

DELIRIUM
IN
CHILDREN AND ADOLESCENTS

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Abbreviations

ADL	Activities of daily living
AIDS	Acquired Immunodeficiency Syndrome
AMS	Acute changes in mental status
APA	American Psychiatric Association
APACHE	Acute Physiology and Chronic Health Evaluation
APOE4	Apolipoprotein E4
CEEU	Clinical Effectiveness and Evaluation Unit
CGI-I	Clinical Global Impression-Improvement
CNS	Central Nervous System
CTD	Cognitive Test for Delirium
CT	Computerised tomography
DAP	Delirium Abatement Program
DC: 0-3R	Diagnostic classification of mental and developmental disorders of infancy and early childhood: Revised edition
DRS	Delirium Rating Scale
DRS-R-98	Delirium Rating Scale-Revised-98
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECT	Electroconvulsive therapy
EEG	Electroencephalogram
FDA	Federal Drug Administration
HIV	Human Immunodeficiency Virus
HAART	Highly active anti-retroviral therapy

ICD	International Classification of Diseases
ICU	Intensive Care Unit
IRIS	Immune Reconstitution Inflammatory Syndrome
IVI	Intravenous
LOC	Level of consciousness
mg	Milligrams
mYPAS	Modified Yale Preoperative Anxiety Scale
NICE	National Institute of Clinical Excellence
NMS	Neuroleptic Malignant Syndrome
PAED	Paediatric Anaesthesia Emergence Delirium
PD	Paediatric delirium
PICU	Paediatric Intensive Care Unit
PIM	Paediatric Index of Mortality
PRISM	Paediatric Risk of Mortality
RCT	Randomised controlled trial
ROC	Receiver operator curve
SLE	Systemic Lupus Erythematosis
SPECT	Single Positron Emission Computerised Tomography
TBSA	Total Body Surface Area
WHO	World Health Organisation

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Abstract

Delirium is increasingly regarded as a spectrum disorder, with subsyndromal forms merging imperceptibly with 'normal' consciousness. The traditional distinction between delirium and dementia has also become eroded, with a growing awareness of the significant residual deficits associated with delirium in adult patients. Delirium in adults has been reconceptualised as a disorder with significant morbidity and mortality, over and above that associated with its underlying causes. However, as a spectrum disorder operationally defined without a 'distress and/or impairment' criterion, the question of where exactly delirium starts and where delirium ends clearly has important implications for management. In addition, the evidence base for pharmacotherapy of delirium in adults remains insubstantial and methodologically flawed.

Through the use of a systematic review of the literature and a case series of children and adolescents diagnosed with delirium, I attempt to highlight relevant continuities and discontinuities between the syndrome of delirium as it presents in childhood and adolescence, and as it presents in adulthood and old age.

Mirroring trends in the adult delirium literature, the scarce literature addressing delirium in children and adolescents suggests that in addition to being common, the disorder may be associated with residual cognitive and behavioural impairments. In paediatric consultation liaison psychiatry settings, the diagnosis of delirium is also associated with a mortality rate as high as 26%.

I also present an illustrated conceptual model of the etiopathogenesis of delirium in children and adolescents, and data supporting the existence of certain high-risk groups. Paediatric delirium may have both a benign and a malignant form, but the correlates of 'malignant paediatric delirium' remain unclear at this time.

The operational diagnostic criteria for delirium currently in use may be at best inadequate, and at worst, inappropriate, for use in children. While the range of symptoms of delirium occurring in all age groups is similar, a relatively unique phenomenological profile and an

increasing awareness of the difficulty in eliciting the currently defined 'core' features of delirium in children suggest that we may need to look beyond DSM IV-TR criteria in the diagnosis of delirium in children. Similarly, delirium rating instruments derived from adult and geriatric delirium research appear to have a degree of face validity in children, and yet their sensitivity, specificity, predictive values and reliability remain unknown in this age group. Synthesizing data obtained from a systematic literature review and case series, I present an argument for the creation of both developmentally sensitive consensus operational diagnostic criteria for delirium in children, and a delirium rating instrument specific to children.

In addition, I report further open, uncontrolled evidence for the modest effectiveness of adjunctive haloperidol and risperidone in children and adolescents with. Lastly, I present a proposal for a treatment algorithm for delirium in children and adolescents, which incorporates threshold indications for the use of antipsychotic medications in child and adolescent delirium.

Preface

The syndrome of delirium is a commonly encountered clinical problem in the context of paediatric consultation-liaison psychiatry.

My first experience of trying to assess and manage a child with a delirium occurred on one of the general paediatric wards at Red Cross Children's Hospital. This involved a 4 ½-year-old boy who had recently returned to the ward from the Paediatric Intensive Care Unit following a liver transplant. He had become psychotic and uncontrollably agitated over the course of 24 hours. The referral to the Consultation-Liaison Psychiatry Unit of the Division of Child and Adolescent Psychiatry was most notable for the level of urgency conveyed by the referrer. Rarely had I encountered a child so agitated and distressed. I found myself having to rely heavily on my experiences with adult and even elderly patients with delirium, and I recall feeling quite inadequately prepared. It was a distinctly unsettling experience. Two renowned child and adolescent psychiatry textbooks proved to be of little assistance, providing only a cursory mention of delirium. I decided to perform a literature search. What I discovered was a quite startling lack of published literature relating to almost any aspect of delirium in children and adolescents. It was also clear that the evidence base for management of the disorder in children remained at the very lowest level of evidence: case series, case report, and expert opinion.

Within a relatively short period of time in the Consultation-Liaison Psychiatry Unit of the Division of Child and Adolescent Psychiatry I also discovered that delirium was a relatively common reason for referral from the inpatient paediatric wards. In light of the scarcity of literature relating to the subject, and the fact that I found myself frequently needing to assess and manage referrals similar to the one described above, I decided to undertake a systematic literature review. The results of my initial *unsystematic* literature search had suggested that, with only a few exceptions, there was little high quality published research on the subject of delirium in children and adolescents. I therefore decided to perform a systematic literature review of all of literature relating to *any* aspect of delirium in this age group in any language. The purpose of this review was fourfold.

1. To identify evidence of both continuities and discontinuities (should they exist) between the syndrome of delirium as it occurs in children and adolescents, and as it occurs in adults.
2. To identify gaps in the knowledge base relating to delirium in children and adolescents - areas where perhaps insufficient literature exists to allow for such continuities and discontinuities to be discerned.
3. To clarify unanswered research questions in relation to delirium in children and adolescents and thus direct further research.
4. To allow me to institute best clinical practice in the management of my child and adolescent patients suffering from delirium, based on the best available current empirical evidence.

To the best of my knowledge, at the time of writing, no systematic literature review addressing all aspects of delirium in children and adolescents has previously been conducted.

Simultaneously, I decided to document in detail the cases of childhood and adolescent delirium I was seeing in the form of a Case Series. Over the course of a 2-year period I have systematically documented my experiences with 23 child and adolescent patients who were referred to the Consultation-Liaison Unit and subsequently diagnosed with delirium. My hope was that my own clinical experiences might address some of the large gaps in the existing knowledge base in this area, and perhaps even begin to answer some of the previously unanswered questions elucidated by my systematic literature review. Additionally, the purpose of the case series was:

1. To describe the first case series of delirium in children and adolescents from a low-income country
2. To evaluate how delirium is best practically assessed and diagnosed in this age group
3. To describe the use of 3 delirium rating instruments in both delirious and non-delirious children and adolescents

4. To describe in detail a non-pharmacological approach to management of delirium in this age group
5. To establish a threshold for the use of antipsychotic medication in children and adolescents with delirium, and
6. To systematically evaluate the effectiveness of both typical and atypical antipsychotic medications in the treatment of childhood and adolescent delirium

The results of these two undertakings, a systematic review of the literature and a case series of children and adolescents with delirium, are presented in this dissertation.

The work is described in 3 main sections.

In Chapter 1, I attempt to provide a conceptual introduction to the subject of delirium and to clarify why childhood delirium, despite its apparent neglect in the literature, is a disorder of potentially great importance. In this section I have also included some thoughts on the origins of delirium's relative neglect by researchers.

In Chapter 2, I present a systematic review of the literature relating to all aspects of delirium in children and adolescents. The results of the systematic review are discussed under several subheadings. In order to place the results of the review in the context of wider research, I have introduced each subsection of the review with an overview of the relevant literature relating to delirium in adult populations. As a contextual 'backdrop' to the review I found it necessary to conduct an unsystematic but thorough review of the existing literature relating to delirium in adult and geriatric patients. The research into delirium in these populations is far more advanced than the research in children and adolescents, and in recent years there has been a vast expansion of the field. This 'secondary' literature review has allowed me to discuss the child and adolescent delirium literature in relation to the data relating to adults, and more clearly elucidate gaps in the literature addressing delirium in children and adolescents. In addition to highlighting gaps in the existing knowledge base, the literature review of adult delirium has also allowed me to elucidate discrepancies between the syndrome of delirium in children, adolescents, adults and the elderly.

In Chapter 3, I describe a Case Series of 23 children and adolescents with delirium that I assessed and managed over the course of a 2-year period during which I was working within the Consultation-Liaison Psychiatry Unit at Red Cross Children's Hospital in Cape Town. In the discussion I place particular emphasis on the management aspects of delirium in these 23 children and adolescents. In addition, I discuss 3 cases of delirium occurring in Human Immunodeficiency Virus (HIV) positive children in some detail in order to illustrate the complexities of assessing and treating delirium in this population.

In my Conclusion to the dissertation I attempt to highlight and summarise to what extent the Case Series addresses the gaps in the literature elucidated by the systematic review of the literature of delirium in children and adolescents. Additionally, I attempt to highlight and summarise the continuities and discontinuities between delirium in children and delirium in older populations evident from my own work and the work of others. Finally, I outline a proposed algorithm (Appendix I) for the management of delirium in children and adolescents. This algorithm has emerged from a synthesis of the existing literature relating to delirium in children, adolescents, adult and geriatric patients, and my own clinical experience with managing delirium in children and adolescents. I also attempt to clarify which gaps in the knowledge base relating to delirium in children and adolescents have *not* been addressed by both the Case Series described above and the work of others who have published in this area. Lastly, I present my thoughts as to how some of the remaining unanswered questions might be addressed using different methodologies.

Chapter 1

Introduction

1.1 The concept and history of delirium

In diseases of the body the mind often goes astray; for it loses its reason and drivels in its speech and often in a profound lethargy is carried into deep and never-ending sleep with drooping eyes and head; out of which it neither hears the voices nor can recognise the faces of those who stand round calling it back to life.

(Lucretius, c.98-55 B.C., translated by Munro, 1952, p.36)

Descriptions of delirium in the literature date back more than 2000 years. Hippocrates in *On Epidemical Diseases*, circa 400 B.C., provided a vivid account of what contemporary clinicians would refer to as a hyperactive delirium.

Erasinus, who liv'd by the Torrent of Bootes, grew very feverish after supper, and had a very bad night. The first day he was easy, but in pain the night. The second, worse in all respects, and at night light-headed. The third, uneasy, and very delirious. The fourth, exceedingly ill, and had no sleep at night, but dream'd and talk'd, and afterwards remarkably worse, frighten'd and impatient. The fifth, betimes in the morning was compos'd and came perfectly to himself, but before noon was so raving mad, that he could not contain himself. His extreme parts were cold, and somewhat livid, his urine stopped and about sunset he dy'd.

(Hippocrates, c. 400 B.C., translated by Clifton, 1752, pp. 75-76)

Hippocrates' description illustrates well the characteristic temporal course of delirium: acute onset, rapidly fluctuating with periods of relative lucidity and nocturnal exacerbations.

The ancient Greeks in fact distinguished two forms of a mental disturbance associated with fever and other serious illnesses. They recognised both *phrenitis* (frenzy) and a quiet form *lethargus* (lethargy), similar to Lipowski's (1983) contemporary hyperactive and hypoactive subtypes of delirium (Francis, 1992).

Celsus was the first to introduce the concept of *delirium* (*de lira*, 'off the path') in the 1st century, using the term to distinguish this entity from mania, depression and hysteria (De Rooij *et al.*, 2005). However, from the time of Celsus until the end of the nineteenth century the meaning of the term 'delirium' remained ambiguous, resulting principally from the fact that the term was used by medical and psychiatric writers in different ways (Lipowski, 1980, p.5). Some writers used the term as a synonym for insanity or a derangement of the mind, whilst others restricted its use to refer to transient, acute mental disorder associated with physical illnesses. Lipowski (1980, pp.5-27) traced the shifting and ambiguous meanings of the term delirium from Celsus in the first century A.D., through Galen (c.A.D. 129-199), Paulus Aegineta (A.D. 625-700), Avicenna (A.D. 980-1037), and into the 19th century and beyond.

According to Lipowski (1980, p.16), Erasmus Darwin, the grandfather of Charles Darwin, was probably the first writer to propose that the manifestations of delirium were a result of impaired or reduced consciousness. Hughlings Jackson (1931, pp.221-222) provided a conceptual schema for interpreting the symptoms of delirium in terms of levels or degrees of consciousness ('there may be slight affections of consciousness, a slight confusion of thought, and from this there are all degrees down to deepest coma').

In 1944, Romano and Engel (1944a; 1944b; 1944c) described the electroencephalogram (EEG) tracings in delirious patients, reporting that their findings suggested diffuse cortical dysfunction. It was not until 1980, however, that the concept of delirium was standardised and operationalised as a nosological and clinical entity in the American Psychiatric Association's *Diagnostic and Statistical Manual*, 3rd edition (DSM-III) (American Psychiatric Association, 1980). The term

'delirium' was selected above other synonyms and a definition proposed. This was also the year that saw the publication of *Delirium: Acute Brain Failure in Man*, a 567-page volume devoted entirely to the subject of delirium (Lipowski, 1980). The previous edition of the *Diagnostic and Statistical Manual* (Second Edition, 1968) had not included the term delirium, but had referred to 'acute organic brain syndromes'.

The term 'delirium' is still used today in the two preferred international diagnostic classification systems – the ICD-10 (World Health Organisation, 1992) and the DSM-IV-TR (American Psychiatric Association, 2000).

Delirium is an etiologically non-specific neuropsychiatric syndrome – a final common pathway for a wide variety of insults to the central nervous system, in much the same way as cardiac failure can be the common expression of a large number of different insults to the cardiovascular system.

As a neuropsychiatric syndrome it is an example of what used to be referred to as the 'organic mental disorders' in the 3rd Revised edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III-R) (American Psychiatric Association, 1987) until the term was dropped in the 4th edition (DSM-IV) because of the unfortunate implication that 'nonorganic' or 'functional' mental disorders do not have a biological etiology or substrate. It is now widely accepted that the 'organic' versus 'psychiatric' dichotomy is ultimately a semantic distinction, determined by our current level of understanding (or lack thereof) of the neurophysiological substrate of central nervous system disturbances.

The concept of delirium has survived two millennia of attempts at definition and redefinition, but remains plagued by what Henry and Mann (1965) termed a 'plethora of diagnostic terms and classificatory rubrics', both across and within different medical disciplines. More than 25 terms are used in the literature to refer to delirium (Pandharipande *et al.*, 2005), the most common of which are 'acute confusional state', 'acute encephalopathy', 'toxic confusional state', and 'intensive

care unit psychosis' (McGuire, 2000). Others include 'subacute befuddlement', 'acute brain dysfunction', 'acute brain failure', 'cinchonism', 'paraneoplastic encephalitis', 'sundowning', 'cerebral insufficiency' and 'acute organic brain syndrome'. The multiplicity of terms used to describe delirium has resulted in ambiguity, confusion, and variable thresholds for making the diagnosis (Meagher, 2001).

Lipowski (1967), referred to delirium as the 'Cinderella' of English-language psychiatry – 'taken for granted, ignored, and not considered worthy of study'. Confusion in the nosology relating to confusional states may well have contributed to delirium's status as relative pariah within psychiatric research (Lipowski, 1980; Meagher, 2001). Another contributing factor to its relative neglect as a subject of research may relate to the fact that delirium, while straddling somewhat uncomfortably the border zone between internal medicine and psychiatry, has always been at risk of falling between the cracks. Delirium is a psychiatric syndrome more often initially presenting to physicians than to psychiatrists - on acute medical wards, intensive care units, and anaesthetic recovery rooms - and is thus more commonly managed by physicians than psychiatrists. Psychiatrists, with the exception of those working in Consultation-Liaison or Old Age Psychiatry, will rarely encounter delirium. Physicians, on the other hand, may encounter it commonly, but may regard it as 'part of the scenery', a nonspecific concomitant of serious physical illness with few implications for treatment or prognosis (Pandharipande *et al.*, 2005).

The subject of delirium is generally looked upon by the practical physician as one of the most obscure in the chain of phenomena he has to deal with; whilst the frequency of its occurrence under various diseased conditions of the system renders the affection not a little familiar to the eye.

(Gallway, 1838; cited in Lipowski, 1980, pp. 26-27)

Delirium is a pleomorphic and characteristically fluctuating condition that can superficially mimic most other psychiatric conditions. It is a nonspecific syndrome-

based diagnosis with no pathognomonic features or definitive tests, and our understanding of its neurochemical basis remains crude. Delirium may well be more accurately conceptualised as a poorly defined zone on a continuum of consciousness or a spectrum disorder (Henry and Mann, 1965; Trepacz *et al.*, 2004; Schieveld, 2008).

Schieveld (2006) has argued convincingly the conceptual similarities between delirium and catatonia as nonspecific, final common pathway 'reaction types of the brain' to a variety of 'organic' disturbances. Both catatonia and delirium have multiple medical etiologies, fluctuating and variable courses, diverse manifestations, and both have 'bipolar' hyperactive and hypoactive forms. Like anaemia or fever, these disorders are most commonly evidence of an underlying disease rather than separate disease entities in themselves.

Delirium has also been termed the 'organ failure' of the brain, analogous to the end-organ damage of other organs resulting from severe systemic disease (Lipowski, 1980; Ouimet *et al.*, 2007a). However, it has also become apparent that the brain is far from a passive end-organ 'victim' in this process, expressing diffuse dysfunction in the form of a delirium. Local central nervous system (CNS) inflammatory responses to a variety of 'insults' have been hypothesized not only to alter brain neuronal function (thereby potentially generating the manifestations of delirium), but also to act as catalyst in the process of *peripheral* cytokine-mediated, multi-organ dysfunction (Pandharipande *et al.*, 2005).

In recent years the conceptual boundaries of delirium have become increasingly eroded. Subsyndromal, 'veiled' and 'emerging' forms of delirium and the existence of *residual* cognitive deficits and functional impairments have blurred the boundaries between both delirium and 'normal' consciousness, and delirium and dementia. Reconceptualised as a 'spectrum disorder' in recent years, the absence of a 'distress and/or impairment' criterion in current DSM-IV-TR operational diagnostic criteria for delirium has created ambiguity in the delineation of where

delirium starts and ends on a continuum of altered consciousness. This has implications for treatment that have not yet been adequately addressed.

Delirium has been subjected to caricature and stereotyping in both lay and medical settings. The layperson commonly equates the term 'delirium' to manic-like states that are not necessarily pathological, as in the phrase 'deliriously happy'. It is also unfortunate that the term 'delirium' is all too often linked with the term '*tremens*' in the minds of many clinicians as well as laypersons. As a result, the common stereotype of the delirious patient is the grossly tremulous, agitated, and floridly psychotic alcohol-dependent person in the throes of severe alcohol withdrawal.

Charles Dickens illustrated this familiar stereotype of delirium with his description of *delirium tremens* in 'The Stroller's Tale' of *The Pickwick Papers*, first published in 1837.

...every way he turned, some obstacle impeded his progress. There were insects, too, hideous crawling things, with eyes that stared upon him, and filled the very air around, glistening horribly amidst the thick darkness of the place. The walls and ceiling were alive with reptiles--the vault expanded to an enormous size - frightful figures flitted to and fro--and the faces of men he knew, rendered hideous by gibing and mouthing, peered out from among them; they were searing him with heated irons, and binding his head with cords till the blood started; and he struggled madly for life.

(Dickens, 1986, pp.46-47)

In Mark Twain's *Adventures of Huckleberry Finn*, originally published in 1884, Huck's father provided another classic literary illustration of the popular stereotype of agitated or hyperactive delirium with prominent psychotic symptoms:

I don't know how long I was asleep, but all of a sudden there was an awful scream and I was up. There was pap looking wild, and skipping

around every which way and yelling about snakes. He said they was crawling up his legs; and then he would give a jump and a scream, and say one had bit him on the cheek – but I couldn't see no snakes. He started and run round and round the cabin, hollering "take him off! He's biting me on the neck!" I never saw a man look so wild in his eyes. Pretty soon he was all fagged out, and fell down panting; then he rolled over and wonderful fast, kicking things every which way, and striking and grabbing at the air with his hands, and screaming and saying there was devils a-hold of him

(Twain, 1994, pp.38-39)

Unfortunately, this image of delirium is an inaccurate, misleading and potentially dangerous stereotype, because it in fact represents the minority of cases and is likely to lead to variable thresholds for diagnosis and the underdetection of somnolent, psychomotorically-retarded delirious patients (Meagher, 2001).

Three major subtypes of delirium have been described – hyperactive, hypoactive, and mixed (Lipowski, 1983). Patients are categorised on the basis of alertness and psychomotor activity. *Hyperactive* delirious patients are restless, agitated or combative, hyperalert and often have hallucinations and delusions. Both Mark Twain and Charles Dickens' depictions would be classified as examples of hyperactive delirium. *Hypoactive* delirious patients, on the other hand, have decreased mental and physical activity, and inattention. They appear lethargic, drowsy and sometimes sedated; they respond slowly to questions and may hardly move spontaneously. Patients who manifest both these above-mentioned characteristics during a single delirium episode are said to have a mixed delirium (Liptzin and Levkoff, 1992). Contrary to the popular stereotype, the pure hyperactive subtype would appear to be comparatively rare, at least in adult populations (Peterson *et al.*, 2003).

Almost 2500 years after Hippocrates' description, the concept of delirium continues to evolve. In 2007, Bhat and Rockwood still felt justified in remarking: 'Can it still

make sense to ask: “what is delirium?”” In proposing novel operational criteria for delirium these authors appeared to answer their question with an affirmative. Since the publication of operational criteria in DSM-III the distinctions between delirium, and both dementia and normal consciousness, have gradually become blurred (Schieveld *et al.*, 2007; Inouye and Ferrucci, 2006). The result is that delirium, as an ambiguously defined, characteristically fluctuating and protean disorder with increasingly indistinct boundaries remains an elusive condition. Amidst the shifting sands of normal childhood development the syndrome of delirium - Bhat and Rockwood’s (2007) ‘unanchored narrative self’ - eludes our grasp even more effectively.

1.2 Definitions

In the DSM-IV-TR, delirium is included in the chapter entitled ‘Delirium, Dementia, and Amnestic and Other Cognitive Disorders’ This brings together disorders in which the predominant disturbance is a clinically significant deficit in cognition which represents a significant change from a previous level of cognitive functioning (American Psychiatric Association, 2000). In DSM-III-R all these disorders would have been grouped under the heading ‘Organic Mental Syndromes and Disorders’ (American Psychiatric Association, 1987).

DSM-IV-TR defines delirium (Box 1.1), as a *disturbance* of consciousness accompanied by a change in cognition that develops over a short period of time, and that cannot be accounted for by a preexisting or evolving dementia (my italics). In addition, there should be evidence from the history, physical examination, or laboratory tests, that the delirium is a *direct* physiological consequence of a general medical condition. DSM-IV-TR then subdivides delirium on the basis of presumed etiology: Delirium Due to a General Medical Condition, Substance-Induced Delirium, Delirium Due to Multiple Etiologies, and lastly, Delirium Not Otherwise Specified, for those instances in which a specific underlying etiology can not be elucidated (American Psychiatric Association, 2000).

Box 1.1 DSM-IV-TR Diagnostic Criteria: Delirium Due to a Medical Condition

- A. Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention.
- B. A change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia.
- C. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.
- D. There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition.

(American Psychiatric Association, 2000, p.143)

ICD-10, in contrast, retains the general term 'Organic Mental Disorders', and includes delirium under this heading (Box 1.2). The ICD-10 *Clinical Descriptions and Diagnostic Guidelines* describes delirium as:

an etiologically nonspecific syndrome characterised by concurrent disturbances of consciousness and attention, perception, thinking, memory, psychomotor behaviour, emotion, and the sleep-wake cycle.

And further:

the distinction that is sometimes made between acute and subacute delirium is of little clinical relevance; the condition should be seen as a unitary syndrome of variable duration and severity ranging from mild to very severe

(World Health Organisation, 1992, pp. 57- 59)

Box 1.2 ICD-10 Diagnostic Guidelines for Delirium

For a definite diagnosis of delirium, ICD-10 requires symptoms in **each** of the following areas:

- A. Impairment of consciousness and attention (on a continuum from clouding to coma, with reduced ability to direct, focus, sustain, and shift attention.)
- B. Global disturbance of cognition (perceptual distortions, illusions and hallucinations – most often visual, impairment of abstract thinking and comprehension, with or without transient delusions, but typically with some degree of incoherence; impairment of immediate recall and recent memory but with relatively intact remote memory; disorientation for time as well as, in more severe cases, for place and person)
- C. Psychomotor disturbance (hypo- or hyperactivity and unpredictable shifts from one to the other; increased reaction time; increased or decreased flow of speech; enhanced startle reaction).
- D. Disturbance of the sleep-wake cycle (insomnia, or in severe cases, total reversal of the sleep-wake cycle; daytime drowsiness; nocturnal worsening of symptoms; disturbing dreams and nightmares which may include hallucinations on waking)
- E. Emotional disturbances – depression, anxiety , fear, irritability , euphoria, apathy or perplexity

The onset is usually rapid, the course diurnally fluctuating, and the total duration of the condition less than 6 months. The above clinical picture is so characteristic that a fairly confident diagnosis of delirium can be made even if the underlying cause is not clearly established. In addition to a history of an underlying physical or brain disease, evidence of cerebral dysfunction (e.g. an abnormal electroencephalogram, usually but not invariably showing slowing of the background activity) may be required if the diagnosis is in doubt.

(World Health Organisation, 1992, pp. 58-59)

ICD-10 criteria for delirium (Box 1.2) are somewhat more restrictive than those of DSM-IV-TR.

The diagnosis of delirium is based on clinical judgment *supplemented* by the use of diagnostic criteria guidelines such as those provided by the DSM-IV-TR and ICD-10. Special investigations like the electroencephalogram (EEG) provide helpful but supportive evidence only. The diagnosis of delirium is arrived at through the recognition of a specific cluster of symptoms and signs with a peculiar temporal course in the context of physical illness or substance use. In the absence of pathognomonic features or special investigations with 100% specificity or sensitivity, the 'gold standard' for the diagnosis of delirium is likely to remain Spitzer's proposed 'LEAD' standard (Spitzer *et al.*, 1983).

'L' – *Longitudinal*

This means that the diagnostic evaluation is not limited to a single examination done at one point in the evolution of the illness, such as an initial evaluation performed on admission to hospital. Symptoms that only emerge or are identified after an initial evaluation are also taken into account in diagnosing the entire episode of illness

(Spitzer et al., 1983, p.408)

In the case of delirium, this is a vital aspect of the diagnostic assessment. Ideally, serial mental state examinations and cognitive evaluations are required. Delirium is a characteristically fluctuating condition, and single 'snapshot' assessments are likely to lead to higher rates of underrecognition and misdiagnosis.

'E' – Expert

The criterion diagnoses are made by expert clinicians who have demonstrated their ability to make reliable diagnoses. These expert clinicians will make independent diagnoses, based on thorough clinical interviews, discuss the reasons for diagnostic disagreement, and then make consensus diagnoses that will constitute criterion measure.

(Spitzer et al., 1983, p.408)

In the case of paediatric delirium, the 'gold standard' would include diagnoses made by an experienced child psychiatrist. Diagnostic consensus would ideally include other child psychiatrists and paediatric neurologists.

'AD' – All Data

The expert clinicians will not only systematically evaluate the subject, but will interview other informants, such as family members, and will have access to data provided by other professionals, such as ward personnel and previous therapists.

(Spitzer et al., 1983, p.408)

In the case of paediatric delirium, 'all data' could potentially include collateral history from the primary paediatric team, nursing staff (including the night nursing staff), allied professional staff, family members, and results of special investigations (in particular the electroencephalogram)

The diagnosis of delirium is essentially a two-part process. The first part involves the diagnosis of the syndrome of delirium. The second part of the diagnosis involves the assignment of a probable etiology, for example, according to DSM-IV-TR, 251.2 'Delirium Due to Hypoglycemia', or, 291.0 'Alcohol Withdrawal Delirium'.

When the etiology is uncertain, the diagnosis can be recorded as 780.09 'Delirium Not Otherwise Specified' or, when a substance is judged to be an etiological factor but the specific substance is unknown, 292.81 'Unknown Substance-Induced Delirium' (American Psychiatric Association, 2000).

Despite the attempts at standardizing both the nomenclature and clinical definition of delirium by both the ICD-10 and the DSM-IV-TR, confusion with regards to definition and terminology remain, particularly between psychiatry and medicine.

1.3 The confusion about confusion

1.3.1 Introduction

The problems relating to terminology extend beyond the common usage of numerous synonyms for delirium by different medical disciplines. One of the reasons why delirium seems to be neglected, often undetected and frequently misdiagnosed may relate to the current psychiatric terminology used to *define* delirium (Bhat and Rockwood, 2007). Even to a psychiatrist the terminology can seem vague and cumbersome, and it should be remembered that delirium is most commonly encountered and managed by non-psychiatrists.

One of the reasons for the 'confusion' relates to the difficult concept of 'consciousness'. The current usage of terms such as normal, diminished, disturbed, restricted or 'clouded' consciousness remain ripe with ambiguity, and create enormous difficulty in the practical assessment of delirium at the bedside. A second area of 'confusion' relates to the current use of both categorical and dimensional models of delirium, and a third relates to the increasingly blurred boundary between delirium and dementia. Each of these problematic aspects will now be addressed in greater detail.

1.3.2 The problem with 'consciousness'

In the DSM-IV-TR diagnostic criteria for delirium, the very first criterion, Criterion A, an essential or core feature of delirium, is defined as 'a disturbance of consciousness' (American Psychiatric Association, 2000). However, the nature of 'consciousness' continues to defy satisfactory definition, potentially approached from phenomenological, spiritual, evolutionary, biological and philosophical standpoints. Lipowski (1980) emphasized that there appeared to be no 'generally accepted definition of consciousness'. Consciousness is clearly not an all-or-none phenomenon, and it is unclear as to what constitutes 'normal' consciousness. Consciousness can be considered from both quantitative and qualitative viewpoints. Fish (1967, pp. 82-85), for example, distinguished 3 broad ways in which consciousness (defined in this instance as 'a state of awareness of the self and the environment') could be altered: dream-like changes of consciousness; lowering of consciousness; and restriction of consciousness. All 3 of Fish's disturbances of consciousness can occur in delirium.

Quantitatively, crude divisions can be drawn between states depending on the relative presence or impairment of consciousness. And yet consciousness is also not a unitary phenomenon. Altered states of consciousness may occur in which certain *aspects* of consciousness, like sensation, perception, memory and judgment are enhanced or impaired relative to other aspects. Levels of consciousness (alertness, awareness, and attentiveness) may be pathologically increased or decreased. A 'disturbance' of consciousness may therefore reflect either a qualitative or quantitative alteration, and if quantitative, may reflect either a decrease *or* increase in conscious level.

Levels of alertness may be increased in association with increased arousal and hypervigilance in certain delirious states, most notably those that are substance-related. Diminished levels of consciousness can be defined on a continuum, and Trzepacz and colleagues (2004), for example, define delirium as a state of consciousness lying on a continuum between normal alertness/wakefulness and

stupor. These authors also acknowledge that the precise delineation between severe hypoactive delirium and stupor is difficult. Sadock (2005, p.858) defines 'stupor' as:

A state of decreased reactivity to stimuli and less than full awareness of one's surroundings; as a disturbance of consciousness, it indicates a condition of partial coma or semicoma.

The DSM-IV-TR defines stupor as 'a state of unresponsiveness with immobility and mutism' (American Psychiatric Association, 2000).

It can be seen that even the first 'core' diagnostic criterion of delirium as currently defined in the DSM-IV-TR is laden with ambiguity, and little guidance is provided as to how a 'disturbance of consciousness' might be evaluated and rated at the bedside (Trzepacz *et al.*, 2004; Bhat and Rockwood, 2007).

When faced with a patient presenting with diminished awareness and responsiveness, clinicians often turn to the Glasgow Coma Scale (Teasdale and Jennet, 1974), which can be objectively used to quantify these aspects of consciousness and facilitate communication between clinicians, without the need for vaguely defined terms like 'stupor', 'torpor', 'semicoma' or 'obtundation'. However, the Glasgow Coma Scale primarily addresses diminished levels of consciousness at the extreme end of the spectrum, providing a crude measure of awareness and responsiveness to voice, touch and pain. The scale is insensitive to the more subtle disturbances of consciousness commonly present in delirium that may manifest with distractibility, inability to sustain attentional focus or shift attention from one task to another. Baseline bedside cognitive tests of attention and vigilance are not routinely performed, and where more subtle deficits might be suspected, clinicians tend to rely more heavily on basic tests of orientation and recent memory, which may be insensitive markers of delirium (Meagher *et al.*, 2007).

Bhat and Rockwood (2007) suggested that at least some of the difficulty in operationalising criteria for delirium, conceptualised as a disorder of consciousness, 'simply reflects the at times impenetrable semantic problems in describing fundamental aspects of everyday human conscious experience'. These authors proposed novel operationalised criteria for the acute disturbance of consciousness associated with delirium, characterised by impairments in arousal (both hyper- and hypoarousal), attention, and altered time perception.

1.3.3 Categorical models, dimensional models and boundary issues

As defined in DSM IV-TR and ICD-10, the syndrome of delirium is a discrete categorical entity. Categorical diagnoses have the advantage of facilitating communication and standardizing research, but are poor at addressing boundary or subthreshold forms of the disorder that may yet have prognostic and functional implications, despite not making the criteria for 'caseness'.

A number of authors have postulated that delirium might better be conceptualised as a spectrum disorder. Hart (1936) referred to 'attenuated deliria' and noted that:

The existence of this graded series makes it difficult to mark out any precisely defined syndrome to which the term "delirium" may properly and exclusively be applied. This difficulty is apparent when we seek, in text-books and elsewhere, for a satisfactory definition.

(Hart, 1936, p. 745)

In 1965, Henry and Mann described what they referred to as 'incipient delirium', which might be 'easily missed unless the patient's medical attendants are sufficiently familiar with these features to recognise the importance of the gathering storm' (Henry and Mann, 1965). 'Partial delirium' and 'subsyndromal delirium' have been described in adult intensive care unit patients and elderly medical patients (Ely *et al.*, 2001; Cole *et al.*, 2003). Schieveld and colleagues (2007) have described

'emerging' or 'veiled' delirium in children and adolescents in the paediatric intensive care setting who presented with cognitive and/or attentional disturbances in the context of severe anxiety, without clear agitation or retardation. Prugh and colleagues (1980) described 'subclinical delirium' in a 10-year-old boy with chronic renal disease who presented with depressed mood and subtle cognitive deficits on formal testing with partially reversible severe slowing and disorganisation on electroencephalogram (EEG). Patients with emerging, partial, or subclinical features of delirium may shift further along the spectrum into full syndromal delirium, and subsequently progress even further into states of stupor and coma. Delirium is a characteristically fluctuating condition and patients may shift back and forth along this continuum over the course of the day or even shorter time periods.

1.3.4 The overlap between delirium and dementia

In addition to recent conceptualisations of delirium as a spectrum disorder, converging lines of recent evidence have even begun to challenge the traditional distinction between dementia and delirium (Inouye and Ferrucci, 2006).

Delirium has traditionally been conceptualised as a relatively global impairment of higher cognitive functions that is both transient and acute in onset. Dementia, on the other hand, has traditionally been conceptualised as a relatively global impairment of higher cognitive functions that is gradual in onset, chronic, and usually progressive. However, these distinctions have become increasingly blurred. Firstly, delirium frequently persists for much longer than previously believed, and has been associated with long-term cognitive decline. Dementia is an important risk factor for delirium in older people, and so in this population delirium often appears to be superimposed on dementia. Dementia with Lewy bodies, which shares features with delirium such as fluctuating course and visual hallucinations, may reflect an overlap syndrome. Lastly, recent research has postulated shared underlying pathogenic mechanisms for these disorders, as both delirium and dementia have been shown to be associated with decreased cerebral oxidative metabolism, cholinergic deficiency, and inflammation (Inouye and Ferrucci, 2006).

1.3.5 Summary

In summary, there remain a bewildering number of synonyms for delirium in common usage. The first core criterion of delirium as defined in the DSM-IV-TR (2000) is ambiguous and vulnerable to different interpretations. Additionally, in recent years it has become clear that the conceptual ‘edges’ of delirium are far from sharply delineated. These factors are likely to contribute to underrecognition, misdiagnosis, interdisciplinary misunderstanding and even mismanagement. The situation appears to be sufficiently problematic to have motivated proposals for new operationalised criteria for delirium in the last 2 years.

1.4 Why is delirium important?

1.4.1 Introduction

In recent years there has been a rapid expansion of the literature relating to delirium in adult and elderly populations. This literature has done much to dispel the notion that delirium is an insignificant concomitant or ‘part of the scenery’ of severe physical illness. It has become increasingly apparent that delirium in adults is common, often persistent, and associated with significantly increased morbidity and mortality. The financial costs associated with delirium are enormous. However, it is a diagnosis that is often missed, misdiagnosed and mismanaged in adults. An evidence base for effective management and prevention of delirium in adults and the elderly has also emerged, suggesting that many of these sequelae might be preventable.

In the following paragraphs I will briefly outline the evidence for the above statements, drawing on the recent literature relating to delirium in adults obtained from my unsystematic but thorough review of the relevant literature published in the last 10 years.

1.4.2 Delirium is highly prevalent

Delirium is a common disorder across treatment settings, and is particularly common in certain populations. Delirium is present in 1-2% of adults in the community, with the prevalence increasing with age, such that the prevalence reaches 14% in those 85 years and older (Folstein *et al.*, 1991; Inouye, 2006). In the adult general hospital population delirium is reported to have an average prevalence of about 20% (Trzepacz, 1996). Siddiqi and colleagues (2006), in a systematic review of the literature, reported a prevalence of delirium on admission to hospital ranging from 10 to 31%, and an incidence of new delirium *per* admission ranging from 3 to 29%. In the intensive care setting delirium has been reported to occur in more than 30% of adults (Ouimet *et al.*, 2007a) and between 70 to 87% of elderly patients (Pisani *et al.*, 2003). Delirium also occurs in 15 to 53% of older people post-operatively (Inouye, 2006).

1.4.3 Delirium is associated with residual deficits

In addition to being common, in adult patients delirium may be slow to resolve, and there is good evidence that symptoms of delirium *persist* in about a third of patients (Young and Inouye, 2007; Siddiqi *et al.*, 2006). There remains controversy relating to the interpretation and meaning of persistent cognitive impairment in long-term follow-up studies of elderly patients with delirium. Some authors have suggested that this may represent damage resulting from the delirium episode itself (Levkoff *et al.*, 1992; Pandharipande *et al.*, 2005; Hopkins and Jackson, 2006), in much the same way as other authors have argued that the psychotic state itself may be 'toxic' to the brain in patients with emerging schizophrenia, resulting in persistent cognitive deficits long after the psychosis has resolved (See McGlashan, 2006 for a discussion of this controversial issue). Other authors have interpreted these persistent deficits as evidence of *pre-existing* 'diminished brain reserve' or subclinical dementia, which only becomes apparent on follow-up when the delirium has in fact resolved (Hopkins and Jackson, 2006).

1.4.4 Delirium is associated with high morbidity and mortality

Delirium, particularly in its more severe form, is associated with increased morbidity, mortality, longer Intensive Care Unit (ICU) stay, and longer hospital stay (Ouimet *et al.*, 2007; Ely *et al.*, 2004). The recent systematic review of Siddiqi and colleagues (2006) reported outcomes for 19 study cohorts and document an increased mortality associated with delirium both at discharge *and* at 12-month follow-up. A rigorous prospective comparison study of medical inpatients with delirium reported a two-fold increase in discharge mortality, an average increase of eight hospital days in the length of stay in hospital, and worse physical and cognitive recovery at 6 and 12 months with increased time in institutional care (McCusker *et al.*, 2003). In non-ICU populations, delirium in hospital is associated with an in-hospital mortality of 25 to 33%, and three times the likelihood of discharge to a nursing home (Pandharipande *et al.*, 2005). Among ICU patients, delirium has been shown to be a strong predictor of mortality in two large prospective studies, and has been associated with a three-fold increase in mortality even *after* controlling for pre-existing comorbidities, severity of illness, and medication use (Pandharipande *et al.*, 2005).

Both hypoactive and hyperactive patients with delirium are at risk of compromising the treatment of their underlying medical condition. Hyperactive delirious patients are frequently uncooperative and aggressive, pulling out intravenous lines and removing dressings, and placing themselves, other patients and staff at risk of injury. Hypoactive patients are apathetic and less able to comply with attempts at rehabilitation. Both subtypes are significantly impaired in their capacity to remain involved in decision-making in relation to their medical treatment.

In addition, the literature suggests high levels of distress in family members and carers (including nursing staff) of patients with delirium. Despite commonly associated memory deficits, 53.5% of adult patients with delirium subsequently recall their delirium as highly distressing (Breitbart *et al.*, 2002). The experience of delirium has even been associated with the secondary development of post-traumatic

stress disorder in adults (Griffiths and Jones, 2007). In addition, the literature suggests that the very development of delirium is associated with fewer interactions and *less* time spent by nurses and physicians in direct patient care (Armstrong-Esther *et al.*, 1986).

1.4.5 Delirium is commonly undetected and misdiagnosed

The literature relating to adults strongly suggests that the diagnosis of delirium is commonly missed across different treatment settings, including primary care, emergency departments, inpatient medical, surgical, and intensive care unit settings (Young and Inouye, 2007; Meagher, 2001; Spiller and Keen, 2006; Weber *et al.*, 2004). Between one- and two- thirds of adult cases are missed across a range of therapeutic settings and by a variety of specialists including psychiatrists and neurologists (Johnson *et al.*, 1992). Bhat and Rockwood (2007) have proposed that one possible explanation for the high rates of underdetection and misdiagnosis may relate to the way in which delirium is defined and conceptualised. Other factors may include delirium's protean, fluctuating nature, and its ability to closely mimic other psychiatric conditions.

Ely and colleagues (2004) reported a survey of 912 healthcare professionals (including 753 physicians), addressing the subject of delirium in an adult intensive care unit. Although 92% of respondents considered delirium to be a serious or very serious problem in the intensive care unit, likely underdiagnosis was acknowledged by 78%. Missed diagnosis of delirium is a significant problem, as non-detection of delirium in emergency departments has been associated with a seven-fold hazard for increased mortality (Young and Inouye, 2007). The situation appears to be worst for those presenting with the hypoactive form of the disorder (Spiller and Keen, 2006; Mittal *et al.*, 2006), despite the fact that the majority of patients present with the hypoactive or mixed form of the disorder rather than the stereotypical hyperactive form (Spiller and Keen, 2006).

When a problem relating to mental state *is* detected in delirious patients, it is commonly misattributed to a primary 'functional' psychiatric diagnosis like schizophrenia, depression, posttraumatic stress disorder, personality disorder, factitious disorder and conversion disorder (Griffiths and Jones, 2007; Spiller and Keen, 2006; Pandharipande *et al.*, 2005), often precipitating the inappropriate use of psychotropic medication (Meagher, 2001). A typical example would be the misdiagnosis of hypoactive delirium as major depression with the subsequent introduction of a tricyclic antidepressant resulting in iatrogenic worsening of the delirium through the medication's anticholinergic effects.

1.4.6 Delirium can be effectively treated

If detected, the underlying precipitant factor of the delirium can often be reversed, removed or at the very least ameliorated. Additionally, symptomatic management of the behavioural disturbances associated with delirium is also effective (Young and Inouye, 2007; Meagher, 2001; Inouye, 2006; Burns *et al.*, 2004). However, despite overwhelming expert consensus in support of both environmental and pharmacological symptomatic treatment of delirium, the empirical evidence for these strategies remains tenuous and flawed.

1.4.7 Delirium is preventable

Simple and inexpensive multicomponent interventions aimed at *preventing* the occurrence of delirium in certain at-risk adult populations have also shown promise (Young and Inouye, 2007; Burns *et al.*, 2004; Weber *et al.*, 2004). These will be discussed in some detail in the 'Prevention' subsection (2.4.17) of the 'Results and Discussion' section of the systematic literature review.

1.4.8 Delirium is costly

Delirium has been reported to complicate the hospitalisation of at least 20% of the 12.5 million patients 65 years and older who are admitted to hospital each year in the United States, increasing the hospital costs by US\$2500 *per* patient, and resulting in about US\$6.9 billion (value in United States dollars in 2004) of Medicare hospital expenditures being attributable to delirium. (Inouye, 2006)

1.4.9 Summary

In certain adult populations delirium is a common and costly condition associated with significantly increased distress, medical morbidity, and even mortality, over and above that associated with its underlying causes. Though a transient condition, its effects on function may be long lasting. It is commonly underrecognised, misdiagnosed and mismanaged, and iatrogenic factors are commonly contributory to its development. Far from being 'part of the scenery' of serious physical illness, delirium, at least amongst adult and geriatric patients, has increasingly been reconceptualised as a serious condition in its own right. An increasing awareness of the significant morbidity and mortality associated with delirium, independent of that associated with its underlying precipitants and predisposing factors, has heralded an era of more aggressive management of delirium.

1.5 Why is Delirium in Children and Adolescents Potentially Important?

[Kinder delirieren bei Intoxikationen und Infektionen verhältnismäßig leicht; gelegentlich zeigen sie dann katatonische Symptome (z.B. Katalepsie), die unter diesen Umständen keine deletäre Bedeutung haben.]

Children with intoxications and infections succumb to delirium relatively easily; at times they then show catatonic symptoms (eg cataplexy), which under these circumstances have no deleterious significance.

(Bleuler, 1920, p. 155)

Leo Kanner, in the 1942, 3rd edition of *Child Psychiatry* remarked that:

It is astonishing that one rarely finds in the literature satisfactory descriptions of delirious reactions of children despite the fact that they are observed so frequently in the various forms of infantile infections.

(Kanner, 1942, p.179)

Although Bleuler's statement in relation to the relative insignificance of the manifestations of paediatric delirium is now increasingly questioned, Kanner's remains largely true to this day. The existing literature relating to all aspects of delirium in children is woefully inadequate (Schieveld, 2008; De Carvalho and Fonseca, 2008; Martini, 2005; Turkel and Tavare, 2003; Trzepacz *et al.*, 2004), and there are very definite dangers associated with extrapolating findings from the adult delirium literature to the paediatric population, particularly with regards treatment. Few firm conclusions can be drawn.

Like old age, childhood is said to be a vulnerable period for the development of delirium (Henry and Mann, 1965; Prugh *et al.*, 1980; Martini *et al.*, 2004; Grace and Holmes, 2006, Williams, 2007; Trzepacz *et al.*, 2004). No reliable estimates of prevalence in the paediatric population exist in order to confirm or disconfirm the anecdotal impressions of the above-mentioned authors that delirium is common in this age group.

Long-term follow-up studies of delirium in adult patients are few and limited by methodological shortcomings. Follow-up studies of delirium in childhood are non-existent. Nevertheless, the suggestion from a steadily growing adult literature that delirium may have significant implications for cognitive functioning in the longer

term and may also act as an independent risk factor for increased mortality, are cause for concern in this vulnerable population at the other end of the age spectrum.

The prognostic impact of delirium in this age group is largely unknown, but one published study raises the possibility that delirium may be associated with longer hospital stay and a higher mortality in children (Turkel and Tavaré, 2003), and another (Prugh *et al.*, 1980) that mild perceptual-motor and cognitive deficits may *persist* for some weeks after recovery from delirium.

At the very least, reports suggest that delirium in children and adolescents can be associated with severe distress (Martini, 2004). Reports of the development of post-traumatic stress disorder secondary to delirium in adults raise the possibility that this might also occur in children and adolescents in the wake of a delirium.

Several recent reports suggest that symptomatic treatment of delirium in childhood is effective, associated with markedly reduced levels of distress (Schieveld *et al.*, 2007; Stoddard *et al.*, 2006; Martini, 2004; Kamik *et al.*, 2007). Medications commonly used in adults with delirium are frequently used in paediatric patients with delirium despite there being little empirical evidence for their effectiveness. There are also reports of preventive psychopharmacology in cases of paediatric emergence delirium (Vlajkovic and Sindjelic, 2007).

1.6 Paediatric Delirium: What the Textbooks Have To Say

As mentioned in the preface, I initially turned to textbooks and diagnostic guidelines for information relating to delirium in children and adolescents. In the following paragraphs I have provided quotations from a selection of well-known textbooks in order to emphasize the degree to which the subject appears to have been neglected. I have included quotations from general psychiatric textbooks and psychiatric diagnostic guidelines, child psychiatry textbooks, general paediatric textbooks, and finally, paediatric neurology textbooks.

1.6.1 General Psychiatric Textbooks and Diagnostic Guidelines

The *Diagnostic and Statistical Manual of Mental Disorders-IV-TR* (American Psychiatric Association, 2000) offers little guidance on the manifestations and diagnosis of delirium in the paediatric patient. There are no specific criteria for making the diagnosis in this population, with the implication being that the existing criteria are assumed to be validly applicable regardless of developmental age.

DSM-IV-TR has the following to say on the subject of delirium in children:

Children may be particularly susceptible to delirium compared with adults (other than the elderly), especially when it is related to febrile illnesses and certain medications (e.g. anticholinergics). This is perhaps due to their immature brain development and physiological differences. In children, delirium may be mistaken for uncooperative behaviour, and eliciting the distinctive cognitive signs may be difficult. If familiar figures cannot soothe the child, this may be suggestive of delirium.

(American Psychiatric Association, 2000, p. 138)

The ICD-10 (World Health Organisation, 1992) offers no further guidance beyond its clinical description and diagnostic guideline (Box 1.2) in relation to delirium in children.

Samuels and Neugroschl (2005), in the 8th edition of *Kaplan and Sadock's Comprehensive Textbook of Psychiatry* (Sadock and Sadock, Editors) had the following to add:

Paediatric patients, too, are at risk of delirium. The rates of delirium in children are ill-defined, but the literature describes delirium in 10 to 40% of preschool children during emergence from anaesthesia...Diagnosis of delirium in children may have

behavioural change as the sole manifestation. Any change of behaviour or a sleep-wake problem in a young child who is not responsive to soothing from familiar figures may be an indication that an underlying medical condition or substance is at the root cause of the behavioural change. Children may be more apt to have a temporary regression of their development early in the delirium recovery. Fever is commonly associated with delirium in children

(Samuels and Neugroschl, 2005, pp. 1054 -1068)

Gill and Mayou (2003), in the *New Oxford Textbook of Psychiatry* (Gelder, López-Ibor, and Andreasen, Editors) contributed the following:

Children are more susceptible to delirium than adults. They may develop delirium with any severe acute illness, most commonly with pyrexia due to an acute infection. Such cases are frequently seen by general practitioners in the community. The underlying cause may be a simple upper respiratory tract infection, or a serious disorder such as pneumonia.

(Gill and Mayou, 2003, pp. 382-387)

Trzepacz, in the 2004 edition of *Yudofsky's Essentials of Neuropsychiatry and Clinical Neurosciences* (Yudofsky and Hales, Editors) notes that delirium is:

unfortunately understudied in children and adolescents...there has been relatively little study of risk factors for delirium in children and adolescents despite a general belief that children are specially vulnerable to delirium

(Trzepacz et al., 2004, pp. 151)

With regard to treatment it adds:

haloperidol use in paediatric patients with delirium is not well-documented

(Trzepacz et al., 2004, pp. 166)

1.6.2 Child and adolescent psychiatry textbooks and diagnostic guidelines

Neither the 1209-page 4th edition of *Child and Adolescent Psychiatry* (Rutter and Taylor, Editors, 2002), nor the 1114-page 3rd edition of the American Psychiatric Publishing's *Textbook of Child and Adolescent Psychiatry* (Dulcan and Wiener, Editors 2004) include the term 'delirium' in the main body of their text.

The American Psychiatric Press's 1566-page *Textbook of Paediatric Neuropsychiatry*, (Coffey and Brumback, Editors, 1998), makes passing reference to the term 'delirium' in suggesting that

The cognitive side effects of ECT include postictal confusion/delirium and impaired memory.

(Fink and Coffey, 1998, p. 1402)

Elsewhere, in the chapter on traumatic brain injury:

Although delirium occurs in the course of recovery from traumatic brain injury, this term is used only infrequently in this context.

(Arffa, 1998, p. 1108)

Lewis' Child and Adolescent Psychiatry – A Comprehensive Textbook (4th Edition, Martin and Volkmar, Editors, 2007) provides a notable and welcome exception to the general neglect of delirium amongst textbooks of child and adolescent psychiatry. Lewis' textbook devotes 4 pages of a chapter to delirium in children and

adolescents in the chapter by Daniel T. Williams entitled 'Delirium and Catatonia' (Williams, 2007, pp. 647-650). The chapter notes the reportedly higher risk in children for developing delirium under circumstances of physiological stress, and goes on to discuss the disorder under the subheadings of: predisposing factors, clinical features, differential diagnosis, assessment and treatment.

Curiously, one of the most comprehensive discussions in relation to childhood delirium in a child psychiatry textbook remains that of Leo Kanner, in whose 1942 edition of *Child Psychiatry*, there is a detailed discussion of the phenomenology and precipitants of paediatric delirium, and several illustrative case histories (Kanner, 1942).

Similarly, Bollea, in the 1969 edition of *Modern Perspectives in International Child Psychiatry* (Howells, Editor., pp. 706-732), provided a detailed discussion of the etiology and phenomenology of delirium in the chapter 'Acute organic psychoses of childhood'. A number of detailed case histories were also provided.

Curiously, delirium seems to have received considerable attention in the earlier textbooks of child psychiatry such as those of Kanner and Howells, but, paradoxically appears to have been neglected in textbooks published after the introduction of operational diagnostic criteria for the disorder in DSM III.

The *Diagnostic Classification of Mental Health and Developmental Disorders of Infancy and Early Childhood: Revised Edition (Zero to Three, DC:0-3R, 2005)* does not contain the term 'delirium', nor does it offer an alternative term for acute/subacute disturbances of consciousness in neonates and infants.

1.6.3 Paediatric and paediatric neurology textbooks

The term 'delirium' is not mentioned in the 16th edition of *Nelson's Textbook of Paediatrics* (Behrman *et al.*, Editors, 2000).

The text *does*, however, contain a chapter on 'Encephalopathies', dominated by a description of cerebral palsy as an example of a 'static' encephalopathy. The term 'encephalopathy' in this instance is loosely defined as 'a generalised disorder of cerebral function'. A description of 'burn encephalopathy' is included under the subtitle 'Other encephalopathies', in which it is suggested that 'altered states of consciousness, hallucinations, and coma may occur' (Haslam, 2000, pp. 1843-1848).

The 5th edition of *Forfar and Arneil's Textbook of Paediatrics* included a paragraph on:

delirium-like conditions...with impairment of consciousness, hallucinations and illusions are common among children with acute infections. Rarely, a non-infectious agent, for instance acute intermittent porphyria, is responsible.

(Hoare *et al.*, 1998, p. 1739)

The 6th edition (2003), however, eschews the term 'delirium' entirely, opting instead for the use of 'encephalopathy', which it suggests is primarily characterised by decreased level of consciousness (Martland, 2003). The Glasgow Coma Scale (Teasdale and Jennet, 1974) is suggested as a suitable tool for its assessment and monitoring. As already mentioned, one of the difficulties is that this scale is designed to detect and rate fairly coarse measures of reduced level of consciousness, not the more subtle impairments commonly associated with delirium.

The 3rd edition of *Brett's Paediatric Neurology* (Brett, Editor, 1997) comes closer to the modern conceptualisation of delirium in its description of 'encephalopathy':

the term encephalopathy implies a disorder of consciousness and it may be applied to the comatose state or to a continuum of worsening altered states of consciousness from being fully alert and responsive to deep coma.

(Tasker and Cole, 1997, pp. 691-725)

The text goes on to state that ‘awareness or cognition, another feature of the normal conscious state’ is altered in encephalopathy (Tasker and Cole, 1997). As Lipowski (1980, p.38) suggested, ‘*Encephalopathy* is a word used mostly by neurologists and not consistently by anybody’. The 4th edition of *Paediatric Neurology – Principles and Practice* (Brett, Editor, 2006), divides disorders associated with ‘impairment of consciousness’ into 2 broad categories – those with ‘activated’ mental state, and those with ‘reduced’ mental state. A description of ‘delirium’ is provided under the subheading of ‘Impairment of consciousness with activated mental state’ as follows:

Delirium is an activated mental state that may include disorientation, irritability, fearful responses and sensory misperception. Patients may be hyperactive and have signs of increased sympathetic tone. Visual hallucinations, when present, are more common than auditory hallucinations, and the patient may experience delusional thoughts or illusion. Delirium is more likely to involve both cerebral hemispheres than one side of the cerebrum or the brainstem alone. Search for the causes, therefore, should begin with consideration of pathology of both hemispheres. In children, common causes include intoxications, infections, fever, metabolic disorders and epilepsy. Night terrors and non-rapid –eye-movement sleep disorders that occur commonly in children can closely resemble the delirious state.

(Taylor and Ashwal, 2006, p. 1378)

Under the subheading ‘Impairment of consciousness with reduced mental state’ are included ‘obtundation’, ‘stupor’, and ‘coma’ (Taylor and Ashwal, 2006)

It can readily be seen that the term 'delirium' means different things to different people across different medical specialities and subspecialities. Paediatricians generally employ a narrow definition of delirium emphasizing a subtype of delirium characterised by hyperactivity and perceptual disturbance (neither of which are regarded as core criteria for the diagnosis). Psychiatrists and child psychiatrists generally employ a broader definition of delirium emphasizing the acute and transient cognitive deficits.

1.7 What are the Origins of Delirium's 'Cinderella status' in Research?

In a survey of 912 healthcare professionals (including 753 physicians), 92% of respondents considered delirium to be a serious or very serious problem (Ely *et al.*, 2004). In the face of this apparent high level of recognition of delirium as a serious disorder, associated with significant negative outcomes, the widely recognised dearth of literature addressing delirium in any age group until recent years may come as a surprise.

The origins of delirium's relative neglect by researchers may in part have its origins in the nature of the syndrome itself (Meagher, 2001). Delirium is protean in its manifestations and transient and fluctuating by nature. The syndrome generally resolves with correction of the underlying cause of the delirium. However, as already emphasized, problems relating to terminology and definition persist. There remain a bewildering number of terms used in the literature to refer to the delirium syndrome, and it is known by different names by different medical disciplines. Even when applying DSM-IV-TR definitions and diagnostic criteria it becomes apparent that there continues to be an element of ambiguity in the terminology used. The threshold for making the diagnosis, particularly in milder cases, is unclear, and in more recent years the conceptual 'edges' of delirium have become increasingly eroded.

The settings in which delirium arises might also have a part to play in its relative neglect. Delirium is a psychiatric syndrome typically seen in medical or surgical contexts and generally treated by non-psychiatrists. The medical ward, emergency department and intensive care unit have not been the traditional territory of psychiatric researchers. On the other hand, delirium might have been neglected by medical and surgical researchers because the syndrome has been seen as lying within the domain of psychiatry. There is also a sense that delirium, particularly in its milder form, has been regarded as a nonspecific manifestation of acute severe physical illness without much relevance for prognosis or treatment, much like fever. This viewpoint is now increasingly challenged (Hopkins and Jackson, 2006; Trzepacz *et al.*, 2004).

Additionally, the treatment of delirium does not easily lend itself to controlled research studies. The primary and overriding treatment of delirium is correction of the underlying cause. In many instances the cause of the delirium is unclear or suspected as being multifactorial. Disentangling the effects of a particular intervention on the course of delirium from symptomatic resolution resulting from correction of the underlying cause of the delirium, natural fluctuation, or even spontaneous resolution poses many challenges.

The following chapter will present the findings of a systematic review of the international literature relating to delirium in children and adolescents.

Chapter 2

A systematic literature review of delirium in children and adolescents

2.1 Introduction

'You don't know much' said the Duchess 'And that's a fact'

(Carroll, 1998, Alices Adventures in Wonderland, p.53)

A systematic review is a summary of research that uses explicit methods to perform a thorough literature search and critical appraisal of individual studies to identify the valid and applicable evidence. A systematic review uses an objective and transparent approach for research synthesis, with the aim of minimising bias.

To the best of my knowledge there has never been a systematic review of all of the literature addressing all aspects of delirium in children and adolescents. A systematic review is required to clarify the existing gaps in the literature and by so doing, guide further research into delirium in this age group.

The existing literature relating to delirium is extremely limited. It sprawls across a wide range of medical disciplines in which delirium is often known by different names. Pockets of literature addressing the subject can be found in the journals of psychiatry, anaesthesiology, emergency medicine, surgery, and neurology, to name but a few. Delirium is frequently published under a pseudonym such as 'burn encephalopathy' or 'confusional migraine', with its true nature only revealed by closer scrutiny of the article.

A systematic review of the literature relating to this neglected field is necessary in order to pull together these various threads and pockets of research under a single banner, that of 'delirium'.

A rapidly expanding body of literature relating to delirium in adults has largely dispelled previously held notions of delirium as an insignificant concomitant of serious physical illness. Research into delirium in adults has confirmed that the disorder is associated with serious morbidity, residual deficits, and high rates of mortality. A systematic review of the literature relating to delirium in children and adolescents is also necessary at this point in time to clarify the continuities and potential discontinuities between delirium in children and delirium in older people. If no discontinuities are apparent, then the current clinical practice of applying adult diagnostic criteria, adult delirium rating instruments, and management strategies developed for use in adults would seem to be appropriate. However, if a systematic review of the literature were able to reveal significant discontinuities between childhood delirium and delirium in adults or elderly people, then this practice might be called into question.

2.2 Objectives

In light of the above, the objectives of the systematic review of the literature relating to delirium in children and adolescents are as follows:

1. To pull together the scattered and often tenuous literature 'threads' relating to delirium in children and adolescents that have been published under a variety of pseudonyms across a wide range of medical journals
2. To analyse this literature in order to elucidate continuities and discontinuities between delirium in children and adolescents, and delirium in older people
3. To clarify gaps in the knowledge base relating to delirium in this age group
4. To generate the pertinent, currently unanswered questions relating to delirium in childhood and adolescence

5. To inform and guide best clinical practice for children and adolescents suffering from delirium
6. To inform and guide further research in this area

2.3 Methods

A broad search strategy was employed to identify *all* published articles in *any* language relating to any aspect of delirium in children and adolescents.

Searching PubMed (10 July 2008) with the MeSH headings 'delirium' or 'confusional state' combined with the MeSH headings 'child*', 'adolescen*' and 'paediatric' produced the following number of 'hits' as tabulated in Table 2.1. With each search the only additional limit included was excluding articles that had been published prior to 1980, when the DSM III first introduced operational criteria for delirium (American Psychiatric Association, 1980).

Table 2.1 Literature Search Results: PubMed (1980 – July 2008)

PubMed search terms	Limit(s)	Hits
Delirium + child*	From 1980 All fields	1259
Delirium + adolescen*	From 1980 All fields	1530
Delirium + paediatric	From 1980 All fields	78
Confusional state + child*	From 1980 All fields	1952
Confusional state + adolescen*	From 1980 All fields	1699

Table 2.1 (continued) Literature Search Results: PubMed (1980 – July 2008)

PubMed search terms	Limit(s)	Hits
Acute encephalopathy + child	From 1980 Title/Abstract	1252
Acute encephalopathy + adolescent*	From 1980 Title/Abstract	678
Acute confusion + child*	From 1980 Title/Abstract	230

The following non-MeSH headings were also searched in combination with the MeSH headings 'child*' and 'adolescen*': 'acute encephalopathy' and 'acute confusion'. Stricter limits were however placed on these searches to exclude articles prior to 1980 *and* to limit the search to those articles in which the search terms appeared in the title or abstract of the article. A similar search was conducted using PsycINFO (15 July 2008), the results of which are tabulated in Table 2.2

Table 2.2 Literature Search Results: PsycINFO (1980 – July 2008)

PsycINFO search terms	Limit(s)	Hits
Delirium + child*	From 1980 All Fields	168
Delirium + adolescen*	From 1980 All Fields	127
Delirium + paediatric	From 1980 All Fields	23
Confusional state + child*	From 1980 All Fields	6
Confusional state + adolescen*	From 1980 All Fields	6
Acute encephalopathy + child*	From 1980 Title/Abstract	3

Title and/or abstract of the identified articles were then screened for relevance. Those selected as relevant were then read in their entirety. The reference lists of all relevant articles identified using the above strategy were then hand-searched for further relevant articles, and experts who have published in the field of delirium were engaged in personal correspondence in an attempt to obtain unpublished material. In addition, a wide range of potentially relevant books and textbooks (and their reference lists) were hand-searched.

Articles or reports published in languages other than English were translated from the original into English, and treated in a similar fashion.

In contrast, the literature review relating to adult delirium was *unsystematic* and intended to provide context for the systematic review of the child and adolescent delirium literature. I performed a search of PubMed and the Cochrane Library in order to identify relevant articles. I restricted my search to the last 10 years (1998 – 2008), English-language articles, and to studies in the form of review articles and clinical trials. The reference lists of these articles were then hand-searched to identify further studies of relevance.

The existing literature addressing delirium in children and adolescents identified by this literature review will be discussed under a series of subheadings, for example 'epidemiology', 'precipitating factors' and 'morbidity'.

Each subheading will be followed by a brief overview of the relevant literature relating to this aspect of delirium in *adults*, in order to provide some contextual background for the child and adolescent literature. The literature relating to *adult* delirium was derived from a thorough but by no means exhaustive literature search of reviews and studies published in the last 10 years. Wherever possible, the literature obtained from the systematic review of the child and adolescent delirium literature will be related to the recent adult literature.

Much of the existing literature relating to delirium in children and adolescents is in the form of individual case reports. In order to synthesize the information from the relatively large number of published individual case reports, I will present relevant findings from the analysis of this body of literature as if these reports together constituted a case series of their own.

2.4 Results and discussion

2.4.1 Overview of the existing literature

2.4.1.1 Introduction

Figure 2.1 illustrates both the literature search strategy and the results of this search. One hundred and nine publications were deemed potentially relevant after screening the title and abstracts of the PubMed and PsycINFO 'hits' obtained by using the search strategy described above. Seventeen of these articles were subsequently excluded after being read in their entirety and being found to be not relevant to the topic, leaving 92 publications in total.

The literature is essentially limited to small case series and case reports including a total of 217 children or adolescents with *definite* (sufficient data recorded to allow application of DSM-IV-TR criteria) delirium, and a further 136 children and adolescents with 'probable delirium'.

There were fourteen case series which included 288 children and adolescents with definite (n=175) or probable (n=113) delirium (see Table 2.3) published between 1980 and July 2008. A further 65 children and adolescents with definite (n=42) or probable (n=23) delirium have been described in the form of case report in 56 published reports between 1980 and 15 July 2008.

In total, the literature published between 1980 and 2008 describes only 353 children and adolescents with definite *or* probable delirium.

Cases of 'probable delirium' were those reports, often documented using one of the many synonyms for delirium ('acute confusional state', 'confusion', 'encephalopathy' etc.), in which sufficient information relating to the phenomenology, temporal course, outcome, investigations (particularly the EEG) and presumed etiology was included in order to make any psychiatric diagnosis other than delirium unlikely. However, insufficient data was included in order to fulfill DSM-IV-TR diagnostic criteria in these cases.

No controlled treatment trials or systematic literature reviews have ever been published.

The vast majority of the published articles relating to delirium in children and adolescents have originated from high-income countries in North America and Europe. The literature relating to delirium in children and adolescents living in low- and middle-income countries (World Health Organization, 2008) is comprised of only 2 case reports (Lee *et al.*, 2003 and Manaboriboon and Chomchai, 2005).

The bulk of the literature published during this period originates from only 2 research groups, namely those of Schieveld, Leentjens and coworkers (The Netherlands), and Turkel, Tavaré, Trzepacz and coworkers (United States of America).

Jan Schieveld and colleagues originally described a cohort of 40 children and adolescents diagnosed with delirium in the setting of a paediatric intensive care unit at University Hospital Maastricht in The Netherlands (Schieveld *et al.*, 2007). This cohort has now grown to include 46 patients in the most recent published contribution from this research group (Leentjens *et al.*, 2008). In total, 5 articles published in peer-reviewed journals have originated from this research group and

this cohort of patients, comprising a significant proportion of the total published literature relating to delirium in this age group (Schieveld *et al.*, 2007; 2008; Leentjens *et al.*, 2008; Schieveld, 2006; Schieveld and Leentjens, 2005).

Turkel and Tavaré (2003) originally published a retrospective chart review of 84 children and adolescents diagnosed with delirium in the setting of a psychiatric consultation-liaison service provided at Childrens Hospital Los Angeles. This remains the largest case series published to date. Subsequently, this research group has produced a further two articles published in peer-reviewed journals in relation to the original cohort of 84 patients (Turkel, Braslow, Tavaré and Trzepacz, 2003; and Turkel, Trzepacz and Tavaré, 2006).

Since 1980, when DSM-III introduced operational diagnostic criteria for the disorder, delirium in children and adolescents would appear to have been neglected by epidemiological, pathophysiological and clinical researchers alike. Delirium has been excluded from all the major epidemiological studies that have addressed community prevalence of mental and behavioural disorders in youth over the past 28 years. The prevalence or incidence of delirium in community samples in this age group remains uncertain.

The majority of journal publications addressing delirium in childhood and adolescence are in fact single case reports, published for the most part in paediatric rather than psychiatric journals (See Tables 2.5.1 to 2.5.7). Few researchers have addressed risk or etiological factors, and even fewer have addressed potential protective factors. Whilst, relative to other aspects of the disorder, the phenomenology of delirium in this age group has been fairly well characterised (Leentjens *et al.*, 2008; Turkel *et al.*, 2006), very few authors have addressed the method of clinical assessment across different developmental ages, and more specifically, how the criterion features described in DSM-IV-TR may be recognised or elicited in youth, particularly in young children. The core issue of whether in fact the DSM-IV-TR criteria for delirium can be validly applied to children and

adolescents in unadjusted form has received very little attention (Turkel *et al.*, 2006; Schieveld and Leentjens, 2005).

The literature identified by the systematic literature search described above will now be introduced. For the sake of clarity I have divided the literature into 3 sections: case series, case reports, and 'other' publications.

2.4.1.2 Published case series of delirium in children and adolescents (1980 to July 2008)

As already mentioned in the introduction to this section, the systematic literature search identified 14 case series published between 1980 and July 2008 which have included 288 children and adolescents with definite (7 case series; n=175) or probable (7 case series; n=113) delirium (see Table 2.3).

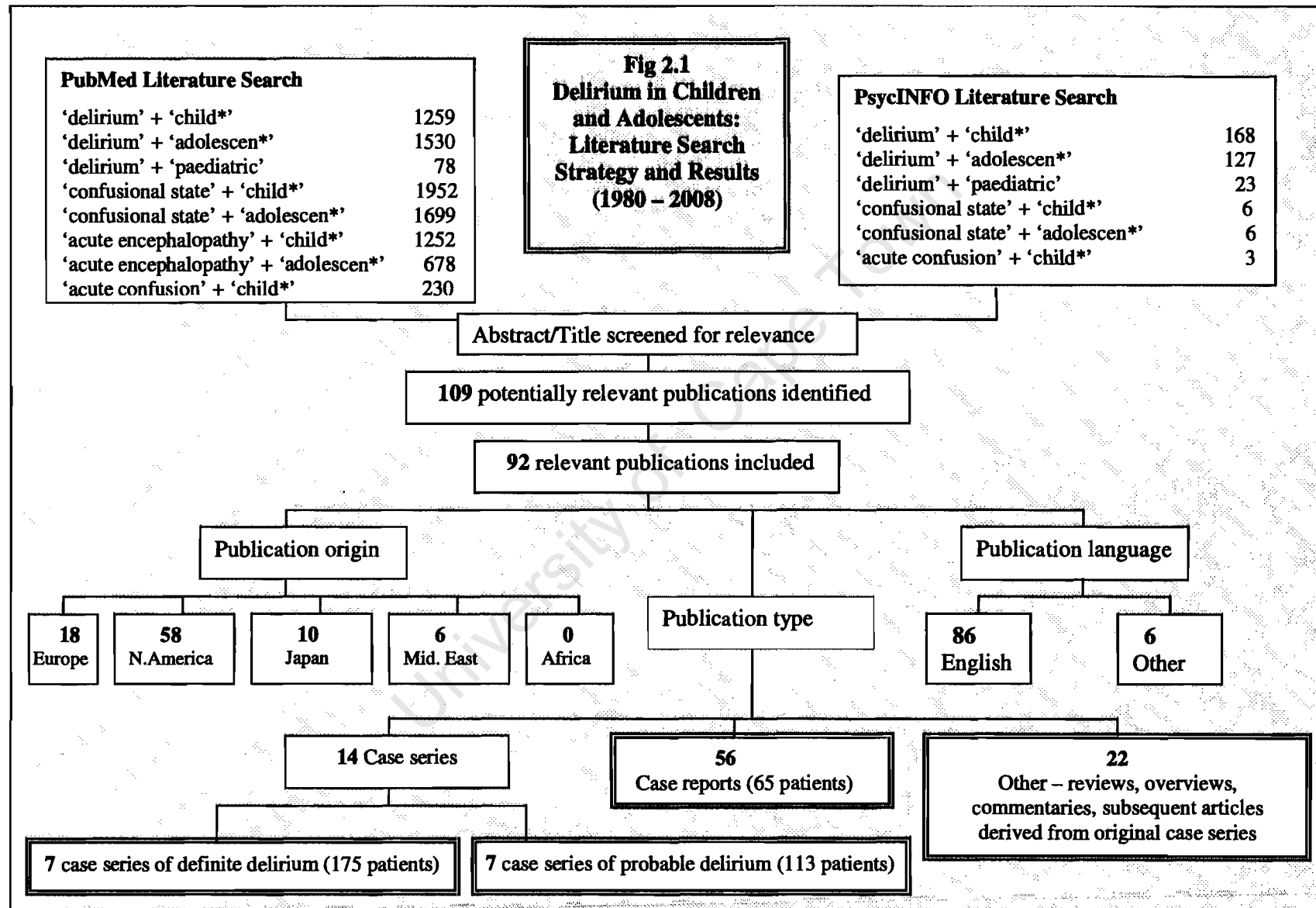
In the following paragraphs I have chosen to summarise the 3 existing cases series of child and adolescent delirium that have arisen from consultation-liaison psychiatry settings (Prugh *et al.*, 1980; Turkel and Tavaré, 2003; Schieveld *et al.*, 2007). These studies also happen to be the largest reported case series of delirium in this age group, making up more than 70% (n= 157) of all reported cases of 'definite delirium' in children and adolescents in the literature published between 1980 and July 2008. Each of these studies is also addressed, where relevant, under the various subheadings of the 'Results and discussion' section of the systematic review. However, as these three studies essentially form the 'backbone' of the existing literature addressing delirium in children and adolescents, I felt it necessary to also address each of these studies separately in some detail.

The largest series to date (Turkel and Tavaré, 2003) described a retrospective chart review of 84 cases of delirium (mean age 10.4 yrs; range 6 months to 18 yrs) identified from 1027 consecutive referrals to the psychiatric consultation-liaison service at the Childrens Hospital Los Angeles over a 4½ year period. Diagnoses were based on DSM-III-R criteria for delirium.

In this series there was a slight male preponderance of 45 males (54%) as compared to 39 females (46%). The most common cause of delirium was infection (n = 29), usually with central nervous system involvement. Medication-related delirium formed the second largest group (n = 16), with delirium associated with a variety of drugs including opioids and anticholinergic agents. Delirium was also found to occur in autoimmune disorders (n = 7), following kidney, lung, heart and bone marrow transplant (n = 7), post-operatively (n = 6), post-trauma (n = 8), in children with neoplastic illness (n = 6), and in those with organ failure (n = 6).

Seventeen (20%) of the 84 patients with delirium died, and the length of hospital stay was long (mean 41 days; range 1 to 255 days), possibly reflecting the severity of the underlying physical illness.

Symptoms of delirium were consistent with descriptions of delirium occurring in adult patients. Impaired attention was found in every patient. Over 90% of the patients manifested sleep disturbance, confusion, impaired concentration, impaired responsiveness and impaired level of consciousness. The majority displayed agitation, irritability, affective lability, nocturnal worsening, and anxiety. Hallucinations were present in 43%, and were most commonly visual and auditory together or visual hallucinations alone. Problems with memory were not commonly noted, and seemed to be more commonly identified amongst older children and adolescents.



The authors noted that antipsychotic medication was effective for sleep disturbance, hallucinations, agitation and 'confusion'. Most patients received high potency antipsychotics (haloperidol in 18 patients, droperidol in 1 patient) orally or intravenously, and a few received low potency agents (thioridazine in 2 patients, chlorpromazine in 1 patient) orally. Low dose intravenous haloperidol was most often used, starting at 0.25mg four times daily and rarely exceeding 1mg total daily dose. Problems with dystonia and cardiac rhythm disturbance were not encountered. Atypical antipsychotic agents were not used during the period of study (1991 – 1995).

The second largest case series is that of Schieveld and colleagues (2007). These authors described the phenomenology, clinical correlates and treatment response of 40 cases of delirium (mean age 7.6 yrs) identified amongst 61 child neuropsychiatry referrals of critically ill children in the setting of a paediatric intensive care unit (PICU) over a period of 4 years (January 2002 to December 2005). Of the 877 acute, non-elective admissions to the intensive care unit, 61 (7%) were referred for a systematic assessment by a child neuropsychiatrist, usually for agitation, anxiety, moaning, discomfort, behavioural disturbance or problematic sedation or pain management, and 40 (61%) of these referrals were diagnosed with a delirium, yielding a cumulative incidence of 5% (boys 5%; girls 4%).

A two-step diagnostic approach was used. The first step was a systematic assessment by a child neuropsychiatrist using DSM-IV criteria for delirium, and included a child psychiatric examination and collateral information on child behaviour and changes in behaviour. Based on the findings of the assessment, patients were then classified as having a (probable) delirium or not. The second step in the diagnostic approach consisted of a daily multidisciplinary consensus meeting attended by the child neuropsychiatrist, the attending paediatric intensivist, and occasionally a geriatric neuropsychiatrist specialised in delirium and/or a child neurologist.

Based on the dominant clinical presentation cases were then classified according to delirium subtype: 'hyperactive' when psychomotor agitation was present and

'hypoactive' when psychomotor retardation was present. In addition, a proportion of children presented with cognitive disturbances in the context of severe anxiety states, often accompanied by moaning and restlessness, but without clear agitation or retardation. This group was classified as 'emerging' or 'veiled' delirium in keeping with the descriptions of 'partial' or 'subsyndromal' delirium described in adult populations.

The underlying somatic or pharmacological features associated with delirium were: a recent increase or decrease in analgesic medication (55%), neurological disorders (52%), infectious disorders (50%) and respiratory disorders (30%). Usually, a combination of these factors was encountered.

A two-track treatment approach consisting of psychosocial/environmental and pharmacological interventions was utilised. Psychosocial/environmental interventions included the parents' presence at the bedside, familiar music, favourite toys, pictures of home and pets, friends and school, and attention to lighting and lighting schedules. All parents received an information leaflet on childhood delirium.

In children with psychomotor agitation that was 'acutely threatening their health status', haloperidol at a loading dose of 0.15 – 0.25mg given intravenously (ivi) was used, given slowly over 30–45 minutes, followed by a maintenance dose of 0.05 to 0.5 mg/kg/24 hours intravenously. In less acute situations, and when an enteral route was available, risperidone at a loading dose of 0.1 – 0.2mg was used, followed by a maintenance dose of 0.2 – 2mg/24 hours. Only 2 of the 40 cases were *not* treated with an antipsychotic medication. Twenty-seven children received haloperidol, 10 children received risperidone, and 1 child received both in succession. The authors described how in the majority of cases beneficial effects of antipsychotic medication were observed rapidly, especially in the hyperactive forms, and often after only a single dose. Two patients receiving haloperidol experienced dystonic reactions. In most cases the antipsychotic was stopped during the Index admission or soon after discharge from hospital.

Five (12.5%) of the 40 children died.

In their discussion of the case series the authors emphasized the difficulties in applying unadjusted DSM-IV criteria for delirium to children, especially in the context of intensive care units where many patients will be artificially ventilated and require opioids and benzodiazepines which may impact on attention. The authors suggested that given the high prevalence of subsyndromal 'emerging delirium' (17/40 or 42.5%) in their series, that overly rigid adherence to DSM-IV criteria for adult delirium might result in persistent underdiagnosis in childhood.

The authors also stressed that paediatric delirium might be subtle and that presentations might be dominated by signs such as: reduction of awareness of the caregiver, or the usual caregiver being unable to console the child, restlessness, autonomic dysregulation and other subtle alterations of higher cortical function. The suggestion was made that paediatric delirium be considered a spectrum disorder.

The limitations of the study discussed by the authors included the absence of systematic screening for delirium and the fact that potentially at least some cases of spontaneous remission may have been misclassified as treatment responders. The authors voiced the opinion, however, that the time-frame of the response in relation to the commencement of antipsychotic medication suggested a medication response rather than spontaneous remission.

In the third largest case series Prugh and coworkers (1980) studied delirium in children and adolescents (6 to 17 years) by comparing a group of hospitalised children and adolescents with 'significant pathophysiological, metabolic, toxic, or traumatic disturbances of central nervous system functioning' of acute onset (presumably delirious) with a control group of children and adolescents hospitalised for elective surgical procedures (presumably not delirious) and matched for age, sex, and socioeconomic status.

An extensive battery of tests was administered to both groups including mental status examination, formal neuropsychological tests, electroencephalography (EEG), and psychodynamic projective tests. The neuropsychological test battery included tests of

perceptuo-motor functioning like astereognosis, graphesthesia, right-left orientation, drawing geometric shapes and copying drawings, and subtraction of serial sevens. The electroencephalograms were independently rated by 3 experts, who assessed the degree of slowing and disorganisation of each EEG trace. A consensus rating of delirium was then reached.

The subject group (presumably delirious) was found to be distinguished at a statistically significant level by 17 of the test items ($p = 0.05$ or less). The authors performed a stepwise discriminant analysis of these distinguishing variables and were able to obtain a weighting for each variable and the best combination of distinguishing variables in terms of the 'probability of being delirious'. The authors were then able to propose a battery of tests that they felt would be best able to distinguish delirious from non-delirious children and adolescents, based on both discriminating ability and clinical utility. This battery included assessment of orientation, memory, examiner-transposition orientation (e.g. patient is asked to touch the examiners left hand with their own right hand), accuracy of copying complex geometric figures, and degree of EEG slowing and disorganisation.

The authors described three cases in detail including a case of 'subclinical delirium' in a 10-year-old boy with chronic renal disease with EEG abnormalities suggestive of delirium in the 'most severe' category. This patient clinically manifested only depressive symptoms, slight confusion, perseveration, and some evidence of tangential thinking.

The authors suggested that in chronic metabolic disorder certain 'compensatory mechanisms' might come into play that might potentially attenuate the overt clinical manifestations of delirium. In such cases clinical evidence of delirium may only become obvious during periods of *more* severe metabolic decompensation. The authors emphasized that in milder cases of delirium in children and adolescents the diagnosis might easily be overlooked and misinterpreted as 'provocative or acting-out behaviour'.

They also stressed the importance of not relying too heavily on a single subtest or procedure in testing for the presence of delirium.

Although the delirious group of children improved on retesting on several test items to the point where they were indistinguishable from the non-delirious group, several other test items (including the degree of EEG organisation and certain perceptual-motor functions) improved on follow-up, but *not* to the point of statistical equivalence with regards the control group. Mild perceptual-motor abnormalities and subtle EEG abnormalities were noted to *persist* for some weeks after clinical resolution of the delirium. The functional implications of these relatively persistent deficits were not discussed.

The authors also discussed certain therapeutic considerations in the management of children and adolescents with delirium including the provision of orientating cues, favorite toys or transitional objects, nightlights to minimise misperceptions, avoidance of sensory deprivation or overstimulation and the judicious withdrawal of drugs from an 'overtreated' patient. The provision of an external or 'auxiliary' ego in the form of a familiar carer who could facilitate orientation, assist in reality testing and provide reassurance, was also emphasized. The authors described how 'modest doses of tranquilizing agents' could be helpful, particularly in anxious patients, but advised caution in the use of psychotropic drugs that might exacerbate the delirium.

Several other studies identified by the systematic literature search describe small case series' of delirium or probable delirium in children and adolescents occurring in particular medical contexts. Many of these studies use poorly-defined synonyms for delirium or overlapping constructs such as 'burn encephalopathy', 'emergence delirium', 'acute confusion' and omit clinical information that may have allowed the application of DSM-IV criteria for delirium. Many of these studies focus more on the disruptive *behaviours* commonly associated with delirium rather than on the cognitive aspects of the disorder, although for the most part sufficient information is provided relating to temporal course (acute/subacute onset, fluctuating course, nocturnal worsening), phenomenology, underlying physical disorder, and investigations (including EEG findings) as to make alternative diagnoses most unlikely.

Three studies each describe a small number of children and adolescents with delirium in the context of severe burn injuries (Brown *et al.*, 1996; Mohnot *et al.*, 1982; Ratcliffe *et al.*, 2004). A further 3 studies from Japan describe small series of children and adolescents with delirium or 'delirious behaviour' in the context of high fever (Okumura *et al.*, 2004; 2006; Onoe *et al.*, 2004). Cole and colleagues (2002), and Przybylo and colleagues (2003) present data in relation to children with delirium in the context of emergence from anaesthesia. DiMario and Packer (1990) described a series of children and adolescents with probable delirium in a paediatric oncology unit, while Turkel and colleagues (2001) briefly reported on 5 children with delirium precipitated by cerebral systemic lupus erythematosus. Lastly, Harrison *et al.* (2002) described 5 paediatric patients with probable delirium in the setting of a paediatric intensive care unit.

These last-mentioned case series of delirium or probable delirium in children and adolescents will be discussed individually in the relevant subsections of the 'Results and discussion' section.

2.4.1.3 Published case reports of delirium in children and adolescents (1980 to July 2008)

As already mentioned, a further 65 children and adolescents with definite (n=42) or probable (n=23) delirium have been described in the form of case report in 56 published reports between 1980 and 15 July 2008 (Tables 2.5.1 to 2.5.7). Few of these reports have been published in psychiatric journals. For the most part, they were identified in 'general' paediatric, emergency medicine or critical care journals, and as a result, few of these publications utilise operational diagnostic criteria for delirium.

For the sake of clarity, I have chosen to divide these published case reports identified by the systematic literature search by presumed etiology into 7 groups: medication-related; metabolic- or endocrine-related; cancer-related; neurologic- or psychiatric related; substance abuse-related; and infection-related delirium in children and adolescents; and finally, delirium in children and adolescents related to 'Other' etiologies.

Table 2.3 Delirium in children and adolescents: Published case series (1980- 2008) in reverse chronological order

Publication	Descriptor	Setting	No.	Definite delirium	Probable delirium	Additional comments
Schieveld <i>et al.</i> , 2007	delirium	Paediatric Intensive Care Unit	40	•		High prevalence of subsyndromal 'emerging' or 'veiled' delirium (17/40)
Okumura <i>et al.</i> , 2006	delirious behaviour	General Paediatric	26		•	In some cases 'febrile delirium' may in fact be triggered by antipyretics or <i>falling</i> body temperature
Okumura <i>et al.</i> , 2004	delirious behaviour	General Paediatric	4		•	'Delirious behaviour' reported in 2% of children with febrile seizures
Onoe <i>et al.</i> , 2004	febrile delirium	General Paediatric	20		•	EEG spectral analysis of 20 children with febrile delirium.
Ratcliffe <i>et al.</i> , 2004	delirium	Paediatric Burn Unit	4	•		Five of 26 children treated with haloperidol had dystonic reactions
Przybylo <i>et al.</i> , 2003	emergence delirium	Anaesthetic Recovery	5	•		DSM criteria applied to 'emergence delirium'
Turkel and Tavare, 2003	delirium	Paediatric consultation liaison psychiatry	84	•		Remains the largest series of its kind
Cole <i>et al.</i> , 2002	emergence delirium (severe restlessness and disorientation)	Anaesthetic Recovery	27		•	Emergence delirium in 10% of children undergoing outpatient abdominal surgery. Prolonged delirium in 2.3%.

Table 2.3 (continued) Delirium in children and adolescents: Published case series (1980- 2008) in reverse chronological order

Publication	Descriptor	Setting	No.	Definite delirium	Probable delirium	Additional comments
Harrison <i>et al.</i> , 2002	'severe agitation or delirium'	Paediatric Intensive Care	5		•	Good response to haloperidol in 5 difficult-to-sedate critically ill children
Turkel <i>et al.</i> , 2001	delirium	Paediatric consultation liaison Psychiatry	5	•		Delirium in systemic lupus erythematosus
Brown <i>et al.</i> , 1996	delirium	Paediatric Burn Unit	4	•		No extrapyramidal side effects with 429 doses of haloperidol in 30 children
DiMario and Packer, 1990	acute change in mental status / encephalopathy	Paediatric oncology	24		•	Children with post-radiation 'somnolence syndrome' (hypoactive delirium) were not classified as having 'acute mental state change', and therefore not included
Mohnot <i>et al.</i> , 1982	burn encephalopathy	Paediatric Burn Unit	7		•	Delirium commonly associated with seizures in this study
Prugh <i>et al.</i> , 1980	delirium	Paediatric consultation liaison psychiatry	33	•		The first of its kind and the first to document the existence of both subsyndromal forms and residual deficits
Total			288	175	113	

2.4.1.4 Other publications relating to delirium in children and adolescents (1980 to July 2008)

Twenty-two other relevant publications were identified by the systematic literature search (Table 2.5). These include unsystematic reviews, overviews, editorials, journal commentaries, and pertinent book chapters relating to delirium in children and adolescents published between 1980 and July 2008. Also included here are further published articles derived from an original case series by the same research group, such as the study described by Leentjens *et al.* (2008), which elaborates and extends the work in relation to the cohort initially described by Schieveld *et al.* (2007). I have also included here articles that closely relate to the subject of delirium in children and adolescents (Jones *et al.*, 1992), or studies like that of Ruha and Yarema (2006), that most likely included child or adolescent patients with delirium, even though the clinical presentations might not have been described as such.

2.4.1.5 Limitations of the existing literature

The existing published literature relating to delirium in childhood and/or adolescence lags significantly behind that which relates to delirium amongst adults in terms of both quality and quantity. It is currently limited to case series, case reports and a motley collection of overviews and commentaries. No systematic literature reviews addressing all aspects of delirium in this age group have been published. The existing literature is significantly compromised by a lack of consistency in relation to terminology and the infrequent use of operational criteria for diagnosis. As a result of these deficiencies much of the published literature could more accurately be described as relating to *probable* delirium in children and adolescents. In relation to management there are no controlled trials and the current evidence is largely anecdotal. No attempts have been made to systematically rate response to treatments, or to control for the influence of environmental factors or changing burden of physical illness. More recent delirium rating instruments capable of repeated measurement in the monitoring of response to treatment have not been tested in children.

TABLE 2.4.1 Medication-related delirium: published case reports in children and adolescents (1980-2008)

Publication	Age (years) and Gender	Presumed etiology	Subtype	Signs and symptoms	Associated neurological features	EEG findings	Temporal course	Psychotropic Pharmacotherapy
1 Al-Rasheed <i>et al.</i> , 2000	8 female	Hypo-magnesemia, Cyclosporin A neurotoxicity	Hypo	Reduced level of consciousness Visual hallucinations	Seizures Babinski sign Increased tone	Marked diffuse slowing. Paroxysmal frontal discharges	Abrupt onset Duration <48 hrs	None
2 Brar <i>et al.</i> , 2005	13 male	Medication-induced (Topiramate)	Hyper	Confusion Agitation Incoherent speech Visual hallucinations	None	None performed	Abrupt onset Fluctuating course Duration 36 hrs	Haloperidol
3 Garza <i>et al.</i> , 2000	3 male	Accidental anticholinergic overdose	Hyper	Agitation Visual hallucinations Inconsolable by parents Confusion Incoherence	Dilated pupils Periods of stupor	None performed	Abrupt onset and offset Fluctuating course Duration 24 hrs	Lorazepam

TABLE 2.4.1 (continued) Medication-related delirium: published case reports in children and adolescents (1980-2008)

Publication	Age (years) and Gender	Presumed etiology	Subtype	Signs and symptoms	Associated neurologic features	EEG findings	Temporal course	Psychotropic Pharmacotherapy
4 Hammerman <i>et al.</i> , 2006	14 female	Medication-induced (aripiprazole)	Hyper	Agitation Disorientation Incoherence Fluctuating consciousness	Drooling Tremor Rigidity	None performed	Abrupt onset Fluctuating course Duration < 48 hrs	Lorazepam
5 Joshi <i>et al.</i> , 2001	14 male	Neuroleptic malignant syndrome (secondary to haloperidol)	Hypo	Confusion Agitation Disorientation Withdrawal Psychomotor retardation	Rigidity Fasciculations Tremor	None performed	Abrupt onset Duration < 7 weeks	None
6 Kuzma <i>et al.</i> , 1995	14 male	Medication-induced (Transdermal fentanyl)	Hyper	Agitation Incoherence Inappropriate speech Insomnia	Involuntary movements	None performed	Abrupt onset and offset Duration 18 hrs	Midazolam Lorazepam
7 Leibold <i>et al.</i> , 2004	15 male	Neuroleptic malignant syndrome secondary to ziprasidone	Hypo	Decreased level of consciousness Incoherence	Rigidity Tremor	Normal	Acute onset Duration < 9 days	None

TABLE 2.4.1 (continued) Medication-related delirium: published case reports in children and adolescents (1980-2008)

Publication	Age (years) and Gender	Presumed etiology	Subtype	Signs and symptoms	Associated neurological features	EEG findings	Temporal course	Psychotropic Pharmacotherapy
8 Livingston <i>et al.</i> , 1983	16 female	Medication-induced (Amitriptyline 50mg)	?	Disorientation Recent memory impairment	None	None performed		None
9 Manaboriboon and Chomchai, 2005	12 female	Medication-induced: (dextromethorphan)	Hypo	Altered level of consciousness Confusion Drowsiness Slow speech	None	None performed	Abrupt onset	None
10 Osterhoudt, 2005	15 female	Dextromethorphan overdose	Mixed	Incoherence Strange behaviour Inattention Somnolence Agitation	Nystagmus	None performed	Abrupt onset Duration <8 hrs	None
11 Ozgur-Oner <i>et al.</i> , 2004	6 male	Medication-induced (risperidone 1mg)	Hyper	Agitation Disorientation Incoherence Anxiety Aggression	None	None performed	Abrupt onset and offset Duration 16 hrs	None

TABLE 2.4.1 (continued) Medication-related delirium: published case reports in children and adolescents (1980-2008)

Publication	Age (years) and Gender	Presumed etiology	Subtype	Signs and symptoms	Associated neurologic features	EEG findings	Temporal course	Psychotropic Pharmacotherapy
12 Penttila <i>et al.</i> , 2006	16 male	Medication-induced (Cephalexin)	Mixed	Amnesia Confusion Paranoia Auditory hallucinations Disorientation Restlessness Emotional lability	None	Normal	Abrupt onset Duration < 48 hrs	None
13 Prugh <i>et al.</i> , 1980	7 male	Atropine intoxication	Hyper	Labile affect Hypervigilance Illusions Delusions Hallucinations Distractable Perseveration Incoherence Disorientation Amnesia	Astereognosis Agraphes- thesia Naming difficulties Drawing difficulties	Severe slowing and disorganisation	Acute onset Duration < 3 days	None

TABLE 2.4.1 (continued) Medication-related delirium: published case reports in children and adolescents (1980-2008)

Publication	Age (years) and Gender	Presumed etiology	Subtype	Signs and symptoms	Associated neurological features	EEG findings	Temporal course	Psychotropic Pharmacotherapy
14 Richardson <i>et al.</i> , 2004	16 male	Antimuscarinic toxidrome (diphenhydramine ingestion)	Hypo	Confusion Mumbling speech Disorganised behaviour Constructional apraxia	None	None performed	Abrupt onset and offset Duration < 12 hrs	None
15 Schwartz and Rodriguez, 1991	4 male	Medication-induced (loperamide)	Hypo	Lethargy Disorientation Visual hallucinations	None	None performed	Duration < 12 hrs	None
16 Sury <i>et al.</i> , 1989	4 male	Midazolam withdrawal	Hyper	Agitation Aggression Uncommunicative Visual hallucinations Disorientated	None	None performed	Abrupt onset Duration < 7 days	Diazepam

TABLE 2.4.1 (continued) Medication-related delirium: published case reports in children and adolescents (1980-2008)

Publication	Age (years) and Gender	Presumed etiology	Subtype	Signs and symptoms	Associated neurologic features	EEG findings	Temporal course	Psychotropic Pharmacotherapy
17 Wells and Rasch, 1999	8 female	Emergence delirium (sevoflurane)	Hyper	Agitation Disorientation Fear Screaming	None	None performed	Abrupt onset Fluctuating course Duration 15 min	None
18 Wells and Rasch, 1999	4 male	Emergence delirium (sevoflurane)	Hyper	Agitation Fear Screaming Inconsolable by parents	None	None performed	Abrupt onset	Midazolam
19 Wilens <i>et al.</i> , 1997	16 male	Cannabis plus nortriptyline	?	Confusion Disorientation Short-term memory loss	None	None performed	Abrupt onset and offset Duration < 24 hrs	None

* Where 2 possible precipitating factors from 2 different broadly-defined etiological categories are reported, the case report has been included in both etiology-related tables

TABLE 2.4.2 Metabolic and endocrine-related delirium: published case reports in children and adolescents (1980-2008)

Publication	Age (years) and Gender	Presumed etiology	Sub-type	Signs and symptoms	Associated neurological features	EEG findings	Tempo-ral course	Psychotro-pic Pharmacotherapy
1 Al-Rasheed <i>et al.</i> , 2000	8 female	Hypo-magnesemia Cyclosporin A neurotoxicity	Hypo	Reduced level of consciousness Visual hallucinations	Seizures Babinski sign Increased tone	Marked diffuse slowing of background and paroxysmal frontal discharges	Abrupt onset Duration <48 hrs	None
2 Belanger-Quintana <i>et al.</i> , 2003	12 male	Hyperammon-emia; N-acetyl glutamate synthetase deficiency	Hypo	Confusion Attention deficits Depressed level of consciousness	Tremor Headache	None performed	Abrupt onset Several episodes < 12 hrs	None

TABLE 2.4.2 (continued) Metabolic and endocrine-related delirium: published case reports in children and adolescents (1980-2008)

Publication	Age (years) and Gender	Presumed etiology	Subtype	Signs and symptoms	Associated neurological features	EEG findings	Temporal course	Psychotropic Pharmacotherapy
3 Budner <i>et al.</i> , 1997	9 female	Hypoglycemia	Hyper	Agitation Distractable Disorientation Visual hallucinations Incoherence	None	None performed	Abrupt onset Fluctuating course Duration < 24 hrs	Haloperidol Lorazepam
4 Decker and Isaacman, 2000	11 female	Wernicke's encephalopathy	Hypo	Drowsy Inattentive Withdrawn	Nystagmus VI nerve palsy Ataxia	None performed	Acute onset <2weeks	None
5 Eschweiler <i>et al.</i> , 1997	16 female	Mild mental retardation (IQ 64) Homocystinuria Emergence from anaesthesia for eye surgery	Hyper	Disorientation Agitation Euphoric Overtalkative Visual and auditory hallucinations Delusions Acalculia	None	None performed	Acute onset Duration 7 days	None

TABLE 2.4.2 (continued) Metabolic and endocrine-related delirium: published case reports in children and adolescents (1980-2008)

Publication	Age (years) and Gender	Presumed etiology	Subtype	Signs and symptoms	Associated neurological features	EEG findings	Temporal course	Psychotropic Pharmacotherapy
6 Hall <i>et al.</i> , 1994	17 female	Hypophosphatemia associated with anorexia nervosa	Mixed	Disorientation Aggression Agitation Delusions Psychomotor retardation	None	Normal	Acute onset Fluctuating course Duration < 12 days	Haloperidol Lorazepam Thorazine Diazepam
7 Kohn <i>et al.</i> , 1998	12 female	Hypophosphatemia Refeeding syndrome Anorexia Nervosa	Mixed	Auditory and visual hallucinations Confusion Disorientation	None	None performed	Abrupt onset Duration < 8 days	None
8 Kohn <i>et al.</i> , 1998	13 female	Hypophosphatemia Refeeding syndrome in Anorexia Nervosa	Hypo	Slow speech and locomotion Acute confusion	None	None performed	Acute onset	None

TABLE 2.4.2 (continued) Metabolic and endocrine-related delirium: published case reports in children and adolescents (1980-2008)

	Publication	Age (years) and Gender	Presumed etiology	Sub-type	Signs and symptoms	Associated neurological features	EEG findings	Temporal course	Psychotropic Pharmacotherapy
9	Miyajima <i>et al.</i> , 1993	9 male	Wernicke's encephalopathy	Hypo	Depressed level of consciousness Memory impairment	Ophthalmoplegia Nystagmus Tremor Drifted into coma	Background slowing	Acute onset Duration <1 month	None
10	Russell <i>et al.</i> , 1990	12 male	Thyrotoxicosis Addison's Disease	Hyper	Hallucinations Disorientation Amnesia Nightmares Inconsolable Aggression Fluctuating LOC	None	None performed	Abrupt onset Fluctuating course Duration <10 days	None

TABLE 2.4.2 (continued) Metabolic and endocrine-related delirium: published case reports in children and adolescents (1980-2008)

Publication	Age (years) and Gender	Presumed etiology	Sub-type	Signs and symptoms	Associated neurological features	EEG findings	Temporal course	Psychotropic Pharmacotherapy
11 Steiner <i>et al.</i> , 1996	16 male	Nonketotic hyperglycinemia	Mix	Lethargy Confusion Agitation 'acute decline in intellectual function'	Ataxia Chorea Gaze palsy	Single irregular L-sided burst of slow waves preceded by a spike	?	None
12 Waternberg <i>et al.</i> , 2000	9 female	Hashimoto's encephalopathy	Mix	Confusion Agitation Disorientation Emotional lability Inattention Lethargy Regression	Seizure	Diffuse slowing of background activity in the theta range	Abrupt onset Duration weeks to months	None

TABLE 2.4.3 Cancer-related delirium: published case reports in children and adolescents (1980- 2008)

Publication	Age (years) & Gender	Presumed etiology	Sub-type	Signs and symptoms	Associated neurological features	EEG findings	Temporal course	Psychotropic pharmacotherapy
1 Karnik <i>et al.</i> , 2007	16 female	Acute lymphoblastic leukemia with CNS involvement	Hypo	Periodic confusion Occasional disorientation Pressured speech Insomnia	None	None performed	Acute onset Fluctuating course Duration 14 days	Risperidone
2 Lee <i>et al.</i> , 2003	15 female	Paraneoplastic syndrome - ovarian teratoma	Hyper	Confusion Incoherence Insomnia Talking nonsense Auditory hallucinations Disorientation 'personality change'	Headache Rigidity Tremor Expressive aphasia	Diffuse slowing	Abrupt onset Fluctuating course	Lorazepam

TABLE 2.4.3 (continued) Cancer-related delirium: published case reports in children and adolescents (1980- 2008)

Publication	Age (years) & Gender	Presumed etiology	Subtype	Signs and symptoms	Associated neurological features	EEG findings	Temporal course	Psychotropic pharmacotherapy
3 Okamura <i>et al.</i> , 1997	15 female	Paraneoplastic syndrome - ovarian teratoma	Hypo	Memory impairment Acute confusion Incoherence 'Loss of contact with reality'	None	Diffuse slowing	Acute onset 1 to 2 months duration	Haloperidol Chlorpromazine
4 Stein-Wexler <i>et al.</i> , 2005	14 female	Paraneoplastic syndrome - ovarian teratoma	Mix	Hallucinations Panic Aggression Pressured speech Incoherence Inattention Somnolence	Headache Slurred speech Abnormal movements Seizure	Focal slowing bilateral temporal and parietal regions	Abrupt onset Fluctuating course	None

TABLE 2.4.4 Neurologic and psychiatric-related delirium: published case reports in children and adolescents (1980-2008)

	Publication	Age (years) & Gender	Presumed etiology	Subtype	Signs and symptoms	Associated neurological features	EEG findings	Temporal course	Psychotropic Pharmacotherapy
1	Amit, 1988	11 female	Nonconvulsive status epilepticus (absence)	Hypo	Disorientation Inattention Memory impairment	None	3/sec spike and wave	Abrupt onset and offset	None
2	Armstrong and Schweitzer, 1997	17 male	Mild learning disability Epilepsy Depression Anticholinergic toxicity – iatrogenic	Hypo	Disorientation to time Disorganisation Memory impairment Lethargic	Slurred speech	None performed	Acute onset Duration <3 days	None

TABLE 2.4.4 (continued) Neurologic and psychiatric-related delirium: published case reports in children and adolescents (1980-2008)

	Publication	Age (years) & Gender	Presumed etiology	Subtype	Signs and symptoms	Associated neurological features	EEG findings	Temporal course	Psychotropic Pharmacotherapy
3	Bechtel, 2004	11 female	Acute confusional migraine	Hypo	Somnolence Disorientation Memory impairment Impaired naming	Dysarthria	None performed	Abrupt onset Fluctuating course Duration < 24 hrs	None
4	Bechtel, 2004	14 male	Acute confusional migraine	Hypo	Somnolence Disorientation Memory impairment Inattention	Dysarthria	None	Abrupt onset Fluctuating course Duration < 24 hrs	None

TABLE 2.4.4 (continued) Neurologic and psychiatric-related delirium: published case reports in children and adolescents (1980-2008)

	Publication	Age (years) & Gender	Presumed etiology	Subtype	Signs and symptoms	Associated neurological features	EEG findings	Temporal course	Psychotropic Pharmacotherapy
5	Grin and DiMario, 1998	11 female	Nonconvulsive status epilepticus (absence)	Hypo	Disorientation Dyspraxia Confusion Memory impairment Inattention	None	3/sec spike and wave	Abrupt onset and offset Duration <12 hrs	Lorazepam
6	Haruda <i>et al.</i> , 1981	10 male	Sickle cell anaemia Transient cerebral ischemia	Hypo	Lethargy Cognitive dulling Distorted drawing and writing	Slurred speech Diplopia Bilateral Babinski sign Frontal release signs	None performed	Acute onset Several episodes < 24 hrs	None

TABLE 2.4.4 (continued) Neurologic and psychiatric-related delirium: published case reports in children and adolescents (1980-2008)

Publication	Age (years) & Gender	Presumed etiology	Subtype	Signs and symptoms	Associated neurological features	EEG findings	Temporal course	Psychotropic Pharmacotherapy
7 Parker <i>et al.</i> , 1997	6 male	Traumatic brain injury Seizures	Hyper	Severe impairment of concentration 'Intolerable' behaviour Impaired consciousness	Seizures Tremor	Diffuse slow waves at 2 Hz Left frontal spikes and high amp slow waves	Abrupt onset Fluctuating course Duration < 4 mo	None
8 Pruett and Rizvi, 2005	16 female	Delirious mania (excited catatonia)	Hyper	Confusion Disorientation Fluctuating alertness Insomnia Agitation Incoherence Hallucinations	Mild rigidity	None performed	Acute onset Fluctuating course Duration days - weeks	Lorazepam Ziprasidone

TABLE 2.4.4 (continued) Neurologic and psychiatric-related delirium: published case reports in children and adolescents (1980-2008)

	Publication	Age (years) & Gender	Presumed etiology	Subtype	Signs and symptoms	Associated neurological features	EEG findings	Temporal course	Psychotropic Pharmacotherapy
9	Nezu <i>et al.</i> , 1997	7 male	Acute confusional migraine	Hypo	Confusion Disorientation Memory impairment	Visual blurring Headache	Posterior slowing	Abrupt onset Fluctuating course Duration <24 hrs	None
10	Nezu <i>et al.</i> , 1997	12 female	Acute confusional migraine	Hypo	Confusion Amnesia	Photophobia Headache Aphasia Hemiplegia	L occipital slowing	Abrupt onset Fluctuating course Duration <24 hrs	None

TABLE 2.4.4 (continued) Neurologic and psychiatric-related delirium: published case reports in children and adolescents (1980-2008)

Publication	Age (years) & Gender	Presumed etiology	Subtype	Signs and symptoms	Associated neurological features	EEG findings	Temporal course	Psychotropic Pharmacotherapy
11 O'Neill <i>et al.</i> , 1992	11 female	Confusional migraine	Hypo	Confusion Disorientation	Slurred speech Headache	Intermittent left occipital slowing	Acute onset Duration <24 hrs	None
12 O'Neill <i>et al.</i> , 1992	11 female	Confusional migraine	Hypo	Disorientation Confusion Amnesia Perseveration	Slurred speech Headache Unsteady gait	Intermittent posterior slowing	Acute onset Duration 6 hrs	None

TABLE 2.4.4 (continued) Neurologic and psychiatric-related delirium: published case reports in children and adolescents (1980-2008)

	Publication	Age (years) & Gender	Presumed etiology	Subtype	Signs and symptoms	Associated neurological features	EEG findings	Temporal course	Psychotropic Pharmacotherapy
13	O'Neill <i>et al.</i> , 1992	11 female	Confusional migraine Hypertension	Hypo	Confusion Disorientation 'unable to talk' Unable to follow instructions Amnesia	Headache	Diffuse occipital slowing	Acute onset Duration 6 hrs	None
14	Yamamoto <i>et al.</i> , 1997	4 male	Bilateral striatal necrosis	Hypo	Hallucinations Incoherence Decreased level of consciousness	Dysarthria Tremor Athetosis Rigidity	None performed	Abrupt onset Days to weeks	None

TABLE 2.4.5 Substance abuse-related delirium: published case reports in children and adolescents (1980-2008)

Publication	Age (years) & Gender	Presumed etiology	Subtype	Signs and symptoms	Associated neurological features	EEG findings	Temporal course	Psychotropic pharmacotherapy
1. Beno <i>et al.</i> , 2004	16 male	Anticholinergic toxicity (Jimson weed ingestion)	Mix	Agitation Hallucinations Incoherence Disorientation Somnolence	None	None performed	Fluctuating course Duration <12 hrs.	None
2. Kurzbaum <i>et al.</i> , 2001	16 male	Anticholinergic toxidrome (Datura Stramonium)	Hyper	Agitation Purposeless movements Uncooperative	None	None performed	?	None
3. Kurzbaum <i>et al.</i> , 2001	17 male	Anticholinergic toxidrome (Datura stramonium)	Hyper	Agitation Purposeless movements Uncooperative	None	None performed	?	None

TABLE 2.4.5 (continued) Substance abuse-related delirium: published case reports in children and adolescents (1980-2008)

Publication	Age (years) & Gender	Presumed etiology	Subtype	Signs and symptoms	Associated neurological features	EEG findings	Temporal course	Psychotropic pharmacotherapy
4 Levy, 1986	14 male	Toxic (typewriter correction fluid)	Hyper	Aggression Confusion Hallucinations Disorientation	Slurred speech Ataxia Brisk reflexes	None performed	Abrupt onset Duration 24 hrs	None
5 Manaboriboon and Chomchai, 2005	12 female	Medication-induced (dextromethorphan)	Hypo	Altered level of consciousness Confusion	None	None performed	Abrupt onset	None
6 Osterhoudt, 2005	15 female	Dextromethorphan overdose	Mix	Incoherence Strange behaviour Inattention Somnolence Agitation	Nystagmus	None performed	Abrupt onset Fluctuating course Duration <8 hrs	None

TABLE 2.4.5 (continued) Substance abuse-related delirium: published case reports in children and adolescents (1980-2008)

Publication	Age (years) & Gender	Presumed etiology	Subtype	Signs and symptoms	Associated neurological features	EEG findings	Temporal course	Psychotropic pharmacotherapy
7 Puustjarvi <i>et al.</i> , 1997	14 female	Unknown overdose of medication and alcohol	Hyper	Confusion Memory deficits Disorientated Thought disorder Labile affect Visual and tactile hallucinations Aggression	Visual impairment	None performed	Acute onset Duration < 36 hrs	None
8 Saito <i>et al.</i> , 1997	16 male	Volatile solvent withdrawal syndrome	Hyper	Hallucinations Confusion	None	None performed	Duration < 1 week	None
9 Wilens <i>et al.</i> , 1997	16 male	Cannabis plus Nortriptyline	Hypo	Confusion Disorientation Short-term memory loss	None	None performed	Abrupt onset and offset Duration < 24 hrs	None

TABLE 2.4.6 Infection-related delirium: published case reports in children and adolescents (1980- 2008)

Publication	Age and Gender	Presumed etiology	Subtype	Signs and symptoms	Associated neurological features	EEG findings	Temporal course	Psychotropic pharmacotherapy
1 Kohsaka <i>et al.</i> , 1984	12 female	Herpes cerebritis	Hyper	Confusion Auditory hallucinations	None	Abnormal	?	None
2 Koranyi, K., 1999	16 female	Ebstein Barr Virus meningo-encephalitis	Hypo	Confusion Disorientation Speech response latency Poor short term memory	Slurred speech Dressing apraxia	None performed	Sudden onset Duration < 48 hrs	None
3 Markov, 1988	11 male	Chickenpox Yersinia infection	Hyper	Auditory and visual hallucinations Fearfulness Insomnia Thought disorder	Abnormal tongue movements	None performed	Acute onset Nocturnal worsening Duration < 36 hrs	None

TABLE 2.4.6 (continued) Infection-related delirium: published case reports in children and adolescents (1980- 2008)

Publication	Age and Gender	Presumed etiology	Subtype	Signs and symptoms	Associated neurological features	EEG findings	Temporal course	Psychotropic pharmacotherapy
4 Mastroianni <i>et al.</i> , 2003	16 month female	Parainfluenza Acute Necrotizing Encephalopathy	Mix	Fluctuating level of consciousness Hyperactivity Jitteriness Insomnia	Tremor	None performed	Abrupt onset Duration weeks	None
5 Scharko <i>et al.</i> , 2006	15 female	Pyrexia HIV-associated dementia	Hyper	Aggression Sexualised behaviour Confusion Fear Paranoia Disorientated Distractable	Tremor Rigidity Parkinsonism	Bilateral continuous slow activity	Acute onset Fluctuating course Duration <3 wks	Poor response to Risperidone Good response to Haloperidol

TABLE 2.4.6 (continued) Infection-related delirium: published case reports in children and adolescents (1980- 2008)

Publication	Age and Gender	Presumed etiology	Subtype	Signs and symptoms	Associated neurological features	EEG findings	Temporal course	Psychotropic pharmacotherapy
6 Schieveld <i>et al.</i> , 2005	2 female	Meningococcal meningitis Septic shock	Hyper	Agitation Inconsolable Yelling Crying	None	None performed	Abrupt onset Duration < 12 hrs	Haloperidol
7 Schieveld <i>et al.</i> , 2005	3 female	Pneumonia Respiratory failure	Hyper	Frightened Inattentive Inconsolable Incoherence Regression	None	None performed	Abrupt onset Duration < 24 hrs	Haloperidol

TABLE 2.4.7 Other published case reports in children and adolescents (1980- 2008)

Publication	Age and Gender	Presumed etiology	Subtype	Signs and symptoms	Associated neurological features	EEG findings	Temporal course	Psychotropic pharmacotherapy
1 Haruda <i>et al.</i> , 1981	10 male	Sickle cell anaemia Transient cerebral ischemia	Hypo	Lethargy Cognitive dulling Distorted drawing and writing	Slurred speech Diplopia Bilateral Babinski sign Frontal release signs	None performed	Acute onset Several episodes < 24 hrs	None
2 Karnik <i>et al.</i> , 2007	14 female	Systemic lupus erythematosus with CNS involvement and high-dose methyl-prednisone	Hyper	Prodrome of anxiety and withdrawal Memory impairment Auditory and visual hallucinations Delusions Agitation Aggression Confusion	None	None performed	Acute onset Duration 8 days	Poor response to risperidone 0.5 mg bd. Rapid response to haloperidol 0.5 mg bd

TABLE 2.4.7 (continued) Other published case reports in children and adolescents (1980- 2008)

Publication	Age and Gender	Presumed etiology	Subtype	Signs and symptoms	Associated neurological features	EEG findings	Temporal course	Psychotropic pharmacotherapy
3 Prugh <i>et al.</i> , 1980	10 Male	Chronic renal failure Post renal transplant	Hypo	Low mood Perseveration 'confusion' Disorganised speech Memory defect	Agraph- asthesia	Severe slowing and disorganisation	?	None
4 Zgurzynski and Manno, 1999	10 male	Malignant hypertension	Mix	Somnolence Disorientation Agitation	Slurred speech Generalised seizure	None performed	Abrupt onset Duration <48 hrs	None

**Table 2.5 Delirium in children and adolescents: Other published literature
(1980-2008)**

Publication	Commentary
De Carvalho and Fonseca, 2008	A commentary which acts as a companion piece to Schieveld <i>et al.</i> (2008), published in the same issue of <i>Critical Care Medicine</i> , which includes a brief overview of delirium pathophysiology, predisposing and precipitating factors in children.
Jones <i>et al.</i> , 1992	The authors present the results of a prospective case series looking at behavioural changes in children on intensive care units as compared to children on general paediatric wards. Although there is little mention of delirium <i>per se</i> the authors report higher levels of anxiety, 'detachment', sadness and weeping in children in the PICU.
Kain <i>et al.</i> , 2004	An important study that showed that high preoperative anxiety can predict emergence delirium in children. Additionally, this study also showed that both high preoperative anxiety and emergence delirium predicts post operative maladaptive behavioural changes up to 2 weeks after surgery.
Karnik <i>et al.</i> , 2007	Published in <i>Psychosomatics</i> , the authors propose a treatment algorithm for the different subtypes of paediatric delirium, advocating risperidone for hypoactive/mixed delirium and haloperidol for hyperactive delirium in children.
Leentjens <i>et al.</i> , 2008	The authors present a comparison of the phenomenology of paediatric, adult and geriatric delirium using the Delirium Rating Scale. The study population appears to be the same as that published as a case series (Schieveld <i>et al.</i> , 2007), with an additional 6 childhood cases added since the first article was published.

Table 2.5 (continued) Delirium in children and adolescents: Other published literature (1980-2008)

Publication	Commentary
Liebelt, 2004	Published in <i>Current Opinion in Paediatrics</i> , the author presents an editorial overview of the therapeutic and toxicology issues associated with the agitated, violent or psychotic paediatric patient. An argument is made for retaining droperidol as a therapeutic option, based on a review of the literature that has emerged since its 'black box' warning in 2001.
Lipowski, 1980	Lipowski's <i>Delirium – Acute Brain Failure in Man</i> , an impressive and comprehensive 567-page book devoted entirely to the subject of delirium, does not contain a chapter addressing delirium in childhood or adolescence. However, it does contain some useful references to delirium in this age group, particularly in relation to precipitants.
Manwooten <i>et al.</i> , 2004	A review of the literature relating to the clinical challenge of differentiating post-operative pain from emergence agitation/delirium in children. An algorithm is proposed to facilitate the decision-making process.
Martini, 2004	A fairly comprehensive review article of delirium in the paediatric emergency unit, published in <i>Clinics in Paediatric Emergency Medicine</i> , which includes etiology, recommended investigations, and management.

Table 2.5 (continued) Delirium in children and adolescents: Other published literature (1980- 2008)

Publication	Commentary
Martini, 2005	A commentary which acts as a companion piece to Schieveld and Leentjens (2005) article, published in the same issue of the <i>Journal of the American Academy of Child and Adolescent Psychiatry</i> , which includes an overview of delirium in paediatric patients and its management
Moos, 2005	A review of emergence delirium in children that highlights the recent trend towards utilizing DSM-IV criteria for delirium in differentiating emergence agitation from emergence delirium. The review focuses particularly on the inhaled anaesthetic sevoflurane.
Ruha and Yarema, 2006	A retrospective chart review of 18 paediatric patients admitted to a PICU with methamphetamine toxicity, all of whom presented with agitation. All were treated with benzodiazepines while 12 received haloperidol. It would seem reasonable to assume that at least some of these patients may have had a hyperactive delirium
Schieveld, 2006	In this article Jan Schieveld draws attention to the parallels between catatonia and delirium in children as final common pathways of 'reaction types of the brain' with kaleidoscopic, fluctuating, 'bipolar' presentations

Table 2.5 (continued) Delirium in children and adolescents: Other published literature (1980-2008)

Publication	Commentary
Schieveld <i>et al.</i> , 2008	Using the same cohort of 40 patients with delirium originally published as a case series (Schieveld <i>et al.</i> , 2007), the authors report on the value of the Paediatric Index of Mortality (PIM) and Paediatric Risk of Mortality (PRISM) in predicting delirium in children in the PICU.
Schieveld, 2008	Jan Schieveld's published PhD thesis <i>On Paediatric Delirium in Critical Illness</i> , that incorporates a number of the articles already published by the research group of Schieveld and colleagues (Schieveld, 2006; Schieveld <i>et al.</i> , 2007; 2008; and Leentjens <i>et al.</i> , 2008), with the addition of a unifying introduction and discussion
Sikich and Lerman, 2004	An important article which bridges the divide between anesthesiology and psychiatry research in addressing 'emergence delirium' in children through the lens of DSM-IV-TR diagnostic criteria. The authors present results supporting the validity and reliability of the Pediatric Anesthesia Emergence Delirium Scale (PAED), developed by the same authors for evaluating delirium in the post-anesthesia setting
Stoddard <i>et al.</i> , 2006	A comprehensive overview of psychopharmacology in pediatric critical care which includes a brief section focusing on the pharmacological management of delirium

Table 2.5 (continued) Delirium in children and adolescents: Other published literature (1980-2008)

Publication	Commentary
Turkel <i>et al.</i> , 2003	The authors report on the retrospective application of the Delirium Rating Scale to the clinical data recorded in the initial assessment of 84 child and adolescent patients with delirium. The study population was the same as that published as a case series earlier the same year.
Turkel <i>et al.</i> , 2006	Published in <i>Psychosomatics</i> , the authors present the results of a MEDLINE search (1966-2003) comparing symptoms of delirium in adults and children. Of note, only one pediatric study met the inclusion criteria – a study published by the same authors in 2003
Van Waarde and van der Mast, 2004	The authors present a case series and literature review of delirium in patients with learning disability that includes two reports of delirium in adolescents with learning disability. Many of the challenges of delirium in children are mirrored by those encountered in people with learning disability
Vlajkovic and Sinjelic, 2007	A review of the literature relating to emergence delirium in children which explores the distinction between emergence agitation (EA) and emergence delirium (ED) with an emphasis on using psychiatric diagnostic criteria. Addresses anaesthesia-, surgery-, and patient-related factors in the etiology of EA/ED in addition to assessment tools, treatment and prevention.

2.4.2 Epidemiology

In this section, I will begin by describing the fairly extensive literature addressing the epidemiology of delirium in adults and geriatric patients. The literature cited here derives from the unsystematic literature review of adult delirium, the methodology of which is described above. I will then describe what limited literature there is that addresses the epidemiology of delirium in children and adolescents, identified by the systematic literature review.

A wealth of epidemiological data addressing delirium in adult and elderly populations has been produced since 1980. The Eastern Baltimore mental health survey (Folstein *et al.*, 1991) documented the prevalence of delirium in the community as increasing significantly with age: 0.4% in those over the age of 18 years, 1.1% in those over the age of 55 years, and 13% in those over 85 years, a figure similar to that reported in a more recent study of older people in Finland (Rahkonen *et al.*, 2001). The study did not assess the prevalence of delirium in those under the age of 18 years.

In hospital populations most studies report prevalences of between 10% and 20% for adult medical inpatients (Burns *et al.*, 2004). A systematic review that identified 42 studies relating to the occurrence of delirium in adult medical inpatients reported rates of between 11% and 42% (Siddiqi *et al.*, 2006).

Rates in adult oncology units have been described, with prevalence and incidence rates of 42% and 45% respectively (Lawlor *et al.*, 2000). The prevalence of delirium in intensive care cohort studies amongst adults has been reported as 20%, 70%, or 80%, depending on the characteristics of the patient population and the instrument used (Ely *et al.*, 2001; Bergeron *et al.*, 2001; McNicoll *et al.*, 2003). The incidence of delirium in the post-operative period amongst adult patients has been reported to be as high as 50% (Tune *et al.*, 1991).

In contrast to the large body of literature testifying to the high incidence and prevalence of delirium in adult, and particularly elderly, people, virtually no information is available to inform even a rough estimate of the prevalence and incidence of delirium amongst children and adolescents. This paucity of data is all the more striking given the commonly-held, but largely anecdotally-informed notion that children represent a population at increased risk of delirium (Henry and Mann, 1965; Prugh *et al.*, 1980; Martini *et al.*, 2004; Grace and Holmes, 2006; Williams, 2007; Trzepacz *et al.*, 2004; Smith *et al.*, 1995). Delirium has been neglected by all of the large epidemiological studies addressing the rates of mental and behavioural disorders amongst children and adolescents in the community, and so we have no conclusive data as to how commonly delirium occurs amongst young people in non-clinical settings.

A curious omission in the literature on delirium is the almost complete lack of reports on its incidence and consequences in childhood. While it is often asserted that delirium is common in children, relevant statistics are missing
(Lipowski, 1967, p. 248)

Unfortunately, not a great deal has changed in this regard since 1967. The following studies identified by the systematic review of the literature provide the only available information relating to incidence and prevalence of child and adolescent delirium in clinical settings.

Schieveld and colleagues' (2007) cohort of children and adolescent patients with delirium has already been described. Out of 877 admissions to the PICU, 61 children and adolescents aged less than 18 years were referred for a psychiatric assessment. Amongst these 61 patients, 40 were assessed as suffering from a delirium (15 girls and 25 boys), with a cumulative incidence of 5% (boys 5%; girls 4%), and a mean age of 7.6 years. The age-specific incidence rates varied from 3% in the 0-3 years age group (boys 3%; girls 3%) to 19% in the 16- 18 years age group (boys 31%; girls 11%). The authors considered the most likely explanation for the comparatively *low* incidence of delirium in this study, when compared to the rates reported for adult ICU patients, to be the low

rate of *recognition* of delirium in young people by parents, paediatric nurses, paediatric intensivists and child neurologists, leading to low rates of referral to psychiatric services.

In the retrospective chart review reported by Turkel and Tavaré (2003) 84 cases of delirium were identified amongst 1027 consecutive psychiatric consultation-liaison referrals at the Childrens Hospital Los Angeles over a 4 and ½- year period, constituting just over 8% of the total referrals to this service.

Although the incidence and prevalence of delirium in general paediatric medical or surgical inpatients are entirely unknown, a number of authors have attempted to estimate the rates of what would probably more accurately be described as 'probable delirium' within certain discrete paediatric settings.

For example, Jones and colleagues (1992) used a prospective methodology to compare the frequency of delirium, anxiety and depressive symptoms in a paediatric intensive care unit as compared to that in a general paediatric medical ward in 43 subjects aged 6 to 17 years. Although the authors did not document the incidence of delirium *per se* in their samples, they did report that 3 out of the 18 (16.7%) PICU subjects were noted as 'confused or disorientated', and 10 out of the 25 ward subjects (40%) and 8 out of the 18 PICU subjects (44.5%) were 'inattentive, distractible'.

As another example, DiMario and coworkers (1990) studied the incidence, etiologies and outcomes of children with cancer who experienced 'acute changes in mental status' (AMS), defined as an abrupt or rapidly evolving loss of consciousness, disorientation, alteration in memory, development of hallucinations, excessive somnolence with diminished arousability, or seizures with or without the presence of other focal neurologic deficits. During the 84-month period of evaluation 89 out of 815 children with systemic cancer developed AMS (11%). Seizures accounted for 60% (53 patients) of AMS, while 'encephalopathy' and stroke accounted for 27% (24 patients) and 13% (11 patients) respectively. An 'encephalopathy' was diagnosed if the acute change in mental status could not be accounted for by seizure or stroke, and was thus a diagnosis of exclusion in this study. It would seem reasonable to postulate a prevalence of delirium

of about 3% in children with cancer in this study, although this is likely to be a gross underestimate as it excludes children with a delirium that might have been *precipitated* by a seizure or a stroke.

In a study that provides some indication of the prevalence of 'probable delirium' in the context of paediatric burn injury, Mohnot and colleagues (1982) reported that of 287 children (range 1 to 7 years; mean 3 years) treated at the burn unit at the Children's Hospital in Birmingham (mean total body surface area burned = 30%), 13 (5%) developed 'burn encephalopathy', defined as the acute onset of change in sensorium *or* the occurrence of seizures or abnormal neurological signs, or both, at any time after the initial burn. Eleven boys and two girls developed 'burn encephalopathy'. The EEG was abnormal (slow and disorganised) in 4 of the 6 patients in which it was done. A similar rate was documented by Brown and colleagues (1996), who examined the medical records of 30 critically-ill paediatric burn patients treated with haloperidol between 1986 and 1992. In 13% (4 out of 30 patients) of those prescribed haloperidol, the indication was for 'delirium with marked disorientation, hallucinations and delusions'. Ratcliffe and colleagues (2004) reported their findings of a retrospective chart review of 26 paediatric burn patients who had received haloperidol. In this series, in 15% (4 out of 26 patients) the major indication for haloperidol was for 'agitation and restlessness in addition to delirium with marked disorientation, hallucinations and delusions'.

A number of Japanese researchers have made a significant contribution to the literature addressing delirium amongst children and adolescents by focusing on 'febrile delirium'. Okumura and coworkers (2004) found an incidence of 'delirious behaviour' of 2% in 203 consecutive patients presenting with febrile seizures. Takahashi *et al.* (1988) reported on 1511 questionnaires relating to the occurrence of delirium associated with fever in children and documented that the highest incidence was at 1 to 4 years of age, with an incidence as high as 28% in this age group.

Several articles from the anaesthesiology literature report on the high incidence of what is referred to as 'emergence delirium' in the paediatric post-anaesthetic setting. The term is often used interchangeably with the more ambiguous term 'emergence agitation'

(Manworren *et al.*, 2004). The term is also not to be confused with 'emerging delirium', described in children by Schievelde and colleagues (2007), which describes a subsyndromal delirium. The incidence of emergence *agitation* in children, characterised by severe restlessness, combativeness, thrashing, kicking, agitation with nonpurposeful movements, disorientation, incoherence and unresponsiveness, has been reported as 12% to 30% (Voepel-Lewis *et al.*, 2003; Cole *et al.*, 2002). A major confounding problem in studies of 'emergence agitation' and delirium is the difficulty in differentiating delirium from inadequately treated pain, fear and anxiety. Cole and colleagues (2002) documented that 27 out of 260 (10%) children (range 10 months to 6 years; mean 2.7 years) experienced emergence *delirium*, in this instance defined as a period of 'severe restlessness and disorientation' on emergence from elective lower abdominal surgery. The rate of emergence delirium was highest in the younger children.

Other authors have suggested that paediatric post-operative delirium may occur in over two-thirds of patients following sevoflurane anaesthesia, and 29% of patients following halothane, with the risk being highest for those under 4 years of age (Keaney *et al.*, 2004). Kain and coworkers (2004) reported an incidence of 19.6% of 'marked symptoms of emergence delirium' in 1279 children undergoing outpatient surgery, with a significantly increased risk in those children with preoperative anxiety. Przybylo *et al.* (2003), using an assessment tool developed from DSM-IV criteria for delirium, reported an incidence of 20% for 'complex symptoms with characteristics of delirium' in a prospective study of 25 children aged 2 to 9 years undergoing surgery for strabismus, with a higher incidence in those children under 62 months old.

In summary, a systematic review of the literature identified few articles relating to the incidence or prevalence of delirium in children and adolescents. The existing literature suggests that delirium in this age group appears to be particularly common in the context of paediatric consultation-liaison psychiatry, where such patients may constitute close to 10% of all referrals. Additionally, delirium appears to be common amongst children and adolescents in the following settings: paediatric intensive care units, hospitalisation for severe burn injuries, children emerging from anaesthesia, paediatric oncology, and paediatric emergency units (with febrile illness). Much of the literature in this area is

obfuscated by a confusing array of synonyms for delirium and different thresholds for diagnosis.

2.4.3 Predisposing factors

Delirium is a disorder that fits well with a multifactorial risk/vulnerability threshold model of causation, in which patients with a high level of pre-existing vulnerability may experience the disorder following only minor physiologic stressors, whereas those with low baseline vulnerability require a more noxious or larger number of 'insults' in order to precipitate the disorder (Young and Inouye, 2007; Inouye and Charpentier, 1996). A number of 'host factors' or predisposing factors have been identified in adults, including old age, male gender, baseline medical comorbidities, and baseline cognitive impairment (Young and Inouye, 2007; Inouye, 2006; Burns *et al.*, 2004; Pandharipande *et al.*, 2005).

Predisposing factors are neither necessary nor sufficient causes for delirium. However, predisposing factors may increase the risk for delirium, and in association with known precipitating factors result in an individual patient crossing the 'threshold' into a clinical delirium. Potential protective factors that might 'buffer' predisposing or precipitating factors and reduce what Henry and Mann (1965) termed 'delirium readiness', have not been adequately researched. Such putative protective factors need not necessarily only be represented by the absence of predisposing factors.

Factors that have been identified as *possible* predisposing factors for delirium in children and adolescents include young age, male gender, pre-existing progressive cognitive impairment, mental retardation, genetic factors, pre-existing psychological problems, physical ill-health, and certain caregiver factors. The literature related to each will now be discussed in turn.

2.4.3.1 Age

The question as to whether childhood represents a particular period of increased vulnerability to the syndrome of delirium, mirroring the increasing risk associated with

increasing age among older adult patients, remains uncertain. No systematic study has yet addressed this question.

However, delirium has been said to be more common in childhood (Prugh *et al.*, 1980; Martini *et al.*, 2004; Grace and Holmes, 2006; Williams, 2007; Trzepacz *et al.*, 2004), with children considered to be particularly vulnerable to delirium precipitated by febrile illness, regardless of cause. Eugene Bleuler (1920, p. 155) remarked that 'children succumb to delirium relatively easily' and Goodman and Sours in the 1967 edition of *The Child Mental Status Examination* suggested that children 'are more apt than adults to respond to fever and infection with delirious and hallucinatory states' (Goodman and Sours, 1994, p.25).

Aono and colleagues (1997) reported a greater incidence of 'emergence delirium' in pre-school children given sevoflurane than in any other age group. The authors controlled for other variables that might increase the risk of delirium, including pain, dehydration and hypoxia. The authors hypothesized that this increased prevalence of emergence delirium in pre-schoolers is a reflection of 'psychological immaturity'. Bhat and Rockwood (2007) also proposed a psychological/developmental underpinning to the apparent relative susceptibility of children to delirium. These authors suggested that immaturity in the development of a 'narrative self' and of time perception might predispose children to delirium.

Martini (2005) has suggested this increased vulnerability apparent in young children might in fact have a biological basis. He proposed that developmental brain changes, particularly in cholinergic function and the hippocampus might mirror the degenerative brain changes associated with ageing, and that these maturational changes in neurotransmitter pathways might provide clues to the 'relative susceptibility' of younger children to delirium.

Paradoxically, however, Kornfeld *et al.* (1965) reported an apparently *reduced* risk of delirium in children as compared to adults amongst post-cardiotomy surgical patients. Of the 20 children from the sample of 119 patients who had undergone open-heart

surgery only one developed delirium (5%), whereas 30% of the adults experienced a delirium. This could of course reflect a higher rate of underrecognition in younger patients, rather than a lower incidence.

In Turkel and Tavare's retrospective series of 84 cases of delirium ranging in age between 6 months and 18 years, the average age was 10.4 years and the median age 11 years (Turkel and Tavare, 2003).

As already mentioned, in the series of 40 patients with delirium in the context of PICU, described by Schieveld and colleagues (2007), the mean age was 7.6 years. These rates, however, are derived from patients referred for psychiatric assessment, and are thus dependent on the sensitivity of the referring agent to detecting the emotional, cognitive or behavioural changes associated with delirium. Rates of underrecognition and misdiagnosis are extremely high even among adults with delirium, and similar if not worse results are to be expected in paediatric populations. Thus, it may be that rates of *recognition* of delirium diminish with the age of the child, with particularly low rates of detection in preverbal children.

In summary, the current systematic review of the literature is unable conclusively to answer the question as to whether young age itself is a risk factor for delirium. However, the evidence from the literature examining emergence delirium, and the anecdotal evidence from a number of experts in the field, would at the very least, tend to support the assertion that delirium is more common in children in certain contexts. The work of Kornfeld and colleagues (1965) raises the interesting question as to whether this heightened age-related vulnerability operates only in certain circumstances. The related question as to whether in fact young age might confer *protection* against delirium in *other* contexts remains equally unanswered. Few authors have attempted to address the possible mechanisms underlying a vulnerability to delirium amongst children. Relative cholinergic deficiency on the basis of differential rates of maturation of neurotransmitter systems, mirroring the normative decline in cholinergic function in old age and the accelerated cholinergic failure of dementia is one proposed explanation. Bhat and Rockwood (2007) on the other hand, propose a multidimensional model of delirium in

which the very experience of a first-person self in time is altered. They propose a metaphor for delirium as the ‘unanchored narrative self’ – ‘the ship lost at sea’- and suggest that children may be at particular risk on the basis of both immature development of self and evolving skills in time perception.

2.4.3.2 Gender

A number of studies examining risk factors for the development of delirium amongst adult and elderly patients have identified male sex as a potential predisposing factor (Elie *et al.*, 1998; Marcontonio *et al.*, 1994). The data available for children and adolescents is limited and inconclusive, but as with many neurodevelopmental disorders encountered in childhood, there would appear to be an increased risk for delirium conferred by male gender, although this awaits confirmation in systematic studies (Martini *et al.*, 2004).

In the PICU case series reported by Schieveld and colleagues (2007), out of 40 cases of delirium (mean age 7.6 years) 25 (62.5%) cases were male and 15 (37.5%) female. The age-specific incidences for delirium amongst 877 consecutive PICU admissions were equal for the 0-3 years group (boys 3%; girls 3%), whereas in the older group 16-18 years there was a higher rate for boys (boys 31%; girls 11%). Turkel and Tavare (2003) reported a series of 84 patients ranging from 6 months to 18 years with delirium in which there was a slight male preponderance of 45 males (54%) and 39 females (46%). In Okumura and colleagues’ (2005) series of 15 children (range 1.8-14.3 years; mean 6.5 years) presenting with ‘delirious behaviour’ in the context of influenza-associated febrile illness there were 10 boys (67%) and 5 girls (33%). In Mohnot and colleagues’ (1982) case series of 13 children diagnosed with ‘burn encephalopathy’ there were 11 boys (85%) and 2 girls (15%). However, in all of the above-mentioned studies the gender ratio of the population being sampled was not reported. For example, in the study of Turkel and Tavare (2003), it would have been valuable to have known the ratio of boys to girls admitted to the hospital during the same time period, as well as the gender ratio of all patients referred to the consultation-liaison psychiatry service.

Male gender, however, has *not* been reported as a risk factor for emergence delirium in children receiving anaesthetic agents.

In summary, as with the hypothesized predisposing factor of young age, male gender *cannot* be said to be a risk factor for delirium in children and adolescents with any degree of certainty. However, the evidence from existing case series of delirium or probable delirium in this age group does suggest a slight male preponderance. However, one could equally suggest that male gender poses, for example, a risk factor for PICU or Burn Unit admission, rather than delirium *per se*.

2.4.3.3 Dementia

Dementia is an important risk factor for delirium in adult populations, with a meta-analysis suggesting a relative risk for delirium of 5.2 (Elie *et al.*, 1998). Pre-existing cognitive impairment is a well-known predisposing factor for delirium in the elderly, and the two occur together in between 22% and 89% of those people greater than 65 years of age (Fick *et al.*, 2002). The mechanisms underlying this increased vulnerability are poorly understood, but are popularly attributed to the effect of 'diminished cognitive reserve' and narrowing of mental adaptability (Martini, 2004).

The incidence of dementia increases fairly predictably with increasing age, and dementia syndromes are rare in childhood. However, at least one report has been published of a child with HIV-related progressive encephalopathy, thought to represent the paediatric form of HIV-associated dementia, experiencing a superimposed episode of delirium (Scharko *et al.*, 2006). Scharko and colleagues (2006) make the point that because children with HIV infection are now living longer with antiretroviral treatment, the risk of late-appearing cognitive disorders such as HIV-associated dementia might increase. In regions of the world where the prevalence of HIV is high amongst children, it is possible that there will be a parallel increase in the incidence of delirium.

2.4.3.4 Learning Disability

Little is known about the incidence or phenomenology of delirium amongst patients with learning disabilities, another population potentially at risk of delirium on the basis of diminished cognitive reserve and adaptive capacity. Van Waarde and coworkers (2004), in reporting the results of a literature search designed to capture articles reporting on any aspect of delirium in patients with learning disability, found only two isolated case reports, *both* of which described adolescent patients.

Armstrong and Schweitzer (1997) reported a 17-year-old boy with mild learning disability and bipolar affective disorder who developed a presumed anticholinergic delirium when prescribed the combination of paroxetine and benztropine, which led to higher serum levels of benztropine than would have occurred if it had been prescribed in isolation. Eschweiler *et al.* (1997) described a 16-year-old girl with mild learning disability and homocystinuria who became delirious on emerging from anaesthesia immediately following eye surgery.

Van Waarde and coworkers (2004) suggested that patients with learning disabilities *do* constitute a group at special risk of delirium, despite the lack of data relating to prevalence and incidence in this population. They postulated that delirium might remain largely undetected and unappreciated in this group of patients owing to the phenomenon of 'diagnostic overshadowing' and difficulties in interpreting behavioural changes in patients with limited ability to express their experiences. Certainly the latter difficulty would appear to apply equally to young children with delirium.

2.4.3.5 Genetic vulnerability

Research into the possibility of a genetic predisposition to delirium is beginning to emerge. Ely and colleagues (2007) recently reported a positive association between the presence of the Apolipoprotein E4 (APOE4) genotype and more 'delirium-positive' days amongst 53 adult intensive care patients.

APOE4 has been used previously as a biologic marker to predict the development of Alzheimer's disease and a poorer outcome after traumatic brain injury. The authors also reported the interesting but unsubstantiated claim that experienced psychiatrists have noted a propensity for similar phenomenological patterns of delirium to recur in patients *and* their families.

The systematic review of the literature was unable to identify any studies examining a genetic contribution to delirium in children and adolescents. Certain genotypes may confer either a general risk for delirium, or a specific susceptibility to particular precipitants. Genotype may also be one of the correlates of what Jan Schieveld (2008) has referred to as 'malignant paediatric delirium'. On the other hand, it is perfectly conceivable that certain genotypes confer protection against delirium

2.4.3.6 Psychiatric disorder

Studies of adult patients with delirium have suggested that *pre-existing* psychopathology may predispose individuals to the development of delirium. Dasgupta and Dumbrell (2006) undertook a systematic review of preoperative risk factors associated with delirium in adult patients undergoing noncardiac surgery. The authors reported a statistically significant association between *pre-surgery* depression and *post-operative* delirium ($p < 0.001$), although they also suggested caution in the interpretation of these results given that there was also significant heterogeneity across studies. Dasgupta and Dumbrell (2006) also reported a statistically significant association between adult psychopathology as assessed by *pre-surgery* rating scores on the Brief Psychiatric Rating Scale and the Global Assessment Scale, and *post-operative* delirium ($p < 0.001$). For this association, pooled effect sizes were reported as medium to large. Alcohol dependence has also been suggested as a factor conferring increased risk for delirium amongst adult patients (Burns *et al.*, 2004).

In contrast, both Dubin and coworkers (1979), and Van der Mast and Roest (1996), on reviewing the available literature pertaining to postcardiotomy delirium in adult patients

concluded that there were no personality or premorbid psychological correlates of delirium.

The relationship between pre-existing psychopathology and/or behavioural disturbance in children and adolescents and delirium remains largely unstudied. Kain *et al.* (2004) have, however, reported an association between preoperative anxiety and emergence delirium in children recovering from the effects of anaesthesia. These authors assessed preoperative anxiety using the modified Yale Preoperative Anxiety Scale (mYPAS; Kain *et al.*, 1997) and found that the odds of having marked symptoms of emergence delirium increased by 10% for each increment of 10 points in the child's modified Yale Preoperative Anxiety (mYPAS) score. The authors hypothesized that *temperamental* differences in stress reactivity and adaptability might mediate this relationship.

Interestingly, preoperative *parental* anxiety in the holding area was also found to be positively associated with emergence delirium in the child. It is interesting to speculate on the possible mechanisms for this association. Could this finding reflect a shared genetic predisposition to both anxiety and delirium, or does parental anxiety exacerbate preoperative childhood anxiety which in turn predisposes to delirium? Kain and colleagues (2007) described the effects of a multicomponent 'family-centred preparation' for elective paediatric surgery using a randomised controlled trial. The intervention included anxiety-reduction strategies, video modeling and education, the presence of the parents during induction, and avoidance of excessive parental reassurance. The authors reported that children exposed to the multicomponent intervention were significantly less anxious while waiting in the preoperative holding area. Parents of children in the multicomponent intervention group were also significantly less anxious in the holding area, and remained less anxious after induction of anaesthesia. Importantly, children in the multicomponent intervention group were also significantly less likely to experience emergence delirium post-operatively.

In contrast, however, Przybylo and colleagues (2003) found no relationship between either exposure to stressful life events or preoperative psychiatric status and post-operative emergence delirium.

Children who are more emotional, more impulsive, less social, and less adaptable to environmental changes have been suggested as being at higher risk of post-anaesthesia delirium (Vlajkovic *et al.*, 2007). De Carvalho and Fonseca (2008) have suggested that children with difficult temperaments, premorbid psychiatric conditions, separation anxiety and pain may be particularly vulnerable.

In summary, high levels of both preoperative parental and child anxiety have been associated with an increased rate of post-operative emergence delirium in children, although the evidence for this is not consistent. However, interventions targeting preoperative anxiety in both children and their parents have been shown to reduce the incidence of post-operative emergence delirium. The evidence for an association with other temperament dimensions such as impulsivity, sociability, reactivity remains anecdotal.

2.4.3.7 Physical ill-health

Physical ill-health can act as both a predisposing and precipitating factor for the development of delirium. The presence and severity of physical ill health have been robustly associated with the risk of delirium in adult patients. Dehydration, malnutrition, severe physical illness, multiple coexisting physical illnesses, chronic renal or hepatic disease, neurologic disease, a history of stroke, metabolic derangements, bone fracture or other trauma, low serum albumin, thiamine deficiency, HIV, immobility and terminal illness have all been identified as predisposing factors for delirium (Inouye 2006; Trzepacz, 1996). Use of physical restraints and bladder catheters, hypertension, active alcohol and tobacco consumption, and high Acute Physiology and Chronic Health Evaluation (APACHE II; Knaus, 1985) scores on admission are also documented risk factors for delirium amongst adult patients (Ouimet *et al.*, 2007a; Weber *et al.*, 2004).

The relationship between physical health and delirium in children and adolescents has not been systematically studied. However, a broad range of underlying physical conditions and substances have been associated with delirium in this age group, which

will be discussed in greater detail in the 'Precipitating factors' section. In the case of physical ill health it is often unclear as to whether it functions as a predisposing factor, precipitating factor, or both. Treatments associated with the physical conditions may also function as both precipitating and predisposing factors for delirium, thereby adding another layer of confounding to the situation.

Schieveld and colleagues (2007), in their series of 40 patients with delirium in a paediatric intensive care unit setting that has already been discussed above, used the Paediatric Index of Mortality (PIM; Shann *et al.*, 1997) and Paediatric Risk of Mortality (PRISM; Pollack *et al.*, 1988) scales in order to systematically document the severity of physical illness in their patients. The mean PIM score was 10% and the mean PRISM score 24%, suggesting that as a group these patients were severely ill. Amongst the 40 cases of delirium, mechanical ventilation was necessary in 85%.

In a separate article (Schieveld *et al.*, 2008) the authors reported on the sensitivity, specificity, and positive and negative predictive values of using the PIM and PRISM to *predict* delirium in children in the intensive care unit, and suggested that although their sensitivity and specificity for delirium were only 'fair', and the positive predictive value 'low', that given the seriousness of delirium in the PICU setting these instruments might still have utility for this purpose

An indirect, proxy measure of illness severity is length of hospital stay. The average length of hospital stay among the 84 delirious paediatric patients described by Turkel and Tavaré (2003) was 41 days, with a maximum of 255 days, reflecting severe underlying physical ill health in this group. However, the authors did not indicate what the average length of hospital stay for patients of a similar age who were *not* referred to psychiatric services with a delirium, or those referred who received a diagnosis *other* than delirium.

In summary, both overall burden of physical illness as reflected in generic measures of illness severity, and long duration of hospital stay have been associated with delirium amongst children and adolescents.

2.4.3.8 Caregiver Factors

De Carvalho and Fonseca (2008) made the assertion that certain caregiver factors might influence the risk for delirium in children and adolescents, including caregiver anxiety, caregiver absence and caregiver pain perceptions. As has already been discussed, Kain and coworkers (2007) reported a significant reduction in emergence delirium from 24% in a control group to 10% in their intervention group that received 'family-centred preparation for surgery'. Perhaps loss of 'auxiliary ego support' through either physical absence or uncontained parental anxiety mediates this association. Bhat and Rockwood's (2007) metaphor for delirium as the 'unanchored narrative self' and 'ship lost at sea' has already been mentioned. In metaphorical terms, perhaps parents struggling to manage their own anxiety are less able to provide the 'anchor' strong enough to hold the ship to its course.

2.4.3.9 Summary of predisposing factors

In summary, a systematic review of the literature relating to delirium in children and adolescents was able to identify a number of putative predisposing factors for the occurrence of delirium in this age group. Of these, the existing literature would seem to support the following underlying variables with the greatest weight of evidence: physical ill health, pre-existing psychiatric disorder, caregiver anxiety or caregiver absence, young age, and possibly male gender.

Clearly there exists some overlap between predisposing and precipitating factors for delirium. Thus, physical ill health and even caregiver absence might conceivably function as both predisposing and precipitating factors in children and adolescents.

2.4.4 Precipitating factors

A number of authors have conceptualised delirium as a final common pathway or symptomatic 'reaction type of the brain' to a wide array of underlying physical disorders

with direct or indirect central nervous system involvement (Trzepacz *et al.*, 2004, Schieveld, 2006).

A lengthy list of cerebral, metabolic, endocrine, cardiopulmonary, infectious, autoimmune, neoplastic, nutritional, toxic, and substance-related conditions have been associated with delirium in adult patients (Inouye, 2006; Meagher, 2001; Burns *et al.*, 2004; Young and Inouye, 2007).

Similarly, a wide variety and large number of underlying physical conditions have been associated with delirium in children and adolescents. Delirium in children and adolescents involves the same categories of etiologies as it does in adult patients. However, some authors have suggested that children may be differentially more susceptible to delirium than adults in certain contexts. For example, Martini (2004) has suggested that young patients are particularly vulnerable to the development of delirium secondary to toxic, metabolic, or traumatic central nervous system insults. Trzepacz and coworkers (2004) have also suggested that, as head trauma and accidental poisonings are more common amongst children than adults, that a correspondingly larger proportion of cases of delirium might be expected to be the result of these two etiologies. Williams (2007) stated that delirium in children and adolescents may be more likely due to illicit substances, hypoxia secondary to foreign body inhalation, near-drowning and asthma, and head injury. Anecdotal evidence also suggests that children are particularly prone to develop delirium in the context of febrile illness, regardless of the underlying cause (Prugh *et al.*, 1980). Paediatricians working in emergency units are very familiar with the presentation of the young child with a high fever who is transiently 'confused', disorientated and 'not making sense'.

Lipowski (1980, p.206) suggested the following list of possible precipitants that should be excluded in delirium among those aged 3 to 16 years:

- Infection: measles, mumps, scarlet fever, rheumatic fever, influenza, meningitis, encephalitis
- Intoxication with drugs, poisonous plants, other poisonous substances

- Epilepsy
- Head trauma
- Acute glomerulonephritis
- Uremia
- Hypoglycemia
- Hyponatremia/hypermnatremia
- Migraine

The results of the systematic review of the literature addressing precipitating factors in relation to child and adolescent delirium will now be discussed under a number of subheadings.

2.4.4.1 Existing paediatric consultation-liaison psychiatry case series

In Turkel and Tavare's retrospective record review (2003) of 84 children and adolescents diagnosed with delirium following referral to a consultation liaison psychiatry service the most common cause of delirium was infectious (n = 28; or 33%), usually with central nervous system involvement. The second most common cause was drug-induced (n = 16; or 19%). Delirium was also found after serious trauma (n = 8; or 9.5%), autoimmune disorders (n = 7; or 8%), following kidney, lung, heart, and bone marrow transplant (n = 7; or 8%) and post-operatively (n = 6; or 7%). Children with neoplastic conditions like leukemia, lymphoma and brain tumours were also represented (n = 6; or 7%), as were children with multiple organ, respiratory, or cardiac failure (n = 6; or 7%).

In Schieveld and colleagues (2007) paediatric ICU series of 40 delirious paediatric patients, 22 (55%) had neurological disorders, 20 (50%) infectious disorders, and 12 (30%) respiratory disorders.

2.4.4.2 Published case reports

Of the 65 published case reports of child or adolescent delirium or probable delirium identified by the systematic review of the literature, 19 (29%) are medication-related, 14

(22%) are associated with central nervous system disorders (including 2 reports of nonconvulsive status epilepsy and 7 reports of confusional migraine), 12 (18%) are of metabolic or endocrine etiology, 4 (6%) neoplastic (including 2 paraneoplastic syndromes), 3 (5%) infectious, and only 2 (3%) involve cases of organ failure (See Tables 2.5.1 – 2.5.7).

Thiamine deficiency has also been suggested as an underappreciated precipitant of and/or predisposing factor for delirium in paediatric intensive care and oncology settings (Trzepacz *et al.*, 2004). Decker and Isaacman (2000) described an 11-year-old girl with a history of prolonged starvation who was admitted to an intensive care unit with a hypoactive delirium associated with nystagmus and ophthalmoplegia. A diagnosis of Wernicke's encephalopathy was made and a dramatic change in her ocular and mental status findings was noted within days of commencing thiamine replacement. Miyajima and colleagues (1993) have also reported a 7-year-old boy who developed a delirium associated with Wernicke's encephalopathy while receiving chemotherapy for acute lymphoblastic leukemia.

2.4.4.3 Post-anaesthetic emergence delirium

A significant contribution to the literature on delirium in children and adolescents comes from the anaesthesiology literature (Manworren *et al.*, 2004; Keaney *et al.*, 2004; Cole *et al.*, 2002; Wells and Rasch, 1999; Kain *et al.*, 2004; 2006; 2007; Moos *et al.*, 2005; Vlajkovic *et al.*, 2007; Przybylo *et al.*, 2003; Sikich *et al.*, 2004).

Children emerging from anaesthesia may experience a range of behavioural disturbances that are often interchangeably referred to in the literature as post-anaesthetic excitement, emergence agitation, and emergence delirium (Vlajkovic *et al.*, 2007). Recent publications, however, have taken pains to differentiate pure motor agitation from motor agitation associated with features of delirium (Moos *et al.*, 2005; Vlajkovic *et al.*, 2007), in some cases applying DSM-IV diagnostic criteria for delirium to children recovering from anaesthesia (Przybylo *et al.*, 2003). Using an assessment tool based on DSM-IV diagnostic criteria for delirium, Przybylo and colleagues (2003) described an incidence

of delirium of 20% in children emerging from anaesthesia for surgery for strabismus. Cole and colleagues (2002) documented a slightly lower incidence, suggesting that just over 10% of children recovering from *elective* abdominal surgery experienced an episode of severe restlessness associated with disorientation on emergence from anaesthesia.

Sikich and Lerman (2004) have recently published reliability and validity data on the Paediatric Anaesthesia Emergence Delirium (PAED) scale (Appendix B). For the purposes of this study, 'emergence delirium' was defined as:

a disturbance in a child's awareness of and attention to his or her environment with disorientation and perceptual alterations including hypersensitivity to stimuli and hyperactive motor behaviour in the immediate post-anaesthesia period

(Sikich and Lerman, 2004, p.1139)

The symptoms and signs described in the anaesthesiology literature are in keeping with the phenomenological descriptions of predominantly hyperactive delirium.

Young children are particularly at risk of emergence delirium, and those aged 2 to 5 years may be most vulnerable (Vlajkovic *et al.*, 2007, Keaney *et al.*, 2004). Children certainly experience post-anaesthesia emergence agitation more often (12-13% as compared to 5.3%) than do adults (Vlajkovic *et al.*, 2007).

Several studies have suggested that *rapid* emergence (as happens more commonly with agents like sevoflurane) increases the likelihood of emergence agitation/delirium, and that surgery involving the tonsils, thyroid, middle ear, and eye likewise increases the risk (Vlajkovic *et al.*, 2007). The reasons for this last finding remain unclear, but might conceivably relate to sensory deprivation (in the case of ear and eye surgery) or communication difficulties (in the case of thyroid and tonsil surgery). Curiously, as has already been mentioned, children with higher levels of preoperative anxiety, and children that are temperamentally more emotional, more impulsive, less social and less

adaptable to environmental changes have also been identified as being at higher risk (Kain *et al.*, 2004; Voepel-Lewis *et al.*, 2003).

In summary, a systematic review of the literature relating to delirium in children and adolescents identified a number of articles referring to 'emergence delirium' in the anaesthesiology literature. Indeed, some of the most interesting aspects of delirium in this age group emerge from an analysis of this body of literature.

Only very recently, however, have psychiatric diagnostic criteria for delirium been applied in this context. Earlier work is obfuscated by a tendency to pool together children with 'emergence agitation' and 'emergence delirium', although it is quite possible that patients with 'emergence agitation' simply have more attenuated forms of emergence delirium in which psychotic features are absent and cognitive features more subtle.

Children less than 5 years of age may be at greatest risk, as is the case with febrile delirium. The observation that children with certain temperamental characteristics and higher levels of anxiety may be at elevated risk of delirium in the post-anaesthesia setting is an important one. If children with these characteristics are more vulnerable to delirium in other contexts as well, then the possibility of screening for these characteristics on history in children admitted, for example, to the Burns Unit or Paediatric Intensive Care Unit clearly merits further study. Such screening might facilitate both early diagnosis and treatment of delirium in such high-risk settings. Additionally, the management of preoperative anxiety may have a role in the prevention of paediatric delirium, even outside of the context of anaesthesia.

2.4.4.4 Burn injuries

Delirium has been well described in children and adolescents who have suffered extensive burn injuries. Mohnot *et al.* (1982) published a series of 13 cases of 'burn encephalopathy' (mean age 3 years; 11 boys and 2 girls). This article provides an example of the confusion that pervades the terminology around delirium. 'Burn

encephalopathy' was defined as 'the acute onset of a change in sensorium or the occurrence of seizures or abnormal neurological signs, or both, at any time after the initial burn'. Only one of the 13 experienced a seizure in isolation, 7 of the cases described are clearly cases of delirium, and a further 3 could be classified as probable delirium. The EEG was abnormal (slow and disorganised) in 4 of the 6 patients in which it was done. The authors suggested that in view of their smaller surface area, higher initial metabolic rate, and developing brain, children are more vulnerable to 'burn encephalopathy' than adults. A variety of metabolic derangements, including hyperglycemia, hypoglycemia, hyponatremia, hypernatremia, hypophosphatemia, hypocalcaemia, anaemia, hypoalbuminemia and sepsis were suggested as likely contributors.

Additionally, there are 3 published series (Ratcliffe *et al.*, 2004; Brown *et al.*, 1996; and Harrison *et al.*, 2002) documenting the use of haloperidol in agitated, critically ill children, two of which (Ratcliffe *et al.*, 2004; Brown *et al.*, 1996) describe the use of haloperidol in children with extensive burn injuries. The presence of both agitation and distress in a hospitalised child with severe burns has a wide differential diagnosis including acute stress disorder, post-traumatic stress disorder, separation anxiety, adjustment disorder, major depression, inadequate pain control and severe neuropathic itching, in addition to delirium. All three studies are retrospective chart reviews that often provide insufficient information as to the cognitive aspects of the presentation.

Ratcliffe and colleagues (2004) described the use of haloperidol in 26 children with an average of 50% total body surface area (TBSA) burns. In 80% (21 of 26 children) the indication for haloperidol was 'agitation and restlessness'. The other indication, in 15% (4%) of cases, was for 'agitation and restlessness in addition to delirium with marked disorientation, hallucinations, and delusions'. Assessment of cognitive function and treatment response would likely have been severely confounded in these patients by the use of concurrent psychotropic medications. In 96% of cases morphine was administered before or concurrently with haloperidol, and lorazepam (a benzodiazepine) and diphenhydramine (a sedating antihistamine) were administered in 81% and 69% of cases respectively, either before or concurrently with haloperidol.

In a similar study, Brown and colleagues (1996) reviewed the medical records of 30 critically ill paediatric patients (mean age 7.0 years) with extensive burn injuries (mean TBSA burn 51%) who were treated with haloperidol. The main indication for the use of haloperidol in this series was for 'marked agitation and restlessness' (80%, or 24 of 30 patients), but in 13% (4 of 30 patients) of cases the indication was 'delirium with marked disorientation, hallucinations, and delusions'. Ninety-seven percent of patients received intravenous morphine sulfate, and 70% received midazolam.

In addition to the use of haloperidol, these authors described their *non*-pharmacological approaches to management, emphasizing the first step in management as the elucidation and treatment of the underlying cause of the agitation (pain, hypoxia, sepsis, metabolic derangements, sleep deprivation, drug effects and drug withdrawal). The authors described several psychosocial and environmental interventions, including the provision of a non-threatening environment, reassurance, continual reorientation, and measures to maintain a normal sleep-wake cycle, but suggested that in their experience these interventions were primarily prophylactic and usually inadequate once the delirium and agitation became manifest.

In summary, this systematic review of the literature suggests that delirium is commonly encountered in the context of extensive burn injuries in children, where it has most frequently been managed using the conventional antipsychotic medication, haloperidol, often in combination with benzodiazepine and opioid analgesic medications. Children may be more vulnerable to delirium in the context of severe burns than are adults.

2.4.4.5 Febrile delirium

The earliest study identified by the systematic literature review (1980 to July 2008) that addressed the relationship between childhood delirium and febrile illness was that of Prugh and colleagues (1980), who suggested that children were more likely than adults to respond to fever and infection with delirium. However, this relationship was clearly apparent to Leo Kanner in 1942, who commented on the remarkable lack of literature

relating to childhood delirium, despite the frequency of its occurrence in 'infantile infections' (Kanner, 1942, p. 179). Hart (1936, p. 748) also remarked on the 'greater liability of children to develop delirium during febrile illnesses'.

A number of Japanese authors have focussed their attention on the features and correlates of 'febrile delirium', in part due to the epidemic of Japanese influenza-associated encephalitis during the 1990's and the need to distinguish potentially fatal influenza-associated cerebral infection from the relatively more benign 'febrile delirium', in children presenting with acutely altered mental states associated with fever. Okumura and coworkers (2006) for example, described 26 children with 'delirious behaviour' associated with high fever (body temperature greater than 39 degrees centigrade). 'Delirious behaviour' was not specifically defined in this study, but commonly included meaningless speech ("A giraffe is dying"; "Run away! Pocket monsters are coming"), unexplained fearfulness, behaviours suggestive of hallucinations ('pointing into space as if something present' associated with 'fearful response'), and disorientation, and lasted between less than an hour and up to 14 hours. The EEG was abnormal in the large majority of subjects. These authors also reported an apparent temporal relationship between the administration of antipyretic medications (most commonly acetaminophen) and the onset of delirious behaviour, and suggested that in some cases delirium may in fact be triggered as the body temperature begins to fall or by the antipyretic medication itself.

Similarly, Okumura and colleagues (2005) studied the 'delirious behaviour' of children with influenza-associated febrile illness in order to differentiate 'simple' febrile delirium from influenza-associated encephalitis in Japanese children. Fifteen consecutive admissions (10 boys and 5 girls; mean age 6.5 years) for 'delirious behaviour' associated with fever were included in the study. 'Delirious behaviour' was not clearly defined in this study, but included a subtle reduction of consciousness (10 children), 'meaningless speech' (8 children), and visual hallucinations (3 children). In 14 of the children the delirious behaviour appeared on the day of onset of the fever or on the following day. The body temperature was 39.0 - 39.9 degrees centigrade in 8 children, and 40.0 degrees or higher in 5 children. Seizures were observed in 5 children, and 3 children exhibited

delirious behaviour soon after seizures. The EEG revealed some mildly abnormal findings in 13 of the 15 children.

Onoe and colleagues (2004) described the use of EEG spectral analysis in 20 children (mean age 6.9 years) with febrile delirium, in this case defined as 'an acute and transient confusional state with high fever'. The authors observed that febrile delirium was observed during the first 3 days of fever, usually occurred at night, and lasted less than 10 minutes. Febrile myoclonus was observed in 25%. A past history of febrile delirium was noted in 15%. Posterior slowing (delta waves) on the EEG was observed in 65% of cases of febrile delirium, and these EEG alterations tended to last for only a few days. Little attention was paid to the phenomenology or clinical findings in this study, and a 'confusional state' was not clearly defined.

Okumura *et al.* (2004) studied 213 consecutive febrile seizures in children with an average age of 2.3 years. 'Delirious behaviour' (not defined) was observed in 4 (2%) of these patients (1.6 to 4.3 years old) and included meaningless speech and behaviour suggestive of a child responding to hallucinatory stimuli. Examples of 'delirious behaviours' included 'clinging to mother saying that many worms are on her bedclothes', 'behaving as if something nonexistent were present' and 'meaningless speech such as "Wolves are coming"'. The duration of the delirious behaviour was 10-15 minutes in 2 patients and 1 hour in the remaining two.

Lastly, Takahashi and coworkers (1988) reported on 1511 questionnaires relating to the occurrence of delirium in children associated with fever and documented that the highest incidence was at 1 to 4 years of age, with an incidence as high as 28%.

In summary, it has long been suspected that children are at higher risk of delirium than older people during febrile illness. The work of Okumura, Onoe, and Takahashi and colleagues has confirmed that delirium is common amongst young children (under 5 years of age) in this context. The delirium occurring in children with high fever manifests with the same symptoms and EEG features as that occurring in more severely ill children. However, delirium occurring in this context is usually very brief, occurring

early in the course of illness and often at night. It is often recurrent during further febrile illnesses, and resolves without the need for antipsychotic medication. Paediatric febrile delirium is perhaps the exemplar of Schieveld's (2008) hypothesized 'benign paediatric delirium'.

2.4.4.6 Delirium associated with cancer

Delirium may also occur in the context of neoplastic illness in children and adolescents. Two cases of paraneoplastic limbic encephalitis presenting with delirium associated with immature ovarian teratomas have been reported in a 14-year-old (Stein-Wexler *et al.*, 2005) and 15-year-old (Lee *et al.*, 2003) girl. DiMario and colleagues (1990) reported on a series of 89 children with systemic cancer (excluding primary central nervous system cancers) all of whom developed 'acute mental status changes'. In this instance, 'acute mental status change' was defined as 'an abrupt or rapidly evolving loss of consciousness, disorientation, alteration in memory, development of hallucinations, excessive somnolence with diminished arousability, or seizures with or without the presence of other focal neurologic deficits'. The acute mental status change occurred as a result of seizures in 53 (60%), 'encephalopathy' in 24 (27%), and a stroke syndrome in 12 (13%). Of the 24 children with 'encephalopathic' acute mental status changes the underlying etiology was found to be coagulopathy in 23%, medication-related in 19%, septic or hypovolemic shock-related in 19%, central nervous system (CNS) infection in 17%, and metabolic disturbance in 6%.

In summary, children and adolescents suffering from a variety of cancers can experience delirium through a number of different mechanisms. Importantly, in occasional patients, delirium associated with paraneoplastic limbic encephalitis may be the first clinical manifestation of an underlying cancer.

2.4.4.7 Confusional migraine

The association between an acute confusional state and migraine in children was first suggested by Gascon and Barlow (1970). These authors reported on 4 patients, aged 8-16 years, in whom the confusional state lasted 4 - 24 hours. A systematic review of the

child and adolescent delirium literature identified a number of articles relating to *probable* delirium in the context of confusional migraine. For example, Shaabat (1996) reported a series of 13 children (6 to 15 years) with confusional migraine. The period of 'confusion' was preceded by headache in all cases and lasted between 2 and 24 hours. The ratio of males to females was 11: 2. A family history of migraine on the maternal side was present in 10 of the 13 cases. Bechtel (2004) described an 11-year-old girl and a 14-year-old boy who developed acute and transient marked disorientation, memory impairment and somnolence associated with headache and dysarthria who received a clinical diagnosis of acute confusional migraine on the basis of history, clinical findings, and negative laboratory findings. O'Neill and colleagues (1992) reported 3 children (all 11-year-old girls), where a transient episode of 'confusion', disorientation and inability to follow simple instructions associated with a history of acute onset of a throbbing headache and nausea resulted in a clinical diagnosis of acute confusional migraine. All 3 cases had posterior EEG slowing. Lastly, Nezu and colleagues (1997) described a 7-year-old boy and a 12-year-old girl with confusional migraine characterised by episodes of 'confusion', disorientation and memory disturbance associated with headache and posterior EEG slowing. The temporal course, mental state features and EEG findings in these reports suggest that these episodes would likely receive a psychiatric diagnosis of delirium.

In summary, a relatively large number of cases of confusional migraine in children and adolescents were identified by the systematic review of the literature. In none of these reports was the term 'delirium' used. However, the combination of transient 'confusion', disorientation, and other cognitive deficits of acute onset, accompanied by EEG features congruent with those reported in delirium, suggests that at least some of these patients were experiencing delirium precipitated by migraine.

2.4.4.8 Medication-related delirium

Commonly prescribed psychoactive medications, such as opioid analgesics, benzodiazepines, and corticosteroids are frequently identified as significant etiological contributors to delirium in adults. Data relating to drug-induced delirium has

accumulated through numerous adult case reports, but in fact very few prospective or retrospective studies have addressed this issue.

However, Gaudreau and colleagues (2005) critically reviewed the evidence for the relationship between delirium in adults and prescribed medications using a literature review. Psychoactive medications, when grouped as a single variable, significantly increased the risk of delirium after adjusting for confounding factors in five studies identified by the review. Among drug classes, benzodiazepines significantly increased the risk of delirium in a single study, as did antipsychotics in another single study. Eight out of 12 studies, however, failed to identify a significant association with opioid medications. The authors concluded that the evidence available for an association between psychoactive medications and delirium in adults is 'rather weak, scarce, and sometimes conflicting'.

Medications are, however, frequently implicated in the etiology of delirium among children and adolescents. Of the 65 case published case reports since 1980 describing cases of delirium or probable delirium in children and adolescents identified by the systematic literature review, almost a third are medication-related. A wide variety of medications have been associated with the development of delirium in this age group (Table 2.5.1).

Although antipsychotic agents are commonly prescribed for the symptomatic treatment of delirium in this age group, it is important to note that there have been a number of published reports of antipsychotic medications *precipitating* delirium in children and adolescents. For example, Joshi and colleagues (1991) described the development of a delirium associated with the neuroleptic malignant syndrome in a 14-year-old boy treated with a combination of haloperidol, trifluoperazine and lithium carbonate for a manic episode. Leibold *et al.* (2004) reported a delirium associated with the neuroleptic malignant syndrome in a 15-year-old male adolescent treated with the atypical antipsychotic ziprasidone. A possible *forme frustre* of the neuroleptic malignant syndrome presenting with agitation, intermittent disorientation and fluctuating consciousness has also been described in a 14-year-old girl treated with aripiprazole

(Hammerman *et al.*, 2006). Oner and colleagues (2004) have also reported the development of an acute confusional state lasting 16 hours in a 6-year-old boy who was commenced on risperidone for the treatment of stereotypic behaviours.

Other agents have also been implicated. Brar and colleagues (2005) reported a 13-year-old boy with no previous psychiatric history who developed a delirium characterised by confusion, emotional lability, disorientation, memory impairment and delusions after ingesting 4 of his friend's 100mg topiramate tablets.

Anticholinergic agents have regularly been reported as causing delirium in children and adolescents by a number of authors, and it has been suggested that relative immaturity of central cholinergic neural networks may underpin a particular vulnerability to 'cholinergic failure' in children that is shared by the elderly (Martini, 2004; Lipowski, 1980). Garza and colleagues (2000), for instance, described a 3-year-old boy who developed a hyperactive delirium with visual hallucinations secondary to accidental orphenadrine ingestion. Baysal *et al.* (2006) reported a 4-year-old boy who developed a delirium characterised by agitation, drowsiness, disorientation, hallucinations and delusions secondary to a central anticholinergic syndrome induced by cyclopentolate eye drops. Elmalem *et al.* (1985) documented a series of accidental anticholinergic overdoses in young children presenting with probable delirium. Livingston and coworkers (1983) reported a 16-year-old girl who developed a delirium associated with the use of amitriptyline in their case series of ten patients with tricyclic antidepressant-associated delirium. Wilens *et al.* (1997) have also described two adolescents aged 18 and 15 years who developed a delirium after smoking marijuana whilst receiving tricyclic antidepressants. Armstrong and Schweitzer (1997) reported an episode of presumably anticholinergic delirium in a 17-year-old boy who experienced a dramatic increase in serum benzotropine levels following the addition of paroxetine to his medication regimen.

Delirium has also been described in children on the basis of acute medication withdrawal syndromes. Sury and colleagues (1989), for example, reported a 4-year-old boy who developed a hyperactive delirium characterised by disorientation, agitation,

aggression, and visual hallucinations on the basis of benzodiazepine withdrawal in an intensive care unit setting.

In summary, a systematic review of the child and adolescent delirium literature suggests that prescribed medications are an important precipitant of delirium in children and adolescents. The evidence is particularly strong for a wide variety of anticholinergic agents and psychotropic medications. Importantly, the systematic review also reveals that a number of medications reported as being useful in the *treatment* of delirium in this age group, including antipsychotic medications, have also been identified as possible precipitants of delirium. Clearly, these reports are important to note when deciding whether or not to treat a child or adolescent with delirium using these medications.

2.4.4.9 Delirium associated with abused substances

Drugs of abuse have also been reported in association with delirium in this age group. Mott and colleagues (1994) documented the neurologic manifestations of cocaine exposure in 41 children and adolescents between the ages of 2 months and 18 years. Cocaine exposure was confirmed by urine toxicology. Nineteen of the 41 children and adolescents were described as having neurologic abnormalities, including 4 (aged 16-19 years) who presented with a delirium. Features of delirium generally resolved within 24 hours.

Osterhoudt (2005) described a case of agitated delirium in a 15-year-old girl secondary to dextrometorphan abuse, a common antitussive ingredient used in over-the counter cough and cold preparations, and abused for its dissociative properties in higher doses. Manaboriboon and Chomchai (2005) have also published a report of the development of confusion and diminished level of consciousness in a 12-year-old and 13-year-old girl following deliberate overdose of dextromethorphan.

A number of cases of delirium have been described in adolescents who ingested the strongly anticholinergic *Datura stramonium* (Jimson weed, moonflower, Devil's trumpet) plant for its hallucinogenic properties. Kurzbaum *et al.* (2001) published a

report of two brothers, 17 and 16 years old, who presented with agitated delirium in the context of an anticholinergic toxidrome after ingesting seeds of the plant. Beno and colleagues (2004) have also reported a 16-year-old boy who developed a delirium characterised by agitation, incoherence, hallucinations and disorientation after ingesting *Datura* seeds.

2.4.4.10 Delirium associated with autoimmune conditions

Delirium has also been documented in children and adolescents in association with autoimmune conditions.

Turkel and colleagues (2001) described the clinical findings in 10 children and adolescents (7.5 to 17 years) with systemic lupus erythematosus (SLE) who were referred to a psychiatric consultation-liaison service, and reported that 5 of the 10 children received a DSM-IV diagnosis of delirium. Electroencephalogram (EEG) findings were unremarkable in the 8 of the patients in which an EEG was performed, including in those with clinical delirium. However, initial Single Positron Emission Computerised Tomography (SPECT) findings were abnormal in all of the patients.

2.4.4.11 Delirium and HIV in children and adolescents

Only a single published case report of delirium occurring in the context of HIV infection in childhood was identified by the systematic literature review (Scharko *et al.*, 2006).

This is somewhat surprising, as paediatric patients with HIV infection are known to develop HIV-related progressive encephalopathy, which is felt to be the childhood equivalent of HIV-associated dementia encountered in adult patients, and would be expected to substantially increase the risk of delirium in this group.

Scharko and colleagues (2006) have described a 15-year-old girl with vertically-acquired HIV infection who developed a hyperactive delirium superimposed on features suggestive of an HIV-associated subcortical dementia.

2.4.4.12 Environmental factors

Other factors reported to increase the risk for delirium in children and adolescents include social isolation, sensory extremes, visual or hearing deficits, immobility as well as environmental novelty or stress (Williams, 2007). No empirical evidence to support these suppositions could be found at the time of writing.

2.4.4.13 Delirium associated with ‘functional’ psychiatric disorder

Commonly regarded as the *sine qua non* of ‘organic’ psychiatric disorders, it may seem contradictory to include psychiatric disorder as a possible precipitant of delirium in children and adolescents. However, as has already been suggested in the introductory chapter of this dissertation, the previously distinct boundary between ‘organic’ and ‘non-organic’ or ‘functional’ psychiatric disorder has increasingly become blurred.

Bells’ mania is a severe form of mania that produces a clinical picture almost indistinguishable from hyperactive delirium, characterised by severe psychomotor agitation, psychosis and diffuse cognitive impairments.

In a study that examined the incidence and risk factors for delirium amongst adult psychiatric inpatients, Ritchie *et al.*, (1996) found that patients with bipolar affective disorder had the highest incidence of delirium (35.5%). Lateralisation to more right-sided fronto-subcortical neural networks in delirium is mirrored by research suggesting a right-sided predominance of frontal and subcortical pathways involved in mania (Blumberg *et al.*, 1999), implying that the this predisposition to delirium in bipolar disorder may have a neuroanatomical basis.

Pruett *et al.*, (2005) have described a case of Bell’s (delirious) mania, associated with excited catatonia (or *furor*) in a 16-year-old girl (Table 2.5.4).

2.4.4.14 Summary of precipitating factors

In conclusion, a systematic review of the literature relating to delirium in children and adolescents reveals a wide variety of precipitants of delirium in this age group. A similar range of conditions has been reported as precipitating delirium in children as that in adults. An analysis of all published case reports of delirium in children and adolescents between 1980 and July 2008, and of the literature relating to post-anaesthetic emergence delirium lends support to the assertion that young people are at particular risk of delirium when exposed to a range of prescribed medications and anaesthetic agents. This is clearly an important conclusion, as it suggests that there may be a *more* significant iatrogenic contribution to delirium in this age group than in older patients. Also of note is the fact that a number of medications reported as effective in the *treatment* of delirium in children and adolescents have been reported as precipitating delirium in these patients.

Toxins and substances of abuse appear to be relatively common causes of delirium in this age group. Children also appear to be differentially more vulnerable to delirium associated with febrile illness and severe burn injuries than at other ages. Migraine syndromes may be an important cause of delirium in older children and young adolescents, particularly when the delirium is recurrent.

No research has been conducted to date that has examined the environmental contribution to the development of delirium in children and adolescents. Possible environmental precipitating factors like social isolation, sensory extremes, sensory deprivation or immobility are important, because these factors, relative to other known predisposing and precipitating factors may be more easily correctable. Addressing such factors could potentially play an important and cost-effective role in preventing delirium in young people.

2.4.5 Protective factors

The role of protective factors for delirium has hardly been studied in any age group.

Hypothetically, protective factors might serve to 'buffer' the influence of predisposing and/or precipitating factors, thereby raising the individual's threshold for delirium. Protective factors are not merely absent risk factors. Protective factors exert their effects through dynamic interaction with risk factors to reduce the likelihood of a negative outcome.

Higher educational attainment might serve as such a protective factor for delirium in older people. Jones and colleagues (2006) reported the results of two studies that indicated that hospitalised elderly patients with low educational attainment were at increased risk of delirium. The authors postulated that educational attainment serves as a marker of diminished 'cognitive reserve', defined in this instance as 'the degree of efficiency with which an individual uses relevant brain networks or cognitive strategies to cope with brain injury' (Jones *et al.*, 2006).

Other potential markers of 'cognitive reserve' in adults include intelligence and occupational achievement.

A systematic review of the literature was unable to locate any literature addressing the subject of protective factors for delirium in children and adolescents. Potential protective factors that merit study would include intelligence, level of education, adaptive functioning, female gender, caregiver factors and genotype.

Figure 2.2 illustrates the interaction of predisposing, precipitating and potential protective factors and their relationship with a hypothetical paediatric delirium 'threshold'.

2.4.6 Pathophysiology

Hart (1936, p. 747) noted that:

In discussing at the present time the possible pathogenesis of delirium we have therefore to leave the sphere of knowledge and enter that of hypothesis and speculation

Unfortunately, the pathophysiologies or underlying mechanisms of how the aforementioned predisposing and precipitating factors interact to produce a delirium remain poorly understood in 2008.

There has been little research into the basic underlying mechanisms of delirium, and what research has been done has related almost entirely to adults. In the paragraphs that follow I have attempted to summarise current theories as to the pathophysiology of delirium and the state of the existing evidence in support of these theories.

The principal mechanisms hypothesized to underlie the development of delirium are neurotransmitter (especially acetylcholine and dopamine) imbalance, inflammatory responses, increased blood-brain barrier permeability, hypercortisolism, regional deficits in cerebral blood flow and decreased cerebral oxidative metabolism.

A significant challenge to such research has been the heterogeneity of the delirium syndrome itself and the populations in which it is studied (Marcantonio *et al.*, 2006). Thus, delirium is a rapidly fluctuating condition that often manifests with extreme behavioural dyscontrol in patients who are critically ill. It is therefore not difficult to imagine the challenges faced by researchers exploring, for example, the functional neuroimaging correlates of delirium.

Some authors have argued that, as a disorder resulting from a wide variety of underlying etiologies and yet having a largely stereotyped 'core' presentation, delirium may be the result of a 'final common neural pathway' (Trzepacz *et al.*, 2004). This final common

pathophysiologic pathway has been hypothesized to be associated with a state of *relative* or absolute low cholinergic and high dopaminergic neurotransmitter imbalance (Trzepacz, 2004). Other authors, however, have suggested that a single dopamine-acetylcholine imbalance hypothesis is oversimplistic and does not adequately account for the two opposite psychomotor presentations of delirium (De Rooij *et al.*, 2005).

Extensive evidence supports the role of cholinergic deficiency or 'cholinergic failure' in the genesis of delirium (Marcantonio *et al.*, 2006). The administration of anticholinergic drugs has been robustly associated with delirium in adults, and serum anticholinergic activity has been reported as being raised in adult patients with delirium, correlating with delirium severity, and improving with resolution of the delirium (Marcantonio *et al.*, 2006). Epidemiologic studies have shown that adult patients with a higher 'anticholinergic burden' of their drug regimes are at higher risk of delirium (Han *et al.*, 2001). Physostigmine has the ability to reverse delirium associated with anticholinergic toxicity (Stern, 1983), and there is a suggestion that the cholinesterase inhibiting drugs may be of benefit in delirium, even in cases where the delirium is not related to the administration of anticholinergic drugs (Inouye, 2006). Centrally acting anticholinergic drugs have also been shown to produce electroencephalographic slowing similar to that produced in patients with delirium (Sloan *et al.*, 1992). In addition, several medical conditions associated with delirium, such as hypoxia, hypoglycemia and thiamine deficiency may reduce acetylcholine by affecting the oxidative metabolism of glucose and the production of acetyl coenzyme A, the rate-limiting step for acetylcholine synthesis (Trzepacz *et al.*, 2004). Opioid analgesics, the post-operative state, and traumatic brain injury have also all been associated with decreased cholinergic activity (Trzepacz *et al.*, 2004).

Dopaminergic excess also appears to play a role in the emergence of delirium in adults. Increased dopamine activity may in fact occur as a result of reduced cholinergic activity, and delirium may arise as a *relative imbalance* of these two interacting neurotransmitter systems, rather than an absolute deficiency or excess of either of these two neurotransmitters (Trzepacz *et al.*, 2004). Hypoxia, for example, results in the increased release of dopamine in addition to reducing acetylcholine (Trzepacz *et al.*, 2004).

Dopaminergic drugs and drugs which enhance dopamine release (e.g cocaine) have been associated with delirium in adults (Wetli *et al.*, 1996) and children (Mott *et al.*, 1994). Antidopaminergic agents like the antipsychotic medications are extensively used to treat delirium in adult patients.

Alterations in *other* neurotransmitters, including norepinephrine, serotonin, gamma-amino butyric acid, glutamate and melatonin have all been implicated in adult delirium. However, the evidence supporting their role is substantially less than that supporting the role of cholinergic deficiency and dopaminergic excess (Marcantonio *et al.*, 2006; Inouye, 2006). However, it has been suggested that alterations in these neurotransmitters may exert their influence through interaction with the hypothesized final common pathway of acetylcholine: dopamine imbalance (Inouye, 2006).

The body's inflammatory responses may also play a role in the genesis of delirium. Delirium is common in a variety of systemic inflammatory states, including infections, the post-operative state, cancer, and autoimmune conditions. Inflammation leads to a breakdown in the blood-brain barrier in addition to decreasing cholinergic transmission (Marcantonio *et al.*, 2006). A variety of inflammatory markers or cytokines, including interleukin -1, interleukin-2, interleukin-6, tumour necrosis factor, and interferon have also been implicated in the pathogenesis of delirium, possibly by increasing the permeability of the blood-brain barrier (Inouye, 2006). The brain responds to systemic infection and extensive injury with an inflammatory response of its own, releasing a variety of cytokines. This local inflammatory response is thought to alter patterns of neuronal activity, possibly resulting in the symptoms and signs of delirium (Pandharipande *et al.*, 2005).

Hypercortisolism associated with chronic stress has also been implicated in delirium pathophysiology. Elevated cortisol levels have been associated with delirium in Cushing's disease and high dose steroid treatment (Marcantonio *et al.*, 2006).

Other researchers have used a variety of neuroimaging techniques in attempt to elucidate underlying mechanisms of delirium in adult patients. Neuroimaging studies in adult

patients with delirium provide evidence of generalised disruption in higher cortical function, with dysfunction in the bilateral or right prefrontal cortex, subcortical structures, thalamus, basal ganglia, frontal and temporoparietal cortex, fusiform cortex, and lingual gyri, particularly on the non-dominant side (Inouye, 2006). The right posterior parietal cortex is crucially involved in sustained attention and attention to the environment (Trzepacz *et al.*, 2004), and both are impaired in delirium. Alsop and colleagues (2006) have reviewed the role of neuroimaging in elucidating the pathophysiology of delirium in adult patients, including data from 18 Single Photon Emission Computer Tomography (SPECT) studies of delirium in adults. In general, delirium has been associated with decreased cerebral blood flow, which usually returns to normal following symptom resolution. Regional deficits in blood flow have also been reported, most commonly in the frontal and parietal regions.

In the absence of existing gold standard tests for identifying delirium, Marcantonio and colleagues (2006) have reviewed the adult literature relating to possible serum 'biomarkers' for delirium, including the apolipoprotein E4 allele (APOE4), the A9 allele of the dopamine transporter, serum anticholinergic activity, serum amino acids, melatonin, cytokines and hypercortisolism. As has already been mentioned, genetic factors may play a role in the vulnerability to delirium, although the mechanisms by which this enhanced genetic vulnerability might come about have not been explored.

As already discussed, several recent lines of evidence have converged in blurring the traditional boundaries between dementia and delirium. One such line of evidence suggests that delirium and dementia might share underlying pathogenic mechanisms, including decreased cerebral oxidative metabolism, cholinergic deficiency, and inflammation (Inouye and Ferrucci, 2006). For example, general anaesthesia has been identified as an important risk factor for both post-operative delirium and more subtle but enduring forms of post-operative cognitive dysfunction (Xie *et al.*, 2006). Beta-amyloid protein generation and accumulation are one of the hallmarks of Alzheimer's dementia, and increasing evidence suggests that cellular apoptosis (programmed cell death) may also play an important role (Xie *et al.*, 2006). Xie and colleagues (2006) recently demonstrated that the inhalational anaesthetic, isoflurane, had the ability to

increase levels of beta-amyloid, increase its fibrillar aggregation, and cause apoptosis. These authors suggested that their results provided a 'plausible and direct link' between the pathogenesis of dementia and delirium. They hypothesized that beta-amyloid neurotoxicity, at least in the setting of anaesthesia, might be responsible for delirium *and* its more durable cognitive sequelae, in much the same way as these mechanisms have been shown to be involved in the pathogenesis of Alzheimer's dementia.

In summary, the literature relating to the pathophysiology of delirium in adults highlights the role of neurotransmitter imbalance (principally of acetyl choline and dopamine), enhanced blood-brain barrier permeability, local brain inflammatory responses, hypercortisolism, regional deficits in cerebral blood flow (principally in the frontal and parietal cortices) and cerebral oxidative metabolism. Beta-amyloid toxicity and cellular apoptosis may also play a role. Some of these mechanisms, particularly inflammation, beta-amyloid neurotoxicity, apoptosis, cholinergic failure and decreased cerebral oxidative metabolism may underlie a spectrum of cognitive disorders ranging from delirium to dementia.

By comparison, the literature addressing underlying mechanisms of delirium in children and adolescents is very limited.

The literature relating to child and adolescent delirium indirectly supports the role of low cholinergic activity in the etiology of the disorder. A number of authors have described the occurrence of delirium in children and adolescents in the context of anticholinergic toxicity, as already described. Prugh and colleagues (1980) have provided a detailed account of an episode of delirium in a 7-year-old boy with atropine intoxication associated with reversible EEG slowing. Paediatric delirium as a result of anticholinergic toxicity has also been described in published case reports by: Richardson *et al.* (2000), Garza *et al.* (2000), Kurzbaum *et al.* (2001), and Beno *et al.* (2004).

Flacker and Lipsitz (1999) demonstrated increased serum anticholinergic activity in elderly patients with fever. There is a growing body of literature describing delirium in children and adolescents associated with pyrexial illness, and a number of authors have

suggested that paediatric patients may be particularly prone to delirium in the context of fever (Williams, 2007). This relationship may at least partially be mediated through increased anticholinergic activity during febrile illness.

Karnik and colleagues (2007) have recently presented an intriguing hypothesis in relating two contrasting case reports of a 16-year-old girl with hypoactive/mixed delirium and a 14-year-old girl with hyperactive delirium. The authors postulated two major pathways to delirium. Firstly, they postulated a high dopaminergic pathway leading to aggressive, agitated hyperactive delirium, and drew parallels with the positive symptoms of schizophrenia in this regard. In contrast, they postulated a low or normal dopaminergic state associated with a cholinergic dysregulation pathway to account for hypoactive/mixed delirium. The authors drew on clinical experience, their dopaminergic/cholinergic imbalance hypothesis, and the differing pharmacokinetics of haloperidol and risperidone in suggesting that hyperactive delirium and hypoactive/mixed delirium might respond better to haloperidol and risperidone respectively.

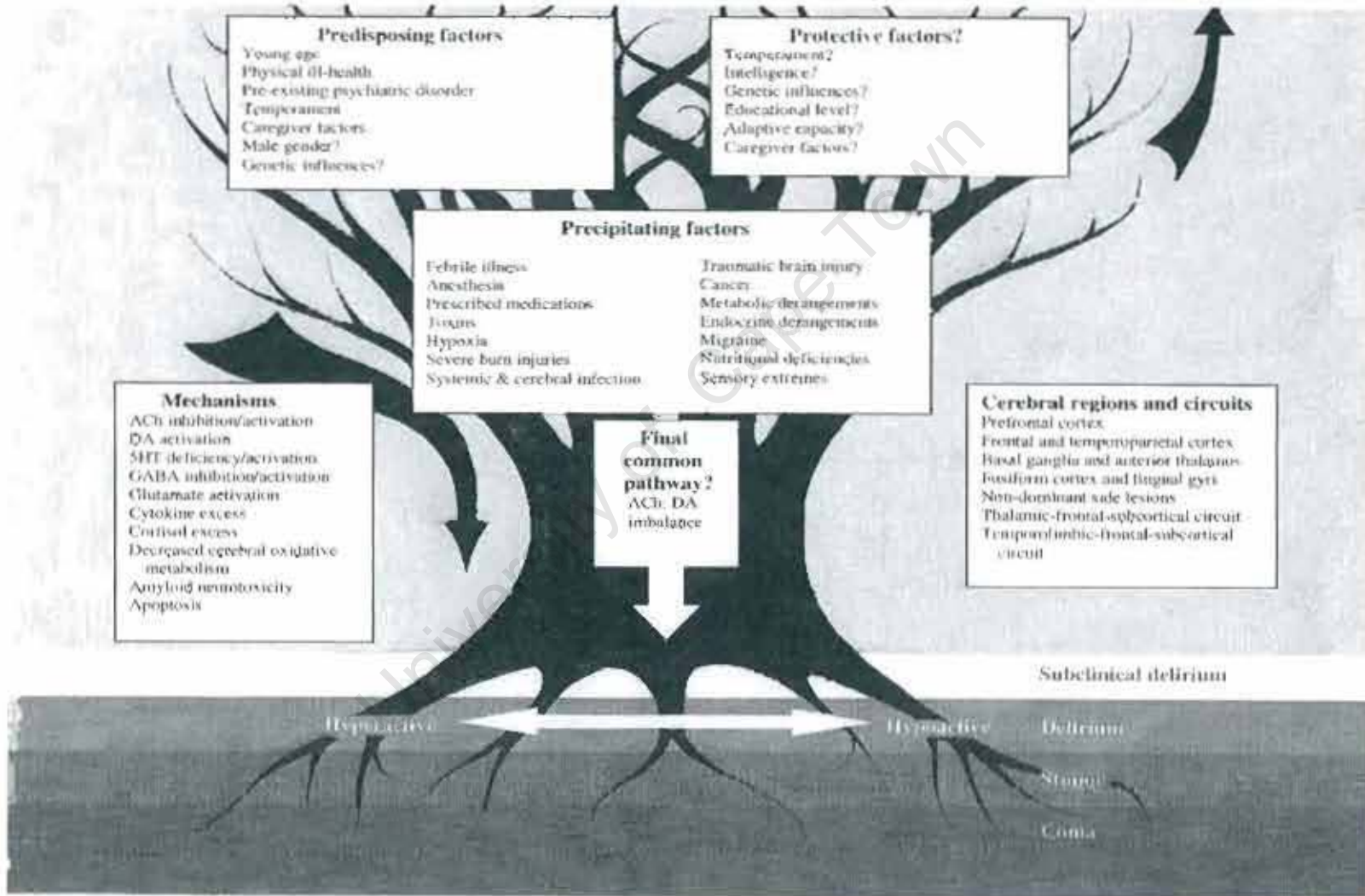
2.4.7 Synthesis

I have attempted to illustrate the pathways to and mechanisms of delirium in children and adolescents in the form of a tree (Figure 2.2). This model is derived from both my systematic review of the literature relating to delirium in children and adolescents, and my own clinical experiences. The highest, smallest branches of the 'delirium tree' represent the most distal influences, namely predisposing factors and potentially, protective factors. These distal influences interact with more proximal ones, namely precipitating factors, represented in the figure as the larger, lower branches of the tree. In addition, protective factors could conceivably interact with predisposing factors to reduce the likelihood of delirium. Distal and proximal influences reach a confluence in the main boughs of the delirium tree, which represent both the main hypothesized pathophysiologic mechanisms of delirium and the main neural circuits involved. These main boughs then combine to represent the hypothesized final common pathway of relative or absolute acetylcholine: dopamine imbalance, which Paula Trzepacz

symbolically represented with a funnel (Trzepacz *et al.* 2004), but which I have chosen to represent with the trunk of the 'delirium tree'. At a certain point (represented by the ground), a patient with a sufficient loading of predisposing and precipitating factors (unbuffered or insufficiently buffered by protective factors), crosses a threshold into subclinical or 'emerging' delirium. Further progression along this path (represented by the roots of the tree) can result in this same patient crossing progressively 'deeper' thresholds into clinical delirium, then stupor, and ultimately coma.

I have represented delirium itself in this figure as a bidimensional spectrum disorder. The first spectrum (represented by the different 'soil' depths) is reminiscent of Trzepacz *et al.*'s hypothesized 'continuum of consciousness' spectrum, in which delirium is represented as a zone between alert/awake and stupor (Trzepacz *et al.*, 2004). The second dimension is that of psychomotor activity, which I have chosen to represent as a dimension rather than the traditionally discrete subtypes of hypoactive, mixed and hyperactive. In this way a patient may move fluidly from hypoactive to hyperactive delirium, and from relative lucidity to subclinical delirium, delirium, stupor and back again. This dynamic spectrum concept is much closer to my own clinical experience with children and adolescents with delirium than the concept of relatively discrete subtypes.

Figure 2.2 The Delirium Tree: Etiology and pathogenesis of delirium in children and adolescents



2.4.8 Comparative Phenomenology: Does delirium in childhood present like delirium in adulthood?

This question is clearly of crucial importance. If it could be shown that delirium in childhood presents with similar manifestations as delirium in adulthood, this would then lend support to the current practice of using unadjusted DSM-IV-TR diagnostic criteria regardless of developmental age. On the other hand, if it could be shown that delirium in children presents with very different clinical manifestations when compared to adults, this would seriously cast doubt on the validity of applying current unadjusted diagnostic criteria to this age group.

Turkel, Trzepacz and Tavare (2006) addressed this important issue using a MEDLINE literature review to identify articles on delirium from 1966 to 2003 which included specific descriptions of the frequency of individual symptoms associated with delirium in both adult and paediatric patients. Among the 2455 articles found, only 10 articles, with a total of 968 adult subjects, were identified that actually listed rates of symptoms associated with delirium. Only 4 studies were identified that directly or indirectly addressed the clinical features of delirium amongst children and adolescents (Turkel and Tavare, 2003; Prugh *et al.*, 1980; Jones *et al.*, 1992; Brown *et al.*, 1996). Only one of these (Turkel and Tavare, 2003), systematically described symptoms of delirium in 84 children and adolescents (mean age 10.4 years) diagnosed with DSM-III-R delirium, and was thus the *only* study relating to delirium in children and adolescents that was included in the review. The results across the adult studies were averaged, and then compared to the results reported in the single child and adolescent study. The authors reported that using this strategy, impaired alertness, apathy, anxiety, disorientation, and hallucinations all occurred with similar rates in children and adults. Hallucinations were reported in 43% of children and adolescents, and ranged from 22% to 55% in seven adult studies, with a combined rate of 29%. About half of adult studies reported on rates of impaired orientation, with a combined rate of 76%. A similar rate of 77% was reported in the Turkel and Tavare (2003) study of children and adolescents. Impaired alertness (or clouded consciousness) had a combined rate of 75% in adult studies, and was not significantly different from the child and adolescent rate. The authors made

particular note of the fact that only 4 studies of delirium in adults reported rates of impaired attention, despite this being a core diagnostic criterion for delirium. Children and adults had equal rates of anxiety (61%), however, children were significantly more likely to have irritable mood (86%) or labile affect (79%) compared with adults (combined rates of 50% and 32% respectively). Adults were significantly more likely to have impaired memory, depressed mood, speech disturbance, delusions and paranoia documented than children and adolescents. No cases of speech disturbance, paranoia or delusions were noted in Turkel and Tavare's child and adolescent series. In contrast, children and adolescents were significantly *more* likely to have evidence of sleep-wake cycle disturbance (combined adult rate 53%; paediatric rate 98%), fluctuation of symptoms (combined adult rate 60%; paediatric rate 100%), agitation (combined adult rate 44%; paediatric rate 69%) and 'confusion' documented, in addition to the higher rates of irritability and affective lability already mentioned above.

Turkel and colleagues (2006) concluded, while acknowledging the dearth of literature relating to the phenomenology of delirium in *both* adults and children, that the same symptoms of delirium appeared to occur in adults and children. They suggested that this data, although limited, supported the clinical practice of making a diagnosis of delirium based on DSM criteria in patients of *any* age. They also suggested that any differences apparent in the reported rates of different symptoms of delirium between children and adults might well reflect observer bias or underreporting of symptoms by different authors due to the underuse of structured or standardised instruments.

Since the review of Turkel and colleagues (2006) that compared symptom rates between children and adults with delirium, Meagher and colleagues (2007) have published a prospective, cross-sectional study of delirium symptoms and cognitive performance amongst 100 consecutive *adult* cases of delirium referred from a palliative care inpatient service. This study provides a useful comparison (See Table 2.6) to the rates of symptoms reported by Turkel and Tavare (2006). Each case was assessed using the Delirium Rating Scale – Revised- 98 (DRS-R-98; Trzepacz *et al.*, 2001) and the Cognitive Test for Delirium (CTD; Hart *et al.*, 1996). The mean age of the cases with delirium only (as opposed to those with delirium plus dementia) was 68.7 years. In this

study, inattention was present in 97%, and other cognitive deficits were also common (76%- 89%), with disorientation being the *least* common. Twenty-four percent had *no* evidence of disorientation present at any level of severity, similar to the findings of Turkel and Tavare (2006) in which no evidence of disorientation was documented in 23% of children and adolescents with delirium. This is a cause for concern, for (as noted by Meagher *et al.*, 2007) many non-psychiatric physicians rely on bedside tests of orientation to time, place and person as their principal mental status examination. Sleep disturbance was noted in 97% of adult cases, motor agitation in 62%, and perceptual disturbances and hallucinations in 50%. These rates in adult patients with delirium are *more* similar to the paediatric rates reported by Turkel and Tavare (2006): 98%; 69%; and 43% respectively.

Thus, the difference in symptom frequencies apparent from Turkel, Trzepacz, and Tavare's literature review (2006) between adult and children/adolescents may well reflect methodological differences rather than dissimilarities in phenomenology. When assessed using structured rating instruments, the differences between adult and childhood presentations of delirium appear even less impressive (Table 2.6).

However, Leentjens and colleagues (2008) recently reported the first study designed to *directly* compare the phenomenology of delirium in children with that in adult and geriatric patients, once again using delirium rating instruments that have only been thoroughly validated in adults. The authors compared Delirium Rating Scale (DRS) scores for 46 children (mean age 8.3 years) admitted to a Paediatric Intensive Care Unit (PICU) with DSM-IV delirium, with DRS scores for 49 adult (mean age 55.4 years) and 70 geriatric (mean age 76.2 years) patients with delirium occurring in a palliative care unit. The authors suggested that their findings indicated that although the *range* of symptoms in all 3 groups was similar, delirium in severely ill children was characterised by a *distinct course and symptom profile*. Specifically, childhood delirium had a more acute onset, less fluctuating course, with less sleep-wake disturbance. Hallucinations, delusions, agitation and lability of mood were *more* severe in children with delirium, while the cognitive deficits were less severe. The authors concurred with Turkel and colleagues (2006) in finding a similar *range* of symptoms of delirium regardless of age.

However, the authors contrasted some of their findings with those of Turkel and colleagues (2006) in relation to comparative phenomenology.

Whereas Turkel and colleagues (2006) noted *more* severe symptom fluctuation and sleep-wake disturbances, Leentjens and colleagues (2008) noted these features to be *less* common than in their adult and elderly counterparts. However, Leentjens and colleagues (2008) made the point that, being a PICU sample, many of their delirious children would have been sedated with opioids and benzodiazepines, which may well have confounded this issue. It is worth noting that the adult and geriatric patients with whom the psychiatrically-referred PICU delirious children were compared were *screened* for delirium in a palliative care setting. Additionally, however, Leentjens and colleagues found delusions to be *more* severe in children and adolescents than in adults, instead of *less* severe as was reported by Turkel and colleagues (2006). Possibly this may also relate to the fact that children with delirium were patients who were *referred* for a psychiatric consultation, rather than screened for delirium. Psychotic symptoms are a common reason for referral of patients with delirium, and this may have biased the results.

In addition, the systematic literature review of delirium in children and adolescents identified 65 published case reports of delirium/probable delirium in children and adolescents between 1980 and 10 July 2008. These cases are generally reported without the use of structured instruments, and as a result the terms used to describe signs and symptoms of delirium vary widely across reports. In addition, many case reports use terms that are vague and poorly defined – ‘confusion’ being a common example. However, by combining these individual case reports into a ‘series’ it is possible to describe the frequency of symptoms and signs of delirium amongst cases that are selected for *publication*. There is clearly an inherent observer, reporting and/or publication bias that needs to be considered when combining these reports. These cases are bound to reflect the more severe and dramatic clinical presentations of delirium. Published case reports of delirium in this age group often describe cases of delirium caused by single, often reversible, and frequently ‘exotic’ precipitants, and so generalisability may be limited. There may, however, still be value in documenting the

frequency of reported features of delirium in this 'series', although it may tell us more about what clinicians *notice* and *look for* in young people presenting with delirium than about the true frequency of these features in the disorder. The study reported by Turkel and Tavaré (2003), being a retrospective chart review of cases assessed without the use of standardised instruments, may also potentially suffer from this limitation. Given this cautionary note regarding the interpretation of these findings, the frequency of symptoms and signs of delirium amongst cases published as individual case reports is as follows: disorientation (51%); agitation (41%); 'confusion' (41%); somnolence / decreased level of consciousness (34%); hallucinations (30%); disorganised speech / thinking (30%); memory impairment (24%); inattention (22%); aggression (17%); apathy/psychomotor retardation (15%); disorganised/purposeless behaviour (11%); fear (9%); inconsolability (9%); sleep disturbance (4%); paranoia (3%) and delusions (2%). In comparison to the findings from the studies already described these findings are notable for the relatively high rates of impairment in orientation and memory, and also of disorganised speech/thinking. If, however, as Meagher and colleagues suggested, clinicians rely more heavily on bedside tests of orientation (and possibly short-term memory) than on tests of attention and vigilance, these findings are then less surprising. Clinicians relying heavily on bedside tests of orientation to place, person, and time and recent memory, rather than on tests assessing the more consistent and core diagnostic feature of inattention, are likely to miss or misdiagnose many cases of delirium, particularly amongst youth.

Table 2.6 compares reported symptom rates between adults (Meagher *et al.*, 2007 and Turkel *et al.*, 2006) and children and adolescents (Tukel *et al.*, 2006, and the 65 case reports identified by the systematic literature review). Note that the recent study by Leentjens and colleagues (2008) has not been included in Table 2.6, as the authors have compared *severity* of symptoms as rated by the Delirium Rating Scale between children, adults and the elderly, rather than symptom percentages.

Table 2.6 Comparing delirium symptom rates between adults, and children and adolescents

	Adult Meagher <i>et al.</i> (2007) n=100 (%)	Adult Turkel <i>et al.</i> (2006) n=84 (%)	Child and adolescent Turkel <i>et al.</i> (2006) n=84 (%)	Child and adolescent (Published case reports) n=65 (%)
Impaired attention	97	65	100	22
Impaired orientation	76	76	77	51
Impaired memory	88	84	52	24
Speech disturbance	54	48	0	30
Delusions	31	26	0	2
Hallucinations	Any severity 50	29	43	30
Hallucinations and perceptual disturbances	Mod. or severe 26			
Agitation	62	44	69	41
Apathy/Retardation	62	59	68	15
Sleep-wake disturbance	97	53	98	4
Fluctuation of symptoms	-	60	100	-
Anxiety	-	61	61	11
Depressed mood	-	52	0	0
Irritable mood	-	50	86	2
Labile affect	53	32	79	4

Additional features of delirium in children that are commonly seen but rarely reported are developmental regression (Prugh *et al.*, 1980; Schieveld *et al.*, 2005) with loss of previously acquired skills, and loss of the caretaker's ability to console the distressed child, and diminished eye contact with the usual caretaker (Schieveld *et al.*, 2005; Sikich *et al.*, 2004).

Schieveld and colleagues (2007) have cautioned that there are accumulating indications that delirium in the paediatric age group may be subtle in presentation. These authors have suggested that adhering too closely to DSM-IV-TR criteria for adult delirium may result in underdiagnosis, particularly in the setting of paediatric intensive care, and that delirium in this context may be dominated by more subtle signs like a reduction of awareness of the caregiver, purposeless actions, and inconsolability. Subtle qualitative changes only apparent to the child's parents or other usual carers may be one of the strongest indicators of delirium in very young children. A parent's comment that 'This is not my child anymore' (Schieveld *et al.* 2007) should be taken very seriously, and trigger a careful search for other subtle indicators of altered consciousness.

In summary, the systematic review of delirium in children and adolescents identified a number of articles addressing the issue of whether delirium in children manifests in the same way as it does in adults. Indeed, this aspect of delirium in youth has perhaps received more attention than any other aspect. As mentioned, this issue is extremely important, as it relates very closely to the question as to whether unmodified DSM-IV-TR criteria can in fact be validly and reliably applied to children.

Recent work by Turkel and colleagues (2006) and Leentjens and colleagues (2008) suggest that hallucinations, agitation and affect lability are consistently identified more commonly amongst children with delirium when compared with adults with delirium, suggesting either a different delirium symptom profile, *or*, that there is a higher rate of underrecognition of mixed/hypoactive forms of delirium in children.

The data in relation to other symptoms of delirium is inconsistent. Turkel and colleagues' (2006) literature review reported that sleep-wake disturbance and fluctuation of symptoms were more frequent in children and adolescents with delirium, whereas these two features of delirium are reported as being *less* frequent in children and adolescents by Leentjens and colleagues (2008). As already stated, however, this discrepancy may be due to different study populations. In particular, the children with delirium in a PICU setting described by Leentjens and colleagues (2008) are more likely to have been prescribed opioid and benzodiazepine medications, which may have reduced the frequency of sleep-wake disturbance and fluctuation of symptoms in their sample.

In addition, as has already been noted, when one compares the symptom rates in children and adolescents with delirium reported by Turkel and colleagues (2006) in their literature review with the rates in adult patients with delirium more recently reported by Meagher and colleagues (2007) the differences become less pronounced. Specifically, differences in the rates of hallucinations, agitation, sleep-wake disturbance and affect lability between children and adults become less prominent. The study by Meagher and colleagues (2007) was a large, prospective, methodologically robust study specifically designed to capture symptom rates in adult patients with delirium, and so it may in fact be more valid to compare the rates reported by Turkel and Tavaré (2003) for children and adolescents with the adult rates reported in this study.

However, all of the existing studies relating to this crucial issue have utilised operationalised diagnostic criteria and rating instruments that were designed for use in adults. The 'true' validity, sensitivity, specificity and reliability of existing diagnostic criteria and delirium rating instruments in children remain unknown.

Two additional features of delirium in children and adolescents were identified by the systematic literature review. Developmental regression with transient loss of previously acquired skills, and the inability of a usual carer to console the child have been suggested as relatively unique features of delirium in children and adolescents.

In conclusion, the results of the systematic review of the literature relating to delirium in children and adolescents suggest that a similar *range* of symptoms of delirium occur in children and adolescents as occur in their adult and geriatric counterparts. The symptom *profile* for delirium in children and adolescents is more similar than it is different to delirium in adult and geriatric patients. Where differences in symptom rates are apparent, however, these differences are relatively small, particularly when one takes methodological and study population differences into account.

The most robust difference in reported symptom rates would seem to be a higher rate of hallucinations and agitation in children and adolescents when compared to adult and elderly patients. This is significant, as hallucinations and behavioural disturbance are the common triggers for referral of young people with delirium to psychiatric services. If this difference were genuine, it could help to explain the anecdotal impressions of a number of authors that delirium is more common in children. Could it be that the particular symptom profile of delirium in children results in a *higher* rate of detection and a lower threshold for referral to psychiatric services?

Despite these differences in reported symptom frequencies and the additional, relatively unique aspects of delirium in children and adolescents, the published literature to date appears to support the *applicability* of unmodified DSM-IV-TR criteria for making the diagnosis of delirium in all age groups. However, despite a degree of face validity, what the above-mentioned literature tells us little about is how the DSM-IV-TR symptoms of delirium in children and adolescents are actually elicited (reflecting clinical utility), and how reliable, sensitive, and specific DSM-IV-TR criteria are when applied to children with delirium.. Could it be that Turkel and colleagues (2006) finding of less prominent speech disturbance and a lower frequency of delusions in children, and Leentjens and colleagues (2008) finding of less cognitive deficits in children, are an artifact of these symptoms simply being both more difficult to elicit and more difficult to distinguish from normality in children? If this is true, at the very least we might expect the DSM-IV-TR diagnostic criteria for delirium to have a lower sensitivity in children, and potentially, lower reliability.

The issue of how symptoms of delirium might be elicited in children is addressed in some detail in both the 'Clinical assessment' section of the Systematic Review (2.4.13) and the 'Diagnostic assessment process' section of the Case Series (3.5.5).

2.4.9 Clinical subtypes of delirium

Lipowski (1983) was the first modern author to classify delirium and describe the now commonly recognised three subtypes, characterised on the basis of psychomotor activity and responsiveness, namely the hyperactive, hypoactive, and mixed subtypes of delirium. However, even in 1965, Henry and Mann recognised a 'quiet' and a 'violent' delirium.

The hyperactive delirious patient conforms more closely to the stereotype of the delirious patient and presents with heightened stimulus responsiveness, increased motor activity, hypervigilance, excitability and often hallucinations and delusions. In contrast, the patient with a hypoactive delirium presents with diminished responsiveness and reduced motor activity. They are often lethargic and somnolent with slow speech, and diminished alertness and awareness. They commonly appear sedated. The third variant, mixed delirium, involves behaviour that fluctuates between the two extremes within an episode of delirium (Liptzin and Levkoff, 1992).

The classification of delirium into these three subtypes has been the subject of several studies of adult and particularly elderly patients with delirium (Lipowski, 1989; Ross *et al.*, 1991; Kobayashi *et al.*, 1992; Meagher *et al.*, 1998; O'Keefe and Lavan, 1999; Camus *et al.*, 2000a; 2000b; Meagher *et al.*, 2000; De Rooij *et al.*, 2005; 2006; Forrest *et al.*, 2007). It has been postulated that the different subtypes of delirium may reflect different underlying etiological and pathogenic pathways, different outcomes, and that different treatment strategies might need to be adopted for the different subtypes of delirium (Trzepacz and Dew, 1995; Sandberg *et al.*, 1999; Meagher *et al.*, 2000; Karnik *et al.*, 2007).

In the paragraphs to follow I will first attempt to summarise the recent contributions to the adult delirium literature in relation to delirium subtypes and their significance. Secondly, I will describe the literature identified by the systematic review of child and adolescent delirium that addresses delirium subtypes in this age group.

Researchers working in the field of adult delirium have shown that the hyperalert-hyperactive subtype of delirium, reminiscent of the familiar stereotype of the patient with *delirium tremens*, is in fact the *least* common subtype. For example, Liptzin and Levkoff (1992) reported the mixed variant to be the most prevalent (52%), followed by the hypoalert-hypoactive variant (19%), with the least prevalent being the hyperalert-hyperactive variant (15%). Similarly, Sandberg and colleagues (1999) reported the mixed variant as being the most prevalent (42%), followed by hypoalert-hypoactive (26%), and then hyperalert-hyperactive (22%). Other authors have documented a similar frequency distribution (Forrest *et al.*, 2007). Spiller and colleagues (2006) have reported an even greater predominance (86%) of hypoactive delirium amongst adult palliative care patients with delirium.

Hypoalert-hypoactive delirious patients are less likely to be *recognised* as suffering from a delirium, and may have a worse outcome than patients with the other two subtypes (Liptzin and Levkoff, 1992). O'Keefe and Lavan (1999), for example, found that hypoactive patients were more likely than delirious patients from other subgroups to have longer hospital admissions and to develop pressure sores. Kiely and colleagues (2007) reported that hypoactive delirious patients were 1.6 more times likely to die during one year follow-up than delirious patients with normal psychomotor activity, whereas both the hyperactive and mixed delirious patients had only nonsignificantly increased risks of dying. Patients with hypoactive delirium also have significantly lower scores on commonly used delirium rating scales such as the DRS, when compared to mixed or hyperactive subtypes (Meagher *et al.*, 2000), which suggests that such rating instruments might have a lower sensitivity for hypoactive delirium.

The literature relating to differential outcomes between delirium subgroups amongst adult patients has not, however, produced consistent findings. Marcantonio *et al.* (2002)

found that, in elderly patients who developed a delirium after acute hip fracture, a purely hypoactive subtype was associated with *better* outcomes in terms of survival, activities of daily living and hospitalisation.

Only a few studies to date have investigated whether the different delirium subtypes in adults benefit from *different* therapeutic approaches.

Patients with hyperactive delirium attract more attention from health care workers, and are thus more likely to be recognised and receive more active management of behavioural disturbances (Mittal *et al.*, 2006; Johnson *et al.*, 1994). Breitbart and colleagues (2002), in reporting their study of delirium-related distress in patients and their families suggested that the experience of hypoactive delirium is *as* distressing as in the hyperactive and mixed subtypes. This finding runs contrary to the popularly held notion amongst clinicians that hypoactive delirium requires a less active therapeutic stance, based on the impression that these patients are somnolent and undistressed. There is, however, some evidence to suggest that hypoactive delirium is somewhat *less* responsive to antipsychotic treatment (Platt *et al.*, 1994; Breitbart *et al.*, 2002b).

Some authors have suggested the use of psychostimulant medications like methylphenidate in adult patients with hypoactive delirium (Morita *et al.*, 2000; Keen and Brown, 2004), while other authors have cautioned that the use of such agents should be avoided in delirious patients with hallucinations and delusions due to the potential risk of exacerbating these psychotic symptoms (Lawlor *et al.*, 2000).

Mittal and colleagues (2006) reported that *hyperactive* adults with delirium were more likely to be referred to psychiatry. Having been referred to psychiatric services, these hyperactive delirious patients were then more likely to be prescribed any psychotropic medications, and specifically more likely to be prescribed atypical antipsychotics and benzodiazepines. They were also more likely to have higher in-hospital mortality, perhaps reflecting greater severity of physical illness.

In summary, the adult literature addressing delirium subtypes challenges the popular stereotype of hyperactive delirium, suggesting in fact that this presentation is the least common manifestation of delirium. The literature suggests that the hypoactive subtype of delirium is at least as clinically significant as its hyperactive counterpart. In fact, the bulk of the literature suggests that the hypoactive subtype of delirium in adults may have a poorer prognosis in terms of both morbidity and mortality, despite being less commonly detected and less actively managed. The adult literature relating to the treatment of hypoactive delirium is extremely limited and inconsistent.

The extent to which the three commonly recognised subtypes of delirium apply equally to children and adolescents has been insufficiently researched, and few authors have addressed this issue until recently.

Schieveld and colleagues (2007) reported that only 14 (35%) of their series of 40 children and adolescents presenting with delirium in the setting of a PICU conformed to the *hyperactive* subtype described in adults. Nine (22.5%) of these 40 patients were classified as hypoactive, while the remaining 17 (42.5%) patients were classified as having a subsyndromal 'emerging delirium'. Patients with 'emerging' delirium were characterised by anxiety, moaning, and/or restlessness accompanied by disturbances of consciousness and cognition. The authors noted that the different forms were not always clear-cut and that some cases fluctuated markedly over time. The authors also commented that the relatively high rate of hyperactive patients in their series might reflect a referral bias in that psychiatric consultation may have been more readily requested in agitated and disruptive patients.

As already described, Karnik and colleagues (2007), have recently reported two contrasted case reports of hypoactive/mixed and hyperactive delirium in two female adolescents, and suggested that these two presentations might respond differentially to risperidone and haloperidol, with the hyperactive variant responding better to haloperidol, and the hypoactive variant responding better to risperidone. The authors proposed a model whereby hyperactive delirium originates from a hyperdopaminergic state, with features reminiscent of the positive features of schizophrenia, whereas, in

contrast, the hypoactive/mixed subtype of delirium is hypothesized to originate from a low or normal dopaminergic state. Risperidone is suggested as being more beneficial in the hypoactive/mixed subtype owing to its ability to increase dopamine levels in the prefrontal areas of the cortex.

Schieveld (2008), however, suggests that Karnik and colleagues' (2007) dichotomy is an oversimplification of what in the reality of clinical practice is 'a form (of delirium) with a frequently changing presentation: from hyperactive to hypoactive, from clinical to subclinical, and from delirium to normal, and then back again'.

The use of methylphenidate or other psychostimulants in the treatment of paediatric patients presenting with hypoactive delirium has, to the best of my knowledge, not been described.

In summary, the systematic review of delirium in children and adolescents identified very few authors that have addressed different subtypes of delirium in this age group. The study by Schieveld and colleagues (2007) does, however, support the adult literature in finding hyperactive delirium *not* to be the most common presentation of delirium amongst children and adolescents. The generalisability of this finding to children and adolescents with delirium occurring *outside* of PICU is uncertain. The model proposed by Karnik and colleagues (2007) is intriguing, and certainly merits further study.

2.4.10 Referral patterns, underdetection and misdiagnosis

Despite the high morbidity, mortality, and economic burden associated with this disorder, an estimated 32% to 67% of cases of delirium go unrecognised on adult general-medical units (Mittal *et al.*, 2006).

Non-detection of delirium in adult patients in emergency department settings has been associated with a sevenfold increased hazard for mortality (Young and Inuoye, 2007). Detection rates of delirium are lowest in adult patients with the hypoactive subtype (Meagher *et al.*, 2000).

Mittal and colleagues (2006) studied the factors associated with referral of 213 adult delirious patients to consultation-liaison psychiatry services (Table 2.7). Patients referred to psychiatric services (n=100) tended to be of younger age and were more likely to have the hyperactive form of delirium than non-referred patients with delirium (n=100). Patients referred by the primary treatment team were significantly more likely to have had their delirium recognised as such by the referring team (50.5% as compared to 20.5%). Patients referred to psychiatry services were also more likely to be treated assertively with psychotropic medications (82% as compared to 34%). In addition, referred patients were more commonly prescribed atypical antipsychotics (50% as compared to 20%), conventional antipsychotics (11% as compared to 6%) and benzodiazepines (18% as compared to 7%). Referral of delirious patients to psychiatric services was associated with statistically significant lower rates of 1-year rehospitalisation on follow-up. Other outcome variables studied, including length of hospital stay, 1-year mortality, or discharge to nursing home, did not, however, differ significantly between referred and non-referred patients.

In summary, an unsystematic review of the adult delirium literature reveals the following in relation to referral patterns, underdetection and misdiagnosis.

Delirium goes undetected in a large proportion of adult patients with delirium, most commonly in patients with the hypoactive subtype. Nondetection of delirium in adult patients is associated with a greatly increased risk of mortality. Adult patients with *hyperactive* delirium are more likely to be referred to psychiatry, and to receive the correct diagnosis prior to psychiatric referral. When adult patients with delirium *are* referred to psychiatry, they receive more active pharmacotherapy and have certain improved outcomes above those who are not referred.

Table 2.7 Patterns of referral to psychiatric services amongst adult patients with delirium
(from Mittal *et al.*, 2006)

	Referred to psychiatry (n=100) Younger (mean = 65 yrs)	Not referred to psychiatry (n=100) Older (mean = 74 yrs)
Age		
Subtype hyperactive	63%	15%
Subtype not hyperactive	37%	85%
Delirium recognised as such by referring team	50.5%	20.5%
Prescribed psychotropic medications	82%	34%
Prescribed atypical antipsychotics	50%	20%
Prescribed conventional antipsychotics	11%	6%
Prescribed benzodiazepines	18%	7%
Outcomes: 1-year rehospitalisation rate	33%	50%
Other outcomes: length of hospital stay, 1-year mortality, discharge to nursing home	Not significantly different	

The literature relating to delirium in children and adolescents that addresses referral patterns, underdetection and misdiagnosis is limited. A number of authors have suggested that the rates of detection and misdiagnosis of delirium in children and

adolescents may be equally low, or even lower than in adult populations (Schieveld *et al.*, 2007; Trzepacz, 2004; Martini, 2005; Smith *et al.*, 1995). Trzepacz (1996) stated that delirium in children and adolescents is underdiagnosed, undertreated and misdiagnosed, with its symptoms commonly being misattributed to nonmedical and psychosocial causes by paediatric nurses and paediatricians. The relationship between delirium subtypes, detection of delirium, misdiagnosis, referral to psychiatric services, psychotropic medication use, and outcomes have not been systematically studied among children and adolescents.

In reviewing the published case reports of delirium in this age group identified by the systematic literature review, however, certain patterns are apparent. Reports of hyperactive delirium greatly exceed the number of reports describing hypoactive delirium. It is uncertain whether this reflects true prevalence differences, underdetection of hypoactive delirium, or publication bias in favour of hyperactive delirium. However, cautious extrapolation from the findings in adult patients would suggest that there is more underrecognition in hypoactive patients. Table 2.8 summarises some of the patterns apparent in relation to referral or non-referral to psychiatric services amongst published case reports of delirium or probable delirium in children and adolescents.

Patients with delirium who are referred to psychiatric services are more likely to have complex, uncertain and multiple possible etiologies which are not rapidly and readily amenable to correction, and are less likely to spontaneously resolve. Referred cases are also more likely to be of the hyperactive subtype, particularly in association with hallucinations, or to be referred from environmental settings with a low 'tolerance' for disruptive behavioural problems like the intensive care unit. However, even amongst those not referred for psychiatric services, there is a predominance of agitated, disruptive or psychotic patients which may reflect underdetection of hypoactive delirium or publication bias in favour of hyperactive delirium. Patients referred for psychiatric services are also more likely to be treated with psychotropic medication, particularly antipsychotics, than those that are managed by paediatricians.

Table 2.8 Referral and non-referral to psychiatric services in published case reports of children and adolescents with delirium (1980-2008)

	Referred to psychiatry	Not referred to psychiatry
Etiologies	Complex multiple causes	Single cause; often toxic (and 'exotic'), idiosyncratic drug reactions
Spontaneous resolution	Unlikely	Likely
Duration	Persisting	Brief
Setting	PICU or general paediatric ward	Accident and Emergency or Anaesthetic recovery room
Physical illness	Multi-system and severe	Less severe
Subtype	Hyperactive – agitated, disruptive, psychotic	Similar bias towards hyperactive
Treatment	More likely to receive antipsychotic medication	More likely to be treated conservatively

In summary, the limited existing literature relating to delirium amongst children and adolescents suggests that those referred to consultation-liaison psychiatry services represent a *subgroup* of patients whose delirium is more complex in etiology, more difficult to treat by simply reversing or removing the underlying precipitant, and more likely to be persistent.

2.4.11 Course and reversibility

Evidence has gradually accumulated in adults to support the notion of delirium as a disorder with potentially persistent cognitive deficits long after the more dramatic behavioural and perceptual disturbances have resolved (Jackson *et al.*, 2004; Hopkins *et al.*, 2006).

The existence of persisting cognitive deficits following apparent resolution of delirium in adults is less controversial than the meaning of this association. Many authors interpret persisting cognitive deficits as being evidence of pre-delirium 'diminished cognitive reserve' or preexisting dementia that has been 'unmasked' by the delirium. Preexisting dementia may go unnoticed prior to the episode of delirium, and only be detected once the delirium has resolved.

The nature of the relationship between delirium and longer-term cognitive impairment remains uncertain. Some authors have suggested that persisting impairments might reflect neuronal damage resulting from the delirium episode itself (Levkoff *et al.*, 1992) in much the same way as other authors have hypothesized that psychosis in the early phases of schizophrenia may in some way be directly toxic to the brain (McGlashan, 2006). Delirium may directly result in damage to certain brain areas, particularly the subcortical regions, limbic structures, prefrontal and parietal cortex (Hopkins *et al.*, 2006).

Thus, the traditional simple dichotomy between delirium and dementia has increasingly been challenged, with emerging evidence suggesting substantial overlap between the two conditions (Inouye, 2006; Young and Inouye, 2007).

A systematic review of the literature of delirium in children and adolescents identified limited data relating to the temporal course of delirium in children and adolescents. Following the pattern described in adult patients with delirium, existing data seems to suggest that in terms of onset, symptom fluctuation, and worsening at night, delirium in younger patients is also characterised by acute onset, marked fluctuation and nocturnal exacerbation. Turkel and Tavare (2003), in their retrospective chart review of 84 cases referred to a consultation-liaison psychiatry service, found exacerbation at night and affective lability to occur in 86% and 82% of children respectively. Martini (2004), in an overview entitled 'Delirium in the Paediatric Emergency Department', emphasized that the characteristically fluctuating course of delirium, with lucid intervals followed by periods of confusion, might lead to missed diagnosis or misdiagnosis in children. Martini (2004) suggested that the correct diagnosis of delirium in children may well

depend on the timing of the assessment. Whilst stressing the acute onset in the majority, Martini also acknowledged that occasional paediatric patients may experience a gradual onset of symptoms, with initial complaints of sleeplessness and nightmares. Schieveld *et al.* (2007) described the difficulties encountered in allocating a subtype to cases of paediatric delirium in an intensive care unit setting in view of the dramatic fluctuations between subtypes in an individual patient over the course of a single episode of delirium. Schieveld *et al.* (2007) also bemoaned the lack of studies addressing the natural course of delirium in childhood and the potential for misclassification of treated patients who have spontaneously resolved as 'responders'.

Very few authors have addressed the possibility of residual, *persisting* cognitive deficits in children and adolescents following resolution of an episode of delirium. Such deficits might substantially add to the morbidity associated with delirium in childhood and adolescence, and lower the threshold for aggressive intervention. Prugh and colleagues (1980) have, however, reported the persistence of disturbed perceptual-motor performance on formal testing, and of EEG abnormalities, even after recovery of the overt signs and symptoms of delirium in a proportion of the children in their series of 33 children with delirium. Kain and colleagues (2004), have also reported that the odds of having one or more new-onset post-operative 'maladaptive behaviour changes' over a 2 week post-operative period is significantly higher in children who experience emergence delirium in the immediate post-operative period.

These two studies (Kain *et al.*, 2004 and Prugh *et al.*, 1980) which report persistent skill deficits and behavioural problems following the resolution of an episode of delirium in children and adolescents challenge the widely held notion that delirium in children is transient and of little significance.

Neither of the two largest case series of delirium in children and adolescents (Turkel and Tavare 2003; Schieveld *et al.*, 2007) addresses the issue of delirium duration in any detail. Little is known of the naturalistic course of delirium in this age group. Even less is known of the relationship between etiology, motoric subtype, severity and duration of delirium in children and adolescents.

Schieveld and colleagues (2007) discussed the difficulties in classifying treatment response and pinpointing remission in a condition that is typified by fluctuation.

Duration of symptoms of delirium also depends on how easily and rapidly the underlying cause or causes of the delirium can be corrected or ameliorated. In some instances, the underlying cause of the delirium may be expected to be of short duration, with correspondingly brief duration of associated symptoms of delirium. Febrile delirium, for example, generally lasts for only a few hours. In Okumura and colleagues (2005) series of 15 children with delirious behaviour associated with high fever, the modal period of duration was 13 – 24 hours. Electroencephalographic abnormalities may lag behind the remission of symptoms, but also generally resolve within a few days (Onoe *et al.*, 2004).

In patients with more severe physical illness we have only indirect, crude, and flawed measures of the duration of symptoms of delirium using the duration of prescription of antipsychotic medication. Ratcliff and colleagues (2004), and Brown and colleagues (1996) reported on the duration of haloperidol use in agitated and delirious paediatric patients with severe burn injuries. Ratcliff and colleagues (2004) reported their longest period of treatment with haloperidol as being 22 days, with the mean number of doses of haloperidol being 12, while in the series reported by Brown and colleagues (1996), the longest period of treatment with haloperidol was 3 months, with the mean number of doses being 14.

In summary, few studies addressing the issue of the temporal course of delirium and of persistent deficits following a delirium were identified in the systematic literature review. The existing literature does, however, suggest that delirium in children and adolescents follows a similar temporal course to that in adults.

Importantly, two studies were identified which suggest that delirium in children and adolescents might have deleterious effects that persist long after the resolution of the more overt features of delirium. If further research was able to confirm the findings of

persistent skill deficits and emotional or behavioural problems associated with delirium, this might further support the argument put forward by Schieveld (2008) that delirium in children and adolescents requires far more active treatment (including pharmacotherapy) than it generally receives at present.

2.4.12 Morbidity

This issue is also central to the risk: benefit analysis in relation to the active pharmacotherapy of delirium in children and adolescents. If research were able to show that the morbidity associated with delirium in this age group greatly outweighed the risk of negative outcomes associated with its treatment, then this too would lend weight to the argument put forward by Schieveld (2008).

Studies of adult patients with delirium have confirmed that delirium is associated with significant morbidity and mortality. In the following paragraphs I will attempt to summarise the literature relating to morbidity associated with delirium in adult patients.

Numerous studies have reported that delirium in adult patients is associated with a significantly increased length of hospital stay (Forman *et al.*, 1995; Francis and Kapoor, 1990; Gustafson *et al.*, 1988; Hales *et al.*, 1988; Levkoff *et al.*, 1992; Pompeii *et al.*, 1994; Thomas *et al.*, 1988), although it would have to be acknowledged that this finding is not universal (Cole *et al.*, 1994, George *et al.*, 1997, Jitapunkul *et al.*, 1992). However, a meta-analysis of eight studies (Cole and Primeau, 1993) *does* support the existence of statistically significant differences in length of hospital stay between patients with delirium and control groups. Subsequent studies have suggested that length of stay may be increased by a median of 11 days in adult patients with delirium (O'Keefe *et al.*, 1997; Holmes *et al.*, 2000).

Delirious patients are less capable of cooperating fully with their medical care or rehabilitation. They may lose the capacity for competent decision-making regarding their medical care (Bostwick and Masterson, 1998). Their behaviour may directly compromise certain medical interventions and investigations, for example by pulling out

nasogastric tubes or removing intravenous lines or bandages. They are more prone to falls and decubitus ulcers, feeding problems and urinary incontinence (Trzepacz *et al.*, 2004).

Delirium also interferes significantly with the accurate assessment and effective management of pain (Breitbart *et al.*, 2002a). Contrary to popular beliefs, the majority of adult patients with delirium *recall* their delirium experience, and often recall it as having been distressing. Notably, patients with hypoactive delirium have been found to recall their experience of delirium as *equally* distressing as those with hyperactive delirium. The experience of delirium-associated psychotic experiences may also result in the later development of posttraumatic stress disorder (Griffiths *et al.*, 2007). Delirium is also a highly distressing experience for family members and nurses, particularly in patients with psychotic symptoms (Breitbart *et al.*, 2002a).

Milbrandt and colleagues (2004) found that, even after controlling for baseline confounding factors like severity of illness and comorbidities, median intensive care unit (ICU) and hospital costs were significantly higher in adult patients with at least one episode of delirium when compared to those without. The presence of delirium resulted in a relative increase in ICU and hospital costs of 40%. Young and Inouye (2007) suggested that an episode of delirium results in additional expenditure of an estimated \$2500 per adult patient.

Amongst adult patients, an episode of delirium during admission is associated with significant functional decline in activities of daily living following discharge (Gustafson *et al.*, 1988; Koponen *et al.*, 1989; Murray *et al.*, 1993). Decreased rates of post-discharge independent living status and increased rates of institutionalisation have been noted by a number of authors (Cole and Primeau, 1993; George *et al.*, 1997; Inouye *et al.*, 1998).

In contrast to the relatively large volume of literature attesting to a significant degree of morbidity associated with delirium in adult patients, the systematic review of the literature relating to delirium in children and adolescents identified almost no data

addressing this crucial question. Very little clarity on this issue has emerged since 1967, when Lipowski remarked that:

It is an important question whether delirium experienced in childhood has any effect on the psychological development of the individual and whether it predisposes him to psychiatric illness such as schizophrenia, anxiety, or dissociative states, in later life

(Lipowski, 1967, p. 232)

The persistence of cognitive and behavioural problems in the wake of an episode of delirium in children and adolescents has, however, been reported by two separate research groups, as described above (Kain *et al.*, 2004 and Prugh *et al.*, 1980). Although the existence of residual deficits following an episode of delirium in adults is now widely acknowledged, the same is not true in youth. The clinical and functional significance of these residual deficits remains unclear, and would, at least in part, depend on their durability.

It has been suggested (Schieveld and Leentjens, 2005) that Turkel and colleagues' (2003) finding of long duration of hospital stay (mean of 41 days) amongst their 84 child and adolescent patients with delirium might indicate, as has been shown in adults, that delirium independently increases hospital stay. However, without a comparison group matched for *physical* illness type, severity and complexity, this finding could equally be attributed to characteristics of the underlying physical illness.

What *is* clear is that delirium in children and adolescents is an extremely disturbing and frightening experience for both the young person themselves and their carers. Kanner's early descriptions of delirium in children illustrate this well:

The emotional tone is one of fear. The patients imagine that something painful or dangerous is being done to them; the dream assumes a highly dramatic shape in which bizarre tortures and persecutions frighten the child. Illusions are often present; the curtains or a towel are mistaken for ghosts or burglars. Imagination

and reality are not kept apart and form together a weird mass of fleeting, tormenting, scary, loose, irrational scenes

(Kanner, 1942, p. 180)

The fragmentation of ego functions and regression to paranoid-schizoid states apparent in childhood delirium are starkly reminiscent of Winnicott's 'primitive agonies' or 'unthinkable anxieties' - going to pieces; having no orientation; having no relation to the body, and falling forever (Winnicott, 1990). Delirium rating scales like the DRS measure 'lability of mood and affect' in the context of delirium, but in my own experience the sheer terror often apparent in children with delirium is more akin to 'annihilation panic' than to anxiety or affect dysregulation.

Schieveld and Leentjens (2005) have suggested that, at the very least, treatment of delirium in this age group restores quality of life and might reduce the incidence of posttraumatic stress.

2.4.13 Mortality

Delirium in adult and elderly patients is commonly associated with serious physical illness, and so it comes as no surprise that delirium is associated with a risk of mortality. However, a diagnosis of delirium has been found to be *independently* associated with increased risk of mortality amongst adult patients, even after adjusting for possible confounding factors like underlying disease severity. Ouimet and colleagues (2007a), for example, studied 243 adult patients with delirium in a large cohort of intensive care unit patients and found that delirium increased mortality in all patients (Odds ratio = 1.47, $p = 0.002$) even *after* adjustment for age and severity of physical illness as measured by APACHE II scores. Similarly, Inouye and colleagues (1998) found that delirium significantly increased the mortality risk even after controlling for age, sex, activities of daily living (ADL) level, and APACHE II scores. McCusker and colleagues (2003), in a prospective comparative study of adult medical patients with delirium, reported a two-fold increase in mortality. Olofsson and colleagues (1996) reported significant differences in index mortality rates dependent on the motoric subtype of delirium, with

the lowest mortality rate (10%) being in the hyperactive group, and the highest (38%) being in the hypoactive group.

The mechanism underlying this independently increased risk of mortality remains unclear. One possible explanation is that the cognitive and behavioural manifestations of delirium interfere to such an extent with medical management and subsequent rehabilitation of the underlying physical illness, that they increase risk of mortality.

However, it has also been proposed that the brain's own inflammatory responses to systemic injury and infection can become 'an engine of inflammation driving the development of multiple organ dysfunction syndrome' (Pandharipande *et al.*, 2005). The local central nervous system immune response has been shown to be accompanied by the production of large amounts of *peripherally produced* tumour necrosis factor- α , interleukin-1 β , and interferon- γ , and it is postulated that these cytokines, as a secondary, peripheral immune response to CNS damage could produce 'downstream' damage in other organ systems. In this way, it is hypothesized that a local brain immune response to damage, whatever its origin, could both produce delirium by altering central neuronal activity, *and* act as a catalyst for multiple organ dysfunction (Pandharipande *et al.*, 2005).

The systematic review of the literature relating to delirium in children and adolescents identified few studies addressing the relationship between mortality and delirium in this age group.

However, Bleuler's (1920, p. 155) assertion that delirium in children, although common, was of little significance, has increasingly been called into question.

What is clear from the limited existing literature is that, as with adult and elderly patients, delirium in children and adolescents in consultation-liaison psychiatry settings is associated with high mortality rates. However, research into delirium in children and adolescents has not yet, as it has in older patients, been able to show that delirium is

associated with an increased risk of mortality *independently* of factors such as age, underlying disease type, severity or complexity.

Five (12.5%) of the 40 children with delirium in a paediatric intensive care setting described by Schieveld and colleagues (2007) died of their underlying disease. In the series of 84 cases described by Turkel and Tavare (2003) there was an overall mortality rate of 20%. Mortality was highest in the multiple organ failure group (67%), and was higher for patients with autoimmune disorders (29%) and following organ transplant (29%). DiMario and Packer (1990), in their series of 24 children with systemic cancer-associated 'encephalopathic acute mental status change' note that 7 of the 24 children (29%) had died seven days after the onset of the mental status change.

The relationship between mortality and delirium in children and adolescents is likely to be complex.

Delirium may function as a proxy marker of physical illness severity, and it is the underlying disease, rather than delirium *per se*, that raises mortality rates. Alternatively, perhaps referral to consultation-liaison psychiatry of child and adolescent patients with delirium serves as a proxy marker of both underlying physical illness severity and of delirium severity. As has already been mentioned, young patients with delirium referred to psychiatry are more likely to have a delirium precipitated by an etiological factor that is complex, multifactorial, and unlikely to spontaneously remit, and to have a delirium that is persistent and associated with severe behavioural disturbance. Thus, particularly with paediatric consultation-liaison psychiatry case series of children and adolescents with delirium, we need to be aware that we are looking at a specific subgroup of patients with delirium. Perhaps referral to consultation-liaison psychiatry services is a potential correlate of Schieveld's 'malignant paediatric delirium'. The association between delirium and mortality may not still hold true for the 'general' population of children with delirium, which includes those youngsters who develop a very brief delirium in the context of fever or of anaesthesia. It may be that delirium in children and adolescents *is* associated with a higher risk of mortality after adjusting for confounding factors, but *only* when the delirium is severe and persistent.

In summary, the existing literature suggests that delirium in children and adolescents in certain contexts is associated with high mortality. No study has yet evaluated whether delirium increases the risk of mortality in this age group *after* controlling for factors like type and severity of underlying physical illness. Studies like that of Ouimet and colleagues (2007a) in adult patients, in which mortality rates were adjusted for measures of physical illness severity, are clearly indicated in children and adolescents.

To what extent aggressive treatment of delirium, including pharmacotherapy might in fact reduce associated morbidity and mortality is not well studied in *any* age group.

2.4.14 The clinical assessment of children and adolescents with delirium

2.4.14.1 Introduction

In order to illustrate the day-to-day pragmatic challenges of utilizing DSM-IV-TR criteria for delirium in children, I have invoked the help of a familiar childhood figure from classical English literature.

Let us imagine for a moment that Lewis Carroll's Alice is brought into a hypothetical Accident and Emergency Department in the early hours of the morning. Let us also imagine that the attending medical officer is fortunate enough to be able to obtain collateral history from an accompanying adult. The history obtained is that Alice has both recently fallen down a rabbit hole, and foolishly drunk from a small bottle labeled only 'Drink me' (Carroll, 1998, pp.1-13). Subsequent to this, Alice acutely developed a markedly altered and rapidly fluctuating mental state characterised by disorientation, perceptual disturbances, severe distress, memory deficits, and an inability to perform simple arithmetical tasks. She is markedly disorientated to both time and person ('Who in the world am I?' and 'I must have been changed for Mabel.' p. 18-19). She is completely unable to perform simple scholastic tasks that only a short while before she would have had no difficulty with ('I'll try if I know all the things I used to know...four

times five is twelve and four times six is thirteen... 'London is the capital of Paris and Paris is the capital of Rome', p.19). Her perceptual disturbances include dysmegalopsia (in which objects are perceived as being of a different size to that which they really are), and frightening visual and auditory hallucinations. For example, she experiences the disembodied head of a Cheshire cat, suspended in mid-air, talking to her (p.59). She is markedly distressed by her experiences to the point of worrying that she might be 'drowned in my own tears' (p.21). Her remarks 'Oh dear what nonsense I'm talking' (p.17), and 'I'm not myself you see' (p. 41) display a degree of insight into these distressing changes. The situation is not greatly helped by the Cheshire cat's statement that 'We're all mad here. I'm mad. You're mad' (p.58)

Let us now imagine that the astute medical officer at least *considers* a delirium as possible diagnosis, rather than attributing the entire episode to a 'curious dream'.

She appears to fulfill DSM-IV-TR Criterion B without difficulty:

A change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia.

She also appears to fulfill Criterion C:

The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.

A head injury sustained during her fall down the rabbit hole might potentially fulfill Criterion C:

There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition

Certainly the temporal relationship might support this as a potential precipitant. However, in addition, we are uncertain as to the contents of the 'Drink me' bottle. Although dysmegalopsia is classically associated with temporal lobe lesions, atropine poisoning is another typical causative factor (Fish, 1967). The associated dry mouth of atropine poisoning might also account for the fact that 'her voice sounded hoarse and strange' (p.19).

However, what about the 'core' DSM-IV-TR Criterion A?

Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain or shift attention)

Here potentially is where our hypothetical medical officer, astute as he or she is, encounters a problem.

To be sure, Alice has diffuse cognitive deficits of acute onset, but to what extent, if any, can the above-mentioned difficulties be accounted for by a 'disturbance of consciousness' defined in DSM-IV-TR as a deficit in attention. In order to be sure, the medical officer will no doubt have to perform bedside tests in order to ascertain her ability to focus, sustain, or shift attention. What tests should he perform? How should he or she interpret evidence of distractibility in a markedly distressed young girl interviewed in a noisy Accident and Emergency Department in the small hours of the morning? Should he or she obtain an electroencephalogram? What if it is interpreted as normal?

As has already been discussed in an earlier section, the extraordinarily high rates of underrecognition and misdiagnosis in adult and elderly patients with delirium, suggests that challenges in the assessment and diagnosis of delirium are not unique to children and adolescents.

Bhat and Rockwood (2007) acknowledged that the 'usual response to underrecognition is to exhort practitioners to do a better job', but suggested that this problem should

instead be seen as 'a daily pragmatic challenge of how delirium is conceptualised'. As previously mentioned, these authors proposed novel operational criteria for delirium as a disorder of consciousness, and a pragmatic approach for how best to assess and measure disturbed consciousness. Bhat and Rockwood (2007) argued that delirium could be recognised through an evaluation of arousal (defined as responsiveness to sensory stimuli and motor activity, which can be increased or decreased in delirium), attention, and temporal orientation. The authors suggested that the following tests could be usefully employed at the bedside to assess impairments of attention: Digit Span Backwards, Digit Cancellation Test, months of the year backwards, and a picture recognition test.

As discussed in the section addressing 'Comparative Phenomenology', the limited existing literature relating to delirium in children and adolescents suggests that there are far more similarities than differences in the phenomenological manifestations between adults and young people.

However, although the list of possible symptoms and signs of delirium may remain largely unchanged between different age groups, at least one author has suggested that the presentation of delirium may be 'more protean' in children (Prugh et al., 1980), which would perhaps concur with Turkel and colleagues (2006) finding of greater fluctuation of symptoms and more affective lability amongst children with delirium.

In addition, although the clinical presentation of the disorder may not differ dramatically across the lifespan, there may still be difficulties in the *eliciting* of the symptoms and signs of delirium, particularly in young children, which may make the application of unadjusted diagnostic criteria at best difficult and at worse invalid.

Van Waarde and colleagues (2004) described similar challenges in the assessment of delirium in patients with learning disabilities and limited ability to relate their experiences. In these instances the clinician may need to rely upon more objective signs such as sleep disturbance, reversal of sleep-wake cycle, a rapid deterioration of pre-existing skills, obvious changes in alertness, and the inference of hallucinations from 'hallucinatory behaviour'. Tzepacz and colleagues (2004) have underscored the

difficulties in the assessment of preverbal or uncommunicative children with delirium, and the greater reliance on inference in such patients.

Kanner (1942, p.179) pointed out that:

It is difficult to state at what earliest age delirious reactions occur. Before disorientation or misinterpretation can take place, the child must have grown old enough to be orientated and capable of correct interpretation and of giving evidence of this capacity as well as its impairment. Typical delirious pictures have been observed in infants as young as 16 months; they were especially outspoken in cases of atropine poisoning. Those babies, in addition to displaying the specific physical signs of the intoxication, were extremely restless and irritable and were seen grasping for imaginary objects and picking things out of the air. Whether delirium exists or, at any rate, can be clearly recognised before that age, remains an open question.

As previously mentioned, the *Diagnostic Classification of Mental Health and Developmental Disorders of Infancy and Early Childhood: Revised Edition (Zero to Three, DC:0-3R, 2005)* does not contain the term 'delirium', nor does it offer an alternative term for acute/subacute disturbances of consciousness in neonates and infants.

2.4.14.2 Assessment and diagnostic approaches to delirium in children and adolescents in previously published case series

The systematic review of the literature relating to delirium in children and adolescents identified only two studies that have specifically outlined an approach to the assessment and diagnosis of delirium in this age group (Prugh *et al.*, 1980 and Schieveld *et al.*, 2007).

Schieveld and colleagues (2007) have illustrated the difficulty in applying DSM-IV-TR criteria for delirium to children and adolescents with their use of a two-step diagnostic

approach. In the first step, a child neuropsychiatrist evaluated whether an individual patient met diagnostic criteria on the basis of:

1. Information from parents, nurses, intensivists, and child neurologists about behaviour and behavioural changes, and
2. A psychiatric examination of the child.

Based on this information, patients were classified as having a (probable) delirium or not. In the second step, in keeping with Spitzer's 'LEAD' suggestions for 'gold standard' psychiatric diagnosis (1983), the provisional diagnosis of delirium was further evaluated in a daily multi-disciplinary consensus meeting with a team consisting of the attending paediatric intensivist, and occasionally a geriatric neuropsychiatrist specialised in delirium and/or a child neurologist. If this team decided that alternative explanations for the change in the child's behaviour were unlikely, then the consensus diagnosis remained one of delirium.

Few authors have documented the actual procedure whereby the core diagnostic *cognitive* features of delirium might be elicited in children.

Schieveld and Leentjens (2005) have emphasized that 'formal' psychiatric assessment, using tests of orientation, memory and language difficulties may not be possible in young children, and that, as a result, a greater reliance on observed behaviour and caretaker information are important. In this context the diagnostician may be forced to infer cognitive deficits from the child's behaviour. Any inferred impairments then need to be evaluated against the temporal course of the change in behaviour – its rapidity of onset, fluctuation across 24 hours, and possible worsening at night, all of which would more strongly suggest a diagnosis of delirium. Schieveld and Leentjens (2005) also place great emphasis on inconsolability (by the caretaker) in the face of acute or subacute behavioural change, and on subtle qualitative interpersonal changes between parent and child.

Prugh and colleagues (1980), in the first systematic study to elaborate on the syndrome of delirium in children and adolescents, had as one of their aims the development of a more reliable 'guide to the psychological, clinical-medical and laboratory diagnosis of delirium in children, where manifestations of delirium may be more protean and confusing than in the adult'.

These authors compared a group of 33 hospitalised children and adolescents diagnosed as having significant pathophysiological, metabolic, toxic, or traumatic disturbances of central nervous system functioning, generally of acute onset, with a control group of children hospitalised for elective surgical procedures who had no central nervous system disorder. An attempt was made to match children in both groups according to age, sex, and socioeconomic background. Evaluations of all subjects were carried out within 48 hours after hospitalisation and were repeated just prior to discharge.

The authors compared the two groups on a wide range of tests of higher cortical functioning including a mental status exam and a number of tests of neuropsychological functioning (double simultaneous tactile stimulation, synkinesia, astereognosis, graphaesthesia, right-left orientation, naming of common objects, drawing of geometric objects, subtraction of serial sevens, and a modified Bender-Gestalt test). In addition, psychological evaluations along psychodynamic lines were administered. The children and adolescents were asked about their dreams, daydreams, magical wishes, and their fantasized future occupations. All subjects had an EEG.

Additional information was derived from the hospital records. A consensus rating of the possibility and severity of delirium was compared with total scores on the authors' 'delirium rating scale'. The authors posited that 'the symptomatic manifestations of delirium in children exist within a spectrum, with clinically evident delirium being a particularly severe form of the disturbance'.

The authors tested two hypotheses:

- Children with known central nervous system (CNS) insults of acute onset would show marked deviations in cognitive functioning from the control group of hospitalised children without CNS involvement, but should improve with time on retesting
- Children with known central nervous system insults of acute onset who did not appear clinically delirious would still differ significantly from the control group on tests of higher cortical function

To test these hypotheses, the following questions were asked:

- Which test items discriminate between the subject group with known CNS disorder (presumably delirious) and the control group without known CNS disorder (presumably nondelirious)?
- Would the subject group (presumably delirious) subsequently improve on later retesting?
- On retesting, would the subject group (presumably delirious) approach the test performance of the control group?

Prugh and colleagues found that 17 of their test items successfully and significantly ($p=0.05$ or less) discriminated between subject and control.

1. memory ($p<0.01$)
2. orientation ($p<0.02$)
3. object identification ; number of errors ($p<0.05$)
4. drawing of geometric objects; organisation ($p<0.05$)
5. drawing of geometric objects; position ($p<0.05$)
6. drawing of geometric objects; circle, form' and angulation ($p<0.05$)
7. Bender-Gestalt # 7 ; relative size ($p<0.01$)
8. Bender-Gestalt # 7 ; form and angulation ($p< 0.01$)
9. Bender-Gestalt # 4 ; form and angulation ($p<0.001$)

10. Draw-a-person; size of figure ($p < 0.05$)
11. Daydreams; number ($p < 0.05$)
12. CNS neurological abnormalities associated ($p < 0.001$)
13. Severity of disease or illness ($p < 0.01$)
14. Clinical rating of delirium ($p < 0.001$)
15. EEG slowing ($p < 0.02$)
16. EEG organisation ($p < 0.01$)
17. Examiner transposition orientation; number of errors ($p < 0.02$)

From this selection of possible tests Prugh and colleagues (1980) proposed a battery of tests (based on both ready availability and *degree* of ability to distinguish delirious from non-delirious subjects) to aid in the assessment and diagnosis of delirium in children and adolescents.

1. Memory ($p < 0.01$)
2. Orientation ($p < 0.02$)
3. Examiner-transposition orientation; number of errors ($p < 0.02$)
4. Bender-Gestalt # 4; form and angulation
5. Bender-Gestalt # 7; relative size ($p < 0.01$) and form and angulation ($p < 0.01$)
6. EEG slowing ($p < 0.02$)
7. EEG organisation ($p < 0.01$)
8. CNS abnormality associated
9. Severity of illness

Regarding the second hypothesis, the authors discovered that amongst the delirious children, several of the study test items (orientation, memory, and EEG slowing) improved on subsequent retesting to the point where subjects were indistinguishable from controls.

However, on several other items (such as EEG organisation and several of the perceptual motor functions) the delirious children improved, but *not* to the point of statistical equivalence with the control group, suggesting that some of the higher cortical deficits

associated with delirium persist for some weeks even after the delirium has clinically resolved.

There are several difficulties potentially associated with this test battery. The literature suggests that clinicians rely overmuch on bedside tests of orientation to person, place and time in assessing cognitive function (Meagher *et al.*, 2007), when almost a quarter of both adult and child and adolescent subjects with delirium do not have any evidence of disorientation (Meagher *et al.*, 2007; Turkel *et al.*, 2006), and almost half of children and adolescents with delirium have no evidence of memory impairment (Turkel *et al.*, 2006). Clinicians tempted to use these items in isolation would potentially miss many cases of delirium. In addition, although many of the test items *indirectly* assess the different domains of attention (ability to focus attention, sustain attention, shift attention) these tests are 'designed' to address 'perceptual-motor' functions, and do not directly address the core diagnostic criterion of attentional impairment. The average age of the subjects in the Prugh *et al.* (1980) study was 11 years 1 month, with a range of 6 to 17 years. Seven of the 17 discriminatory test items require the subject to draw or copy a figure. This will largely preclude children who are not yet of a developmental age that allows them to comply with these test instructions. Additionally, many clinicians faced with a potentially delirious patient will not be readily able to access an electroencephalogram, and will therefore be forced to rely more heavily on bedside cognitive testing. Lastly, Smith and coworkers (1995) suggested that the statistical analysis of the results of this study were 'questionable', in that only chi-squared tests were reported.

The problem remains that delirium is conceptualised primarily as a disorder of altered consciousness and cognition according to DSM IV-TR, and yet there exist no guidelines for the clinician as to how best the two core criteria of 'reduced clarity of awareness of the environment, with reduced ability to focus, sustain, or shift attention' and 'a change in cognition (such as memory deficit, disorientation, language disturbance)' might best be elicited, particularly in young children.

2.4.14.3 The importance of associated neurological signs in child and adolescent delirium

My analysis of the 65 published case reports of delirium occurring in children and adolescents that were identified by the systematic review reveals an additional point in relation to the assessment of possible delirium presenting in this age group. It is worth recalling that only 15 of these cases have been published in psychiatric journals, and that the large majority of these cases have been assessed and managed by non-psychiatrists, and then published in non-psychiatric journals. With this in mind, it is perhaps notable that associated *neurological* symptoms and signs (dysarthria, diplopia, frontal release signs, nystagmus and tremor, for example) are documented in over 50% of these cases. This would seem to further underscore the need for psychiatrists and child psychiatrists to perform a thorough neurological examination in patients presenting with acute emotional, behavioural or perceptual changes in the context of physical illness. Associated neurological features may provide supportive evidence of a diagnosis of delirium in cases where the list of possible differential diagnoses is often extensive.

2.4.14.4 Practical considerations in the assessment of delirium in children

Developmental factors influence the assessment of both the core and associated features of delirium in the paediatric population. The core diagnostic criterion of attentional impairment is rarely recorded in case reports describing children and adolescents with delirium, and instead, greater emphasis is generally placed on the non-criterion associated features like agitation and disorganised behaviour. The associated features of delirium are often more clinically obvious and dramatic, but have less diagnostic specificity and therefore a wider differential diagnosis. There is a risk that the subtle and yet more diagnostically specific core cognitive criteria are neglected and underreported. The obvious consequence of this is likely to be a higher rate of misdiagnosis in cases reported as delirium.

Bedside tests of attention, memory, orientation and mental flexibility commonly used in the assessment of adults may be wholly inappropriate in younger patients. Children with

or without a delirium may be fearful and uncooperative with testing in the foreign environment of the hospital. Younger children may not be able to describe their subjective experience of changes in mental state. Responses to testing need to take into account not only the premorbid level of cognitive functioning in the individual child being tested, but also an appreciation of how other children of a similar developmental age might respond under similar environmental conditions. The potential confounding effects of acute hospitalisation itself, separation from carers, educational level, cultural dissonance with the interviewer, socioeconomic deprivation, stranger anxiety and environmental over- or under-stimulation also need to be considered in each assessment.

Level of familiarity with the person conducting the testing may also play a role in children. Ideally, one should be able to approach bedside cognitive testing with a clear understanding of the child's developmental age, premorbid cognitive strengths and weaknesses, premorbid educational attainment and socioeconomic and cultural background, based on a thorough history from a carer, collateral history from a teacher, or even the results of previous psychometric testing. In the setting of acute and severe physical illness, however, one rarely has the luxury of having all this information at one's disposal prior to examining the child. A parent is usually able to give an estimation of how well their child might usually perform on a particular test, but may also be prone to overestimating their child's premorbid abilities.

Delirium is characteristically a fluctuating condition, and so there is great value in *serial* assessments of cognitive function. The fluctuating course of the disorder frequently leads to lucid periods followed by periods of altered cognition, and so the correct diagnosis may depend upon the timing of the clinical assessments.

A particular difficulty lies in the differentiation of delirium from fear, anger, severe anxiety or inadequately controlled pain in young children with limited verbal skills. Differentiation in preverbal children or children unable to speak for other reasons (for example, ventilated patients in paediatric ICU) is especially challenging. This problem commonly arises in the post-anaesthetic and intensive care settings. Poorly controlled pain in young children may present as restlessness, agitation, uncooperativeness, visible

distress, irritability, fear, regression and even problems in focusing and sustaining attention. A child preoccupied by pain is not likely to perform to their usual level of ability in simple bedside tests of attention, concentration and memory. Likewise, severe anxiety or stress-related disorders like acute stress disorder, post-traumatic stress disorder and even specific hospital-related phobias and separation anxiety associated with hospitalisation may present with agitation, panic, uncooperativeness, regression and attentional deficits. Panic-like states are commonly associated with transient diffuse cognitive deficits, and these children are also unlikely to perform well in testing.

A relatively common dilemma occurs in the child who has suffered a severe burn injury. These children may experience acute stress disorder or post-traumatic stress disorder in the aftermath of the injury. Anxiety is exacerbated by the lack of familiarity with the hospital environment and frequently by separation from carers. They may also experience persistent pain and neuropathic itching from their injuries and graft surgery. They commonly have multiple metabolic derangements and are treated with cocktails of medications with psychotropic effects, in addition to being repeatedly exposed to anaesthetic agents.

In this context, the young child or infant presenting with distress and agitation may commonly be misdiagnosed as having inadequately controlled pain or post-traumatic stress disorder. The result of such misdiagnoses is often the addition of further psychotropic medications like opiates or benzodiazepines, thus worsening the delirium, resulting in escalating doses of analgesic and anxiolytic medications.

2.4.14.5 Bhat and Rockwood's criteria applied to children

It is worth considering how Bhat and Rockwood's (2007) recently proposed novel operationalised criteria for altered level of consciousness and delirium (changes in arousal level, attention, and temporal orientation) might be employed in children.

Assessing level of arousal probably presents the least difficulty of the three in this young age group. With the help of a usual caretaker at the bedside an acute or subacute change

in 'responsiveness to sensory stimuli and motor activity' should be readily recognised. With very young children and infants, however, Winnicott's assertion that there is 'no such thing as a baby' should be recalled (1964). What Winnicott meant, of course, was that infants and neonates are assessed in an interpersonal context – usually a mother-baby dyad ('if you set out to describe a baby, you will find you are describing a baby and someone'). In this setting, subtle alterations in attachment behaviours, quality of responsiveness and rhythmicity may provide the best clue to both altered arousal and attention.

The assessment of both attention and temporal orientation arguably provide more of a challenge than that of altered arousal. Children and adolescents may of course not be cooperative with bedside cognitive testing, but this is not a problem unique to child and adolescent psychiatry, as many adults with delirium are equally uncooperative. Cooperative older children and adolescents can certainly be engaged with tests like months of the year or days of the week backwards. Picture or story memory tests may also be useful in this age group. In the 'Diagnostic assessment process' (3.4.8) section of the Case Series (Chapter 3), which follows, I have attempted to illustrate a number of techniques that I have found useful in the assessment of the different elements of attention in children. My experiences with bedside cognitive testing with children in the context of physical illness, pain, hospitalisation and separation from loved ones has taught me that such tests need to include an element of fun and humour. The assessment of temporal orientation in children potentially creates a problem in the setting of hospitalisation. Normal children rapidly become disorientated to time in the hospital setting, and as Bhat and Rockwood (2007) point out, children may be especially vulnerable to delirium on the basis of still developing abilities in time perception.

2.4.14.6 Summary

In summary, the existing literature (with the notable exception of the 2 above-mentioned studies) has paid scant attention to the crucial question of how best to actually elicit the symptoms and signs of delirium in children. The related question of how best to establish the diagnosis of delirium with the greatest degree of certainty has been equally

neglected. The assessment strategies described by Prugh and colleagues (1980) and Schievelde and colleagues (2007) have in common the use of information derived from a variety of sources. Prugh and colleagues (1980) suggested an approach utilizing information from cognitive and electroencephalogram testing, combined with evidence from a variety of sources (history, mental state, general physical and neurological examination, laboratory indicators) of both 'central nervous system abnormality' and severe physical illness. Schievelde and colleagues (2007) have advocated an approach combining history, collateral information from a wide range of sources, psychiatric interview, and multidisciplinary consensus.

To date, the question of whether delirium rating instruments can be used to facilitate the assessment and diagnosis of delirium has only been addressed by Turkel and colleagues (2003), Leentjens and colleagues (2008), and Sikich and Lerman (2004). The use of rating instruments in the assessment, diagnosis and severity rating of delirium in both adults and children will be discussed in the following section.

2.4.15 The use of rating instruments in the assessment and diagnosis of delirium

More than 10 different instruments have been proposed to assess the symptoms and signs of delirium for screening, diagnosis, severity rating, and monitoring response to therapeutic interventions in adult populations (Trzepacz, *et al.*, 1994). These instruments include the Delirium Rating Scale (Trzepacz, *et al.*, 1988), the Confusion Assessment Method (Inouye *et al.*, 1990), and the Memorial Delirium Assessment Scale (Breitbart *et al.*, 1997). Many of these instruments consist of operationalised DSM or ICD diagnostic criteria, usually in the form of a checklist that incorporates information from direct patient observation and medical records.

Smith and colleagues (1995, pp. 69-70) suggested that:

It is reasonable to assume that for teenagers (in general, children older than 13 years), adult instruments can be used. In younger children, specific criteria for

child delirium have yet to be developed, and only child psychiatrists' judgements can be used for formal diagnosis. For the 6- to 17-year-old age group the Prugh Battery (Prugh et al., 1980) might be considered, but for younger age groups delirium-evaluation instruments have yet to be developed. Nevertheless, numerous cognitive tests calibrated for children of different age groups have been developed for learning disorders (even for preverbal children). Their use should be investigated as screening instruments in any study on childhood delirium

Sixteen rating scales have been applied to the assessment of agitation with or without what has been termed 'emergence delirium' in children following anaesthesia (Sikich and Lerman, 2004). However, these scales lack specificity for delirium, as they include behaviours like crying, agitation and lack of cooperation that could just as easily be accounted for by pain, fear or anger in the post-anaesthetic context.

More recently, however, Sikich and Lerman (2004) have reported on the development of the Paediatric Anaesthesia Emergence Delirium (PAED) scale, a rating instrument specifically designed to detect delirium in children, albeit specific to the post-anaesthetic setting (Appendix B). Receiver operator curve (ROC) analysis of the PAED scale, however, suggests, at a PAED scale score of 10 or greater, a true-positive rate (sensitivity) of only 0.64, and a false-positive rate (1-specificity) of 0.14. These results are not particularly impressive, and cannot necessarily be generalised to delirium occurring outside of the post-anaesthetic context.

Przybylo and colleagues (2003) developed another paediatric assessment tool based on the DSM-IV criteria for delirium for use in the post-anaesthetic setting. The Post-anaesthetic behaviour assessment (PABA) scale was developed as an observational instrument to detect emergence delirium in children, but was unfortunately based only on perceptual disturbances (scored out of a maximum of 3), hallucination type (scored out of a maximum of 6), and psychomotor behaviour (scored out of a maximum of 3). No attempt was made to assess cognitive deficits, or to incorporate cognitive features into the rating instrument. In their conclusion, however, the authors acknowledged this

as a significant limitation of their study, and stated their intention to evaluate 'orientation and cognitive behaviour' in future studies.

The Delirium Rating Scale (DRS; Trzepacz *et al.*, 1988; Appendix A) has been extensively evaluated in adults and translated into 10 languages, and is the most widely used instrument for diagnosing and rating the severity of delirium in adults. The DRS assesses delirium symptoms as rated by a psychiatrist or trained clinician with a high degree of specificity, sensitivity and reliability. Inter-rater reliability using intraclass correlation coefficients for the DRS ranges from 0.86 to 0.97 for psychiatric or geriatric physicians, specificity ranges from 0.82 to 0.94, and sensitivity from 0.82 to 0.94 (Trzepacz *et al.*, 2001). The DRS may also be useful in predicting outcomes, with lower DRS scores correlating with milder illness course in adults. It has, however, been criticized for favouring agitation over retardation in the scoring of psychomotor behaviour, and for not operationalising inattention (Smith *et al.*, 1995).

Importantly, the DRS does not specifically integrate cognitive testing, but leaves it up to the rater's discretion as to what testing is necessary to evaluate the cognitive domain (Smith *et al.*, 1995). Particularly in relation to young children, this potentially poses a problem, as different clinicians may use different strategies to elicit cognitive deficits in children. The related question, as to what actually constitutes a symptom or sign (of, for example, inattention), or where the threshold for defining a symptom like inattention lies, is equally problematic in children.

The DRS is composed of 10 items: two items to determine the temporal onset of symptoms and their relationship to a physical disorder, and eight to evaluate the major symptoms of delirium. These eight items rate perceptual disturbances, hallucinations, delusions, psychomotor behaviour, diffuse cognitive dysfunction, disturbances of the sleep-wake cycle, lability of mood, and variability of symptoms. The cognitive dysfunction item includes impairment of attention, concentration, and memory. Individual item scores range from 0 to 2, 0 to 3, or 0 to 4 points, and the maximum total score on the scale is 32 points. A score of 13 or more indicates a diagnosis of delirium.

One further criticism of the DRS is that it does not lend itself particularly well to measuring the *severity* of delirium or monitoring *response* to interventions (Smith *et al.*, 1995).

A systematic review of the literature relating to delirium in children and adolescents identified four groups of researchers (Przybylo *et al.*, 2003; Turkel *et al.*, 2003; Sikich and Lerman, 2004; and Leentjens *et al.*, 2008) that have reported on the use of delirium rating instruments in this age group. The use of the PAED scale (Sikich and Lerman, 2004) and the PABA scale (Przybylo *et al.*, 2003) in the context of post-anaesthetic emergence delirium have already been discussed.

The first group to describe the use of a delirium rating scale in children and adolescents was that of Turkel and colleagues (2003), who reported the retrospective application of the Delirium Rating Scale to a group of 84 patients aged 6 months to 19 years (average age 10.4 years) diagnosed with delirium according to DSM-III-R criteria. The scale was found to be 'applicable' to children, with scores ranging from 14 to 32 points (where a score of 13 or more indicates delirium), and a mean total score of 25. These scores are comparable to those reported for adults with delirium.

More recently, Leentjens and colleagues (2008) compared DRS scores in 46 children (mean age 8.3 years) admitted to a PICU and diagnosed with DSM-IV delirium, with the DRS scores in 49 adults (mean age 55.4 years) and 70 geriatric (mean age 76.2 years) patients with delirium occurring in a palliative care setting. The authors reported a similar *range* of DRS symptoms in delirious children to adults and geriatric patients, but a distinct DRS *profile* for children, with higher average scores for acute onset, hallucinations, delusions, agitation and lability of mood, but lower scores for cognitive deficits, fluctuation and sleep-wake disturbance.

Some of the shortcomings of the DRS, particularly relating to its use in phenomenologic and longitudinal treatment research, have been addressed in a substantially revised version of the scale, the Delirium Rating Scale– Revised-98 (DRS-R-98) (Trzepacz *et al.*, 2001). Three of the DRS items which focus on features relating to differential

diagnosis (temporal onset of symptoms, fluctuation of symptoms, and physical etiology) add to specificity, but are not easy to rate repeatedly during serial administrations within an episode of delirium.

Some researchers have addressed this problem by modifying the DRS to a 7- or 8- item scale after the initial administration (Trzepacz, 2004). Additionally, the DRS 'psychomotor behaviour' item *combines* hypoactivity and hyperactivity, limiting its usefulness in assessing motoric subtypes of delirium.

In contrast, the DRS-R-98 includes two sections, the first diagnostic and the second severity. The 13-item severity scale can be used for repeated measures and for monitoring change over time. The DRS-R-98 is a 16-item scale with a maximum total scale score of 46 points (including the 3 diagnostic items) and a maximum severity score of 39 points (Appendix C). Trzepacz *et al.* (2001) have reported the results of a receiver operating curve (ROC) analysis of the DRS-R-98 when applied to adults, showing a sensitivity of 92% and a specificity of 93%, using a cut-off score of 15.25 on the severity scale. De Negreiros and colleagues (2008), using a cut-off of 20 with the Portuguese version of the DRS-R-98 reported a sensitivity of 92.6% and specificity of 94.6% in adults.

The systematic review did not identify any literature describing the use of the DRS-R-98 in children and adolescents.

In summary, both the Delirium Rating Scale and the Paediatric Anaesthesia Emergence Delirium scale have been described as having utility in the assessment of delirium in children and adolescents. Given that the PAED scale has been specifically designed to assess delirium in the post-anaesthetic setting, and has been reported as having a sensitivity of only 0.64 even in this context, the DRS would potentially seem to be a more practically useful instrument in children and adolescents outside of the post-anaesthetic (and possibly PICU) setting. Delirium rating scales could potentially play an important role in screening, diagnostic assessment, rating of severity, and response to treatment of delirium in this age group. The application of the DRS-R-98 to children and

adolescents with delirium, given its superiority over the DRS in terms of differentiating delirium subtypes, rating severity, and monitoring response to treatment merits further research.

2.4.16 Investigations

Investigations may have two purposes in the assessment of cases of possible delirium, regardless of age. The most common indication for further investigations in suspected cases of delirium is in order to establish causation, or factors which may be exacerbating or perpetuating the delirium. The second indication for investigation is to obtain supportive evidence of a clinically suspected delirium. To date, the electroencephalogram (EEG) is the only investigation that has been shown to have clinical utility in supporting the diagnosis of delirium.

In the paragraphs to follow I will begin by discussing the use of the EEG in both adult, and child and adolescent patients with delirium. Having discussed the use of the EEG, I will proceed to discuss the use of other investigations, including neuroimaging in the assessment of delirium.

Romano and Engel (1944a; 1944b; 1944c), in their pioneering studies of delirium amongst 53 adult patients, were the first to systematically document the reversible abnormalities to be found on the EEG. The EEG abnormalities described were those of:

1. Decrease in frequency
2. Disorganisation and
3. Reorganisation at a lower energy level

Romano and Engel reported reversible slowing of the dominant frequencies, with the degree of slowing roughly correlated with the severity of the delirium. They also commented that:

The character of the electroencephalographic change appeared to be independent of the specific underlying disease process but was directly related to the intensity, duration and reversibility of the noxious factors

(Romano and Engel, 1944b, p.374)

Romano and Engel also emphasized that a single normal EEG does *not* exclude delirium as the patient's predelirious EEG record may have been faster. In other words, the slowing of the EEG is *relative* to the patient's premorbid tracing, and may still fall within the normal range.

Unfortunately, however, the EEG falls far short of being a 'gold standard' diagnostic assessment tool for delirium in any age group. Inouye (2006) asserted that, having a false negative rate of 17 percent and a false positive rate of 22 percent, the EEG had only a limited role in the diagnosis of delirium in adult patients.

The systematic review of the literature relating to delirium in children and adolescents identified four research groups that have addressed the use of the EEG in children and adolescents with delirium (Prugh *et al.*, 1980; Mohnot *et al.*, 1982; Onoe *et al.*, 2004; and Okamura *et al.*, 2005). Their findings will now be discussed.

Prugh and colleagues (1980) were the first to systematically study EEG changes in 33 children and adolescents with probable delirium. Two EEG's were performed on each subject in both the delirium and control group and were rated independently by two judges with interrater reliability reported as being over 90% agreement. The extent of slowing of the EEG was found to discriminate between children and adolescents in the probable delirium group and the control group to a statistically significant degree ($p < 0.02$). Likewise, the extent of disorganisation of the EEG was also found to significantly discriminate between the two groups ($p < 0.01$). The authors noted that, in their experience, the abnormal EEG tracings were found to 'wax and wane' in parallel with the characteristically fluctuating clinical findings. This suggests that the utility of the EEG as supportive evidence in the diagnosis of a delirium may also depend on the

timing of the investigation. It may therefore be possible to obtain a normal EEG tracing during a period of relative lucidity.

It should also be borne in mind that many patients with delirium characteristically experience symptomatic exacerbations during the night – the time that an EEG is least likely to be performed. Prugh and colleagues (1980) also described a case of ‘subclinical delirium’ with only very mild deficits found on cognitive testing but severe abnormalities on the EEG that was performed just prior to the clinical evaluation. In this particular case the cognitive deficits improved with time whilst ‘borderline abnormalities’ on the EEG persisted. As a group, the degree of slowing in the EEG of the delirious children improved on retesting to the point where subject and control groups were virtually indistinguishable. However, whereas the degree of EEG disorganisation did in fact improve in the delirious group on retesting, this was *not* to the point of statistical equivalence of the two groups, suggesting some *persistence* of certain aspects of the abnormal tracing, even in the face of clinical improvement. The authors postulated that ‘adaptive and compensatory mechanisms’ might account for this discrepancy between clinical remission and delayed EEG normalisation. They concluded that the EEG is a sensitive and worthwhile investigation in the diagnosis of delirium in children and adolescent patients, but also emphasized that no single test should be relied upon given the variability of findings.

Mohnot *et al.* (1982), in their series of children with ‘burn encephalopathy’ documented that slowing and disorganisation of the EEG was present in 4 of the 6 children in which an EEG was performed. Onoe and colleagues (2004), in their series of 20 cases of ‘febrile delirium’ (mean age 6.9 years) found posterior slowing of the EEG in 65% of cases. The duration of the EEG changes was only a few days. Okumura and coworkers (2005) reported mildly abnormal EEG findings with slowing of the background activity and insertion of semirhythmic high voltage slow waves in 13 of 15 children presenting with ‘delirious behaviour’ in the context of influenza infection.

Of the 65 published case reports of delirium/probable delirium identified by the systematic literature review, an EEG was performed in only 22 cases. However, the

EEG was noted to be abnormal in 19 (86%) of the 22 cases in which one was performed. Diffuse slowing was noted in 8/22 (36%); focal slowing in 6/22 (27%); disorganisation and slowing in 3/22 (13%); and in 2 cases (with nonconvulsive absence status epilepsy) the EEG showed the 3/second spike and wave characteristic of this condition.

In summary, the EEG appears to have only a limited role in the assessment and diagnosis of delirium in children and adolescents owing most particularly to its relatively poor level of sensitivity. It may, however, still have a role in differentiating hypoactive delirium from so-called 'functional' psychiatric disorders like depression, and in identifying those patients whose delirium has occurred on the basis of seizure activity.

As mentioned at the beginning of this section, the EEG is the only investigation suggested as having clinical utility in making or supporting the diagnosis of delirium. Marcantonio and colleagues (2006) have reviewed the literature relating to a variety of putative 'biomarkers' of delirium in adults, but the literature exploring this aspect of delirium remains extremely limited. Alsop and colleagues (2006) have provided a review of the neuroimaging research into delirium in adult subjects. At the present time, neuroimaging techniques remain more pertinent to research into underlying mechanisms of delirium than clinical assessment.

As discussed, the other indication for investigations in a patient with a delirium is to elucidate precipitating, predisposing, and/or perpetuating factors. We have already described how a similar range of precipitating factors have been reported in the literature as being precipitants of delirium in all age groups. It should therefore come as no surprise that a similar range of special investigations have been suggested in order to elucidate possible precipitating factors in children and adolescents.

Martini (2004), in his article 'Delirium in the Paediatric Emergency Department' provides an outline of suggested investigations in determining underlying causes of delirium in young patients (Table 2.9).

Table 2.9 Laboratory investigations in child and adolescent delirium

Basic laboratory tests Consider for all patients with delirium	Blood chemistry: serum electrolytes, glucose, calcium, albumin, urea, creatinine, bilirubin, transaminases, alkaline phosphatase, magnesium, phosphorus
	Full blood count
	Electrocardiogram
	Chest X-ray
	Oxygen saturation or arterial blood gas
	Urinalysis
	Urine culture
Additional laboratory tests – as indicated by clinical condition	Urine drug screen
	Vit B12 and folate, autoimmune screen, ammonia, urinary porphyrins, HIV
	Blood cultures
	Serum medication levels
	Lumbar puncture
	CT or MRI brain
	EEG

(Adapted from Martini, 2004)

Nadel and colleagues (1999) examined the utility of emergency cranial computerised tomography (CT) in the acute management of 'acute febrile encephalopathy', which was defined in this study as fever together with persistent alteration of conscious level, focal neurological signs and/or seizures. Cranial CT is often performed as an emergency procedure in children presenting with altered level of consciousness accompanied by fever, especially where there is a clinical suspicion of raised intracranial pressure, in which case lumbar puncture is contraindicated. The authors reported on a retrospective cohort of 39 children who presented to PICU with 'acute febrile encephalopathy' and

had an emergency cranial CT performed within 12 hours of admission. Although an abnormality was noted in 36% of cranial scans, subsequent management was influenced by the findings of the emergency cranial CT in only one case. Cranial CT scanning was found to be an insensitive tool for predicting the presence of raised intracranial pressure in this context.

An analysis of the 65 published case reports of delirium in children and adolescents over the last 28 years provides a potentially useful source of information for directing further investigations in cases of delirium where no underlying cause is initially found. As a collection of published reports they are, however, likely biased towards the more unusual, interesting or 'exotic' precipitants of delirium. In the investigation of a child with a delirium where the initial battery of tests aimed at elucidating an underlying cause have come back negative, it may be useful to consider the following underlying precipitants of delirium.

- Paraneoplastic limbic encephalitis – a number of case reports document the emergence of delirium as the initial presenting feature of 'occult' neoplasias, particularly ovarian tumours in adolescent girls (Table 2.5.3)
- Anticholinergic toxidrome – numerous case reports document the occurrence of delirium associated with the deliberate or accidental ingestion of strongly anticholinergic plants or medications (Tables 2.5.1 and 2.5.5)
- Wernicke's encephalopathy – in children with chronic malabsorption or malnutrition presenting with delirium it would be wise to check thiamine levels, as a number of case reports of delirium associated with thiamine deficiency in children have been published (Table 2.5.4)
- Neuroleptic malignant syndrome (NMS) – this diagnosis is always worth considering in delirious children and adolescents who have been prescribed psychotropic medications, or those that might have had access to these medications. NMS has been described in young people using newer 'atypical' antipsychotics (Table 2.5.1) and even certain antidepressants (Halman and

Goldbloom, 1990). A plasma creatine kinase level will help to exclude this diagnosis.

- Serotonin Syndrome – this diagnosis should also always be considered in delirious children and adolescents prescribed a wide variety of psychotropic medications, but most especially, the antidepressants. As with NMS, accidental or deliberate overdoses of a family member's medication should also be considered.
- Acute confusional migraine - this diagnosis should be considered in children and adolescents presenting with recurrent episodes of 'confusion' without any obvious cause being found. A personal history of headache, nausea or vomiting, or a family history of migraine headaches may provide clues to the diagnosis (Table 2.5.4).
- Other diagnoses to be considered in children and adolescents with delirium of unknown etiology, based on published case reports, are autoimmune conditions like systemic lupus erythematosus and endocrine conditions like Hashimoto's encephalopathy.

2.4.17 Management of delirium

The management of delirium in children and adolescents is arguably the most neglected aspect of this disorder in the existing literature.

The systematic review of the literature relating to delirium in this age group has suggested that delirium is not only common, but also associated with prolonged hospitalisation, persistent cognitive and behavioural deficits and high mortality rates.

In the light of these findings, research into the effective management and prevention of delirium in children and adolescents would seem to be imperative.

For this reason, I have devoted a proportionally larger amount of space to the discussion of the management aspects of delirium. I discovered that in order to place the existing

research into the management of child and adolescent delirium into proper context, I needed to perform a thorough review of the existing literature relating to the management of delirium in adults. In discussing the results of the unsystematic but thorough review of the *adult* delirium literature I have therefore included not only review articles, published clinical guidelines and clinical trials, but also (given the current scarcity of literature relating to the use of the newer 'atypical' antipsychotic medications in delirium), case series and case reports.

A detailed discussion of the literature relating to the management of delirium in *adults* will therefore precede the results of the systematic review of the literature relating to the management of delirium in children and adolescents.

2.4.17.1 Clinical guidelines and recent reviews relating to the management of delirium in adults

In a way, the treatment of delirium presents the physician with a paradoxical situation. We have all been trained in the tradition of treating causes rather than symptoms; and delirium, being a symptom-complex, should provide a striking example of the efficacy and practicability of this principle. But if we insist on treating only causal factors in delirium and ignore the mere symptoms, the symptoms themselves may have so exhausted or debilitated the patient, or the consequences of the patient's actions may have proved so disastrous, that the patient may expire while we are patiently awaiting an opportunity to "get at the cause". But, on the other hand, we may be tempted to go too far and too quickly in our zeal to control the acute symptoms. For example, it is now possible, with drugs and other agents at our disposal, to dampen down the acute signs and symptoms of delirium in a fairly short time; but this may leave us with a patient who is tranquil and manageable but still gravely ill, and whose mental "improvement" may lull us into a false sense of security

(Henry and Mann, 1965, p. 1158)

Although paraldehyde and insulin therapy are fortunately no longer part of the suggested management of delirium, Henry and Mann's general comments in relation to treatment remain pertinent in 2008.

The primary and overarching aim in the management of delirium, regardless of age, is rapid correction of the precipitating cause wherever possible. Prompt attention to all possible perpetuating or exacerbating factors, including iatrogenic factors, should be an early focus of management. Even in 1944, Romano and Engel recognised that:

Regardless of the mechanisms, however, it is clear from this data that the intelligent treatment of delirium must include efforts to reverse the major physiologic derangements accompanying the underlying disease

(Romano and Engel, 1944c, p. 378)

Once all correctable precipitating, perpetuating or predisposing factors have been addressed, management strategies can be divided into environmental and pharmacological interventions.

Several clinical guidelines have been published for the management of delirium in adult and geriatric patients. In the absence of existing guidelines for the management of delirium in children and adolescents it is my impression that management guidelines designed for use in adult and geriatric patients are being applied to younger patients with the only modification being the use of more conservative medication dosing strategies.

The Clinical Effectiveness and Evaluation Unit (CEEU) of the College of Physicians (UK) has developed evidence-based good practice guidelines for the management of delirium in adults in collaboration with the National Institute for Health and Clinical Excellence (British Geriatrics Society and Royal College of Physicians, 2006). These guidelines strongly emphasize identification and treatment of the underlying cause as the most important action to be taken in patients with delirium. They stress that early identification and prompt treatment of the underlying cause may reduce the severity and duration of delirium. The guidelines encourage the use of a multidisciplinary approach

and stress the importance of environmental manipulation, optimal sensory stimulation and reality orientation. It recommends that the use of sedative medications and major tranquillisers be kept to a minimum and be used *only* in specific circumstances:

1. In order to carry out essential investigations or treatment.
2. To prevent patient endangering themselves or others.
3. To relieve distress in a highly agitated or hallucinating patient.

Monotherapy with low-dose haloperidol is recommended, with a benzodiazepine such as lorazepam to be used in patients unable to tolerate antipsychotic medications.

The American Psychiatric Association's *Practice Guideline for the Treatment of Patients with Delirium* was published in 1999 (American Psychiatric Association, 1999), but has subsequently been updated with an American Psychiatric Association *Guideline Watch* (Cook, 2004), which integrates findings from research published since 1999.

Similar in many ways to the more recent CEEU/NICE practice guidelines outlined above, the APA guideline emphasizes ensuring safety of the patient from behavioural disturbance while simultaneously identifying and treating the presumed underlying etiology. The 2004 update adds to the earlier guideline in relation to management of the patient's environment in providing evidence for the introduction of low-tech but potentially labour-intensive changes in nurse-patient interactions, as well as the need for flexibility within hospital systems to facilitate the provision of individually tailored care for delirious patients.

In terms of pharmacological management, the 1999 *Practice Guideline* recommends using the typical antipsychotic haloperidol, owing to its few anticholinergic side effects, few active metabolites, few sedating effects, and ready availability in oral, intramuscular and intravenous routes. The 2004 *Guideline Watch* is, however, less prescriptive in its recommendations in regard to antipsychotics, and outlines the expanding but still limited evidence-base for the use of atypical antipsychotics like risperidone, olanzapine, quetiapine and ziprasidone in delirium. The 2004 *Guideline Watch* continues to

recommend the avoidance of benzodiazepines *except* in cases of delirium related to alcohol withdrawal and seizures.

Sharon Inouye provided a review article for the *New England Journal of Medicine* in 2006, in which she details an algorithmic approach to the management of delirium in older persons. Once a delirium has been confirmed, three parallel management strategies are initiated in concert: Identify and address predisposing and precipitating factors; provide supportive care and prevent complications; and manage symptoms of delirium. Nonpharmacologic strategies are recommended for *all* patients with a delirium, and include reorientation, avoidance of physical restraints, music, massage, relaxation techniques, maintenance of mobility, and normalisation of the sleep-wake cycle. Pharmacologic management is reserved for patients with severe agitation at risk for interruption of essential medical care, or who pose a safety hazard to themselves or staff.

When pharmacologic management is initiated, Inouye (2006) recommends that haloperidol be the agent of choice in older persons with delirium, but that the atypical antipsychotics such as risperidone, olanzapine and quetiapine might be considered as alternatives. Benzodiazepines are regarded as 'second line' agents, reserved for use in patients with sedative and alcohol withdrawal, and those with neuroleptic malignant syndrome.

The following paragraphs will provide a thorough but not exhaustive overview of the current state of the evidence for both environmental and pharmacological interventions in adults with delirium before describing the available evidence in children and adolescents derived from systematic review.

2.4.17.2 Environmental interventions for adults with delirium

The use of environmental strategies in the management of delirium is frequently quoted but clearly understudied (Michaud *et al.*, 2007; Inouye, 2006; Grace *et al.*, 2006; Trzepacz *et al.*, 2004; Meagher, 2001; Meagher *et al.*, 1996; Lipowski, 1980; Henry and Mann, 1965).

Although there are no randomised controlled trials of interventions like noise control, light intensity control, sleep-hygiene, improved staff-patient communication, reassurance and stimulus modification, these environmental manipulations continue to be a recommended part of the management of any delirious patient, regardless of age (Michaud *et al.*, 2007; Inouye, 2006; Burns *et al.*, 2004).

Lipowski (1980) suggested that the delirious patient be cared for in a quiet, well-lighted room with a dimmed light at night. A single room is preferable, and the patient should not be exposed to the noise and bustle of the ward. However, ward staff should 'use their judgement in adjusting the patient's environment according to his or her individual needs rather than following mechanically a set of iron rules'.

The patient should be offered an 'adequate flow of orientating, reassuring, and unambiguous information'. Soothing music might have a role in calming the agitated delirious patient. Lipowski underlined the importance of ward flexibility with delirious patients, allowing a friend or relative to stay with the patient over and above usual visiting hours, in order to provide a familiar social environment. He also suggested that 'family members should be asked to orientate the patient, that is, state the date, and names of the hospital, doctors, and nurses in attendance, and also to talk about matters that interest him', and additionally that 'it is preferable to restrict the number of visitors and staff interacting with the patient so as to avoid information overload, excitement, and fatigue' (Lipowski, 1980)

Good nursing care is a prerequisite for optimal management of patients with delirium with a focus on consistency, safety, frequent re-orientation, patient and carer education, and provision of an appropriate level of sensory stimulation (Lipowski, 1980; Bergmann *et al.*, 2005). Providing sufficient and consistent staffing also assists in orienting, educating and protecting delirious patients. Orienting cues often quoted as being useful in the management of adult patients with delirium include a large clock, a calendar, a well-lit room, and provision of spectacles and hearing aides if required (Michaud *et al.*, 2007; Bergmann *et al.*, 2005; Samuels and Neugroschl, 2005). Familiar objects from the

patient's home may also assist with orientation and relief of distress. Close involvement of supportive family members can also provide orientation cues, patient reassurance and important observational data (Michaud *et al.*, 2007).

Meagher and colleagues (1996) have documented the relative neglect of simple environmental strategies in the management of adult patients with delirium. These authors studied the pattern, frequency, and clinical correlates of the implementation of environmental strategies and psychotropic medication in 46 consecutive referrals (mean age 60.1 years) to a consultation-liaison psychiatry service, each of whom met ICD-10 criteria for delirium. Patients were divided into hyperactive, hypoactive, and mixed subtypes, and then rated according to severity. The implementation of 8 basic nursing strategies was assessed:

1. Frequent observation (4 hourly or more)
2. Efforts by staff to repeatedly orientate the patient to surroundings recognised as a specific part of the management plan
3. Effort made to avoid excessive staff changes e.g. special nurse, key nurse
4. Nurse in a single room
5. Uncluttered nursing environment (no more than two non-orientating, non-vital objects in vicinity of bed, and beds spaced an adequate distance apart)
6. Use of an individual night light
7. Specific efforts to minimise noise levels
8. Relatives or friends specifically requested to visit regularly in an effort to enhance re-orientation

Of the 46 patients with delirium, 30% (n= 14) of the patients were diagnosed with the hyperactive subtype of delirium, 24% (n=11) hypoactive and 46% (n= 21) mixed. Psychotropic medication was given to 56.6% of patients prior to psychiatric consultation and this was significantly associated with severity of delirium and in particular, with hyperactive subtype. Of the 8 environmental strategies only 4 were instituted in over 50% of the patients prior to consultation. The application of these strategies was positively associated with the overall severity of the delirium, agitation, mood lability

and sleep-wake disturbance. It was not associated with either the severity of disorientation or with disturbed thinking or perception

The authors concluded that simple and easy-to-implement environmental strategies were frequently overlooked in the management of delirium. They also concluded that the implementation of these strategies occurred primarily in response to behavioural challenges and difficulty in ward management rather than severity of cognitive disturbance.

In a recent study of hospitalised adults, Inouye *et al.* (2003) developed an intervention strategy that was found to decrease both the frequency and severity of symptoms of delirium. The strategy emphasized re-orientation, sleep hygiene, adequate hydration, and compensation for sensory deficits. When staff members adhered to the protocol, rates of delirium decreased.

Bergmann and colleagues (2005) described a nurse-led, unit-based model for the management of adult delirious post-acute care patients derived from 'best practices as defined by the peer-reviewed literature'. Their Delirium Abatement Program (DAP) included standardised screening for delirium, assessment and treatment of causes, prevention and management of complications of delirium (catheterisation, pressure ulcers, falls, injuries, sleep disorders and malnutrition), and restoration of cognitive and self-care function. These last two modules included recommendations like close nurse monitoring, social engagement, avoidance of physical restraints and sedatives, a sleep hygiene protocol, continuity of nursing assignment, checking of sensory aids, a large-print calendar, a large-faced bedside clock, and a brochure on delirium designed for a nurse to review with family members. Caregivers were prompted to communicate with patients in a calm, non-confrontational manner and to re-orientate them to person, date, time, location, and reasons for stay at least once per shift. During each patient contact, the staff were to inform the patient who they were and what they would be doing and why. No efficacy data for the program has been presented to the best of my knowledge. Lundstrom and colleagues (2005) investigated whether a staff education program and reorganisation of nursing care from a task-allocation care system to a patient-allocation

system with individualised care improved the outcome of older delirious patients when compared to patients managed on a 'control' ward. The authors found that delirium was equally common on the day of admission to the two wards, *but* that fewer patients *remained* delirious on day 7 on the intervention ward ($p=0.001$). The mean length of stay was significantly lower on the intervention ward, especially for delirious patients ($p<0.001$). Two delirious patients in the intervention ward and nine in the control ward died during hospitalisation ($p=0.03$).

Michaud and colleagues (2007) published a systematic review in which they presented a rating of the level of evidence and grade of recommendation for a variety of interventions for delirium, based on the Oxford classification (Phillips *et al.*, 2001; http://www.cebm.net/levels_of_evidence.asp; see Appendix D). Non-pharmacological sleep promotion and limiting sensory overload or 'underload' were given a Grade A rating (Level I evidence, or Level II/III evidence with high consensus). Improved communication (regular verbal communication, use of short sentences, frequent information on place, reason for hospitalisation, information and reassurance about medical procedures) was given a Grade B recommendation rating (Level II/III evidence, or Level IV/V evidence with high consensus), while the involvement in management of significant others, and support of significant others, were given a Grade C recommendation rating (Level IV/V evidence with sufficient consensus between experts).

In summary, although there would appear to be a consensus that non-pharmacologic strategies are important in the management of delirium in adult and elderly patients, the empirical evidence for these interventions is slim. However, recent research has provided evidence that such strategies might not only reduce the incidence of delirium, but also reduce its duration, and the mortality associated with delirium. It remains unknown whether medication *in combination* with non-pharmacologic measures provide greater benefits over non-pharmacologic measures *alone* in adult patients with delirium (Lacasse *et al.*, 2006).

2.4.17.3 Environmental interventions with children and adolescents with delirium

A systematic review of the literature relating to delirium in children and adolescents identified very few articles discussing the environmental aspects of the management of delirium in this age group.

Schieveld *et al.* (2007) described their 'two-track' treatment approach with children and adolescents with delirium in a PICU setting, using both psychosocial and pharmacological interventions in conjunction. Psychosocial interventions included the parents' constant presence and comforting, familiar music, favorite toys, pictures of home and pets, friends, school, lighting schedules and sometimes even fragrances. The parents also received an information leaflet on childhood delirium.

Physical restraints are generally not recommended among delirious children, and should be used with caution (Martini, 2004). Their use in adults has been shown to increase the risk of delirium (Michaud L *et al.*, 2007).

Despite the paucity of literature addressing environmental aspects of delirium management in children and adolescents, common sense suggests that close involvement of carers in providing orientation and reassurance and the provision of familiar toys, special transitional objects, and family photos might well be beneficial for younger patients.

2.4.17.4 Antipsychotic medications in the treatment of adult delirium

After due consideration of these basic physiologic factors, further management of the patient should not be complicated by the superimposition of new noxious agents, such as the indiscriminate use of chemical sedatives. If sedation is necessary the ideal means is the use of a continuous tub bath

(Romano and Engel, 1944a, p. 635)

Although much has changed since Romano and Engel's groundbreaking work on delirium in the early 1940's, their caution in relation to the use of medication in the management of delirium remains pertinent, as almost all of the agents used in its pharmacological management have also been implicated in its causation. In some patients the simplest and most effective strategy may well be the cessation of 'deliriogenic drugs' (Burns *et al.*, 2004).

Not one medication has been approved by the United States Food and Drug Administration (FDA) for use in the treatment of delirium in *any* age group. A careful risk: benefit analysis should therefore be carried out in each individual case before embarking on pharmacological treatment. Importantly, early identification of the symptoms of delirium has been shown to result in reduced usage of medications (Breitbart *et al.*, 1996). With the exception of cases of delirium associated with some withdrawal states, antipsychotic medications remain the treatment of choice, often resulting in clinical improvement before the elucidation and correction of the underlying etiology of the delirium (Nakamura *et al.*, 1997).

In keeping with both the CEEU/NICE (2006) and APA (1999) practice guidelines, The Society of Critical Care Medicine guidelines (2002) recommend haloperidol as the drug of choice in adults, although it is acknowledged that this is based on sparse outcomes data from nonrandomised case series and anecdotal reports. Nevertheless, haloperidol remains the most widely used antipsychotic agent for delirium in adults (Ely *et al.*, 2004). However, the typical antipsychotics like haloperidol have a greater propensity to cause extrapyramidal side effects like dystonic reactions and parkinsonism, particularly in vulnerable populations such as the elderly *and* in children.

Antipsychotic medications are reported to be effective in *all* subtypes of delirium, including the hypoactive (lethargic) subtype characterised by psychomotor retardation and sedation (Breitbart *et al.*, 1996; Platt *et al.*, 1994; Schieveld *et al.*, 2007). The evidence-base for the use of antipsychotics in hypoactive delirium, however, remains extremely flimsy (Breitbart *et al.*, 2002b; Platt *et al.*, 1994; Lonergan *et al.*, 2007, Michaud *et al.*, 2007). In fact, Michaud and colleagues (2007), in their systematic review

of the evidence for interventions for delirium give a Grade I level recommendation for the use of drug treatment in hypoactive delirium, suggesting that there is 'no sufficient evidence or no sufficient consensus to formulate any recommendation (i.e. studies or expert opinion are contradictory)'.

My own unsystematic review of the adult literature of the last 10 years reveals that one Cochrane review, five other systematic reviews, and one unsystematic review published within the last 6 years have addressed the use of antipsychotic medications in the treatment of adult patients with delirium (Lonergan *et al.*, 2007; Seitz *et al.*, 2007; Rea *et al.*, 2007; Lacasse *et al.*, 2006; Boettger and Breitbart, 2005; Weber *et al.*, 2004; and Schwartz *et al.*, 2002).

Schwartz and colleagues (2002), Lonergan *et al.* (2007), Rea *et al.* (2007), and Boettger and Breitbart (2005) have specifically addressed the role of *atypical* or 'second generation' antipsychotics in the treatment of delirium. The results of each of these reviews will now be discussed in some detail, as each has used slightly different methodology.

The Cochrane review of Lonergan, Britton, and Wyller (2007) addressing the use of typical and atypical antipsychotics in delirium concluded that there was no evidence that low dosage haloperidol has lesser efficacy or greater frequency of adverse effects than olanzapine or risperidone, although *high-dose* haloperidol was associated with higher rates of extrapyramidal side-effects. In relation to delirium *prevention*, the review concluded that low-dose haloperidol might decrease the degree and duration, but not the incidence of delirium in adults with post-operative delirium. It should be noted that these conclusions were derived from the analysis of only three studies that satisfied the reviewer's selection criteria for inclusion.

Rea *et al.* (2007) searched MEDLINE (1977 – September 2006) and International Pharmaceutical Abstracts (1997 – September 2006) for English-language publications of clinical trials that compared haloperidol with atypical antipsychotics in the treatment of hospitalised acutely ill adults with delirium. Only four trials were identified: one double

blind, randomised study (risperidone *versus* haloperidol), one single blind, randomised study (olanzapine *versus* haloperidol), and two retrospective studies (olanzapine *versus* haloperidol and quetiapine *versus* haloperidol). Rea and colleagues (2007) concluded their review by suggesting that haloperidol and atypical antipsychotics were equally efficacious for the treatment of delirium in acutely ill hospitalised patients, and that atypical antipsychotics might be safer in relation to their side effect profile. In relation to the treatment of hypoactive delirium, these authors suggested that the existing data was inconclusive.

Seitz *et al.* (2007) undertook a systematic review using MEDLINE (July 1980 to July 2005) and Cochrane databases for English language articles reporting prospective studies with standardised diagnostic criteria for delirium. Fourteen studies (9 single agent studies and 5 comparison trials) met the author's inclusion criteria with a total of 448 patients. No study that included a placebo comparison to account for spontaneous improvements was identified. Other major methodological limitations of the studies identified included inadequate blinding, randomisation and the handling of participant withdrawals from studies. Studies included in the review tended to be of short duration (less than 7 days in many cases). Observational studies have shown that delirium is often a transient disorder with prompt treatment of the underlying precipitating medical illness. For example, several studies have shown that delirium in adult post-operative populations lasts between 1 and 4 days in most cases (Edlund *et al.*, 2001; Williams-Russo *et al.*, 1992; Galanakis *et al.*, 2001; Liptzin *et al.*, 2005), and that delirium in adult medical patients tends to have a similar time course as that noted for post-surgical patients (Martin *et al.*, 2000; Rudberg *et al.*, 1997; Rockwood, 1989). Delirium characteristically also has a *fluctuating* course of symptoms, so that in studies that were too short or where subjects were examined too infrequently, some individuals may appeared to have recovered when in fact what was being observed was a 'natural' and temporary fluctuation in symptoms. The study medications in this review (Seitz *et al.*, 2007) included haloperidol, chlorpromazine, olanzapine, risperidone and quetiapine. Improvements in delirium severity were reported with all of these medications, with improvements occurring soon after initiation using relatively low doses of the medications. Delirium severity as measured on the various delirium scales was reduced

by 43% to 70% in the 12 studies that reported this outcome. Serious adverse events attributed to antipsychotic medications were uncommon, although side effects were not systematically evaluated in *any* of the studies identified. These authors also noted that several studies have documented increased risk of the development of delirium with exposure to psychoactive medications, *including* antipsychotics. Additionally, they noted that the available evidence suggested that many cases of delirium could be successfully managed *without* medications using environmental strategies, but that these strategies were often underutilised. Three comparison studies identified higher rates of minor adverse events with haloperidol when compared to olanzapine and risperidone. In these studies the increased adverse events with haloperidol was due to mild extrapyramidal symptoms.

The authors concluded that in the absence of any published, double blind, randomised, placebo-controlled trials, it was difficult to determine whether the observed improvements in delirium severity could be attributed to the study medications, the natural history of the disorder, or correction of the underlying medical condition. They also acknowledged that several studies (Lundstrom *et al.*, 2005; Cole, 2002) have observed substantial improvements in delirium without reliance on antipsychotic medications. Cole and colleagues, for instance, conducted a randomised trial of the systematic detection and nonpharmacological intervention of delirium in older medical inpatients. The authors found significant rates of improvement both in the intervention group and the usual care group (48% and 45% respectively). Seitz and colleagues (2007) emphasized the need for placebo-controlled studies, particularly in the light of the negative results obtained in two recent randomised placebo-controlled trials for the *prevention* of delirium in adult patients using haloperidol and donepezil.

Lacasse and colleagues (2006) reported on a systematic review of trials evaluating the pharmacological treatment of delirium in adult medically or surgically ill patients. The authors searched a wider range of databases than Seitz *et al.* 2007, including PsycINFO and EMBASE (in addition to MEDLINE and the Cochrane Central Register of Controlled Trials) to July 2006. Only prospective, randomised, controlled trials comparing the clinical effects of antipsychotic therapy with placebo *or* comparing two

antipsychotic treatments in an acute care setting were selected. Only 4 studies met these inclusion criteria. Three of these trials compared haloperidol with other agents including atypical antipsychotics, first generation antipsychotics, or benzodiazepines. No study using a placebo-controlled methodology was identified.

The authors concluded that on the basis of the comparative studies examined in their review, antipsychotic medications appeared to be efficacious and safe for the treatment of delirium in adult patients. Haloperidol was the most studied agent, and was associated with more frequent extrapyramidal side effects, although overall, all agents were well tolerated. They also concluded that the recommendation of one antipsychotic agent over another in the first-line pharmacological treatment of hospital-associated delirium in adult patients was limited by the quality and quantity of the available data, and that *no* rigorous scientific data clearly supported the widely accepted recommendation that haloperidol be the pharmacotherapeutic treatment of choice. They also noted the lack of data addressing the question of whether antipsychotics in combination with environmental strategies provided greater benefits than either alone.

Weber and colleagues (2004) reviewed the evidence for both treatment and prevention of delirium using a search of the published literature in the MEDLINE and Cochrane databases. The authors concluded that at the time of writing the best available evidence for pharmacological intervention in the symptomatic treatment of delirium in adults was strongest for the use of haloperidol and chlorpromazine. This recommendation was based largely on the findings of one of only two randomised controlled trials identified by the authors' search strategy; namely the study of Breitbart *et al.* (1996). Breitbart and colleagues (1996) randomised 31 delirious AIDS patients to haloperidol (n=13), chlorpromazine (n=13), or lorazepam (n=6). Treatment with either haloperidol or chlorpromazine resulted in significant improvement, whereas *no* improvement was found in the lorazepam group. Treatment with haloperidol or chlorpromazine was associated with extremely low prevalence of extrapyramidal side effects. *All* patients receiving lorazepam, however, developed treatment-limiting adverse effects that included oversedation, disinhibition, ataxia, and increased confusion.

Schwartz *et al.* (2002) reviewed the scarce available literature on the use of the *atypical* antipsychotics, olanzapine, risperidone, and quetiapine in treating delirium amongst adult patients. This review was based on two retrospective case reports (Sipahimalani and Masand, 1997), a retrospective follow-up of 11 consecutive patients (aged 14-74 years) (Sipahimalani *et al.*, 1997), and a case series of 7 patients with psychotic delirious symptoms (Furmaga *et al.*, 1997), in the case of risperidone. For olanzapine, the data consisted of a retrospective study (Sipahimalani and Masand, 1998) of 11 delirious adults treated with olanzapine (8.2 +/- 3.4mg/day) compared to a group of 11 delirious adults treated with haloperidol (5.1 +/- 3.5mg/day). According to the DRS, five of the 11 olanzapine-treated patients and six of the 11 haloperidol-treated patients experienced a greater than 50% reduction in delirium severity. The peak clinical response occurred in 6.8 +/- 3.5 days with olanzapine and in 7.2 +/- 4.9 days with haloperidol. These between-group differences were insignificant. Haloperidol, however, was more poorly tolerated: five patients taking haloperidol as compared to none of those taking olanzapine developed extrapyramidal symptoms. For quetiapine, the review conclusions were based on a single retrospective study (Schwartz and Masand, 2000) comparing haloperidol with quetiapine in adult patients with delirium with 11 patients in each arm of the study. Of the 11 patients in each group 10 showed improvements in DRS scores, with a reduction of more than 50% in global delirium symptoms.

The authors of the review (Schwartz *et al.*, 2002) concluded that on the basis of their experience and the limited available evidence, an atypical antipsychotic agent was a reasonable *first-line* approach to the pharmacological treatment of delirium. In the authors clinical practice risperidone was used as the agent of choice, although if this agent failed, the medical and psychiatric diagnosis was reevaluated and haloperidol was instituted as suggested by the American Psychiatric Association guidelines (American Psychiatric Association, 1999). The authors also noted that if an enteral route for administration was not available because of the patient's medical condition, level of agitation, or refusal to take oral medication, then intramuscular or intravenous haloperidol might be a more reasonable choice.

Boettger and Breitbart (2005) conducted a PubMed, PsycLIT and Embase literature search for studies using atypical antipsychotics in the treatment of adults with delirium (1996 to April 15, 2005). These authors identified 13 studies examining the use of risperidone, olanzapine, and quetiapine, and two case reports using ziprasidone. No publications were found on aripiprazole. Of these studies, three used a retrospective design, nine were prospective and open label, and only one study was double blinded. The authors concluded that although atypical antipsychotics were widely used in the treatment of delirium in adults, well-designed studies did not exist. Even the prospective, double blind study of Han and Kim (2004) did not report the end score in both of the treatment groups nor measure side effect burden. Some studies included patients with drug intoxication and other readily reversible causes of delirium. Few studies differentiated between delirium subtypes. Among the existing studies, stronger data supported the use of risperidone and olanzapine, and these agents appeared to be safe, with a low burden of side effects. The authors also suggested that there might only be limited efficacy in the use of olanzapine in the hypoactive delirium subtype in elderly patients.

Since the review by Schwartz and colleagues (2002), a number of further publications have described the use of risperidone in the treatment of adult patients with delirium, including two prospective open trials of risperidone and one double-blind trial of risperidone *versus* haloperidol (Bougeois and Hilty, 2005; Gupta *et al.*, 2005; Han and Kim, 2004; Liu *et al.*, 2004; Parellada *et al.*, 2004; Tune *et al.*, 2002).

Horikawa and colleagues (2003) carried out a prospective open trial of 10 patients with delirium, and found that, with a relatively low dose of 1.7mg/day, risperidone was effective in 80% of patients, with the effect appearing within a few days. There were no serious adverse effects. However, sleepiness (30%) and mild drug-induced parkinsonism (10%) were observed. The authors concluded that the observed improvement was considered to have occurred in response to the risperidone rather than correction of underlying cause, because patients in whom the etiological factors of delirium could be eliminated, and those whose delirium was quite likely to resolve spontaneously, were excluded from the study.

Table 2.10 Recent reviews and systematic reviews of the use of anti-psychotics in adults with delirium

Publication	Nature of review	Nature of the studies identified by the review	Authors and date of publication of included studies	Anti-psychotic medications	Conclusions of review
Loneragan <i>et al.</i> , 2007	Cochrane systematic literature review	3 studies satisfied the reviewer's selection criteria for inclusion. 1 randomised, placebo-controlled study 1 randomised, double-blind, placebo-controlled study (prevention) and 1 randomised, double-blind study	Hu <i>et al.</i> , 2004 Han and Kim., 2004 Kalisvaart <i>et al.</i> , 2005 (prevention study)	Haloperidol Olanzapine Risperidone	No evidence that <i>low</i> dosage haloperidol has lesser efficacy or greater frequency of adverse effects than olanzapine or risperidone. High-dose haloperidol was associated with higher rates of extrapyramidal side-effects
Rea <i>et al.</i> , 2007	Systematic review of MEDLINE (1977 to September 2006) and International Pharmaceutical Abstracts (1997 to September 2006) for English language haloperidol vs atypical comparator trials	Four haloperidol versus atypical antipsychotic comparator trials were identified 2 retrospective studies 1 double-blind, randomised study 1 single-blind, randomised study	Han & Kim, 2004 Skrobik <i>et al.</i> , 2004 Schwartz & Masand, 2000 Sipahimalani & Masand, 1998	Haloperidol Risperidone Olanzapine Quetiapine	Atypical antipsychotics are as efficacious as haloperidol and are associated with fewer adverse effects The sedative potential of olanzapine and quetiapine may be beneficial in hyperactive delirium The data is inconclusive in relation to hypoactive delirium Additional prospective, randomised, controlled trials are needed

Table 2.10 (continued) Recent reviews and systematic reviews of the use of anti-psychotics in adults with delirium

Publication	Nature of review	Nature of the studies identified by the review	Authors and date of publication of included studies	Anti-psychotic medications	Conclusions of review
Seitz <i>et al.</i> , 2007	Systematic review using MEDLINE (July 1980 to July 2005) and Cochrane databases for English language articles	14 studies (9 single agent studies and 5 comparison trials) met the author's inclusion criteria with a total of 448 patients. 12 of the 14 studies were not double-blind 4 of the 5 comparison studies were not adequately randomized No placebo-controlled studies identified	Akechi <i>et al.</i> , 1996 Kim, K. <i>et al.</i> , 2001; 2003; Kim, J. <i>et al.</i> , 2005 Breitbart <i>et al.</i> , 1996; 2002b Horikawa <i>et al.</i> , 2003 Mittal <i>et al.</i> , 2004 Parellada <i>et al.</i> , 2004 Sasaki <i>et al.</i> , 2003 Pae <i>et al.</i> , 2004 Nakamura <i>et al.</i> , 1995 Han & Kim, 2004 Skrobik <i>et al.</i> , 2004	Haloperidol Chlorpromazine Olanzapine Risperidone Quetiapine	Delirium severity as measured on the various delirium scales was reduced by 43% to 70% in the 12 studies that reported this outcome. Serious side-effects uncommon Three comparison studies identified higher rates of extrapyramidal adverse events with haloperidol when compared to olanzapine and risperidone 'In the absence of any controlled trials, it is difficult to determine whether the observed improvements in delirium severity are due to study medications, the natural history of the disorder, or treatment of the underlying medical conditions'

Table 2.10 (continued) Recent reviews and systematic reviews of the use of anti-psychotics in adults with delirium

Publication	Nature of review	Nature of the studies identified by the review	Authors and date of publication of included studies	Anti-psychotic medications	Conclusions of review
Lacasse <i>et al.</i> , 2006	Systematic review using PsycINFO, EMBASE, MEDLINE and the Cochrane Central Register of Controlled Trials to July 2006	Only 4 studies met inclusion criteria. No study using a placebo-controlled methodology was identified. 2 randomised, double-blind studies 2 prospective, open comparison studies	Breitbart <i>et al.</i> , 1996 Han <i>et al.</i> , 2004 Lee <i>et al.</i> , 2005 Skrobik <i>et al.</i> , 2004	Haloperidol Chlorpromazine Risperidone Olanzapine Amisulpride Quetiapine	Antipsychotics appeared to be efficacious and safe for the treatment of delirium in adult patients. Haloperidol was the most studied agent, and was associated with more frequent extrapyramidal side effects, although overall, all agents were well tolerated. Recommendation of one antipsychotic over another in the 1st-line drug treatment of delirium in adult patients was limited by the quality and quantity of the available data. No rigorous scientific data clearly supported the widely accepted recommendation that haloperidol be the antipsychotic of choice.

Table 2.10 (continued) Recent reviews and systematic reviews of the use of anti-psychotics in adults with delirium

Publication	Nature of review	Nature of the studies identified by the review	Authors and date of publication of included studies	Anti-psychotic medications	Conclusions of review
Boettger and Breitbart, 2005	Systematic review using PubMed, PsycLIT and Embase (1996 to April 2005) for studies using atypical antipsychotics in the treatment of delirium.	13 publications examining the use of risperidone, olanzapine, and quetiapine, and two case reports using ziprasidone 3 retrospective studies 9 prospective, open-label Only one double-blind study identified using risperidone	Horikawa <i>et al.</i> , 2003 Mittal <i>et al.</i> , 2004 Parellada <i>et al.</i> , 2004 Liu <i>et al.</i> , 2004 Han & Kim, 2004 Sipahimalani & Masand, 1998 Kim, K. <i>et al.</i> , 2001; 2003 Skrobik <i>et al.</i> , 2004 Breitbart <i>et al.</i> , 2002 Schwartz & Masand, 2000 Sasaki <i>et al.</i> , 2003 Pae <i>et al.</i> , 2004	Risperidone, Olanzapine, Quetiapine, Ziprasidone	The authors concluded that although atypical antipsychotics were widely used in the treatment of delirium in adults, well-designed studies did not exist. Among the existing studies, stronger data supported the use of risperidone and olanzapine, and these agents appeared to be safe, with a low burden of side effects. The authors also suggested that atypical antipsychotics might only have limited efficacy in the management of hypoactive delirium Many studies neglect to differentiate between subtypes

Table 2.10 (continued) Recent reviews and systematic reviews of the use of anti-psychotics in adults with delirium

Publication	Nature of review	Nature of the studies identified by the review	Authors and date of publication of included studies	Anti-psychotic medications	Conclusions of review
Weber <i>et al.</i> , 2004	Systematic literature review using MEDLINE and the Cochrane databases	One RCT One open controlled trial One open uncontrolled trial Three case reports	Breitbart <i>et al.</i> , 1996; 2002 Kim <i>et al.</i> , 2001 Sipahimalani & Masand, 1997 Passik & Cooper, 1999	Haldol Chlorpromazine Olanzapine Risperidone	'The current evidence for pharmacological interventions in the symptomatic treatment of delirium is strongest for the use of haloperidol and chlorpromazine. Substantially less evidence suggests that...olanzapine might also be efficacious and have fewer side-effects than the typical neuroleptic medications'
Schwartz <i>et al.</i> , 2002	Unsystematic literature review of atypical antipsychotics in the treatment of delirium in adult patients Methodology not described	4 case reports 1 open retrospective study 2 retrospective comparison study 1 case-series	Sipahimalani & Masand, 1997; 1998 Sipahimalani <i>et al.</i> , 1997 Furmaga <i>et al.</i> , 1997 Passik & Cooper, 1999 Schwartz & Masand, 2000 Leso & Schwartz, 2002	Risperidone Olanzapine Quetiapine Ziprasidone	'the use of an atypical antipsychotic is a reasonable first-line approach to the drug treatment of delirium' No conclusions were drawn with respect to adverse effects

Mittal and colleagues (2004) undertook a prospective open-label 6-day trial of risperidone in medically-ill adults with DSM IV delirium and a Delirium Rating Scale score of greater than or equal to 13. Daily assessments included DRS, Cognitive Test for Delirium (CTD), and a modified Extrapyramidal Symptom Rating Scale. The Cumulative Illness Rating Scale (for the assessment of medical burden) was assessed at Day 1 and Day 6. Ten patients (mean age 64.7 years) were treated with a mean daily maintenance dose of 0.75mg. Eight out of ten patients improved on most measures of delirium. Improvement occurred *despite* the absence of a decrease in the overall medical burden as measured by the Cumulative Illness Rating Scale, supporting the conclusion that improvement in delirium preceded improvement in total medical illness. The authors acknowledged, however, that as the Cumulative Illness Rating Scale is relatively insensitive to *rapid* changes in medical burden, definite conclusions could not be drawn. Other than sedation, no adverse events occurred that could be clearly attributed to risperidone.

Han *et al.* (2004) reported on a double-blind, randomised trial of 28 adult patients with delirium using a flexible-dose regimen of haloperidol or risperidone. The severity of delirium was measured using the Memorial Delirium Assessment Scale. Scores for both groups decreased significantly over the 7 days of the trial. However, no significant differences in mean Memorial Delirium Assessment Scale scores were found between the two groups. In addition, there was no significant difference in the frequency of response to the drugs between the two groups (haloperidol group response: 75%, n=9; risperidone group response: 42%, n=5; p= 0.11). One patient in the haloperidol group experienced mild akathisia, but no other patients reported clinically significant side effects.

There has, however, also been a report that warned of a *risk* of delirium associated with risperidone treatment, especially in the elderly and in those receiving other medications or having other disorders affecting the central nervous system (Ravona-Springer *et al.*, 1998). Tavcar and Demovsek (1998) have also reported a case of delirium seemingly induced by risperidone.

Since the review by Schwartz *et al.* (2002), a randomised, *placebo-controlled* trial comparing haloperidol and olanzapine (Hu *et al.*, 2004), and an open trial of olanzapine (Breitbart *et al.*, 2002b) for the treatment of delirium in hospitalised adult cancer patients have been reported.

Breitbart and colleagues (2002b) conducted an open-label, prospective trial of olanzapine in 79 patients with DSM IV delirium over the course of a 7-day treatment period. Fifty-seven patients (76%) had complete resolution of their delirium on olanzapine. No patients experienced extrapyramidal side-effects, however, 30% experienced sedation. In this study both the presence of the hypoactive subtype and severity of delirium as measured by the Memorial Delirium Assessment Scale (greater than 23) predicted *poorer* response. Of note, two patients treated with olanzapine seemed to have a *worsening* of their delirium requiring cessation of the drug. The authors suggested that olanzapine's muscarinic antagonist properties could theoretically have played a role in the exacerbation of delirium. The authors also suggested that olanzapine's sedative properties may have contributed to the poorer response of patients in the hypoactive group.

Hu and colleagues (2004) reported the results of a randomised, placebo-controlled trial of 175 elderly patients with delirium randomised to olanzapine (74 patients), haloperidol (72 patients) or placebo (29 patients). To the best of my knowledge, at the time of writing, this is the only randomised, placebo-controlled trial to be conducted in the treatment of delirium in *any* age group. This study met inclusion criteria for the Cochrane Review of Lonergan *et al.* (2007). The authors concluded that olanzapine (1.25- 2mg per day), as compared to haloperidol (2.5- 10mg per day), improved delirium more rapidly and was associated with fewer side effects, although there was no difference in the 7th day persistence of delirium.

It is notable in this study that the Delirium Rating Score of *placebo* patients fell by 24.7% at Day 7, although this was significantly less than the decreases observed with olanzapine (72.2% reduction) and haloperidol (70.4% reduction). Kim *et al.* (2001) have

also assessed the efficacy and safety of olanzapine for the treatment of delirium in 21 adult Korean patients. Scores on a delirium rating scale improved significantly from the time of pre-treatment to the time of post-treatment. No patients had significant side effects.

Two relatively recent surveys addressing, amongst other aspects, the opinions of correspondents regarding the optimal treatment of delirium have been published. Someya and colleagues (2001) conducted a survey of 28 psychiatric departments in Japan regarding the drug therapy of delirium. Haloperidol was used in 67% of cases. Haloperidol was also considered the drug of first choice by 97% of psychiatric facilities, while 57% thought this drug had few side effects and was easy to use. Ely and colleagues (2004) surveyed a convenience sample of physicians (n=753), nurses (n=113), pharmacists (n=13), physician assistants (n=12), and respiratory care practitioners (n=8), regarding the treatment of delirium in the intensive care unit. Delirium was treated with haloperidol by 66% of correspondents, with lorazepam by 12%, and with atypical antipsychotics by less than 5%.

In summary, the evidence for the treatment of delirium in adult patients remains rather limited. The available literature has many limitations. Trials are generally of very short duration, and utilizing, for the most part, single-agent, open-label methodologies without placebo control in the case of pharmacological strategies. Only one randomised, placebo-controlled study of delirium treatment has been published (Hu *et al.*, 2004). Given that delirium is by nature a fluctuating condition with high rates of spontaneous remission over short periods of time, this last problem constitutes a major flaw in the evidence. In addition, according to clinical practice guidelines, any intervention must proceed in concert with correction of the underlying medical cause wherever possible. Few studies have addressed this important confounding factor using measures of medical illness burden over time, and where this has been addressed, the measure of medical burden has been relatively insensitive to sudden changes in overall medical condition. Thus, it remains to be proven with any scientific rigor that any improvements in delirium symptoms documented in clinical trials are not better accounted for by prompt correction of the precipitating medical illness. The available literature suggests

that potentially beneficial environmental strategies are frequently neglected. Medication use in delirium appears to be correlated with disruptive behaviours rather than severity of cognitive disturbance, and is therefore more commonly used in the hyperactive subtype. This is concerning, as Platt and colleagues (1994) have suggested that the hypoactive subtype may well respond as favourably to antipsychotic medication as the hyperactive subtype. In recent years an emerging but flawed evidence base for the use of atypical antipsychotics has arisen. However, clinician surveys (Ely *et al.*, 2004; Someya *et al.*, 2001) reveal that haloperidol remains the drug treatment of first choice in delirium, in keeping with recommendations from current practice guidelines.

2.4.17.5 Antipsychotic medication treatment of children and adolescents with delirium

Having just acknowledged the considerable limitations of the evidence-base for the use of medication in the treatment of adult patients with delirium, it has to be said that the evidence for their efficacy and safety in children and adolescents with delirium is substantially more limited.

In the paragraphs that follow I have attempted to both summarise and discuss the results of my systematic literature review of delirium in children and adolescents in relation to antipsychotic medication treatment of delirium in this age group.

Karnik *et al.* (2007) recently reported two cases of delirium in adolescent girls, as mentioned in an earlier section. They described the apparent differential responsiveness of the girl with the hyperactive subtype of delirium to haloperidol, and of the girl with the 'hypoactive/mixed' subtype of delirium to risperidone. The authors provided a suggested treatment algorithm for paediatric delirium based on a theoretical model of two different neurochemical pathways leading to the different subtypes of delirium, and described a theoretical framework to account for the apparent better response of hyperactive delirium to haloperidol, and of hypoactive/mixed delirium to risperidone. In the first case, these authors described a 16-year-old girl with a hypoactive/mixed type of delirium characterised by confusion, disorientation, pressured speech and insomnia that

showed a good response to risperidone 0.5 mg twice-daily. In the second case, the authors described a 14-year-old girl with a hyperactive delirium characterised by hallucinations, delusions, agitation and aggression who exhibited a poor response to increasing doses (average 3mg per day) of risperidone over a 5 day period. This patient responded rapidly when the antipsychotic was switched to haloperidol 0.5mg twice daily. The authors suggested that risperidone's ability to increase dopamine levels in the medial prefrontal cortex *via* indirect activation of 5-hydroxytryptamine 1A (5HT_{1A}) receptors might result in better cognitive enhancement in hypoactive delirium, in the same way that this mechanism has been suggested to improve cognition and negative symptoms in patients with the negative symptoms of schizophrenia.

This report is similar to the experience of Scharko and colleagues (2006) who described a 15-year-old with an agitated delirium in the context of presumed HIV-dementia who responded poorly to an initial trial of risperidone, but whose symptoms rapidly resolved on switching to haloperidol.

Martini (2004), in his recent review 'Delirium in the Paediatric Emergency Department', recommended that haloperidol remain the drug treatment of choice in children and adolescents with delirium after a careful risk: benefit analysis in each individual case. Individual doses of 1 to 2 mg orally or 1mg intramuscularly were recommended. The author warned of the potential for extrapyramidal side effects, and specifically warned of the risk of neuroleptic malignant syndrome with haloperidol, a presentation that includes symptoms of delirium and is potentially fatal.

Stoddard and colleagues (2006), in their review of 'Psychopharmacology in Paediatric Critical Care' were of the opinion that brief use of intravenous haloperidol with later substitution of an atypical antipsychotic was increasingly becoming the case with children presenting with a delirium in the United States. The authors suggested that, in their experience with older children, haloperidol was a safe, inexpensive, and highly effective treatment for the rapid remission of acute delirium, particularly in alleviating insomnia associated with delirium. In their experience, intravenous haloperidol could be used sagely for short periods in older children and adolescents who were 'selected

carefully and monitored for cardiovascular and other adverse effects'. In these authors' center haloperidol has been used effectively to relieve the symptoms of different subtypes of delirium in children and adolescents, including delirium associated with burns in more than 80 older children. They reported no emergence of acute dystonias while the causes of the delirium were being sought and corrected. The authors suggested that haloperidol was required for only 1 to 3 days until the delirium resolved. Low doses, between 0.5 and 3 mg given slowly by intravenous push were usually sufficient, repeated every 6 to 8 hours once the appropriate dose had been identified. The authors noted that haloperidol had not been approved by the FDA for intravenous route in children or adults. If children were able to tolerate oral, nasogastric, or gastrostomy tube medications, these authors suggested that after 24 – 48 hours of intravenous haloperidol, substitution of an atypical antipsychotic such as risperidone, olanzapine or quetiapine might be appropriate.

Schieveld *et al.* (2007) reported on the therapeutic approach and treatment response of 40 patients with paediatric delirium (mean age 7.6 years) in a paediatric intensive care unit setting. A two-track treatment approach was utilised, with pharmacological strategies proceeding in parallel with environmental strategies. In this series all but two children with delirium received antipsychotic medication. In children with marked agitation that was sufficiently severe to threaten their health status, haloperidol at a loading dose of 0.15-0.25 mg/dose intravenously was used, given slowly over 30-45 minutes, followed by a maintenance dose of 0.05-0.5 mg/kg/24 hours, also by intravenous route. In less acute situations, however, and when an oral route for medication administration was possible, risperidone at a loading dose of 0.1- 0.2mg/dose by mouth, followed by a total daily maintenance dose of 0.2-2.0 mg/24 hours was used as the treatment of choice. Clinical responses and side-effects were recorded by the child neuropsychiatrist and the paediatric intensivists. Children were followed up at 6 weeks after discharge. Twenty-seven patients were given haloperidol, 10 risperidone, and 1 child received both drugs in succession. In the majority of cases a response was rapidly observed, especially in the hyperactive forms, often even after a single dose. Two patients experienced acute dystonia as a likely side effect of haloperidol that responded well to biperidene. In most cases the medication was stopped or tapered successfully

during hospitalisation or after discharge. Limitations of this study noted by the authors included the fact that no severity scale for delirium was used, because none existed for the paediatric population. In addition, the authors acknowledged that as no data existed on the natural course of childhood delirium that has established the rate of spontaneous remission of delirium in this age group, cases of spontaneous remission might have erroneously been classified as treatment responders. In the opinion of the authors, however, the time frame of the responses pointed towards a medication effect rather than spontaneous remission. No rating scale was used to estimate antipsychotic effectiveness.

In a separate article, Schieveld and Leentjens (2005) described the use of intravenous haloperidol for the treatment of delirium in two girls aged 28 months and 42 months. In both cases good responses were obtained from a single dose of intravenous haloperidol. The 28-month-old girl received a single dose of 0.25 mg haloperidol administered slowly intravenously and made a complete recovery within 30 minutes. The 42-month-old girl received a single dose of 0.15 mg haloperidol, administered in the same way, and had made a full recovery on waking the next morning. These authors were of the opinion that delirium in children, regardless of subtype, should be treated actively with antipsychotic medications rather than conservatively, for the following reasons. Firstly, because it is important to control agitation in order to prevent the child from harming themselves by, for example, extubating themselves, pulling out intravenous lines, or falling out of bed. Secondly, the authors asserted that reducing the stress associated with a delirium facilitates recovery of the somatic condition, and quoted Turkel and Tavaré (2003) in postulating a longer hospital stay and higher mortality in children with delirium. Lastly, these authors suggested that active treatment of childhood delirium might reduce the impact of an experience that is frightening to both children and their carers, and might reduce posttraumatic stress. Suggested dosages for children younger than 4 years of age were given as 0.25 mg/dose slowly intravenously over 30- 45 minutes as a loading dose and 0.05 to 0.5 mg/kg/24 hours intravenously as a continuing dose.

The authors concluded that pharmacological treatment should be part of the *routine* care of delirious young children, and did not restrict their recommendations to children and adolescents with delirium in the PICU setting.

Turkel and Tavaré (2003), in reporting their retrospective series of 84 children and adolescents with delirium referred to a consultation-liaison psychiatry service, provided little comment on the treatment of these cases, other than noting that 'antipsychotic drugs were found to be helpful in controlling symptoms of delirium in the paediatric patients in this study'.

Brown and colleagues (1996) documented their experience of the safety and efficacy of haloperidol in the treatment of 30 agitated, critically ill paediatric patients with burn injuries. The mean age of the patients in this study was 7 years (8 months to 18 years), with a mean weight of 32.7 +/- 4.3kg. Ninety percent of these patients required ICU monitoring for a significant proportion of their hospitalisation. The main indication for the use of haloperidol was 'marked agitation and restlessness' (80%), followed by 'delirium with marked disorientation, hallucinations and delusions' (13%) and insomnia (7%). The mean individual dose of haloperidol was 0.047 mg/kg/dose. The longest period of treatment with haloperidol was 3 months. Forty-three percent of doses were intravenous, and 57% were enteral. On an 'efficacy score' of 0 to 3 (0 = no effect, 1 = fair, 2 = good, 3 = excellent), 67% of patients had an efficacy score of 3. Haloperidol had no beneficial effect in 17%. The enteral route was used in 4 of the 5 cases in which haloperidol had no effect. Of the 429 doses of haloperidol administered, adverse effects were noted on only two occasions. Extrapyramidal effects were not observed. The authors went on to note that as haloperidol undergoes extensive first pass metabolism in the liver, the enteral route might result in a reduction in bioavailability of 40% when compared to the intravenous route. They also noted that the intravenous route has actually been associated with significantly reduced rather than increased incidence of extrapyramidal effects (Menza *et al.*, 1987).

Harrison *et al.* (2002) also documented the prompt behavioural control obtained with 5 'difficult-to-sedate' critically ill children with intravenous haloperidol. The ages of these

patients were 9 and 11 months, and 12, 14, and 16 years. Nursing notes described them as being 'agitated, thrashing, disorientated or combative'. The patients in this report received loading doses of haloperidol ranging from 0.025 to 0.10 mg/kg/dose intravenously. The maintenance regimen ranged from 0.06 to 0.45 mg/kg/24 hours divided into 3- 4 daily doses. These authors noted the increased risk of dystonic extrapyramidal reactions in young children, especially boys, but also went on to note the reduced likelihood of this effect by using the intravenous route. In this small series of 5 patients haloperidol was well tolerated in 4 out of 5 patients. One patient developed an oculogyric crisis.

Ruha and colleagues (2006) have recently documented the adjunctive use of haloperidol in 12 children (mean age 21.2 months) presenting with agitation and distress in the context of acute methamphetamine toxicity. Many of these children are likely to have been experiencing an intoxication delirium. All patients were treated with a benzodiazepine in addition to haloperidol. No patient received haloperidol without first receiving a benzodiazepine. Two patients received haloperidol in the emergency department, with individual doses of 0.17 and 0.02 mg/kg/dose administered, while the remaining patients were treated in the intensive care unit, with individual haloperidol doses ranging from 0.02 to 0.67 mg/kg/dose (mean 0.14mg/kg/dose; median 0.05 mg/kg/dose). Patients received between 1 and 4 doses of haloperidol in total. There were no reports of QT prolongation, dystonic reactions or cardiac dysrhythmias. All patients received continuous cardiac monitoring.

However, not all authors have documented the safe use of haloperidol in agitated, acutely ill paediatric patients. Ratcliffe and colleagues (2004), for example, assessed the effectiveness and safety of haloperidol by a retrospective chart review of 855 acutely ill children treated consecutively over a 3-year period. A total of 26 of these acutely ill children received haloperidol and were therefore included in the study. The mean age of these children was 11.7 years, with a mean weight of 51.4 kg. The major indication for the use of haloperidol was 'marked agitation and restlessness' (85%). The other indication was for 'agitation and restlessness in addition to delirium with marked disorientation, hallucinations and delusions' (15%). A total of 308 doses of haloperidol

were administered. The mean dose used was 0.057 mg/kg/dose. The longest period of administration was 22 days. Of the doses, 53% were intravenous and 47% enteral. The effectiveness of haloperidol was retrospectively assessed using a scale of 0 to 3 (0 = no effect, 1 = fair, 2 = good, 3 = excellent). The mean effectiveness score for haloperidol was 1.73 (fair to good). An effectiveness score of 0 was observed in 19% of cases, 1 in 31%, 2 in 8% and a score of 3 in 43%. In terms of adverse effects, of the 308 doses administered, adverse effects or complications were noted in one of five (20%) patients that had an effectiveness score of 0 (no effect). Patients who were given an effectiveness score of 2 or 3, however, did not experience a side effect from haloperidol. Of the 26 patients, 6 patients (23%) had adverse reactions to the medication. Four patients experienced dystonic reactions, one hyperpyrexia, and another hyperpyrexia and a dystonic reaction. The overall incidence of acute dystonic reactions was 19.2%. The authors concluded that the use of haloperidol was accompanied by an unacceptably high incidence of side effects in the critically ill paediatric population. The authors no longer use haloperidol in this patient group at their institution. Unfortunately, the authors do not go on to discuss whether they have substituted another medication for haloperidol in the treatment of these patients.

Amongst the 65 published cases reports of delirium or probable delirium in children and adolescents between 1980 and 2008 identified by the search strategy, only 8 patients received antipsychotic medication (haloperidol in 7 patients, ziprasidone in 1). Of these 8 patients, 6 were classified as having a hyperactive delirium, 1 a mixed delirium, and 1 a hypoactive delirium, on the basis of the information available in the reports. Seven of the 65 cases were treated with a benzodiazepine alone (most often lorazepam). In 4 cases an antipsychotic medication was used in combination with a benzodiazepine.

This low rate of antipsychotic use (16%) in published case reports of children and adolescents with delirium is in striking contradistinction to the high rate (95%) documented by Schieveld and colleagues (2007), and deserves further scrutiny. Schieveld and Leentjens (2005) strongly recommended an active rather than conservative therapeutic stance in the management of all cases of delirium in childhood, regardless of subtype, and suggest that antipsychotic use should be part of 'routine'

management. They argue that in the context of a delirium, active management with antipsychotic medication reduces stress (and possibly the incidence of post-traumatic stress disorder), the risk of self-injury, and may reduce hospital stay and even mortality (extrapolating from the literature relating to delirious adults). Bearing in mind the *caveats* already mentioned in generalizing data derived from a conglomerated 'series' of individual published case reports, it is interesting to note that current practice in settings *outside* of PICU does not seem to conform to the recommendations of Schievelde and Leentjens (2005) regarding antipsychotic use. There may be several reasons for this. Schievelde and colleagues (2005; 2007) described a series of cases of delirium in the setting of a paediatric intensive care unit (PICU). For the most part, individual published case reports reflect cases of delirium presenting in the setting of a paediatric accident and emergency unit or general paediatric medical ward. Cases presenting in a PICU are likely to be more medically compromised, and the potential negative consequences such as agitation, combative, disorganised, or uncooperative behaviour (accidental extubation, pulling out of intravenous or arterial lines, and wound dehiscence) are likely to be greater. In these instances the risk: benefit analysis for antipsychotic usage is perhaps more likely to fall in favour of active pharmacological treatment. A large proportion of published case reports of child and adolescent delirium or probable delirium have seemingly been managed conservatively (38 of 56 cases; 67%), without mention of any psychotropic medication. However, by looking at the presumed precipitating cause of the delirium in these case reports, it can be seen that almost a third (32%) can be classified as having a readily and rapidly correctable single cause. In contrast, the PICU series described by Schievelde and colleagues (2007) reflect cases of delirium in a very sick population of children and adolescents (mean Paediatric Risk of Mortality score 23.54; mechanically ventilated in 85%) that are likely to have multi-organ impairment and multifactorial etiologies for the delirium. These cases of delirium are far less likely to have a readily and rapidly correctable cause, and therefore are more likely to require active treatment with psychotropic medication whilst complex and multiple underlying etiologies are being addressed. In addition, 42% of the individual published case reports of delirium or probable delirium can be classified as having an underlying cause that is likely to resolve spontaneously in less than 48 hours. Almost a third (32%) of these cases were presumed to be toxic or medication-related. Of the

individual published case reports in which the delirium was seemingly managed conservatively without mention of any psychotropic medication, the median duration of delirium was 24 hours or less.

It can therefore be seen that the risk: benefit analysis for the use of antipsychotic medication in children and adolescents with delirium is influenced by factors other than symptomatology. The etiology (single or multiple, simple or complex, readily and rapidly correctable or not), likely duration, severity, symptom profile, age of the patient and environmental setting (intensive care unit or accident and emergency unit) all influence this decision in clinical practice.

In summary, the evidence-base for the use of antipsychotic medication in cases of child and adolescent delirium is extremely slim. No controlled trials have yet been reported. What published literature that there is, seems to support the use of antipsychotic medication, particularly in cases where the presumed underlying etiology is unclear, multifactorial, complex, and unlikely to be readily and rapidly correctable or to resolve spontaneously over a short time period. In addition, the potential risks of agitated, combative, disorganised or uncooperative behaviour in particular environmental contexts need to be carefully evaluated. The evidence for the use of antipsychotic medication is currently at the lowest levels on the hierarchy of evidence-based medicine (Levels 4 and 5; Appendix D), consisting of a handful of small case series and expert opinion. In those studies that have attempted to standardise the rating of response to antipsychotic medication amongst children and adolescents with delirium, the measures have most often been crude and retrospective, with little if any attention paid to major potential confounding factors like spontaneous remission, natural fluctuation, and correction of underlying etiologies. Of the antipsychotic medications, there is most support for the use of haloperidol (see Table 2.10), which has been detailed in over 200 children or adolescents presenting with delirium or probable delirium since 1980 (Schieveld *et al.*, 2005, 2007; Rahu *et al.*, 2006; Brown *et al.*, 1996; Harrison *et al.*, 2002; Ratcliffe *et al.*, 2004; Stoddard *et al.*, 2006; Turkel and Tavare, 2003; Brar *et al.*, 2005; Hall *et al.*, 1994; Okamura *et al.*, 1997; Budner *et al.*, 1997; Scharko *et al.*, 2006; Karnik *et al.*, 2007). Haloperidol has the advantages of being available for parenteral

administration when the enteral route cannot be used. The intravenous route may also have the added advantage of lowering the risk of extrapyramidal side effects (Menza *et al.*, 1987; 1988). Schieveld *et al.* (2007) and Harrison *et al.* (2002) recommend haloperidol in doses of 0.05 to 0.5 mg/kg/day, and 0.06 and 0.45 mg/kg/day respectively, given in 3-4 divided doses. In the PICU setting, Schieveld and colleagues (2008), in reporting their uncontrolled, open experience with intravenous haloperidol, suggest that it is often rapidly effective, 'usually within 2 to 6 hours, and sometimes after a single IV dosage'. The study of Brown and colleagues (1996) used a mean dose of 0.047 mg/kg/dose in their series. Using their mean patient weight of 32.7 kg, this equates to an average individual dose of 1.53 mg. Ratcliffe *et al.* (2004) reported a mean individual dose of haloperidol of 0.057 mg/kg/dose. Using their mean patient weight of 51.4 kg, this equates to an average individual dose of 2.93 mg, which may explain the higher incidence of extrapyramidal side effects reported in this study. Martini (2004) recommended individual doses of 1 to 2 mg by mouth or 1mg intramuscularly. Stoddard *et al.* (2006), drawing on their experience of delirium in older children recommended individual doses of between 0.5 and 3 mg given slowly by intravenous push and repeated every 6 to 8 hours until an appropriate dosage is identified. In the context of medically ill delirious children and adolescents, higher doses of haloperidol would appear to be associated with a higher risk of extrapyramidal side effects, and so the old adage of 'start low and go slow' would seem particularly appropriate in this context, given the higher rates of extrapyramidal symptoms in the younger age group.

Table 2.10 presents those case series of children and adolescents with definite or probable delirium treated with haloperidol that were identified by the systematic review.

Droperidol, an analog of haloperidol, has also been suggested to have a role in the treatment of agitated, violent or psychotic paediatric patients (Sorrento, 2004) and in adults with delirium (Meagher, 2001). Droperidol is more sedating and has a faster onset of action than haloperidol, an effect that may have added benefit in extremely agitated and combative patients. A great deal of controversy has surrounded droperidol since the United States Food and Drug Administration (FDA) issued a 'black box' warning, cautioning in relation to droperidol's dose-dependent prolongation of the QT interval on

electrocardiogram, and the potential for cardiac dysrhythmias. Since then, several published studies have disputed this point (Chase and Biros, 2002; Kao *et al.*, 2003).

The risk of extrapyramidal side-effects such as dystonia, especially with conventional antipsychotics like haloperidol, may be greater in young patients than in adults because the number of striatal dopamine D2 receptors declines after childhood. With this in mind, there is emerging evidence for the role of risperidone, an atypical antipsychotic, in medically-compromised children and adolescents with delirium (Schieveld *et al.*, 2007; Stoddard *et al.*, 2006; Martini, 2004). Risperidone was used to good effect in 11 of the PICU cases described by Schieveld and colleagues (2007). The authors expressed a preference for risperidone in non-acute situations because of the theoretically lower risk of extrapyramidal side effects. In cases where an oral route of administration was possible, risperidone was started with a loading dose of 0.1- 0.2 mg, followed by a maintenance dose of 0.2-2.0 mg/24 hours. Stoddard and colleagues (2006) have suggested that there has been an increase in the use of atypical antipsychotics in the management of delirium in children and adolescents, with patients frequently being switched from intravenous haloperidol to an atypical antipsychotic like risperidone, olanzapine, or quetiapine as soon as the enteral route becomes available. However, the reports of Karnik *et al.* (2007) and Scharko *et al.* (2006) raise the possibility that risperidone may be *less* effective in hyperactive/agitated cases of delirium amongst adolescent patients. Karnik and colleagues (2007) suggested that risperidone might have a particular role in hypoactive cases of paediatric delirium, based on wider receptor effects and potential to selectively increase dopamine in the prefrontal area.

Table 2.11 Haloperidol in the treatment of children and adolescents with definite or probable delirium: Published reports (1980- 2008)

Publication	Setting	Indication	No.	Age	Route	Dose	Side effects	Response
Schieveld <i>et al.</i> , 2007	PICU	Delirium; Hyperactive (10) Hypoactive (5) Emerging (13)	27	Mean 7.6 years	ivi	0.15 - 0.25mg loading dose; maintenance 0.05 - 0.5mg/kg/24 hrs	Dystonic reactions in 2 patients (7.4%)	'Successful in all patients...In most cases, the beneficial effects were observed rapidly... sometimes even after a single dose'
Schieveld <i>et al.</i> , 2005	PICU	Probable delirium	2	28 months and 42 months	ivi	0.15 - 0.25 mg single dose in each patient	No side effects reported	Complete remission following single ivi dose within 30 min and 12 hours respectively

Table 2.11 (continued) Haloperidol in the treatment of children and adolescents with definite or probable delirium: Published reports (1980- 2008)

Publication	Setting	Indication	No.	Age	Route	Dose	Side effects	Response
Brown <i>et al.</i> , 1996	Burns Unit	Marked agitation + restlessness (24 patients; 80%) Delirium with marked disorientation, hallucinations + delusions (4 patients; 13%) Insomnia (2 patients; 7%)	30	Mean 7.0 years	ivi (18 patients; 60%) enteral (11 patients; 37%) imi (1 patient; 3%)	Mean dose 0.047 mg/kg/dose Largest cumulative 24-hour period dose = 0.455mg/kg	Adverse effect noted in only 2 of 429 doses: Excessive sedation and hypotension in one patient each (3..3%)	Mean efficacy score = 2.3 Efficacy score: 3 in 20 patients (67%); 2 in 4 patients (13%); 1 in 1 patient (3%) 0 in 5 patients (17%) (where 0= no effect; 1= fair; 2= good; and 3= excellent)
Harrison <i>et al.</i> , 2002	PICU	Agitated (2) Thrashing (1) Disorientated (1) Combative (1)	5	Mean 8.9 years	ivi	Loading doses 0.025 - 0.10 mg/kg Maintenance 0.06-0.45 mg/kg/24 hrs	Dystonic reaction in one patient (20%)	Uniformly good response rapidly achieved

Table 2.11 (continued) Haloperidol in the treatment of children and adolescents with definite or probable delirium: Published reports (1980- 2008)

Publication	Setting	Indication	No.	Age	Route	Dose	Side effects	Response
Ratcliffe <i>et al.</i> , 2004	Burns Unit	Marked agitation and restlessness (85%) As above plus marked disorientation, hallucinations + delusions (15%)	26	Mean 11.7 years	ivi (164 of total of 308 doses; 53%) enteral (144 of total of 308 doses; 47%)	Mean dose 0.057 mg/kg/dose Largest cumulative 24-hour period dose = 0.957mg/kg	Dystonic reaction (4 patients; 19.2%) Hyperpyrexia (2 patients; 7.6%) No adverse effects noted in those with effectiveness score of 2 or 3 Adverse effects in 1 of 5 (20%) with effectiveness score of 0	Mean efficacy score = 1.73 Efficacy score; 3 in 11 patients (42%) 2 in 2 patients (8%) 1 in 8 patients (31%) 0 in 5 patients (19%) (where 0 = no effect; 1 = fair; 2 = good; and 3 = excellent)
Rahu <i>et al.</i> , 2006	PICU and Emergency	Acute methamphetamine toxicity with agitation and distress	12	19 months	ivi	0.02-0.67 mg/kg/dose; mean 0.14 mg/kg/dose; median 0.05 mg/kg/dose	No dystonias or QT prolongation	The authors of this report do not comment on efficacy

Table 2.11 (continued) Haloperidol in the treatment of children and adolescents with definite or probable delirium: Published reports (1980- 2008)

Publication	Setting	Indication	No.	Age	Route	Dose	Side effects	Response
Stoddard <i>et al.</i> , 2006*	Burns	delirium	>80	'older children'	Mostly ivi	0.5 to 3.0mg per dose as slow ivi push, repeated every 6 to 8 hours	No dystonias	The authors comment only that haloperidol resulted in 'excellent calming effects'
Turkel and Tavare, 2003	Consultation liaison psychiatry	delirium	18	Mean 10.4 years	Mostly ivi	'starting at 0.25mg qds and rarely exceeding 1mg total daily dose'	No dystonias	'effective for sleep disturbance, hallucinations, agitation and confusion'

Table 2.12 Risperidone in the treatment of delirium in children and adolescents: published reports (1980 – 2008)

Publication	Descriptor	Number of patients	Age (mean)	Dose	Adverse effects	Response	Additional comments
Schieveld <i>et al.</i> , 2007	Delirium	Total=11	7 years	Loading dose of 0.1 to 0.2 mg per dose; maintenance dose of 0.2 to 2.0 mg per 24 hours	None reported	'successful in all patients'	Most of these patients were subsyndromal
	Hyperactive	4	4.75 years				
	Hypoactive	2	12.0 years				
	Emerging (subsyndromal)	5	4.1 years				
Karnik <i>et al.</i> , 2007	Delirium	Total=2		0.5 mg to 1mg twice daily	None reported	Complete remission over 5 days in 1 patient	Adjunctive zolpidem for persistent insomnia
	Hypoactive/mixed	1	16 years				
	Hyperactive	1	14 years				
Scharko <i>et al.</i> , 2006	Delirium Hyperactive	1	15 years	Gradually increased to maximum of 1mg twice daily	None reported	No response – discontinued after 11 days and switched to haloperidol, which resulted in rapid remission	This patient HIV+ve patient likely had underlying HIV-associated dementia
Total		14					

In summary, the existing evidence base for the use of antipsychotics in *hyperactive* delirium in children and adolescents is comprised of small case series, case reports, and expert opinion. All reports of the use of antipsychotic medication in delirium in this age group have been open and uncontrolled. This is hardly surprising given the state of the evidence in relation to the use of antipsychotic medications in adults with delirium, which is only slightly more robust. Of the antipsychotic medications, there is most support in the literature for haloperidol, used in much smaller doses than commonly prescribed in adult patients. Based on this review, and to the best of my knowledge, the use of haloperidol has only been documented in any detail in approximately 200 children and adolescents with delirium or probable delirium in the literature published since 1980. However, the relatively high incidence of dystonic reactions (see Table 2.10) with haloperidol in the context of severe physical illness in this age group remains a concern. The literature tentatively suggests that the risk of extrapyramidal side effects such as dystonia might be reduced through the use of intravenous administration, in addition to using small dosages. The systematic literature review also identified only four articles referring to the use of the atypical antipsychotic, risperidone in children and adolescents suffering from delirium (Karnik *et al.*, 2007; Scharko *et al.*, 2006; Stoddard *et al.*, 2006, and Schieveld *et al.*, 2007). Based on this review, and to the best of my knowledge, the use of risperidone has only been documented in 14 children and adolescents with delirium in the published literature since 1980. However, as Stoddard and colleagues (2006) suggest, the use of atypical antipsychotics such as risperidone in the treatment of delirium in this age group appears to be increasingly common in clinical practice.

2.4.17.6 Benzodiazepines in the treatment of delirium

The other group of medications that is commonly used in the treatment of delirium is the benzodiazepines. Pandharipande and colleagues (2005), in their review of the management of delirium in adult patients, suggested that benzodiazepines are *not* recommended because of the risk of oversedation, exacerbation of confusion, paradoxical agitation, and respiratory depression. The exception is delirium tremens (and other withdrawal syndromes) for which the benzodiazepines remain the drugs of choice. Likewise, Grace and Holmes (2006), in their review of the management of the

behavioural and psychiatric symptoms of delirium in adults, while acknowledging that the benzodiazepines are often used as the first-line agents, warned of the concerns about their potential for oversedation, respiratory depression and disinhibition. Considering that lorazepam and other benzodiazepines are widely believed to be 'deliriogenic', with the capacity for worsening or prolonging the syndrome (Gaudreau *et al.*, 2005; Pandharipande *et al.*, 2005; Marcantonio *et al.*, 1994), it is interesting to note that 16% of the healthcare professionals surveyed by Ely and colleagues (2004) reported treating delirium in the intensive care unit with benzodiazepines.

Gaudreau and colleagues (2005), in their review of the literature, identified 11 studies examining benzodiazepines as possible precipitants of delirium in adults, with positive associations reported in only four of these. Breitbart and colleagues (1996), in their series of 31 delirious AIDS patients reported that all 6 patients treated in the lorazepam arm of the study developed adverse side effects including oversedation, disinhibition, ataxia, and increased confusion. Lorazepam *alone* appeared to be ineffective for the treatment of delirium. Some authors, however, have advocated the *combination* of intravenous haloperidol and lorazepam, suggesting that this combination may in fact reduce the risk of extrapyramidal side effects as compared with haloperidol alone (Menza *et al.*, 1988). Meagher (2001) has suggested that benzodiazepines may have a particular adjunctive role in patients unable to tolerate antipsychotics drugs, possibly allowing for lower doses of antipsychotics to be used. This 'antipsychotic sparing' effect may be particularly pertinent to paediatric delirium, but this issue remains largely unstudied.

Of the 65 individual case reports of child and adolescent delirium identified by the search strategy, 7 (12.5%) were treated solely with a benzodiazepine (most commonly lorazepam), and 4 (7%) were treated with an antipsychotic in combination with a benzodiazepine. Stoddard and colleagues (2006) suggested that, in the management of child and adolescent delirium in the paediatric critical care setting, intravenous benzodiazepines, in particular lorazepam and midazolam, were safe and short-acting alternative agents that in some cases relieved some of the symptoms of delirium. They warned, however, of the risk of sedation, paradoxical disinhibition, and worsening

delirium significantly compromising the assessment and management in some cases. Martini (2004) also warned of the risk of disinhibition in an already behaviourally disturbed child with the use of benzodiazepines in delirium. Schievelde and colleagues (2007) reported that 55% of their cases of PICU delirium were associated with a recent increase or decrease in analgesedative medication (opioids and/or benzodiazepines), but did not document the rates of coadministration of benzodiazepines with antipsychotic treatment. Williams (2007) suggested that benzodiazepines should generally be reserved for delirium due to alcohol or sedative-hypnotic withdrawal, but that occasionally lorazepam might be used as an *adjunct* with haloperidol when agitation and insomnia persist.

In summary, while most authors warn of the risk for adverse effects and even worsening of delirium associated with the use of benzodiazepines, there does appear to be some limited evidence that short-acting benzodiazepines as adjunctive medications to the use of antipsychotic medications may have a role in the treatment of delirium in children and adolescents. They may have a particular adjunctive role in helping to control agitation and insomnia when these symptoms do not adequately respond to antipsychotic medications, and may also provide a useful 'dose-sparing effect' in relation to antipsychotic medication.

2.4.17.7 Psychostimulants in the treatment of hypoactive delirium

Trzepacz and colleagues (2004) cautioned that psychostimulants could worsen delirium, presumably through increasing dopaminergic activity. However, a number of authors have described the successful use of psychostimulants such as methylphenidate for the treatment of hypoactive delirium (Morita *et al.*, 2000; Keen and Brown, 2004; Gagnon *et al.*, 2005). Moein and colleagues (2006) were able to show that methylphenidate reduced both duration of intensive care unit and hospital stay in patients admitted to an intensive care unit following moderate to severe traumatic brain injury.

This systematic review of the literature was unable to identify any literature relating to the treatment of hypoactive delirium in children and adolescents.

To the best of my knowledge, the efficacy of psychostimulant medication combined with antipsychotic medication for the treatment of delirium has not been studied in any age group.

Other medications used in the treatment of delirium

Other medications with limited evidence for effectiveness in the treatment of adult and elderly patients with delirium include the tetracyclic antidepressant, mianserin (Nakamura *et al.*, 1995; 1997), and the cholinesterase inhibitor, donepezil (Sampson *et al.*, 2007). However, a recent Cochrane review (Overshott *et al.*, 2008) found no evidence from controlled trials of donepezil's effectiveness in delirium.

This systematic literature review was unable to identify and publications relating to the treatment of delirium in children and adolescents with either of these medications.

2.4.18 Prevention

There is a growing body of literature attesting to the effectiveness of preventative delirium interventions in adult and elderly at-risk populations (Young and Inouye, 2007; Michaud *et al.*, 2007; Weber *et al.*, 2004; Siddiqi *et al.*, 2007). Such interventions have included the implementation of pre-operative proactive geriatric consultation in combination with a structured protocol addressing pain, unnecessary medications, appropriate environmental stimulation, and early mobilisation amongst other risk factors (Marcantonio *et al.*, 2001). A nurse-led intervention using education, systematic cognitive screening, and a pain protocol has been shown to reduce the duration and severity (but not incidence) of delirium in elderly hip-fracture patients (Milisen *et al.*, 2001). Inouye and colleagues (1999) have also demonstrated the effectiveness of a multicomponent protocol in preventing delirium and reducing its duration. In another trial, low-dose haloperidol prophylaxis for at-risk elderly hip-surgery patients was shown to reduce delirium severity and duration, but not its incidence (Kalisvaart *et al.*, 2005). Levanen and colleagues (1995) have documented the finding of reduced

ketamine-induced post-anaesthetic delirium in adult patients premedicated with dexmedetomidine.

In comparison, almost nothing has been published relating to the prevention of delirium in children and adolescents. Vlajkovic and Sindjelic (2007) review some of the existing paediatric anaesthesiology literature exploring a variety of pharmacological strategies aimed at reducing emergence agitation and delirium in children. These interventions have included the use of clonidine, dexmedetomidine and midazolam. The authors concluded that the literature relating to the prevention of emergence agitation and delirium in children remains conflicting.

The most intriguing report in relation to the prevention of paediatric delirium comes from Kain and colleagues (2007). As briefly discussed in the 'Predisposing factors' section, these authors conducted a randomised controlled trial in which a multicomponent 'family-centered' preparatory intervention prior to elective paediatric surgery was compared to 3 other groups. The 3 other groups included a control group of 'standard care', a 'parental presence' group, in which a parent was allowed to be present during induction with anaesthesia, and a 'midazolam group' in which participants received standard care plus 0.5 mg/kg oral midazolam 30 minutes before being separated from parents and moved to the operating room. The multicomponent intervention included anxiety reduction strategies, video modeling and education, the presence of the parents during induction, coaching, and the avoidance of excessive reassurance by parents. The authors reported that their multicomponent intervention significantly reduced preoperative anxiety in both child and parent. The multicomponent intervention also significantly reduced the incidence of post-operative emergence delirium, when compared with the control, midazolam, and parental presence groups (10% versus 24% versus 21% versus 16%; $p = 0.038$). This study suggests that simple prophylactic psychosocial interventions may reduce the incidence of emergence delirium in children. The question as to whether such interventions might reduce the incidence, severity and/or duration of paediatric delirium in *other* contexts and in relation to other precipitants, remains unanswered.

2.5 Summary

To the best of my knowledge, this review represents the first systematic review of the literature relating to all aspects of the syndrome of delirium in children and adolescents. The only other published literature searches relating to this subject that I was able to identify were those of Turkel *et al.* (2006) and Schieveld (2008).

The literature review by Turkel *et al.* (2006), however, was much more limited in scope, having the specific aim of identifying 'articles with specific descriptions of the frequency of individual symptoms associated with delirium in both adult and paediatric patients'. These authors based the results and discussion of their review on 10 adult delirium articles and just *one* paediatric delirium study that met their inclusion criteria. The single article relating to paediatric delirium identified by this review which met the authors inclusion criteria, was a study previously reported by the same authors of the review itself (Turkel and Tavare, 2003).

Jan Schieveld (2008) documented the limited number of publications identified relating to delirium in children, in comparison to the relatively large number identified relating to delirium in adults, using a PubMed search in May 2007. However, the literature search was principally used to highlight the fact that the number of publications of delirium in children (1438) was roughly 10% of that in adults. The identified articles themselves were not discussed.

A systematic review of the literature addressing the subject of delirium in children and adolescents was urgently required in the light of rapid developments in the field of delirium in adults and the elderly over the last decade or so. Research into delirium in adult and elderly patients has confirmed that the disorder is associated with significant morbidity, residual cognitive deficits and high mortality, even when results are adjusted for possible confounding factors such as type, severity, and complexity of physical illness. The brain's own inflammatory response to injury may trigger not only delirium, but may also act as a catalyst for cytokine-related multi-organ damage outside of the central nervous system. With an increasing awareness of the negative outcomes

associated with delirium, the field has seen a rapid increase in studies evaluating both treatment and prevention of delirium in adult and elderly patients. Additionally, recent researchers have begun to challenge the longstanding divisions between delirium and dementia, and have proposed a more inclusive conceptualisation of delirium as a spectrum disorder, with subsyndromal forms merging imperceptibly with 'normal' consciousness, and more severe forms merging into stupor and then coma. Despite an increasing awareness of the clinical significance of delirium, current guidelines for the management of delirium in adult and elderly patients derive mainly from uncontrolled trials and case series. Only one randomised, placebo-controlled study was identified by the unsystematic but thorough literature review of delirium in adult and elderly patients (Hu *et al.* 2004). Recent research into the management of delirium in adult patients has documented a rapid increase in the use of the novel atypical antipsychotic medications, and these agents are increasingly being utilised in clinical practice for the management of delirium in adults.

The existing literature relating to all aspects of delirium in children and adolescents lags significantly behind that in older people. More particularly, the literature relating to the management of delirium in children and adolescents is extremely limited. In the absence of clear management guidelines for delirium occurring in this age group, clinicians are left to extrapolate as best they can from the data available in adults and even the elderly. This may not in itself be particularly problematic, so long as minimal discontinuities exist between the syndrome as it occurs in children, and the syndrome as it occurs in older patients, and as long as developmental influences on the use of psychotropic medications in young people are borne in mind.

However, without sufficient research into the causative factors, manifestations, temporal course, morbidity, mortality, and response to treatment in children with delirium we may be unable to discern such discontinuities, should they exist. For example, discontinuities in the treatment response to conventional antipsychotic medications between adults and children with delirium could profoundly influence the risk: benefit analysis required for each patient when considering initiating such medications.

A useful corollary can perhaps be found in the literature relating to depression in children. A wealth of literature in adult patients attests to the efficacy of the tricyclic antidepressant medications in the treatment of depression (Guaiana *et al.*, 2007). Until quite recently, tricyclic antidepressants were commonly being prescribed to children and adolescents with depression, based largely on the extrapolation of data from studies in adults. However, in recent years a rapidly expanding body of literature has highlighted significant discontinuities between the syndrome of major depression as it occurs in children, and as it occurs in adults. Not least of these discontinuities is a poor response amongst children with depression to the tricyclic antidepressant medications. A systematic review of the literature relating to the use of these medications in children with depression by Hazell *et al.* (2002) was able to show that these medications are in fact ineffective for depression in this age group. Tricyclic antidepressants are associated with significant adverse effects in young people. The work of Hazell *et al.* (2002) and others has probably done much to prevent children being exposed to potentially harmful medications prescribed for an indication for which they are probably ineffective. It is quite conceivable that similar discontinuities exist between delirium in children and delirium in adults, with similar implications for management.

A systematic literature review can assist in elucidating apparent continuities and discontinuities between delirium in children and adolescents, and delirium in adults and geriatric patients. In this way, a systematic review can either support or refute the current clinical practice of basing the treatment of delirium in children and adolescents largely on data obtained from adult delirium research. Such a review can also expose gaps in the existing knowledge base relating to delirium in youth, and assist in directing new research. With this in mind I conducted a systematic review of all of the literature relating to any aspect of delirium in children and adolescents published in any language since 1980. The results of the systematic literature search, utilizing a broad search strategy, identified only a small number of published case series and 65 published case reports of definite or probable delirium in children and adolescents.

An analysis of the literature identified by this search strategy can be summarised as follows. Delirium is a disorder that is commonly encountered in clinical settings

amongst children and adolescents. Clinical settings in which it is particularly common are paediatric consultation-liaison psychiatry, paediatric anaesthesia, the paediatric intensive care unit, and paediatric burn units, oncology and emergency units. However, it is commonly undetected and frequently misdiagnosed, possibly even more so than in adults.

A similar range of etiological factors is associated with delirium in children and adolescents as is found in adult patients. However, children, and perhaps adolescents, appear to be especially vulnerable to delirium in the context of emergence from anaesthesia, febrile illness, severe burn injuries, migraine, prescribed medications, toxins and abused substances. This increased vulnerability to delirium may be related to immature development of the neural networks implicated in the pathogenesis of delirium (particularly cholinergic networks) and/or to psychological immaturity.

Delirium in children and adolescents manifests in a similar way to delirium in other age groups. Certain features, however, such as agitation and hallucinations, appear to occur with greater frequency in delirious youth. Delirium in children may present more subtly than in adults, with less obvious cognitive impairments. In addition, certain relatively unique features of delirium in this age group have been described, most notably developmental regression with transient loss of skills, and inconsolability by a usual caretaker. The same subtypes of delirium as have been described in adults have also been described in children. However, clear delineation between these subtypes may be more problematic in children. Subtle variants of delirium have been described in children and adolescents, such as subclinical, 'veiled' or 'emerging delirium'. Delirium may be more difficult to diagnose in children, as the core features of disturbance of consciousness and cognitive impairments may be more difficult to elicit, and more subtle in their manifestations.

Delirium is associated with significant morbidity and mortality in children and adolescents, as it is in adults. However, existing research has not yet addressed the question, as it has in adults, as to whether these associations hold true after adjusting for physical illness type, severity, and complexity. As is the case with adults, delirium in

children and adolescents has been associated with residual cognitive deficits and behavioural problems long after the resolution of the delirium itself.

Existing delirium rating scales designed for use in adults appear to have a role in the assessment and diagnosis of delirium in children and adolescents. The Delirium Rating Scale (DRS) has been used most commonly in this population, with scores reported as being similar to those in adults. The use of the Delirium Rating Scale-Revised-98, superior to the DRS in that it is better at distinguishing delirium subtypes, rating severity of delirium, and of monitoring change in severity with time or intervention, has been described by a number of researchers in adult and elderly patients with delirium. Its use in children and adolescents has not been described.

Similar management strategies recommended in adult and elderly patients with delirium are being recommended in the literature for use in children and adolescents with delirium. These recommendations are, however, being recommended on the basis of slim empirical evidence. The existing evidence relating to the treatment of delirium in children and adolescents is based entirely on open and uncontrolled studies, case reports, anecdote, and expert opinion. To a large extent recommendations for management appear to be heavily derived from the evidence base in adults with delirium, which is, as I have taken pains to point out, perilously slim. The situation appears to be particularly fraught in relation to the pharmacological management of hypoactive delirium.

In the light of the developments in the adult literature, and the (albeit limited) evidence for increased morbidity and mortality associated with delirium in children and adolescents, one research group, that of Schieveld, Leentjens and coworkers, has advocated an aggressive approach to the management of delirium in this age group, and the 'routine' use of antipsychotic medications in young children suffering from delirium.

With regards medication management, there is most evidence for the use of haloperidol, which has been used for the treatment of delirium and probable delirium in children or adolescents in over 200 patients detailed in the published literature since 1980. In comparison, the use of risperidone has only been documented in 14 children and

adolescents with delirium in the published literature since 1980. However, as Stoddarc and colleagues (2006) suggested, the use of atypical antipsychotics such as risperidone in the treatment of delirium in this age group appears to be increasingly common in clinical practice. The treatment of hypoactive delirium in children with psychostimulant medications has not been studied.

2.6 Limitations of the systematic review

This review did not include articles published prior to 1980. In addition, delirium has such an array of synonyms in common usage that even employing as broad a search strategy as was used in this review may not have captured all articles relating to this subject. Given that delirium appears in many guises and under a variety of names in the published literature, a number of the articles discussed in this review may, strictly speaking, refer to 'probable delirium'. Few reports, other than those originating from consultation-liaison psychiatry services, have employed DSM diagnostic criteria.

The vast majority of the published literature relating to definite or probable delirium in children and adolescents addresses predominantly hyperactive delirium. Thus, the extent to which the findings of the review can be generalised to predominantly hypoactive delirium is uncertain.

In addition, this review analysed the literature relating to delirium in children and that relating to delirium in adolescents together, based on the assumption that delirium in adolescence might reasonably be expected to overlap considerably with delirium in childhood. This assumption may of course be flawed, as delirium in adolescence may have more in common with delirium in adulthood than with delirium in childhood. Significant discontinuities may exist between pre- and postpubertal delirium, and by combining the literature addressing delirium in both groups, this review may inadvertently have obscured potential discontinuities. The vast majority of the subjects with delirium included in this review were hospitalised children and adolescents. The

extent to which the findings of this review can be generalised to the wider population of children and adolescents with delirium, including those with brief delirium, is uncertain.

2.8 Strengths of the systematic review

The review employed a very broad search strategy and included a number of delirium's common pseudonyms such as 'confusional state' and 'encephalopathy'. The review also included articles published in languages other than English. In combination with a time period covering the last 28 years, it is to be hoped that these attributes might significantly reduce the chances of relevant articles being missed. In addition, the reference lists of relevant articles were hand-searched for other relevant articles and a wide variety of textbooks were consulted. Great pains were taken to be able to relate the articles identified by the literature search to the existing body of rapidly expanding literature addressing the subject of delirium in adult and geriatric patients. To this end, a second literature review was conducted of delirium in these older patients. Despite being more modest in scope and less rigorous in methodology, this secondary review was nevertheless reasonably comprehensive. In addition, articles identified in this secondary search of adult and geriatric delirium were then hand-searched for passages pertaining to delirium in children and adolescents.

2.9 Conclusion

The existing literature points to a great degree of continuity between many aspects of delirium in children and adolescents, and delirium in adult and elderly patients. Far more continuities than discontinuities exist in relation to predisposing and precipitating factors, clinical manifestations, temporal course, and associated morbidity and mortality. Where discontinuities do appear to exist, for example in relation to phenomenology, they appear to be relatively minor.

Given the immaturity of the field, and the scarcity of research into delirium in children and adolescents, it also has to be acknowledged that the existing knowledge base is

currently inadequate for the purpose of elucidating possible discontinuities in certain areas. Unfortunately, response to treatment is one of these areas. Few firm conclusions in relation to treatment can be drawn from a systematic review of the existing literature relating to delirium in children and adolescents.

As has already been mentioned, the other motivations for undertaking this systematic review were to more clearly highlight gaps in the existing literature relating to delirium in children and adolescents, and to guide further research. There remain serious gaps in our knowledge relating to almost every aspect of delirium in this age group, and a thorough exploration of the published literature produces more questions than answers. Particularly pertinent questions that remain either wholly or only partially answered include:

- *Are children generally at higher risk of delirium compared to adolescents or adults, or are they only differentially more vulnerable to certain precipitants?*
- *What are the protective factors, if any, in relation to delirium in this age group?*
- *What is the relationship, if any, between temperament, the vulnerability to delirium, and its different subtypes?*
- *What is the prognostic significance of delirium in children, and how durable are the residual cognitive and behavioural deficits?*
- *Does delirium itself increase the risk of mortality in critically-ill children?*
- *Can delirium in children be prevented?*
- *How can delirium best be assessed and diagnosed in young and very young children?*

- *How can delirium rating instruments assist in the assessment and management of children and adolescents with delirium?*
- *How can delirium in children and adolescents be best treated?*
- *What are the indications for antipsychotic medications in delirious children?*

The case series described in the following chapter was motivated by a desire to address the last 4 of these questions in particular.

University of Cape Town

Chapter 3

A case series of children and adolescents with delirium

3.1 Introduction

The systematic review of the literature relating to delirium in children and adolescents described in Chapter 2 identified only three case series of child or adolescent delirium patients that had utilised DSM operational criteria for making the diagnosis (Turkel *et al.*, 2003; Przybylo *et al.*, 2003; and Schieveld *et al.*, 2007). The total number of children and adolescents included in these series is only 129. The largest series reported to-date has been the study of Turkel and Tavare (2003), which included 84 patients identified over a 4-year period. Only three case series of delirium in children and adolescents have been described in the setting of consultation-liaison psychiatry since 1980 (Prugh *et al.*, 1980; Turkel *et al.*, 2003; and Schieveld *et al.*, 2007), only two of which utilised DSM operational criteria for establishing the diagnosis, as described above. All of these above-mentioned case series have been reported from high-income countries in North America or Europe.

It needs to be emphasized that given the immaturity of the field, each of these studies has provided a massive contribution to the knowledge base relating to delirium in children and adolescents. However, in addition to relatively small patient numbers, the studies described above have had a number of other limitations, particularly in relation to the assessment of treatment effectiveness.

The published articles produced by the research group of Turkel, Tavare, Braslow and Trzepakz (Turkel and Tavare, 2003; Turkel *et al.*, 2003; 2006) were based on a case series derived from a retrospective record review of 84 child and adolescents patients who were assessed as suffering from a delirium over a 4-year period by the paediatric consultation-liaison psychiatry service at Childrens Hospital Los Angeles, based on DSM-III-R criteria. The data derived from this case series has several limitations. Firstly, the study was retrospective in nature, and the patients were assessed and managed by a

variety of clinicians. The inter-rater reliability in the application of DSM-III-R diagnostic criteria for delirium across these clinicians is unknown, and this may have introduced considerable inconsistency. Secondly, the authors reported very little data in relation to management of these patients (Turkel and Tavaré, 2003). Their conclusions in relation to pharmacological management were restricted to documenting that 'antipsychotic medications were effective for sleep disturbance, hallucinations, agitation, or confusion', and that 'atypical antipsychotics were not used during the period of this study' (1991-1995). In a later article, (Turkel *et al.*, 2003), the authors documented for the first time the use of a delirium rating instrument, the Delirium Rating Scale, in children and adolescents with delirium. However, the scale was retrospectively applied to the clinical records, and a non-delirious control group was not used to compare scores with the delirious group. As has already been mentioned, no firm conclusions can thus be drawn in relation to the specificity, sensitivity, predictive values and reliability of the DRS when applied to children and adolescents.

The published works of the research group of Schieveld, Leentjens and colleagues (Schieveld, 2008; Schieveld *et al.*, 2008, Schieveld *et al.*, 2007; Leentjens *et al.*, 2008; Schieveld and Leentjens, 2005) have been based on a series of 40 children (more recently 46 children in Leentjens *et al.*, 2008), assessed as having a delirium in the Paediatric Intensive Care Unit of the Maastricht University Hospital in the Netherlands. These diagnoses were based on DSM-IV criteria for delirium. Schieveld *et al.* (2007) described their management approach, both environmental and pharmacological, in some detail. However, the authors provided very little information in relation to treatment effectiveness and how treatment response was assessed. The authors documented only that 'In most cases the beneficial results (of antipsychotic medications) were observed rapidly, especially in hyperactive forms, sometimes even after a single dose' (Schieveld *et al.*, 2007). This research group has also documented the application of the Delirium Rating Scale to children and adolescents with delirium (Leentjens *et al.*, 2008). However, although the authors compared DRS scores with adult and elderly patients with delirium, they did not use a non-delirious paediatric control group. Without comparison to suitable non-delirious age-matched control groups, the reliability and validity of the DRS in this age group remains uncertain.

In summary, existing published case series of child and adolescent patients with delirium suffer from a number of limitations. None of these studies attempted to rate delirium severity using more contemporary delirium rating instruments than the DRS. Several limitations of the DRS have already been mentioned. Notably, It has a limited ability to distinguish hyperactive from hypoactive delirium, and additionally, a limited ability to rate delirium severity, especially in response to treatment. Additionally, none of the above-mentioned studies attempted to systematically rate response to treatment in relation to delirium severity or delirium subtype. None of these studies attempted to assess response to treatment of delirium in relation to changing measures of physical illness severity. Only Schieveld *et al.* (2007) described the use of atypical antipsychotics such as risperidone in the treatment of children and adolescents with delirium, although as previously mentioned, this has been reported in case reports by Scharko *et al.* (2006) and Karnik *et al.* (2007).

Other case series of delirium or probable delirium in children and adolescents are comprised of patients where the diagnosis has not been made according to operational criteria, and where, for the most part, the core diagnostic features of delirium have been poorly characterised.

3.2 Objectives

The objectives of this case series were principally to address some of the unanswered questions identified by the systematic review of child and adolescent delirium, already described in Chapter 2, and more specifically, to address some of the limitations of previously reported case series of delirium in this age group.

As already mentioned in the concluding paragraphs of the section devoted to the systematic literature review, this case series was conceived in the hope that it might shed additional light on four of the wholly or only partially answered questions identified by the review:

- *How can delirium be best assessed and diagnosed in young and very young children?*
- *How can delirium rating instruments assist in the assessment and management of delirium in children and adolescents?*
- *How can delirium in children and adolescents be best treated?*
- *What are the indications for antipsychotic medications in child and adolescent delirium?*

Specifically, it was hoped that this case series might address some of the limitations of previously reported case series, particularly in relation to the use of rating scales and the assessment of treatment effectiveness. With this in mind, the objectives of the case series were:

- *To document a case series of delirium in children and adolescents from an urban African setting*
- *To document the use of the revised version of the DRS, the DRS-R-98, in rating the severity of delirium in children and adolescents. The use of the DRS-R-98 has previously not been described in children and adolescents.*
- *To assess the applicability and utility of the PAED scale in a setting other than the emergence from anaesthesia*
- *To compare the DRS, DRS-R-98 and PAED scale scores between children and adolescents with delirium, and a suitable control group of non-delirious children and adolescents.*
- *To systematically assess treatment effectiveness, albeit in an open and uncontrolled way*

- *To assess treatment effectiveness in relation to both conventional and atypical antipsychotic medications, delirium severity as measured by the DRS-R-98 Severity Scale, and delirium subtype.*

Additionally, I sought to document in detail my experiences with assessing and managing HIV-positive children and adolescents with delirium, a group that has received almost no attention from researchers until now.

Secondary objectives, given the paucity of existing research into this area, were to add to the knowledge base in relation to the etiology, phenomenology, morbidity and mortality associated with delirium in children and adolescents in an urban African setting.

3.3 Methods

3.3.1 The setting

The Red Cross War Memorial Children's Hospital is situated in Cape Town, and is the only specialist hospital dedicated entirely to children in sub-Saharan Africa. Most of the approximately 250 000 patients seen at the hospital each year come from severely disadvantaged communities throughout South Africa and the rest of the continent. The hospital has 288 beds at present, and approximately 8000 surgical operations are performed each year. Despite being a hospital for children, a relatively large number of adolescents are also treated at the hospital, in keeping with a culture of retaining longstanding paediatric patients with chronic illnesses within a youth-friendly therapeutic environment until they (and their paediatricians) are 'ready' to transition to adult services.

The wider context of children and adolescents living in South Africa is dominated by poverty and HIV/AIDS. In 2007/2008 the South African Child Gauge (Proudlock *et al.*, 2008) reported that 68% of children in South Africa were living in households with an

income of less than R1,200 (approximately 150 United States dollars in 2008) per month. The HIV prevalence amongst pregnant women in the 9 provinces of South Africa in 2006 ranged from 15% in the Western Cape, in which the Red Cross Children's Hospital is situated, to 39% in KwaZulu-Natal province. The HIV prevalence amongst children in 2006 ranged from 0.8% in the Western Cape to 3.2% in KwaZulu-Natal province. In 2006, 21% of the estimated 18.2 million children living in South Africa were classified as 'orphans', in that they were without a living biological mother, father, or both parents. Also in 2006 it was estimated that 5% of children in the Western Cape Province were living in households without basic sanitation, 7% without access to drinking water on site, and 6% without an electricity connection. Although shocking, it also has to be acknowledged that these statistics represent, without exception, the best of those for the nine provinces in South Africa. However, as has already been mentioned, as the only tertiary teaching hospital in South Africa, and even subSaharan Africa, dedicated entirely to children, the Red Cross Children's Hospital treats children from all around the country, including the very poorest and disadvantaged regions.

The Consultation-Liaison Psychiatry Unit of the Division of Child and Adolescent Psychiatry assesses and treats both inpatient and outpatient children and adolescents, referred by their primary paediatric treatment teams with a range of emotional, behavioural and sometimes cognitive problems.

3.3.2 The sample

The patients included in this case series were derived from referral of hospitalised children and adolescents to the Consultation-Liaison Psychiatry Unit of the Division of Child and Adolescent Psychiatry over a 2-year period from 1 January 2006 to 1 January 2008. The patients were referred by a variety of primary paediatric treatment teams for the assessment and recommendations for management of inpatient children and adolescents presenting with a variety of behavioural, emotional or cognitive problems in the context of physical illness, but all received a psychiatric diagnosis of delirium.

The patients were all assessed and managed (at least from a psychiatric perspective) by myself during this period. The assessment and management of these patients was naturalistic, in that it reflects current clinical practice at Red Cross Children's Hospital in the management of children and adolescents suffering from delirium.

3.3.3 Measures

Three rating scales were retrospectively applied to the data recorded in the clinical records of these patients – the DRS, DRS-R-98, and the PAED. A control group was selected in order to provide comparison between rating scale scores of delirious children and adolescents, and a similar aged group of children without delirium. Twenty-five consecutive patients with a wide range of psychiatric diagnoses attending the Outpatient Unit of the Division of Child and Adolescent Psychiatry were recruited as controls.

The assessment of treatment effectiveness was conducted in an open and uncontrolled fashion. Clinical Global Impression – Improvement (CGI-I) scores, rated by myself in relation to *sustained* improvement within the first 48 hours of instituting combined pharmacological and environmental management were used as a crude measure of effectiveness. CGI-I scores were not, however, assessed in relation to changing measures of physical illness severity.

3.4 Ethical issues

The study was formally approved by the Research Ethics Committee of the University of Cape Town. The study was also approved by Red Cross War Memorial Children's Hospital. Verbal consent was obtained and documented for the anonymous use of all case material presented. In cases where no parent was available, consent was obtained from the legal guardian. All of the cases were children and adolescents who were admitted to hospital for reasons relating to their physical illness. They were all referred to the Consultation-Liaison Psychiatry Unit for assessment and management of

behavioural and/or emotional problems and all ultimately received a diagnosis of delirium. No screening for cases of delirium took place.

The study was naturalistic in that it did not involve any interventions or clinical assessments not already being routinely used in the management of delirium in children and adolescents at Red Cross Children's Hospital. Decisions as to which of the commonly used antipsychotic medications to prescribe were based on individual aspects of the clinical picture, underlying physical illness, route of administration and side-effect profile, within a 'treatment as usual' framework. The study itself in no way influenced the choice of medication used, and did not in any way inconvenience patients or their carers. The rating instruments were scored based on the findings from the routine mental state examination, and so did not require a longer interview, further interviews, or in any way burden the patient or carers.

3.5 Results and discussion

3.5.1 Demographics

Twenty- three clinical diagnoses of delirium were made during this period, and these cases comprise the case series detailed below. These patients were referred from a variety of inpatient settings including PICU (22%), Paediatric Surgery/Trauma (22%), Paediatric Subspecialty Wards (22%) and General Paediatric Wards (22%). Of the 3 remaining patients, 2 were referred from the Paediatric Acute Admissions Ward, and 1 from the Anaesthetic Recovery Room.

One hundred and twenty seven new referrals of inpatients to the Consultation-Liaison Unit were received during this period. The 23 cases of delirium therefore made up 18% of the total number of referred cases during the study period. This is very much in line with Lipowski's (1980) estimate that 15 to 20% of patients (adults in this instance) referred for psychiatric consultation from medical and surgical wards and special units suffer from delirium.

Table 3.1 A consultation liaison psychiatry case series of children and adolescents diagnosed with delirium: Demographics, precipitants, delirium subtypes and physical setting

Patient	Age (years)	Gender	Presumed etiology	Delirium subtype	Setting
1	5	Male	Multifactorial Post-liver transplant Psychoactive polypharmacy	Hyperactive	Paediatric Subspeciality Ward
2	10	Male	Medication-induced	Mixed	Acute admissions ward
3	9	Female	Multifactorial Severe burn injury Psychoactive polypharmacy	Hyperactive	Paediatric surgery ward
4	2	Female	Multifactorial Severe burn injury Psychoactive polypharmacy		PICU
5	12	Male	Multifactorial Polytrauma Psychoactive polypharmacy	Hyperactive	Paediatric Trauma Unit
6	11	Male	Multifactorial Polytrauma Head injury Psychoactive polypharmacy	Mixed	PICU

Table 3.1 (continued) A consultation liaison psychiatry case series of children and adolescents diagnosed with delirium: Demographics, precipitants, delirium subtypes and physical setting

Patient	Age (years)	Gender	Presumed etiology	Delirium subtype	Setting
7	12	Male	Multifactorial Ruptured appendix Psychoactive polypharmacy	Mixed	PICU
8	8	Female	Traumatic brain injury	Hyperactive	Paediatric Trauma Unit
9	13	Female	Post-cardiac surgery	Hyperactive	Paediatric Surgery Ward
10	12	Female	Multifactorial Systemic Lupus Psychoactive polypharmacy	Mixed	Paediatric Subspeciality Ward
11	4	Male	Multifactorial Sepsis Hepatic failure	Hypoactive	Paediatric Surgery Ward
12	16	Female	Multifactorial Post-renal transplant	Hypoactive	Paediatric Subspeciality Ward

Table 3.1 (continued) A consultation liaison psychiatry case series of children and adolescents diagnosed with delirium: Demographics, precipitants, delirium subtypes and physical setting

Patient	Age (years)	Gender	Presumed etiology	Delirium subtype	Setting
13	4	Male	Sevoflurane emergence delirium	Hyperactive	Anaesthetic Recovery Room
14	9	Female	Multifactorial HIV on HAART Sepsis Malnutrition	Hyperactive	General Paediatric Ward
15	9	Female	Multifactorial HIV on HAART Tuberculosis Renal failure	Hyperactive	General Paediatric Ward
16	6	Male	Multifactorial Post-renal transplant Sepsis	Hyperactive	Paediatric Subspecialty Ward
17	10	Male	Traumatic brain injury	Mixed	General Paediatric Ward

Table 3.1 (continued) A consultation liaison psychiatry case series of children and adolescents diagnosed with delirium: Demographics, precipitants, delirium subtypes and physical setting

Patient	Age (years)	Gender	Presumed etiology	Delirium subtype	Setting
18	11	Female	Multifactorial Hepatic failure Hyperammonemia Sepsis	Mixed	General Paediatric Ward
19	9	Male	Multifactorial Severe burn injury Sepsis Psychoactive polypharmacy	Mixed	PICU
20	12	Female	Cyclical vomiting Pre-renal failure	Mixed	Acute Admissions ward
21	13	Male	Multifactorial Severe burn injury Sepsis Psychoactive polypharmacy	Hypoactive	PICU
22	15	Female	Multifactorial Post-renal transplant Psychoactive polypharmacy	Mixed	Paediatric Subspeciality Ward
23	11	Female	Multifactorial HIV on HAART Tuberculous meningitis	Hyperactive	General Paediatric Ward

Of the 23 children and adolescents with delirium, 11 were male and 12 female. The mean age for the total sample was 117 months (9.75 years), with the mean age for the male patients (n=11; mean age=105 months) being slightly younger than that of the female patients (n=12; mean age=128 months). The age range for the sample was from 28 months to 16 years.

3.5.2 Physical status

As a group, these patients were severely physically compromised (Table 3.2). Of the 23 patients, 9 (39%) required Paediatric Intensive Care Unit admission at some point during their index admission. Four of the cases of delirium occurred in the context of extensive burn injuries. Four occurred in the context of recent solid organ transplantation and three in the context of HIV infection and antiretroviral treatment. The vast majority of cases of delirium occurred in the context of clinical and/or laboratory evidence of *multisystem* involvement.

3.5.3 Etiology

As can be seen from Table 3.3, cases of delirium in which there was thought to be a single clear precipitant make up only a small minority of the cases. These cases tended to be medication/toxin ingestion or head trauma related, and more frequently occurred in previously well children. Similarly, cases in which it was felt likely that the delirium would resolve spontaneously or be readily and rapidly treatable (by removing or reversing the likely precipitant) comprised only a very small proportion of referred cases.

Intuitively, one suspects that referrers are more likely to make a correct diagnosis of delirium in cases presenting with a clearly identified precipitant, and are more likely to manage the case (be timeously removing or reversing the likely precipitant) without necessitating a referral to psychiatric services for diagnostic clarification or recommendations for management.

In the large majority of cases the exact cause of the delirium was in fact uncertain and most likely multifactorial. The majority presented with evidence of multiple organ system compromise, often with multiple and complex biochemical and/or metabolic abnormalities. The majority of the patients were managed with complex polypharmacy regimens for their physical condition where there was a strong possibility of an iatrogenic contribution to the etiology of the delirium. In over half of the cases it was felt likely that prescribed medications could be contributing to the etiology.

**Table 3.2 A consultation liaison psychiatry case series of children and adolescents diagnosed with delirium:
Likely Precipitant(s)**

Likely precipitant(s)	Number of patients (Total = 23)*
Polytrauma	2
Head injury related	3
Burn injury	4
Post solid organ transplant	4
HIV-associated	3
Sepsis	5
Renal failure	7
Hepatic failure	4

*In a number of instances more than one precipitant was associated with delirium in an individual patient

**Table 3.3 A consultation-liaison psychiatry case series of children and adolescents diagnosed with delirium:
Nature of precipitant(s)**

Nature of precipitant(s)	Number of patients (Total = 23)
Single clear precipitant	5
Rapid spontaneous resolution likely (e.g. toxic ingestion)	3
Readily and rapidly correctible cause	2
Likely complex and multifactorial	19
Significant uncertainty as to exact cause	16
Probable iatrogenic contribution	13

3.5.4 Phenomenology

Of the features noted, the 5 commonest, in descending order of frequency, were: marked fluctuation of mental state (91%), acute onset of changes in mental state (87%), agitation/restlessness (83%), attentional deficits and insomnia (both 78%). It is notable that the two commonest features of delirium in this sample related to *temporal* aspects of the change in mental state, rather than specific symptoms or signs, further underscoring the need for a longitudinal assessment and serial interviews in order to ensure the correct diagnosis is made. The two next most common features (anxiety/fearfulness and mood lability) are relatively nonspecific, occurring relatively commonly in the hospitalised child in the context of anxiety, pain or medication side effects. Turkel and colleagues (2006) reported the following rates in their series: fluctuation (100%), attentional disturbance (100%), sleep-wake disturbance (98%), and agitation (69%). Notable differences from the series reported by Turkel and colleagues were the comparatively higher rates in this series of speech disturbance (52% vs 0%), and delusions (22% vs 0%). Also of note is a high rate of hallucinations during delirium in this series, most commonly visual hallucinations, which were present in over half of cases (52%).

Twenty-two percent presented with an apparent prodrome, characterised by apathy, dysphoria, and withdrawal, which appeared to last anywhere between a few days to a week or more prior to the onset of the full delirium syndrome.

As can be readily seen from Table 3.5, the majority of cases were categorised as either being hyperactive or mixed.

It is worth noting that in all three of the patients with hypoactive delirium the diagnosis was not suspected by the primary treating team, and all three patients were in fact referred with suspected depression and an assessment for possible antidepressant medication. In all three cases the onset of the delirium was relatively insidious over a period of at least a month. These cases presented with marked psychomotor retardation, apathy, social withdrawal, poverty of speech, blunting of affect and decreased reactivity of mood. The key to the diagnosis in these cases was serial bedside cognitive assessments, which revealed markedly fluctuating levels of alertness and ability to focus and sustain attention. In two of the cases the sleep-wake cycle was markedly abnormal. An electroencephalogram showing diffuse slowing supported the diagnosis of a hypoactive delirium in two of the three cases. Two of the three patients with hypoactive delirium subsequently died. One of these died in hospital during the index admission, and was seen to drift back and forth between periods of relative alertness, hypoactive delirium, and stupor before finally lapsing into coma and eventually dying.

Table 3.4 A consultation-liaison psychiatry case series of children and adolescents diagnosed with delirium:
Symptom profile (N=23)

Symptom domain	Symptom	N	%
Behavioural disturbance	Agitation / restlessness	19	83
	Insomnia	18	78
	Disinhibition	8	35
	Aggression	5	22
	Marked developmental regression	6	26
	Motor retardation	7	30
Perceptual disturbance	Visual hallucinations	12	52
	Auditory hallucinations	8	35
	Other hallucinations	1	4
	Nightmares	7	30
	Delusions	5	22

Table 3.4 (continued) A consultation-liaison psychiatry case series of children and adolescents diagnosed with delirium:
Symptom profile (N=23)

Symptom domain	Symptom	N	%
Affective disturbance	Marked mood lability	13	57
	Irritability	5	22
	Distress/tearfulness	11	48
	Anxiety/fearfulness	14	61
	Apathy	4	17
Cognitive disturbance	Attentional deficits	18	78
	Orientation deficits	10	43
	Memory deficits	5	22
	Executive function deficits (set shift/maintenance problems and/or perseveration)	9	39

Table 3.4 (continued) A consultation-liaison psychiatry case series of children and adolescents diagnosed with delirium:
Symptom profile (N=23)

Symptom domain	Symptom	N	%
Speech disturbance	Incoherence	12	52
	Shouting/screaming	10	43
Temporal course	Acute onset	20	87
	Marked fluctuation	21	91
	Worse at night	14	61
Apparent prodrome		5	22
Inconsolability	Carer unable to console	8	50

Patients classified as having a 'mixed' delirium manifested features of both hyperactive and hypoactive delirium within the same episode of delirium, usually within a 24-hour period. A number of these patients appeared to have initially presented with predominantly hypoactive features (somnolence, psychomotor retardation, withdrawal, diminished alertness and other cognitive deficits), but were only referred once they 'switched' into a predominantly hyperactive form. These 'switches' occasionally occurred quite rapidly, often over the course of 24 hours, reminiscent of the dramatic 'switches' often seen in patients with catatonia from catatonic *stupor* to catatonic *furor*. Other patients classified as 'mixed' appeared to move fluidly back and forth along a spectrum of psychomotor disturbance. Such patients, for example, might appear markedly agitated at one point only to sink into somnolence and diminished responsiveness a short while later.

The patients that I have classified as 'hyperactive' might best have been classified as 'predominantly hyperactive', as even these patients rarely presented with 'pure' psychomotor agitation over the course of their illness. Over the course of days it becomes difficult to distinguish hyperactive delirium with marked disruption of the sleep-wake cycle from a 'mixed' delirium in a child who is predominantly agitated, sleeps poorly at night, and falls exhausted into deep sleep for short periods during the daytime.

In the case of the patients classified as 'hypoactive', these might best have been described as 'purely hypoactive', as these 3 patients showed no evidence of psychomotor agitation over the course of their illness. These patients, however, often seemed to cross the indistinct boundary into stupor and even coma, in the same fluid fashion as patients with 'mixed' delirium shifted from psychomotor agitation to psychomotor retardation and back.

**Table 3.5 A consultation liaison psychiatry case series of children and adolescents diagnosed with delirium:
Delirium subtypes (N=23)**

Delirium subtype	N	%
Hyperactive	10	43.5
Hypoactive	3	13.0
Mixed	10	43.5

3.5.5 Diagnostic assessment process

Delirium remains a clinical diagnosis. Many aspects of its phenomenology are not specific to delirium, and so its cross-sectional presentation in particular can mimic a wide variety of psychiatric conditions. However, the *gestalt* clinical picture of a peculiar cluster of symptoms and signs presenting with a characteristic temporal course (acute onset, marked fluctuation, worse at night) in the context of physical illness or substance/medication use is readily recognised.

In the patients described above, the diagnosis of delirium was established using serial clinical interview with the young person and their usual carer, serial bedside cognitive assessment, longitudinal collateral history from a variety of other professional sources (nursing interview and nursing notes, treating clinician interview and clinical notes, and frequently a number of other professionals including physiotherapists, occupational therapists etc.). The clinical interviews and cognitive assessments were all conducted by myself.

When assessing children for a possible diagnosis of delirium, one of the central difficulties is that children, and particularly young children, may not have the verbal skills to adequately describe their subjective experience. In addition, these children are inevitably interviewed by an unfamiliar adult (myself, in this instance) in the bewildering and frightening setting of a hospital admission. Add to this the context of

serious physical illness, pain, anticipatory anxiety, multiple medications, lack of sleep, aversive past experiences with doctors, and anxious parents at the bedside and it is not difficult to imagine how a child's motivation for cooperation with assessment might be seriously compromised. For these reasons it is often necessary to infer subjective phenomenology from behavioural manifestations in young children. For example, a child may not be able to volunteer in interview that she is seeing frightening snakes in the corner of her well-lit room, but her expression of terror, pointing at the corner of the room and cries of "Snakes!" may allow us to infer that she may be experiencing visual hallucinations. However, certain signs and symptoms may be more difficult to infer from behavioural manifestations in uncooperative children or those with limited verbal abilities. This is particularly the case with the cognitive features of delirium, which in fact comprises the phenomenological 'core' of delirium. Thus, what constitutes valid and reliable evidence of a 'disturbance of consciousness with reduced ability to focus, sustain, or shift attention' (Criterion A DSM-IV-TR) in a frightened, uncooperative, and physically ill 3-year-old interviewed in an Emergency Department at 3 o'clock in the morning?

Additionally, the requirement that there be evidence of 'a change in cognition' (DSM-IV-TR) from baseline functioning implies that in order to make the diagnosis there must at least be some idea of the child's cognitive functioning prior to developing the illness.

In the paragraphs that follow, I have attempted to describe in some detail exactly how the DSM-IV-TR criteria for delirium were interpreted and their features elicited in the patients included in this case series.

3.5.5.1 DSM-IV-TR Criterion A:

Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention

In older children and adolescents who were cooperative with testing, Criterion A was evaluated by serial evaluations of the ability to say the days of the week and/or months of the year backwards, or to perform simple Go-No Go tests. Other tests used to

supplement these tests were forward and backward digit span, serial subtraction of 7's or 3's, story memory and picture memory. However, the first two of these tests proved problematic in our most impoverished and poorly educated patients. Even with cooperative and well-educated patients we were left with the problem of how to interpret findings in the absence of premorbid or baseline test results in our individual patients. Often the most informative findings were the presence of dramatic fluctuations in performance over time rather than the absolute score on these tests. For these reasons a variety of simple Go – No Go tests specifically aimed at evaluating ability to focus and sustain attention and then shift set proved to have the greatest utility with patients from a wide spectrum of cultural and educational backgrounds.

As an example, patients were first instructed to raise their hand each time they heard the number '3' read out aloud from a list of random numbers from zero to ten. Each patient was allowed a 'test run' in order to assess whether they had understood the instructions. A list of 20 numbers from zero to ten was then read out aloud to the patient in which the number '3' was listed three times. More than two errors of omission (not raising the hand for the number 3) or commission (raising the hand for numbers other than 3) were regarded as clinically significant. Younger children who were anxious or in discomfort proved difficult to engage with this method, and such bedside tests as 'days of the week backwards' were clearly impossible in patients who were unable to speak.

A simple bedside test which proved invaluable in these instances, and which often facilitated engagement, reduced performance anxiety, and often elicited laughter was what I took to calling the Clap Trap Test. This test could be used with children as young as 3 years of age and rapidly provided a measure of the young person's ability to focus attention, maintain attention, shift mental set with changing rules, and inhibit actions. Essentially, the Clap Trap Test involves the interviewer sitting opposite the child and instructing the child to copy exactly what the interviewer does with his hands. The interviewer then claps his hands together twice to see whether the child has understood the instructions. The interviewer persists with this until it becomes clear that the child has understood and is able to follow through with these basic instructions, reminding the child to copy exactly what the interviewer does with his hands. The interviewer then

begins to clap out rhythmic sequences gradually increasing in complexity, beginning with simple one-clap-pause-two-claps-pause-one clap sequences and later moving on to more complex percussion rhythms. Only the most somnolent, agitated or frightened of children were unable to engage with this simple test, and the majority enjoyed it immensely. Repeated errors at the 1-2-1 or 2-1-2 stage were interpreted as significant. Significant attention deficits can become apparent with many tests of attention in the context of severe anxiety, pain, or lack of motivation or cooperation even in non-delirious patients. The advantage of the Clap Trap Test under these circumstances lies in the non-threatening quality of the interaction between interviewer and child, facilitating rapport, reducing anxiety, and frequently injecting some humour into the assessment.

Another useful test for the bedside assessment of attentional capacity, working memory, and simple arithmetic involved the counting up of a small handful of coins that the interviewer produced from his pocket. The majority of our patients with limited education were still quite adept at adding up small change to see whether they had enough money to purchase a chocolate at the hospital tuckshop. Older children were able to work out how much change they might expect from the shopkeeper. At the end of the test the children were allowed to keep the coins. This test provided a familiar 'real-life' assessment of cognition for which the majority of children could summon up sufficient motivation. Once again, often the most significant finding was of dramatic fluctuation in performance over serial assessments rather than absolute cross-sectional ability.

For the youngest of our patients even these simple bedside tests proved inappropriate. In these instances, and in others in which the child was not able to be cooperatively engaged, the careful observation of aspects of the child's interaction with a familiar carer (most frequently the parent) proved extremely useful. Sustained eye contact with the parent, persistent attention to the parent's instructions or reassurance, and the child's capacity to be consoled by the parent's reassurances were used as proxy measures of attention in such cases. The Paediatric Anaesthetic Emergence Delirium (PAED) scale (Sikich *et al.*, 2004), is the only formal delirium assessment measure that addresses this important feature of delirium in young children. Item 1 (The child makes eye contact

with the caregiver) and Item 5 (The child is inconsolable) are each assessed on a scale from 0 to 4.

3.5.5.2 DSM IV-TR Criterion B

A change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established or evolving dementia.

Once again, practical difficulties abound in the assessment of these problems in children, particularly young children, in the context of significant physical illness, discomfort and the bewildering hospital setting. Some children, particularly the older ones, were able to cooperate with some of the 'traditional' bedside tests of 'short-term' memory, like repeating 3 unconnected named objects and recalling them correctly after a brief interval. Younger children often responded better to questions about the names of the children in neighbouring beds, or what they had eaten for breakfast that morning.

An alternative method which taps both attention and short-term verbal memory, and which additionally proved a useful tool for engagement, was reading a passage from an *unfamiliar* children's storybook and assessing their recall of the passage immediately after reading it aloud to the child, and then again at the end of the interview. This test was, however, frequently confounded by the absence of a baseline premorbid assessment, verbal ability, language and potentially educational and cultural factors. Short-term visual memory of a complex picture from an *unfamiliar* picture book was often used as an alternative.

In relation to orientation, even non-delirious children seem prone to quite marked disorientation for time when hospitalised, and at least in children, this problem makes the implementation of Bhat and Rockwood's (2007) proposed operationalised criteria difficult and potentially invalid. Most mobile non-delirious children were, however to relate how they would navigate their way to the bathroom or nursing station, or find their way back to their bed from elsewhere in the ward. Likewise, most non-delirious

children were able to identify (even if not by name), children in neighbouring beds, nurses, primary caregivers and the interviewer (if serially assessed).

Frequently I was left with the question as to what in fact constituted a symptom or sign of a 'change in cognition' in the extraordinary circumstances in which delirious children are almost invariably interviewed. I found that having a primary caregiver alongside the bed during cognitive testing not only provided containment for the child, but also a crude yardstick against which apparent deficits could be measured. The caregiver (most often a parent) was usually able to give an idea as to how their child might *usually* be expected to perform on these simple tests of attention, memory and orientation, even taking into account the unfamiliar and anxiety-provoking setting of the hospital ward. The parent's account was also invaluable in the assessment of perceptual disturbances. Children often have difficulty verbalizing confusing and frightening experiences, and in these instances a parent's account of a child appearing to be "seeing things that aren't there" or appearing to respond to hallucinatory voices were extremely helpful. In addition, parents were often able to describe a subtle qualitative alteration in the manner of the child's relating to them, frequently ascribed to a change in 'personality'.

3.5.5.3 DSM IV-TR Criterion C

The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.

For the most part, clinicians assessing children and adolescents for delirium are spared the difficulty frequently encountered in geriatric psychiatry, in which a 'change in cognition' needs to be evaluated against a backdrop of the gradual cognitive deterioration of a dementia. This is not always the case, however, and in two of our cases we were required to assess the possibility of a delirium superimposed on a possible gradually progressive HIV 'encephalopathy'. In both cases the finding of markedly fluctuating performances on bedside cognitive testing from day to day (in addition to other features) strongly suggested a delirium.

A particular difficulty was encountered in the case of children or adolescents with a hypoactive delirium, frequently referred with a query as to the possibility of depression. In these cases it often seemed likely, on reviewing the medical and nursing notes, that the delirium had been present but unnoticed for days and even weeks. In these behaviourally less dramatic cases the assessment of the time of onset and rapidity of symptom evolution was often unclear. As with many of the features, the presence of marked fluctuation in presentation within each day, often with worsening at night, was highly suggestive.

3.5.5.4 DSM IV-TR Criterion D

There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition/substance intoxication/medication use or withdrawal syndrome

On first glance this criterion might seem to be the least ambiguous of the four DSM IV-TR criteria, but in my experience this last criterion can be one of the most problematic. Frequently I was confronted by a cluster of symptoms and signs occurring in the context of physical illness and medication use but with no means of establishing cause and effect.

A question that often arose was to what *extent* an abnormal physiological parameter needed to be deranged to adequately account for the delirium. At what level of hyponatremia could it be said with any certainty that an apparent delirium was likely to be etiologically related to low plasma sodium? Once again, temporal aspects of the presentation frequently came to the rescue, in that I was able to retrospectively link onset of delirium with the onset or exacerbation of a physiological derangement, introduction of a new medication or increase in dose of an already prescribed medication. Parallel exacerbations or relative remission of symptoms of delirium coincident with documented worsening or improvement of physiological parameters was equally suggestive.

Notably, the DSM IV-TR *still* allows a diagnosis of delirium in cases where ‘a clinical presentation of delirium that is suspected to be due to a general medical condition or substance use but for which there is insufficient evidence to establish a specific etiology’.

In essence, my own diagnostic strategy involved:

1. Eliciting and interpreting symptoms and signs of the delirium syndrome within a developmental framework using developmentally appropriate bedside tests
2. A strong emphasis on establishing a detailed picture of the temporal aspects of the presentation (rapidity of onset, fluctuation, worsening at night) and the temporal relationship between symptoms and physiological parameters and changes to the prescription chart
3. Always having a familiar caregiver at the bedside for all assessments wherever possible
4. Obtaining frequent *serial* mental state examinations and bedside cognitive assessments in order to provide a longitudinal picture of the child or adolescent’s presentation.
5. Using information from as many sources as possible

3.5.6 Morbidity and mortality

Of the 23 patients diagnosed with delirium 6 died (26%).

The extent to which delirium *per se* may or may not have played a role in this extremely high mortality rate is not a question that the present study can address. Referral to psychiatric services for assessment of delirium may merely act as a proxy indicator of

physical illness severity. This case series is not likely to represent the 'general population' of children with delirium in the hospital setting. As cases referred to a Paediatric Consultation-liaison Psychiatry service they likely represent a subgroup with more severe and/or chronic delirium, where frequently the severity or complexity of the underlying physical illness did not lend itself to rapid reversal with consequent resolution of the delirium.

The morbidity directly related to delirium itself was difficult to quantify in these patients, and the pattern of morbidity tended to vary according to delirium subtype. Delirium contributed significantly to the levels of distress and low quality of life experienced by these patients, particularly those who experienced hallucinations, paranoid delusions, fearfulness and marked mood lability. Parents frequently experienced severe distress on finding their child behaving markedly out of character, fearful, responding to hallucinations, difficult to engage and seemingly inconsolable.

Delirium also significantly contributed to levels of staff distress, particularly in those instances where there was aggression, uncooperativeness, inconsolable distress or marked regression. In the worst of these instances nursing staff were subjected to a continual barrage of verbal abuse and had faeces and bedpans thrown at them. Presentations such as these also caused a great deal of distress amongst other patients and their families sharing a ward with the delirious individual.

Patients frequently removed intravenous lines, wound dressings and nasogastric tubes, and picked and tore at skin grafts and surgical wounds. Some of these patients had required physical restraint prior to psychiatric assessment in order to minimise the possibility of injury to themselves or others.

Hypoactive delirium contributed to morbidity in a quite different fashion. Patients presenting with an altered level of consciousness associated with apathy, withdrawal, psychomotor retardation and emotional blunting are less able to engage and cooperate with treatment and rehabilitation efforts. Particularly if the delirium is chronic, these patients can be unrewarding patients to nurse, and this may contribute to relative neglect

and even social isolation in an inpatient setting. These hypoactive patients were often seriously compromised in their ability to engage with a variety of rehabilitative interventions such as physiotherapy and occupational therapy, and in many instances this was felt likely to have contributed to prolonged hospital stays. Their ability to engage in treatment-related decisions and planning was severely compromised, as was their ability to self-care.

In a number of instances morbidity was associated with misdiagnosis and misguided intervention. A number of these children were prescribed increasing doses of inappropriate psychotropic medications (morphine, benzodiazepines) in cases where behavioural disturbance associated with delirium was misinterpreted as an expression of pain, anxiety, or even willful defiance. In many of these cases escalating polypharmacy was felt to have contributed to worsening severity of delirium.

3.5.7 Rating Scales

De Carvalho and Fonseca (2008) recently bemoaned the absence of a reliable and validated assessment tool for delirium in children and adolescents.

In this series, rating scales were not employed to facilitate the diagnostic assessment, but were retrospectively applied to the detailed clinical notes. To our knowledge, at the time of writing, the use of delirium rating scales in the child and adolescent population has only been reported by Leentjens *et al.*(2008), Turkel *et al.*(2003), and Sikich and Lerman (2004). These studies were discussed in some detail in the literature review section. Turkel *et al.* (2003) previously reported on the retrospective use of the Delirium Rating Scale (DRS) in a group of 84 patients (aged 6 months to 19 years; average 10.4 years) diagnosed with delirium according to DSM-III-R criteria, and documented a mean score of 25 out of a maximum of 32 (range 14 to 32). Sikich and Lerman (2004) have previously reported on the use of the PAED, a scale devised by the authors for use in delirium occurring in children in the immediate post-anaesthetic setting, and documented its sensitivity and specificity for detecting delirium with a cut-off score of 10. Its use outside of the post-anaesthetic setting has not been reported.

Three rating instruments were retrospectively applied in this series in order to gauge their validity, applicability and clinical utility in the paediatric population – the Delirium Rating Scale (Trzepacz *et al.*, 1988), the Paediatric Anaesthesia Emergence Delirium scale (PAED) (Sikich and Lerman, 2004), and the Delirium Rating Scale– Revised-98 (DRS-R-98) (Trzepacz *et al.*, 2001).

To the best of my knowledge, at the time of writing, the use of the DRS-R-98 has not been reported in children and adolescents.

The 3 rating scales described above were then prospectively applied to a control group of 25 consecutive children and adolescents attending outpatient appointments at the Division of Child and Adolescent Psychiatry. The control group was comprised of children and adolescents with a variety of psychiatric disorders, many of whom also suffered from comorbid physical disorders. The mean age of our control group was 10.5 years (mean age delirium group = 9.75 years).

3.5.7.1 The Delirium Rating Scale

Sufficient clinical data was available to complete full DRS ratings on 20 of the 23 patients. The remaining 3 patients had missing data that did not allow for rating on one of the DRS items each.

Missing scale item data was handled using two different strategies (Appendix E). In the first strategy, these three patients were scored with the missing item *omitted* from the total scale score, and then given a score as a proportion of a slightly lower total. In the second strategy, these three patients were scored with the missing scale items scored as *midway*, and then given a score out of the maximum possible scale score of 32. For example, in a scale item with a possible score ranging from 0 to 3, a patient with data missing in relation to this item was scored as 1.5, using the second strategy.

For each patient a percentage score was calculated which resulted in a mean DRS percentage score of 69.4% (missing items omitted) or 69.2% (missing items scored midway). This translates into a mean DRS score of 22.2 (missing items omitted) or 22.1 (missing items scored midway), which correlates well with Turkel and colleagues (2006) findings in delirious children and adolescents (mean DRS = 25). The DRS scores for our sample ranged from 14 to a maximum of 28 out of 32. Of note, the two lowest DRS scores (14 and 17) were obtained in patients with hypoactive delirium. Although these are above the clinical cut-off score of 13 (Turkel *et al.*, 2003), our findings suggest that the DRS may prove less sensitive in identifying children and adolescents with hypoactive delirium.

In our control group (Appendix F) of 25 consecutive child and adolescent psychiatric outpatient attenders with a range of diagnoses including psychotic disorders, autism, disruptive behaviour disorders and mood disorders, the mean DRS score was 5.04 (range 1 – 10).

In summary, when applied to children and adolescents the DRS appears to have a degree of face, predictive, and discriminant validity. Its clinical utility as a screening instrument may be limited by its lower sensitivity for hypoactive delirium in children and adolescents. Its clinical utility in relation to monitoring changes in delirium severity over time, and in response to treatment may be limited in comparison to the DRS-R-98, which includes a severity scale. Further research is necessary to determine the sensitivity, specificity, predictive values and reliability of the DRS in children and adolescents of different ages.

3.5.7.2 The Delirium Rating Scale-Revised- 98

De Rooij and colleagues (2006) reported a mean *severity* DRS-R-98 score of 22 in 23 delirious hospitalised *elderly* patients in a study aimed at determining the validity and reliability of the Dutch version of the DRS-98-R. Trzepacz and colleagues (2001) reported mean DRS-R-98 *total* scores of 26.9 (range 11-39) and DRS-R-98 *severity* scores of 21.3 (range 6-33) in a sample of 24 delirious *adult* patients. The mean DRS

score in this sample was 18.4. Analysis of the receiver operator curve revealed that for the DRS-R-98 total score a cut-off of 15.25 resulted in a sensitivity of 92% and specificity of 86% when comparing delirious patients with patients with a variety of other psychiatric diagnoses including dementia, schizophrenia and depression. A higher cut-off of 17.75 resulted in a sensitivity of 92% and specificity of 95%. Lastly, De Negreiros and colleagues (2008) assessed the validity and reliability of the Portuguese version of the DRS-R-98 in a sample of 64 *elderly* patients and reported a mean DRS-R-98 total score of 27.3 and a mean severity score of 21.7 in those patients with a delirium. Analysis of the receiver operator curve revealed a sensitivity and specificity of 92.6% and 94.6% respectively at a DRS-R-98 total cut-off value of 20 when comparing patients with delirium with patients with a variety of other psychiatric diagnoses.

The scoring of the DRS-R-98 in my own study suffered from missing item data to a greater extent than the DRS. In part this was due to the DRS-R-98 simply requiring a greater number of items to be scored. Items relating to specific cognitive parameters (visuospatial skills, long term memory, orientation etc.) were frequently unable to be scored in children, particularly in the context of lack of cooperation or motivation. Missing data for the DRS-98-R was handled in a similar way to that from the DRS using the two strategies described above (Appendix E).

The mean DRS-R-98 Total score was 27.4 (59.6%) when missing scale items were simply omitted, and 26 (56.5%), when missing scale items were scored midway. The mean DRS-R-98 Severity score was 21 (54%), when missing items were omitted, and 20 (52%) when scored midway. The range for total scores when missing items were rated midway (as is suggested by Trzepacz *et al.*, 2001) was 18-34.

In our control group (Appendix G) of 25 child and adolescent psychiatry outpatient attenders the mean DRS-R-98 Severity Score was 5.56 (range 1- 13), and the mean DRS-R-98 Total score was 7 (range 1 – 15).

Table 3.8 compares DRS-R-98 scores amongst the studies described above and this present case series of children and adolescents with delirium.

Table 3.6 Comparing DRS-R-98 scores in geriatric, adult, and child and adolescent patients with delirium

	This case series 2008	Trzepacz <i>et al.</i>, 2001	De Rooij <i>et al.</i>, 2006	De Negreiros <i>et al.</i>, 2008
Population	Children and adolescents	Adults (mean age 64 years)	Elderly adults (mean age 80.5 years)	Elderly adults (mean age 77.3 years)
DRS-R-98 Total (mean)	26 (18-34)	26.9 (11-39)		27.3 (14-37)
DRS-R-98 Severity (mean)	20 (12-28)	21.3 (6-33)	22 (7-39)	21.7 (10-30)

In summary, despite lacking developmentally sensitive scale items, the DRS-R-98 appears to have a degree of face, predictive, and discriminant validity when applied to children and adolescents. As is the case with the DRS, however, its sensitivity, specificity, predictive values and reliability in this age group is unknown. It has the advantage of a severity scale for measuring changes in delirium severity over time, and in response to treatment, and would thus seem a better instrument for use in treatment effectiveness studies.

3.5.7.3 The Paediatric Anaesthesia Emergence Delirium scale

The PAED was developed for use in a very specific setting – in paediatric patients emerging from anaesthesia (Sikich and Lerman, 2004). It is a simple and brief scale likely biased to detecting hyperactive rather than hypoactive delirium. It is, however, at the time of writing, the only delirium rating scale *specifically* designed for use in children, and as such it includes two very useful items describing features of delirium in young children, namely:

1. The child makes eye contact with the carer, and
5. The child is inconsolable.

Both these items are rated on a scale of 0 to 4.

In our experience, particularly in the context of a young child presenting with agitation and severe distress, the absence of eye contact with the primary caregiver at the bedside and the inability of a *primary caregiver* to console the child are extremely valuable supportive features of a diagnosis of delirium.

Difficulties encountered when applying the scale, particularly retrospectively, were the relative ambiguity of items 2 and 3:

2. The child's actions are purposeful
3. The child is aware of his/her surroundings.

The mean PAED score (with missing items scored midway) for this sample (Appendix E) was 12.3 (range 6 - 16). The mean PAED score in our control group (Appendix H) of child and adolescent psychiatry outpatient attenders was 4.8 (range 1 - 9).

Sikich and Lerman (2004), reported that an ROC curve analysis of the PAED scale revealed that at a PAED scale score of 10 or greater, the PAED had a true-positive rate (sensitivity) of 0.64, and a false-positive rate (1-specificity) of 0.14 for emergence delirium in a paediatric sample.

In summary, the PAED scale appears to have a degree of face, predictive, and discriminant validity when applied to children and adolescents in a context other than emergence from anaesthesia. It is the only available scale to utilise developmentally sensitive items in the assessment of delirium. It is quick and easy to use. However, some of its items (listed above) may be prone to ambiguity outside of the immediate post-anaesthetic setting. The sensitivity, specificity, predictive values and reliability of the PAED outside of the post-anaesthetic setting remains unknown.

3.5.8 Electroencephalogram findings

The EEG was abnormal in 5 of the 7 cases in which an EEG was obtained. Marked and diffuse slowing was found in all of the abnormal EEGs. The EEG was disproportionately requested in cases of hypoactive delirium and where there was significant initial uncertainty as to the correct diagnosis.

Of note, in the two instances where the EEG was found to be normal, the rationale for requesting the investigation was not in fact to clarify the diagnosis, but to aid in excluding seizure activity. In both these cases the diagnosis of delirium was not in any doubt, as both presented with the abrupt onset of markedly fluctuating behavioural disturbance and florid psychotic features, accompanied by clear evidence of an altered level of consciousness.

3.5.9 Management

3.5.9.1 Environmental management

Regardless of whether antipsychotic medication was used or not, all 23 cases received active environmental management.

A relatively high proportion of the patients in this case series were successfully managed using environmental strategies in combination with efforts to reverse or ameliorate the precipitant. Five of the 23 (22%) patients were managed conservatively without antipsychotic medication. In three of these five cases the delirium was associated with a clearly identified precipitant. In all three cases the precipitant was assessed as being either very likely to spontaneously resolve (in the case of the two which were medication-related), or, being readily easily addressed with an expectation of rapid resolution. Three of these cases resolved in less than 12 hours.

The overarching goal of environmental management was to provide a consistent, containing, and predictable therapeutic space for delirious patients that specifically addressed the challenges associated with the cognitive deficits of inattention, disorientation and amnesia. Many aspects of the environmental management (reorientation, reality testing, reassurance and explanation, and anxiety reduction) could also be seen as providing an 'auxiliary ego' to patients experiencing severe psychic fragmentation.

3.5.9.1.1 Physical environment

Two of the primary goals for the management of the physical environment were optimisation of the level of sensory stimulation and the provision of consistent reorienting cues.

In cases of hyperactive delirium the patient, wherever possible, was moved from the communal ward to a quiet single room, ideally positioned close to the nursing station. Particular difficulties were encountered in attempting to reduce sensory overstimulation in patients with hyperactive and mixed delirium encountered in the paediatric intensive care unit (PICU) setting where no single rooms were available. Delirious patients in the PICU were often subjected to an excessive degree of bewildering noise, light, and activity that limited their sense of containment and exacerbated existing difficulties in their maintaining a normal sleep-wake cycle. In these instances we were limited to positioning hyperactive delirious patients in a relatively partitioned part of the PICU, and focusing instead on staff consistency, staff activity scheduling, and family interventions.

In cases of hypoactive delirium the patients were actually moved from the quieter parts of the ward or single rooms to the main body of the ward and close to the nursing station in order to *increase* the level of social interaction. Sometimes a television or radio was placed in close proximity to the patient in order to increase the level of sensory stimulation.

Attention was also paid to lighting. One of the particularly agitated and distressed patients benefited greatly from the simple measure of keeping the blinds on a large window adjacent to her bed drawn during the period of the day when bright sunshine would usually have streamed into her single room. In all cases a dim nightlight was suggested to reduce the likelihood of misperceptions and fearfulness at night, when many patients with delirium experience an exacerbation of their symptoms.

Families were actively encouraged to bring favourite toys and transitional objects to the bedside. In some cases families were also encouraged to bring photographs of family members, pets or even soothing familiar music from the home, particularly for those times when carers could not themselves be present at the bedside.

3.5.9.1.2 Staff

Staff psychoeducation relating to the nature and management of delirium proved vital in all cases, and was particularly helpful for nursing staff. Nursing staff often found the rapid and dramatic fluctuations in mental state difficult to understand, and not infrequently interpreted uncooperative or aggressive behaviour as being conscious and voluntary. Reinterpreting erratic behavioural disturbance as an expression of a characteristically fluctuating mental disorder helped nursing staff to resist acting out in a punitive, retaliatory way with difficult patients.

A strong emphasis was placed on achieving and maintaining consistency of staffing with individual patients to the greatest extent possible given the constraints of rapidly changing nursing rosters. Staff were urged to provide constant reorientation and reassurance to patients with each patient contact, repeatedly making sure that the patient knew who they were, what their role was, what they would be doing and why, what time of day it was, what meal was to be expected next, where they were and why they were in hospital. Staff members were also encouraged to engage in constant reality testing and reality reorientation with patients, particularly those experiencing illusions, paranoid ideation, delusions and hallucinations.

Another vital aspect of the environmental management in patients who were severely physically ill and requiring numerous interventions from a variety of treating teams was staff activity scheduling. This was particularly important for the delirious burn patients, who were often exposed to a confusing and seemingly never ending stream of frequently changing professionals on a daily basis. Thus, these patients received frequent interventions from nursing staff, medical staff, physiotherapy, occupational therapy, and pain management staff with little hope of knowing who was likely to be coming when, and when they might expect to be left alone. A simple but valuable intervention in these instances was to liaise with all the treating teams and devise a predictable schedule of expected activities that was then displayed on a large chart next to the bedside as a plan of the week's daily activities. Once again, treating teams were strongly urged to minimise inconsistency amongst the professionals attending an individual patient.

3.5.9.1.3 Carers

A cornerstone of the environmental management of young delirious patients proved to be working with their primary caregivers, who form an integral part of the management team. A great deal of time was spent in providing psychoeducation about delirium.

Many parents were bewildered and frightened by the dramatic and frequent changes in mental state of their children. Many parents would become demoralised after a period of apparent return to normality proved to be only a relative period of lucidity in a naturally fluctuating disorder. Many also found the experience of not being able to console their child extremely distressing.

Many parents questioned whether the changes in their child's 'personality' would be permanent if they did in fact recover from their physical illness. Containing the anxiety of the primary caregiver at the bedside proved an essential element of management, and there were a number of instances when explanation and (where appropriate) reassurance offered to the bedside caregiver resulted in a marked improvement in the delirious child's level of distress.

Primary caregivers were strongly encouraged to remain at the bedside in order to provide constant familiarity, reassurance and reorientation. Where two caregivers were available, they were encouraged to take their bedside duties in shifts in order to allow for adequate rest. Similar to what was asked of the nursing staff, primary caregivers were urged to provide repeated reorientation to time, place, person and the reason for being in hospital to their children.

3.5.9.2 Pharmacological management

Pharmacological management with an antipsychotic medication was instituted in the following instances following a careful and individualised risk-benefit analysis.

1. Presence of significant psychotic symptoms.
2. Behavioural disturbance (agitation, aggression, uncooperativeness) associated with significant risk of harm to self or others.
3. Significant interference with necessary medical investigations, treatment or rehabilitation.
4. Severe distress.
5. Difficulty or non-response to reversing or ameliorating presumed precipitating or perpetuating factor(s) AND poor or only partial response to environmental management PLUS 1,2,3 or 4.

Eighteen of the 23 patients (78%) received an antipsychotic medication. Twelve of these 18 patients (67%) received haloperidol, six received risperidone (26%), one patient received sulpiride and another droperidol. Two patients initially received haloperidol, but needed to be switched to risperidone after experiencing extrapyramidal side effects with haloperidol.

Haloperidol was the initial agent of choice in the following instances:

1. No enteral route available for administering oral medication.
2. *Severe* agitation or combative behaviour.

3. Severe physical illness.
4. Significant hepatic or cardiac impairment.

Two patients (both male) experienced intolerable extrapyramidal side effects with haloperidol that necessitated a switch to risperidone. One patient (18kg) experienced severe akathisia with 1mg intravenous haloperidol given in two divided doses, and another (24kg) experienced an acute dystonic reaction with 1.5mg intravenous haloperidol given in two divided doses. No patients receiving risperidone experienced clinically significant extrapyramidal side effects.

Six of the 12 patients who were prescribed haloperidol received it via the intravenous route. The patient who received droperidol was also given this via the intravenous route.

Clinical Global Impression – Improvement scores were used to reflect the degree of sustained improvement or deterioration in mental state within 48 hours of commencing an antipsychotic medication.

In hyperactive/mixed delirious patients, improvement was regarded as a reduction in agitation and/or aggression, psychosis, or distress. In hypoactive delirious patients it was assumed that an improvement would be reflected in reduced psychomotor retardation and improved clarity of awareness.

Of the 18 patients treated with antipsychotic medications, 12 (66.7%) were rated as very much or much improved, whilst 6 patients had little or no improvement. Five patients were rated as minimally improved (27.7%) and with one patient antipsychotic medication produced no change. Of the 12 patients treated with haloperidol, 9 were rated as very much or much improved (75%). Of the 4 patients initially treated with risperidone, 2 (50%) were rated as very much or much improved, with 2 of the 4 having little or no improvement.

Effectiveness of antipsychotic medication also appeared to vary according to both delirium subtype and delirium severity. For example, seventy-eight percent of the

patients with a hyperactive delirium and 71% of those with a mixed delirium who were treated with antipsychotic medication were rated as very much or much improved. In contrast, two of the 3 patients diagnosed with a pure hypoactive delirium were treated with an antipsychotic (one with risperidone and one with sulpiride), and neither experienced more than minimal improvement.

It is notable that only 4 (22%) of the 18 patients treated with antipsychotics were rated as being 'very much improved'. It is also notable that 3 (75%) of these 4 'very much improved' patients were treated with *intravenous* butyrophenones (2 with haloperidol; 1 with droperidol).

Sixty-nine percent (9 of 13) of the patients with a DRS-R-98 score greater than 20 responded as very much (3/13) or much (6/13) improved, while 60% (3 of 5) of those with a DRS-R-98 score of less than 20 were rated as 'much improved', with *none* of these patients being 'very much improved'.

Six (33%) of the 18 patients treated with antipsychotics also received a benzodiazepine. Lorazepam was used in patients with hyperactive delirium with severe agitation, aggression, or insomnia that was unresponsive or relatively unresponsive to antipsychotic medication. None of the patients who received adjunctive lorazepam experienced a paradoxical reaction or deterioration of their delirium. My impression was that in a number of patients low-dose adjunctive lorazepam was effective in restoring a normal sleep-wake cycle and may have had a dose-sparing effect on the use of antipsychotic medication.

Table 3.7 A consultation-liaison psychiatry case series of children and adolescents diagnosed with delirium: Antipsychotic efficacy

Clinical Global Impression – Improvement	Haloperidol		Risperidone*	Other**	Delirium subtype			Delirium Severity	
	0.05 – 0.4mg/kg/24 hours		0.25 – 2mg per 24 hours %		Hyper %	Hypo %	Mixed %	DRS-R-98 >20 %	DRS-R-98 <20 %
	Intravenous %	Enteral %							
Very much or much improved	4/6 67.0	5/6 82.0	2/4 50	1/2 50	7/9 78.0	0/2 0.0	5/7 71.0	9/13 69.0	3/5 60.0
Minimally improved or no change	2/6 33.0	1/6 18.0	2/4 50	1/2 50	2/9 22.0	2/2 100.0	2/7 29.0	4/13 31.0	2/5 40.0

* Risperidone – Although a total of 6 patients received risperidone, 2 of these patients were switched to risperidone after experiencing extrapyramidal side-effects from haloperidol. Both patients were already much improved on haloperidol, and their improvement was sustained on switching to risperidone

** Other – 1 patient received a single dose of intravenous droperidol and was assessed as rapidly being 'very much improved'; 1 patient received oral sulpiride and experienced only minimal improvement

Table 3.8 A consultation-liaison psychiatry case series of children and adolescents diagnosed with delirium: Environmental management

Target of environmental management	Strategy	Objective(s)	Hypothesized predisposing or precipitating factor targeted
Physical environment	Optimise lighting (increase or decrease as appropriate)	Optimise level of sensory stimulation	Sensory extremes, insomnia, disrupted sleep-wake cycle
	Optimise noise level (increase or decrease as appropriate)		
	Dim nightlight	Reduce risk of visual misperceptions; anxiety containment	Sensory extremes; high levels of patient anxiety
	Provide familiar toys and transitional objects	Anxiety containment	High levels of patient anxiety
	Provide photographs of family, home and pets		Social isolation: unfamiliarity
	Provide familiar music		Immobility, social isolation
	Avoid physical restraints		

Table 3.8 (continued) A consultation liaison psychiatry case series of children and adolescents diagnosed with delirium: Environmental management

Target of environmental management	Strategy	Objective(s)	Hypothesized predisposing or precipitating factor targeted
Social environment	Psychoeducation about delirium	Enhance auxiliary ego functions	High level of patient anxiety
Staff	Staff consistency	Anxiety containment and orientation to person	Social isolation
	Staff activity scheduling	Facilitate temporal orientation through predictable routine	Persistent disorientation; unfamiliarity; disruption of routine
	Staff provide constant reorientation to time, place and person		
	Staff provide constant reality testing and orientation		
Social environment	Carers present at bedside	Anxiety containment	Carer absence
Carers	Explanation and appropriate reassurance for carers	Enhance auxiliary ego functions (anxiety regulation, reality testing, orientation)	High levels of carer anxiety Social isolation
	Anxiety management for carers		Persistent disorientation; unfamiliarity; disruption of routine
	Carers provide constant reorientation to time, place and person		
	Carers provide constant reality testing and orientation		

3.5.10 Case examples: HIV-related delirium in children

As case examples I have chosen to present in more detail the 3 cases of delirium associated with HIV infection, as they illustrate not only the unique challenges involved in the assessment, diagnosis, and management of delirium in this age group, but also the not insignificant challenges of providing a paediatric consultation-liaison psychiatry service in a Sub-Saharan African setting. I will focus on the pharmacological rather than environmental/psychosocial aspects of management of these cases, as the latter were essentially the same for all the cases and have already been described in some detail. I will, however, highlight when certain components of environmental/psychosocial management were compromised owing to the particulars of each case.

Patient 14

This 9-year-old Xhosa-speaking girl was admitted to hospital on the 26 October 2006 in a desperate physical condition. She had been sexually abused by a distant relative in 2004 and had been abandoned by her biological mother in June 2006. She had been left with an 18-year-old aunt in an informal settlement on the outskirts of Cape Town, while her mother returned to the Eastern Cape to remarry. In September 2006 she presented to hospital with a 1-year history of chronic severe diarrhea associated with faecal and urinary incontinence. She was in a shockingly neglected state. She was dehydrated, emaciated, and her skin was covered in bullous impetigo skin lesions. She weighed only 16 kilograms. She had oral candidiasis and a vaginal discharge from which *Neisseria Gonorrhoea* was later cultured. She was noted to be 'very quiet' on admission.

Most of her blood laboratory parameters were grossly abnormal. She was severely anemic (Hb 6.7g/dl) and thrombocytopenic (platelets 39 thous/mcl). She was also severely hyponatremic (serum sodium 121 mmol/L), hypomagnesemic (serum magnesium 0.46 mmol/L), hypophosphatemic (serum phosphate 0.37 mmol/L),

hypokalemic (serum potassium 3 mmol/L), and hypochloremic (serum chloride 91 mmol/L). Remarkably, she had a serum albumin of only 7 g/dl. She was tested for HIV and found to be positive. Her absolute CD4 ('helper' T-cell lymphocyte) count on admission was 9 cells/ μ L (0.08%). A strain of *Shigella* was cultured from both her stool and blood. A lumbar puncture proved to be normal.

She was commenced on broad-spectrum antibiotics (ceftriaxone and cloxacillin) for her bacterial infection and an antifungal agent (fluconazole).

Her clinical notes during the early phase of her admission described her as apathetic and withdrawn, and it was even suggested that she might be clinically depressed. Though for the most part she was noted to be alert, occasional mention was made in the nursing documentation of her being incoherent or 'confused'. A possible hypoactive delirium was not considered at this stage, although clearly this would have been one of the first diagnoses to exclude.

On Day 7 of ceftriaxone and Day 8 of cloxacillin treatment (Day 8 of her admission) she was clearly noted to be 'confused', especially at night. Her speech was 'inappropriate' and she was inexplicably spitting out food, despite appearing hungry. Her mood state fluctuated dramatically and she shouted out and wailed. Her muscle tone was noted to be increased and her peripheral reflexes abnormally brisk. A CT scan of her brain at this point revealed only marked and diffuse atrophy of the cerebral cortex and cerebellum. She remained desperately ill and pyrexial at this stage, and indeed, her hemoglobin reached its lowest point (Hb 5.4 g/dl) on this day. She was also noted to have herpes stomatitis and so acyclovir was added to her medication regimen. Her antibiotics were changed to meropenem and ciprofloxacin as she continued to spike temperatures. Her severe diarrhea continued and she remained between 16 and 17 kg in weight 11 days into her admission. On Day 18 of her admission she was noted to be 'miserable, anxious, lethargic and complaining of being eaten by insects'. She was refusing food and pulling

out her intravenous cannulas. It was only on Day 35 of her admission (Day 28 since the first documented mention of 'confusion') that she was referred to the Paediatric Consultation-liaison Psychiatry Unit. Simultaneously she was commenced on antiretroviral treatment (stavudine, lamivudine and efavirenz).

At about this time her mental state worsened. She became extremely agitated and grossly disinhibited. She was markedly distressed and appeared terrified. She screamed and shouted loudly that she was seeing snakes and feeling them moving over her body. These features were notably worse at night, and fluctuated dramatically from hour to hour. At times she was paranoid and would refuse both food and medication only to present as 'alert, playful and cooperative' and 'demanding Kentucky Fried Chicken' the next morning. Her affect oscillated between euphoria accompanied by singing, tearfulness, and fear. The nursing staff reported that she slept very poorly and that she seemed to experience nightmares. In interview she proved difficult to engage being so distractable. She was orientated to place and person, but it was noted that she had discrete periods when she "drifts into a world of her own". Her speech and behaviour were noted to be perseverative and she appeared to be responding to both auditory and visual hallucinations.

A clinical diagnosis of a hyperactive delirium was made, the precise etiology of which was uncertain, but being almost certainly complex and multifactorial. She remained anemic, hyponatremic (Na 126 mmol/L) with an albumin of only 7 g/dl at the time of the onset of the delirium, and she continued to spike temperatures. Low serum albumin is a significant risk for delirium in any age group (Trzepacz *et al.*, 2004), one of the reasons being that hypoalbuminemia results in a greater bioavailability of many drugs that are transported in the bloodstream by albumin.

She scored 23 on the DRS, 24/36 on the DRS-R-98 Total and 18/30 on the DRS-R-98 Severity scale. An electroencephalogram at this point was reported as being within normal limits. No prior EEG was available for comparison.

Owing to her extremely poor physical condition, the severity of her agitation and the fact that she was able to accept oral medication, a decision was made to treat her with very low dose oral haloperidol (0.25mg twice-daily by mouth) on Day 37 of her admission, following the psychiatry consultation. This was augmented with lorazepam at night in order to help reestablish a normal sleep-wake cycle. At the same time as the haloperidol was commenced, it was decided to switch the efavirenz to nevirapine, based on the concern that the efavirenz might be exacerbating a pre-existing delirium (see discussion to follow).

Over the first 48 hours her mental state showed a sustained improvement in that she seemed less distressed and agitated, but continued to fluctuate with exacerbations occurring particularly at night. The psychosocial management of her delirium was greatly compromised by the absence of a primary caregiver at the bedside. On Day 42 of her admission she was noted to be 'happy and calm'. Symptoms of delirium did not return after this. By Day 49 her weight was starting to pick up and she was active and playing appropriately with other children on the ward.

She was discharged from hospital on Day 54 and the haloperidol was then discontinued. She was discharged to St Joseph's Home, a children's home specializing in looking after children with chronic illness' who cannot be cared for by their families. She was followed up in the Neuropsychiatry outpatient clinic with no evidence of residual cognitive impairment. At her latest review appointment she presented as a charming, cheerful and intelligent girl who was clearly forming close bonds with friends and carers at the home.

Patient 15

This 9-year 1-month-old girl, who had defaulted on her treatment for pulmonary tuberculosis, was admitted to a general paediatric ward in acute renal failure secondary to severe vomiting and diarrhea on the 2nd May 2007. She was in a severely emaciated state and weighed only 26kg. Her mother had died 18 months previously of an HIV-related illness and she had never known her father. She had been cared for by a foster aunt after watching her mother die in front of her at the community clinic. Her highest level of education was Grade 3, but she had not attended a school in at least a year. HIV testing revealed that she was positive, and that her CD4 count was only 77 cells/ μ L (1.4%). She was commenced on a highly active antiretroviral treatment (HAART) regimen on the 25 May that included stavudine, lamivudine, ritonavir and lopinovir. She was noted to have an abnormally wide-based gait, dyskinetic tongue movements, poor balance and abnormal muscle tone. Her CT brain revealed diffuse and marked cerebral and cerebellar atrophy, as with the previously described case.

As with Patient 14, initial concerns relating to her mental state centered about a possible major depressive episode. Her presentation at the beginning of June was characterised by lethargy, social withdrawal, tearfulness, apathy and anhedonia. She was hopeless and expressing ideas of guilt, punishment and passive suicidality. She had stopped eating and her physical state was not improving. On mental state examination she was difficult to engage, markedly psychomotor retarded and severely blunted in affect. She had poverty of speech with marked response latency. She had no obvious cognitive deficits on bedside testing. There were no additional features of post-traumatic stress disorder, although this was not entirely excluded as a possible differential diagnosis. During this period she continued to spike temperatures in excess of 39 degrees centigrade, and on Day 36 the team elected to commence antituberculous treatment, consisting of rifampicin, isoniazid, pyrazinamide and ethionamide.

A decision was taken to cautiously introduce fluoxetine at a dose of only 5mg daily on the 12th June, Day 40 of her admission. After only 3 doses of fluoxetine her mental state rapidly and dramatically deteriorated over a period of not more than 24 hours. She became extremely agitated and distressed. She seemed terrified and appeared to be experiencing frightening visual hallucinations of snakes and dead bodies in the ward. In fact, her mental state in terms of psychotic phenomena was quite strikingly similar to that of the previously described case. She was markedly disinhibited and her affect changed rapidly between tearfulness, euphoria, and fear. She was grossly thought-disordered and appeared to be experiencing persecutory delusions. She slept very poorly at night, and when she did sleep was noted to suffer nightmares. She appeared to have additional catatonic features including seemingly involuntary facial grimacing and odd sustained periods of posturing. She was orientated only to person and she was markedly inattentive and distractible. Her level of consciousness shifted rapidly between being narrowed and hypervigilant, and somnolent and poorly responsive. Her concentration was extremely impaired and she was markedly distractible. Her short-term memory was very impaired and she had marked visuospatial deficits when compared to her earlier bedside testing. Her speech was perseverative. Particularly striking features of her presentation were the rapidity of onset, extreme and rapid fluctuation in her symptoms from hour to hour, and dramatic exacerbations at night.

The diagnoses considered at this point were:

1. A hyperactive delirium (with catatonic features)
2. A major depressive episode with melancholic features that had 'switched' into a manic or mixed affective episode with psychotic and catatonic features secondary to the fluoxetine. Bell's (delirious) mania has also been described in adolescents (Table 2.5.4).
3. A psychotic disorder secondary to a general medical condition
4. Likely progressive 'HIV encephalopathy'/HIV-associated dementia as a background disturbance to one of the above

5. A neuropsychiatric Immune Reconstitution Inflammatory Syndrome (IRIS)

She scored 28 on the DRS, 30/46 on the Total DRS-R-98, and 23/39 on the DRS-R-98 Severity scales. An electroencephalogram obtained at this time was reported as normal, as was a repeat lumbar puncture.

Despite the normal electroencephalogram, the temporal course (abrupt onset, markedly fluctuating course and nocturnal worsening), prominent visual hallucinations, catatonic features and diffuse cognitive deficits in the context of severe physical illness and polypharmacy swung the paediatric consultation-liaison psychiatry team towards a consensus diagnosis of a delirium.

Possible precipitants for the delirium included drug-drug interactions, serotonin syndrome, neuroleptic malignant syndrome (which has on occasion been described with fluoxetine alone; Halman and Goldbloom, 1990), infection, a neuropsychiatric Immune Reconstitution Inflammatory Syndrome (IRIS), thiamine deficiency, or other metabolic derangements. Uremia is associated with increased blood-brain barrier permeability and thus poses a significant risk factor for delirium (Trzepacz *et al.*, 2004). Given that the delirium had occurred abruptly after only 3 doses of fluoxetine, a ritonavir-fluoxetine-isoniazid interaction precipitating a serotonin syndrome was suspected, and the fluoxetine was discontinued. Physical symptoms of the serotonin syndrome may well have been obscured by her longstanding diarrhea, infective fever and premorbid movement abnormalities. IRIS is a not uncommon paradoxical worsening of the patient's clinical condition seen in patients with AIDS in the weeks to months following the commencement of antiretroviral therapy. I will discuss the possible neuropsychiatric manifestations of this recently recognised syndrome in greater detail in the discussion section to follow.

The environmental/psychosocial management of her delirium was greatly compromised by the absence of a regular carer such as a parent at the bedside. However, she benefited greatly from being placed in a side-room adjacent to the nursing station, and being allocated a single student nurse to be consistently available to her throughout the day. At night a dim light was kept on to reduce the risk of frightening visual illusions.

Haloperidol was commenced at a dose of 0.25mg three times daily, augmented with lorazepam 0.5mg twice daily. At the same time, the isoniazid and fluoxetine were discontinued. Within 48 hours there was a sustained and marked improvement in her mental state. Her delirium resolved completely within 5 days and her psychotropic medication was then discontinued. On resolution of the delirium there was no evidence of residual depressive symptoms and she was appropriate, bright in mood and playing with other children on the ward. She was followed up as an outpatient with no return of depressive symptoms and remains well at the time of writing.

Given the abruptness of onset, temporal course, and rapidity of complete resolution, the team felt that the diagnosis of delirium had been correct, and in retrospect wondered whether the depression-like presentation preceding the delirium represented a delirium prodrome or even a hypoactive delirium overlaid with depressive features, rather than a true major depressive episode. The probable HIV-associated subcortical dementia pre-dating the delirium may also have complicated the assessment of depressive symptoms. Diminished cognitive reserve may also then have increased her baseline vulnerability to delirium, as is seen so often in elderly dementing patients.

Patient 23

This Xhosa-speaking 11-year and 4-month-old girl and her HIV+ve mother shared a shack with 6 other people in a nearby informal settlement. She had a Grade 3 education but had not attended school for many months.

In July 2006 she was diagnosed with pulmonary tuberculosis and commenced on antituberculous treatment (rifampicin, pyrazinamide, isoniazid, and ethionamide). In December of the same year she presented in a severely malnourished state with a hemiplegia secondary to cryptococcal meningitis. Her CT brain revealed diffuse cerebral atrophy and she had an absolute CD 4 count of 25 cells/ μ L (0.86%). She tested positive for HIV and was therefore commenced on HAART (efavirenz, stavudine and lamivudine) shortly after commencing amphotericin B.

In February 2007, after having been on HAART for approximately one month, she re-presented with raised intracranial pressure, seizures, and severe hyponatremia. It was felt likely that her dramatic deterioration represented an Immune Reconstitution Inflammatory Syndrome (IRIS), a seemingly paradoxical deterioration occurring shortly after the introduction of antiretrovirals. At this point she was also referred to the paediatric consultation-liaison psychiatry unit because of concern about a possible depression. She was socially withdrawn, apathetic, lethargic, and anhedonic with poor oral intake. A possible HIV-associated subcortical dementia was considered at this stage in view of her atrophy on neuroimaging, focal neurological signs and depression-like clinical picture. She performed well on bedside cognitive testing, however, but her mother remained adamant that relative to her usual performance she was significantly cognitively sluggish. It was decided to hold off on antidepressant medication, and fortunately her mental state improved significantly over the next two weeks as her physical condition improved. She was soon discharged on a combination of HAART and antituberculous medications.

In September 2007 she was readmitted to hospital after failing to attend outpatient appointments and documented non-adherence of her antiretroviral and antituberculous medications. Her mother had had insufficient money to afford the taxi fare to the hospital to attend follow-up appointments. Her absolute CD 4 count was 175 cells/ μ L, and this

time she presented with a hemiplegia on the opposite side. She was diagnosed with tuberculous meningitis on this occasion, associated with marked hydrocephalus. Her antiretroviral and antituberculous medications were recommenced. During her admission she developed a VIth cranial nerve palsy secondary to raised intracranial pressure, which was treated with acetazolamide, steroids, and regular therapeutic lumbar punctures.

In December, during this same admission, she abruptly became confused. She became extremely agitated and appeared very frightened. Her mood was markedly labile and she was disinhibited. She appeared to be experiencing paranoid persecutory delusions and both auditory and visual hallucinations. These symptoms were particularly prominent at night and fluctuated from hour to hour. She slept very little, if at all at night, but had periods when she was somnolent and difficult to engage during the day. She was markedly inattentive and distractible, to the extent that she could not be engaged in even simple bedside tests of memory and orientation. She also had evidence of motor perseveration. She prayed continually in a fearful way. Her prescription chart at this point included isoniazid, rifampicin, pyrazinamide, ethionamide, lamivudine, stavudine, efavirenz, fluconazole, acetazolamide, and prednisone 60mg daily.

She scored 27 on the DRS, 23 on the DRS-R-98 Total and 17 on the DRS-R-98 Severity scales. An electroencephalogram obtained at this point was normal.

Her precipitant of her delirium was felt likely to be complex and multifactorial (meningitis, raised intracranial pressure, high-dose steroids, polypharmacy) and all possible contributory culprits were addressed to the greatest extent possible. Her prednisone dose was reduced and it was recommended that her efavirenz be discontinued.

She was commenced on haloperidol 0.5mg in the morning and 1mg at night, augmented with lorazepam 0.5mg at night. The sustained improvement in her level of distress and

degree of agitation was rated as very much improved on the CGI-I within the first 48 hours. Her delirium settled completely over the course of a week.

Unfortunately, over the next 2 weeks her physical condition further deteriorated and she eventually lapsed into coma. She died in hospital.

3.5.11 Discussion: HIV-associated delirium in children and adolescents

To the best of our knowledge, at the time of writing, only one other case of delirium in an HIV-positive child or adolescent has been published in the literature. Scharko and colleagues (2006) described the difficulties in the assessment and management of a 15-year-old girl with apparent HIV-associated dementia who developed a superimposed hyperactive delirium in the context of an intercurrent febrile illness.

The authors described how this adolescent with a history of vertically acquired HIV infection and a background of extreme poverty was admitted to hospital with a CD4 count of only 1 cell/uL. On Day 10 of her admission a psychiatric consultation was requested because she was agitated, aggressive, biting and displaying sexual aggression. At times she also appeared confused, frightened, and paranoid alternating with periods of relative lucidity. On mental status examination she was hyperalert, disorientated, paranoid, thought-disordered, responding to hallucinations and distractible. On physical examination she had a coarse resting tremor of her upper limbs and she had a shuffling narrow-based gait.

In this case the authors were fortunate to have not only the results of neuropsychological testing and the Vineland Adaptive Behaviour assessment performed 4 months prior to their examination but additionally, the results of similar testing from 3 years earlier. Her psychiatric history was notable for an episode of major depression diagnosed at the age of

12 years. Additionally, the patient had been admitted to the inpatient child psychiatry unit for disruptive behaviour associated with depression only 4 months prior to her medical admission and had been commenced on Citalopram 10mg daily.

Magnetic resonance imaging of her brain revealed static diffuse cerebral atrophy which had not altered from numerous previous scans. The authors made a diagnosis of delirium superimposed on an HIV-associated dementia, based on the history, clinical presentation, and MRI findings, in association with a dramatic loss of adaptive *functioning* over a 3-year period (despite her Verbal, Performance, and Full Scale IQ remaining essentially static). An EEG showed bilateral continuous slow activity that further supported this diagnosis.

She was commenced on risperidone 0.5mg daily that was increased to a maximum of 1mg twice daily. Her citalopram was continued at a dose of 30mg daily. On day 14, the risperidone was discontinued on the basis of poor response, and she was then commenced on haloperidol 0.5 mg twice daily. She tolerated this well, and her mental state settled considerably over the next 3 days. Once her delirium was completely resolved, she was noted to still have occasional perseveration and echolalia in addition to speech response latency.

In their discussion, these authors emphasized the lack of data relating to the presentation of HIV progressive encephalopathy or HIV-associated dementia in adolescents, and the challenges inherent in establishing the diagnosis beyond question. Similarly, they highlighted the lack of guidance in the available literature relating to the treatment of delirium in this age group.

In a letter of response to the editor Kapetanovic and colleagues (2006) addressed in greater detail possible exacerbating factors of this patient's delirium, focusing on drug-drug interactions. The authors postulated a possible neuroleptic malignant syndrome

precipitated by two potential 2D6 inhibitors (ritonavir and citalopram) elevating the plasma risperidone to toxic levels...They also stressed the importance of noting the patient's ethnic background in view of the impact 2D6 polymorphisms may have on drug metabolism.

Certain continuities between these 4 cases discussed above are worth highlighting. In all these cases the patients were admitted in poor physical condition with very low CD4 counts, and all were treated with antiretroviral medications. In each case there was a history of a depressive episode or, at the very least, a depression-like episode which had attracted clinical attention. In two of these cases such episodes immediately preceded the delirium, and in 2 cases the patients were being prescribed selective serotonin reuptake inhibitor (SSRI) antidepressants at the onset of the delirium. In each case the diagnosis was of a hyperactive delirium associated with extreme agitation and hallucinations.

In all 4 cases there was concern as to the possibility of an underlying progressive or static HIV encephalopathy predating the delirium, on the basis of abnormal neuroimaging, abnormal neurological findings, or a documented decline in adaptive functioning over a lengthy period. This potentially greatly complicates the interpretation of apparent cognitive deficits, particularly, as was common to all 3 of our own cases, where there no previously documented neuroimaging results or cognitive assessments. Chronic underlying progressive or static cognitive impairment may increase what Henry and Mann termed 'delirium readiness' (Henry and Mann, 1965), leaving these young patients vulnerable to delirium in the face of further CNS insults.

Notably, in all 3 of the patients with HIV-associated delirium described in this case series, the EEG was reported as being within normal limits. However, in all 3 cases, no pre-delirium EEG tracing was available for comparison. An EEG tracing within normal limits recorded at a single point in time does *not* exclude a delirium, as the characteristic (but not invariable) EEG finding in delirium is of *relative* slowing (with or without

disorganisation). Thus a patient with a relatively fast awake EEG trace (albeit within normal limits) may have a significant degree of slowing when delirious and still remain within normal limits. In addition, as has already been described, the EEG features of delirium characteristically wax and wane much as the clinical manifestations of delirium characteristically fluctuate. The sensitivity of the EEG to delirium may then to a certain extent depend on the timing of the tracing. The value of serial EEG recordings in these instances is unknown.

All 4 cases responded well or very well to oral haloperidol, which was well tolerated and most often effective within a few days of initiation. All 4 cases were complicated by extensive polypharmacy. The use of psychotropic medications in HIV-positive patients is greatly complicated by the potential for drug-drug interactions. In Patient 15, fluoxetine 5mg was added to an antiretroviral regimen that included ritonavir and isoniazid, and this may well have precipitated a serotonin syndrome. The initial dose of fluoxetine was deliberately reduced to 5mg in order to reduce the likelihood of interactions, but in a patient this cachectic, 5mg of a serotonin reuptake inhibitor with as long a half-life as fluoxetine's may have been sufficient. With the benefit of hindsight, the introduction of even 5mg of fluoxetine to this patient's medication regimen may have been an error of judgment, and it may have been better to have adopted a 'wait and see' approach to her depressive symptoms while her physical state improved. However, at the time, the severity of her depression and the fact that her physical state was not improving provided rationale for a trial of a low-dose antidepressant. In retrospect, citalopram may have been a safer option.

DeSilva and colleagues (2001) have described 5 cases of serotonin syndrome in adult patients with HIV treated with antidepressants. All 5 cases involved the use of fluoxetine. Fluoxetine is metabolised primarily by P450 2D6 to an active metabolite, norfluoxetine, which is then further metabolised by 2D6. Ritonavir is known to markedly inhibit 2D6 even at therapeutic doses, and this may have led to much higher plasma levels of both

fluoxetine and norfluoxetine than expected in our patient. In addition, the antituberculous agent, isoniazid has certainly been implicated in the serotonin syndrome in combination with other serotonergic medications (Gillman, 2005). Genetics may also have played a role in this interaction. A deficiency of the 2D6 isoenzyme has been reported in 8.5% of African Americans and 5-8% of white people (Cohen *et al.*, 1996). One study has indicated no apparent interaction between ritonavir and the serotonin reuptake inhibitor, escitalopram (Gutierrez *et al.*, 2003), and in our own paediatric consultation-liaison psychiatry unit we have taken to initiating citalopram as the antidepressant of first choice in depressed children with HIV who are taking antiretroviral medications. It is also worth noting that significant interactions have been reported between the benzodiazepines commonly used as adjunctive agents in children with severe delirium and certain antiretroviral medications. Midazolam, for example, is dependent on CYP 3A4 for its metabolism, which is potently inhibited by ritonavir. Such inhibition of metabolism could result in diminished clearance of midazolam and potentially fatal oversedation. Lorazepam, on the other hand, is metabolised by glucuronidation. Drugs that increase the activity of glucuronidation, like ritonavir, may lower the plasma levels of lorazepam and render it ineffective for sedation (Thompson *et al.*, 2006).

Ritonavir is the antiretroviral medication most often implicated in these types of interactions with psychotropic medications (DeSilva *et al.*, 2001; Thompson *et al.*, 2006). A case of delirium that rapidly progressed into a reversible coma has been reported (Jover *et al.*, 2002) in an HIV-positive adult when risperidone prescribed for a manic episode was added to an antiretroviral regimen that included ritonavir. Risperidone is also a 2D6 substrate, and ritonavir may elevate plasma levels to the point of toxicity, and even theoretically precipitate a neuroleptic malignant syndrome. There are to date 16 published case reports of neuroleptic malignant syndrome in children and adolescents associated with the atypical antipsychotics (Croarkin *et al.*, 2008). In our own unit we have stuck to using low doses of the 'old' typical haloperidol in our HIV-positive children who have developed delirium. None of the instances of extrapyramidal side effects in our case

series occurred in any of those patients who were HIV-positive. The work of Breitbart and colleagues (1996) lends support to the effectiveness of haloperidol in hospitalised HIV-positive adults with delirium.

Zidovudine and efavirenz have both been associated with severe manic-like presentations in adult patients with AIDS (Wright *et al.*, 1989; Shah *et al.*, 2003). A psychotic disorder (notable for disorientation and a 'confused appearance') has also been described in a 12-year-old HIV-positive girl associated with markedly raised serum efavirenz levels on the basis of a particular genetic polymorphism which had interfered with the drug's metabolism (Lowenhaupt *et al.*, 2007). Unfortunately, the literature relating to possible neuropsychiatric adverse effects of antiretroviral medications in children and adolescents remains remarkably scarce.

Should paediatricians be taking greater cognisance of these neuropsychiatric adverse effects, particularly when prescribing antiretroviral medications to HIV-positive children with possible HIV-associated dementia/encephalopathy, emotional and/or behavioural problems, or family history of serious mental illness? Should we be selecting specific antiretroviral regimens for children and adolescents with 'diminished cognitive reserve' or other markers of a 'vulnerable brain'? There is an urgent need for research in this area.

Notably, in 2 of the HIV-positive patients described in this series the delirium occurred within 2 months of the initiation or recommencement of antiretroviral medication, and in the 3rd patient the initiation of antiretroviral medications coincided with a dramatic deterioration in the symptoms of delirium. Immune Reconstitution Inflammatory Syndrome (IRIS) is a recently recognised condition that manifests as a paradoxical worsening of the patient's condition attributable to the recovery of the immune system after the initiation of antiretroviral therapy in the form of HAART. The syndrome most often occurs within 3 months of commencing HAART during the early rapid immune recovery phase. IRIS can also occur when a patient on a failing HAART regimen is

switched to a more successful viral suppressive regimen, or when HAART is recommenced after an interruption in medication adherence. The paradoxical deterioration seen in this subgroup of patients following the initiation of HAART is thought to reflect the rapid and dysregulated restoration of antigen-specific immune responses. Various antigens may be the targets of this dysregulated immune response, including viable and replicating infective antigens, dead and dying infective antigens, and even the patient's own antigens in the case of autoimmune IRIS.

The most commonly recognised forms of IRIS are related to underlying opportunistic infections with mycobacteria, viruses, and fungi that become 'unmasked' as the patient's immune response is restored. Between 15 to 25% of patients receiving HAART develop IRIS within the first few months of therapy, making this a common condition that is thought to be grossly underrecognised and misdiagnosed (Riedel *et al.*, 2006).

IRIS may play a role in a variety of AIDS-related disorders of the central nervous system, including tuberculosis, cryptococcal disease, cytomegalovirus retinitis, and progressive multifocal leukoencephalopathy. However, a number of cases of HIV dementia or HIV encephalitis presenting with an acute deterioration shortly after the initiation of HAART that were consistent with IRIS have also been described. The pathophysiology of this IRIS-associated worsening of HIV dementia or HIV encephalitis is poorly understood. In the few patients in whom histopathology was available, brain infiltration with CD8+ cytotoxic T cells has been found (Dhasmana *et al.*, 2008). Whether the dysregulated immune response in these instances is targeting host antigen, the HIV virus itself, or an unrecognised opportunistic infection is unclear.

In addition to a temporal relationship with the initiation or recommencement of antiretroviral medication, in all 3 of the HIV-positive patients with delirium described above there was concern as to the possibility of an underlying HIV 'encephalopathy'/dementia which predated the delirium. The literature relating to

possible neuropsychiatric manifestations of IRIS are currently limited to reports of deteriorating HIV-associated dementia in the context of recent HAART initiation and immune restoration amongst adult patients. However, as I have pointed out on a number of occasions throughout this dissertation, the traditionally crisp distinction between dementia and delirium no longer exists. There is an increasing recognition of overlap between the two syndromes in relation to both clinical manifestations and pathogenesis.

With this in mind, it would seem feasible for a severe and prolonged paediatric delirium occurring within 2 months of the commencement of HAART to occur as a result of a neuropsychiatric IRIS, particularly in the context of suspected paediatric HIV-associated dementia/encephalopathy'. The correct diagnosis of neuropsychiatric IRIS syndromes may be crucial in determining optimal management. At present, the use of systemic corticosteroids in IRIS syndromes is well described but remains controversial (Riedel *et al.*, 2006; Dhasmana *et al.*, 2008). However, just as systemic corticosteroids have been used in the management of delirium associated with CNS involvement in autoimmune conditions like systemic lupus erythematosus (Turkel *et al.*, 2001), these agents may be important to consider in severe neuropsychiatric IRIS syndromes.

If these 4 cases considered together can teach us any lesson in relation to psychotropic pharmacotherapy, it is that psychotropic medications should be used with great caution in acutely and severely ill HIV-positive children and adolescents, as the risk of clinically significant drug-drug interactions with antiretroviral medications (and antituberculous agents) is high. Clinicians should be vigilant to the possibility of both the serotonin syndrome and neuroleptic malignant syndrome in this context, as even very small doses may precipitate serious side effects in this vulnerable population. If psychotropic medications are to be used for the treatment of agitated delirium in these patients, the limited literature and clinical experience suggest that low doses of haloperidol may be the best alternative, and that if benzodiazepine augmentation is required, lorazepam or oxazepam be the agents of first choice.

I would also like to suggest that a subset of HIV-positive children would benefit from having a *baseline* EEG recorded. This would allow for comparison with later EEG's recorded at a time of deterioration in mental state or cognitive functioning. A baseline EEG might be considered in HIV-positive children with either 'hard' (cerebral atrophy, focal neurological signs, developmental delay) or 'soft' (emotional and/or behavioural disorders) markers of a 'vulnerable brain'.

3.6 Summary

To the best of my knowledge, at the time of writing, only 3 other case series' of definite delirium in children and adolescents with larger sample sizes have ever been reported in the literature (Turkel and Tavare, 2003, n=84; Schieveld *et al.*, 2007, n=40; Prugh *et al.*, 1980, n=33).

The data from this case series confirm the reports of these authors in finding the syndrome of delirium in children and adolescents to be a relatively common diagnosis in the context of inpatient Paediatric Consultation-liaison Psychiatry, in this instance constituting 18% of inpatient referrals over a 2-year period.

A male preponderance has been suggested by other authors, but was not found in this series. However, the mean age of male subjects with delirium was younger than the mean age of female subjects, and so it is conceivable that in children a larger 'deliriogenic' insult is required in females than in males in order for them to cross the threshold into delirium.

The syndrome manifests in a similar fashion to that in adults, but developmental constraints present particular challenges in the eliciting and interpretation of symptoms and signs. Visual hallucinations (52%), delusions (22%) and incoherence (52%) were

particularly prevalent in this series. Two features have been suggested as being relatively unique to delirium in children and adolescents – transient developmental regression and inconsolability with a primary caregiver (Schieveld, 2008). In this series, inconsolability in the presence of a primary caregiver was present in 50% of the patients who were assessed with a primary caregiver at the bedside. Transient regression with loss of skills was present in 26% of our patients with delirium.

In this series, a number of patients were seen to ‘switch’ after a fairly prolonged period in hypoactive delirium into hyperactive delirium, and it was often only after this ‘switch’ occurred that a referral to psychiatry was triggered.

Additionally, child and adolescent patients with delirium who were referred to psychiatry appeared to represent a subgroup of patients in which the delirium was usually characterised by severe behavioural disturbance or psychotic features, persistent, and for which either a single obvious precipitant or perpetuating factor could not be identified, or the precipitant or perpetuating factor proved resistant to reversal or amelioration.

Additionally, 22% of our patients appeared to have an apparently prodromal alteration in mental state in the week or weeks preceding the delirium. Most commonly, this apparent prodrome manifested with depressive features, particularly low mood, blunting of affect, apathy, and social withdrawal, rather than the anxiety that characterised Schieveld *et al.*'s (2007) ‘emerging delirium’. Leo Kanner (1942, p.179) also described an apparent ‘prodromal’ or subsyndromal phase in paediatric delirium:

The fully-fledged syndrome with disorientation, fear, hallucinations, and dramatic dream production is usually preceded by a state of general malaise, drowsiness, and blunting of the sensorium

Lipowski (1980) has also described a prodromal phase of delirium in adults characterised by anxiety, irritability, fatigue, insomnia and vivid dreams.

However, in light of the information obtained from the systematic literature review, this apparent prodrome could also be interpreted in other ways. For example, pre-existing depression might act as a predisposing factor for delirium (Kain *et al.*, 2004; Vlajkovic *et al.*, 2007; De Carvalho and Fonseca, 2008). Secondly, these 'prodromal' features could also represent more subtle manifestations of the 'delirium spectrum' (Ouimet *et al.*, 2007b). Thirdly, these apparent prodromal alterations in mental state could in fact represent undiagnosed or misdiagnosed instances of hypoactive delirium that have later abruptly 'switched' to hypoactive delirium's 'bipolar' counterpart – hyperactive delirium, as frequently occurs in patients with catatonia (Schieveld, 2006).

Traditional bedside assessments of cognition were often found to be inappropriate in children for the assessment of delirium in the context of physical illness, hospitalisation and pain. Developmentally sensitive tests that incorporated a measure of fun and humour proved to be significantly better in engaging children in cooperating with cognitive evaluations.

Delirium was associated with a quite extraordinarily high mortality rate (26% in this series) amongst patients referred to psychiatry from inpatient paediatric wards. This likely reflects a referral bias favouring those paediatric inpatients who present with more severe and persistent mental disturbance, and whose delirium has proved to be more difficult or impossible to reverse or ameliorate by addressing the underlying cause. Referral to psychiatry may in this way function as a proxy measure of the burden of underlying physical illness severity.

It is also conceivable that referral to psychiatry may also act as a proxy indicator of the level of anxiety amongst clinicians in the primary treatment team relating to their patients deteriorating course and prospect of dying.

Findings from the use of delirium rating scales in this case series and a control group of psychiatric outpatients with a variety of diagnoses suggest that the DRS and the DRS-R-98 in particular may have clinical and research utility in delirious children and adolescents. Scores on both these scales in our series are similar to those reported in delirious adults and, in the case of the DRS, similar to those reported by Turkel *et al.* (2003) in children and adolescents. The DRS-R-98 may be particularly useful for measuring delirium severity and documenting response to treatment.

Electroencephalogram findings in this series provide further support for the use of this investigation, particularly amongst patients with a hypoactive delirium, which can mimic severe psychomotor retarded depression very closely. It should, however, be noted that a number of our clinically clear-cut cases of delirium had electroencephalograms reported as normal during an episode.

With regards the management of delirium in this population, this case series provides further supportive, open, and uncontrolled evidence for the modest effectiveness of low-dose antipsychotic medication. The most rapid and dramatic responses were obtained in patients with hyperactive delirium treated with the conventional butyrophenone antipsychotics (haloperidol and droperidol) administered via the intravenous route. In contrast, there was essentially very little or no response to antipsychotic medication in the 2 patients with hypoactive delirium.

This study also provides further supportive, open, and uncontrolled evidence for the modest effectiveness of the atypical antipsychotic, risperidone in carefully selected patients.

I have also described in some detail the naturalistic psychosocial/environmental management of these 23 cases. Five of the 23 cases (22%) were managed without antipsychotic medication in this way, in parallel with concomitant attempts at reversing or at least ameliorating the underlying cause of the delirium.

3.7 Conclusion

In concluding, I would like to return to the list of wholly or only partially unanswered questions in relation to delirium in children and adolescents that were generated in response to my systematic review of the literature, and then highlighted under the 'Objectives' section of the Case Series.

Question 1

How can delirium be best assessed and diagnosed in young and very young children?

In relation to this first question, I can concur with Schieveld and colleagues (Schieveld *et al.*, 2007; Schieveld and Leentjens, 2005) and Prugh *et al.* (1980) in finding the diagnosis of delirium in children, and especially young children, extremely challenging.

In young children especially, hyperactive delirium can be difficult to distinguish from inadequately treated pain, severe anxiety, acute stress disorder and post-traumatic stress disorder. Delirium in this age group often presents in a more subtle form, particularly in the earliest stages, that appears to merge imperceptibly at times with an apparent prodromal state. In these instances, close attention to temporal aspects of the presentation, particularly in relation to rapidity of onset, marked fluctuation, nocturnal worsening, and parallel changes in physical health and/or prescribed medications, often provide clues to the correct diagnosis. Additionally, close attention to relational aspects

of the presentation can provide important information. Complete inconsolability in the presence of a primary caregiver may provide an important clue to differentiating delirium from the other conditions listed above.

In the case of hypoactive delirium, this can be extremely difficult to distinguish from demoralisation and depression in the context of physical illness, particularly in young children. In this instance, close attention to temporal aspects such as fluctuating performance on bedside cognitive tests can be crucial. The EEG can also provide supportive evidence of a diagnosis of delirium in these cases, but is a relative insensitive instrument for delirium in children.

In putting forward my recommendations in relation to the assessment and diagnosis of delirium in children, I have attempted to collate the assessment strategies described by Schieveld *et al.* (2007), Prugh *et al.* (1980) and Przybyło *et al.* (2003) with my own clinical experiences.

Delirium in young children is best assessed and diagnosed using information obtained from a variety of sources over the course of a longitudinal rather than cross-sectional assessment. These sources include historical information from both caregivers and staff.

In my own experience I have found the nursing documentation of the night-shift nursing staff particularly helpful in obtaining information relating to sleep-wake cycle and nocturnal worsening of symptoms. Caregivers are clearly able to provide vital information in relation to premorbid cognitive abilities and temperament, amongst other things. Careful observation of caregiver and child interactions, particularly mother-child dyads, in relation to eye contact and consolability can provide useful information.

Serial clinical interviews with the child, preferably at different times of day and with cognisance of the timing of sedative medications are vital to obtaining a longitudinal

assessment of mental state. Particular attention should be paid to serial bedside cognitive tests, which need to be developmentally appropriate and engaging. I have described a number of techniques that I have found useful and fun in the bedside cognitive assessment of young children. Lastly, as already mentioned, the EEG can provide supportive evidence for a diagnosis of delirium if abnormal. When the EEG is reported as normal, however, this should not be taken as evidence of a diagnosis other than delirium. The value of serial EEG's in particularly vexing cases is uncertain.

Question 2

How can delirium rating instruments assist in the assessment and management of delirium in children and adolescents?

With regards to this second question, this study provides further supportive evidence for the applicability of the Delirium Rating Scale (DRS) to children and adolescents, in reporting DRS scores of delirious children and adolescents comparable to those reported in adults and in a previous study in children and adolescents (Turkel *et al.*, 2006). Further supportive evidence of the validity of the DRS in this age group is provided in the comparison of DRS scores of a delirious group of children and adolescents with those of a control group of psychiatry outpatients with a range of diagnoses.

The DRS-R-98 also appears to have a degree of validity in this age group, with scores similar to those reported in adults with delirium. The DRS-R-98 appears to be a useful instrument for assessing the severity of delirium in children and adolescents, and importantly, for objectively documenting response to treatment.

In relation to the PAED, I found two of its items, addressing eye contact with a primary caregiver and inconsolability in the presence of a primary caregiver, to be so useful as to incorporate them into my routine assessment of children suspected of suffering from a

delirium. As a whole, my impression was that the PAED scale is probably most useful in the setting it was designed for, that of emergence from anaesthesia, although it may have a particular role in the assessment of delirium in the paediatric intensive care unit as well.

Question 3

How can delirium in children and adolescents be best treated?

With regards the third question, it will be necessary for me to place my own experiences in the context of that of other researchers in the field of child and adolescent delirium, particularly the recent contributions of Schieveld *et al.* (2007), Karnik *et al.*, (2007) and Scharko *et al.* (2006) in relation to the pharmacotherapy of delirium in this age group.

Antipsychotic medications appear to have at least modest efficacy in the management of hyperactive and mixed subtypes of delirium, with approximately two-thirds of patients responding within 48 hours with a reduction in agitation, psychotic symptoms, distress and insomnia. Children and adolescents with hyperactive or mixed delirium of high severity as measured by the DRS-R-98 may respond particularly well. Intravenous haloperidol in small dosages appears to be particularly effective in severe hyperactive delirium in children and adolescents. Risperidone appears to be a reasonable alternative when an enteral route is available.

Although these conclusions concur for the most part with those of Schieveld *et al.* (2007), certain discrepancies are apparent.

Schieveld *et al.* (2007) report a seemingly universally good response to both haloperidol and risperidone in patients with both hyperactive and hypoactive delirium. My own results were less impressive, with a third of patients treated with either haloperidol or risperidone having only minimal or no improvement. My experience with treating two

patients with 'pure' hypoactive delirium with antipsychotic medications was particularly disappointing, with both patients experiencing minimal improvement. These results contrast in some respects with those of Schieveld and colleagues (2007), who reported positive responses to antipsychotic medication amongst their nine hypoactive delirious patients, who formed 22% of their sample.

In addition, only 5% (2/40) of delirious patients in the case series reported by Schieveld *et al.* (2007) were managed *without* antipsychotic medication, despite only 14 (35%) of the 40 patients having been classified as having a hyperactive delirium. The authors reported that 'Treatment with haloperidol or risperidone was successful in all patients'.

Schieveld and Leentjens (2005) urged clinicians to treat delirium in children actively and not conservatively, and suggested that pharmacological management should be 'part of the routine care of delirious young children'. The authors went on to conclude:

We fear that this child psychiatric emergency often goes unrecognised and is undertreated; the complex combination of a serious illness and polypharmacy in a young child often results in reluctance and a delayed decision to add yet another medication to treat the delirium. We hope that this clinical perspective will allay this reluctance and lead to a more active therapeutic approach to treating delirium.

(Schieveld and Leentjens, 2005, p.394)

Although I agree wholeheartedly with these authors concerns regarding underrecognition, undertreatment, and the need for a more active therapeutic stance in the management of delirium in this age group, my own approach has been somewhat more conservative.

Although the evidence base for the use of antipsychotics in children with hyperactive delirium remains extremely slim, it is substantially more robust than the evidence for their use in hypoactive delirium. Even in adults with hypoactive delirium, the evidence for the use of antipsychotics is far from conclusive.

I would like to suggest that 'mild' delirium in children and adolescents may be amenable to *active* psychosocial/environmental management, in concert with addressing the underlying cause of the delirium as rapidly as possible. In more severe cases characterised by marked agitation, distress or psychotic features, particularly when these are compromising medical care, and in circumstances where the underlying cause is unknown or not readily reversed, I would suggest a trial of low-dose antipsychotic medication. I concur with Schieveld and colleagues in favouring haloperidol in these instances, particularly in its intravenous form. I suspect that the bioavailability of oral antipsychotics in children with multi-organ impairment is in many cases markedly compromised, making intravenous preparations a more attractive alternative. In cases complicated by persistent agitation and insomnia low doses of short-acting benzodiazepines appear to be useful adjunctive agents when used in combination with antipsychotic medications. In this context low-dose, short-acting benzodiazepines may provide a dose-saving effect in relation to antipsychotic medications.

In cases of hypoactive delirium in children and adolescents the argument for antipsychotic medications is less clear. Schieveld and colleagues (2007) have argued for the use of antipsychotic medication in these cases. If the published literature is anything to go by, these authors would appear to have the most experience (n=9) in treating hypoactive delirium in children with antipsychotic medications. Karnik and colleagues (2007) argued for a particular role for the atypical antipsychotic, risperidone, in the treatment of children and adolescents with hypoactive/mixed delirium.

My own current clinical practice with children and adolescents with hypoactive delirium is to rapidly institute environmental management strategies, in particular optimizing the level of sensory and social stimulation. This proceeds in parallel with attempts to elucidate and address the underlying precipitants and perpetuating factors of the delirium.

I pay careful attention to all psychoactive prescribed medications, particularly opioids and medications with anticholinergic side effects.

If these combined strategies produce little or no improvement, and the delirium is of sufficient severity to significantly interfere with necessary medical treatment or rehabilitation, I then consider a trial of low-dose risperidone, so long as an enteral route of administration is available. I do, however, believe that it is crucial in these instances to closely monitor and document response to treatment using a delirium rating instrument such as the DRS-R-98. It is vital that clinicians bear in mind what symptom domains they hope or expect to see improvement in when commencing antipsychotic medication, and that they monitor patients closely for any evidence of deteriorating psychomotor retardation or cognitive deficits.

Anecdotally, one of my most effective interventions with all these patients was the active psychoeducation and support provided to primary carers, most commonly the parents. In addressing parents' fears and reducing their anxiety levels I feel I was able to increase their capacity to contain the fear and distress in their delirious children. This alone, in a number of instances, seemed to significantly reduce distress and agitation in delirious patients.

Question 4

What are the indications for antipsychotic medications in child and adolescent delirium?

I have attempted to answer this final question by drawing on both my own clinical experience and the results of a systematic review of the literature described above. I have come to the conclusion that antipsychotic medications should be strongly considered under the following circumstances in a child or adolescent suffering from a delirium:

1. Presence of significant psychotic symptoms
2. Behavioural disturbance (agitation, aggression, uncooperativeness) associated with significant risk of harm to self or others
3. Significant interference with necessary medical investigations, treatment or rehabilitation
4. Marked distress
5. Difficulty or nonresponse to reversing or ameliorating presumed precipitating and perpetuating factor(s) AND poor or only partial response to environmental management PLUS 1,2,3 or 4

It should be noted that these recommendations are comparatively conservative in relation to those of other workers in the field.

3.8 Limitations of the Case Series

One of the greatest limitations of this study is the small sample size. As a sample of psychiatrically-referred inpatient cases of delirium, my findings might not be generalisable to the wider population of delirious children and adolescents. This patient sample also had very few cases of hypoactive delirium, and so my comments relating to this subgroup of delirious patients, particularly with regards treatment, should be interpreted with caution. I would suggest that in any study of delirium in this age group that one of the crucial questions to be asked is precisely how the diagnosis was established. One of the weaknesses of this study was that the diagnosis of delirium was made based on the clinical assessment of a single psychiatrist, with supportive evidence from laboratory investigations like the encephalogram. To counterbalance this weakness every attempt was made to obtain a longitudinal and comprehensive assessment using serial clinical interviews with both patient and carer, supplemented with collateral information from as many sources as possible. In relation to this issue, the diagnostic strategy employed by Schieveld and colleagues (2007), using a multidisciplinary clinical

consensus to supplement the clinical assessment of the child and collateral information from parents, nurses, intensivists and child neurologists, is particularly laudable.

Rating scales were retrospectively applied to the clinical data recorded in the patient's clinical and nursing notes, rather than prospectively at the time of the initial assessment. This resulted in a certain scale items being unable to be rated. Additionally, this meant that the DRS-R98 was unable to be used as a repeated measure for monitoring and rating response to treatment.

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In addition, the control group was a child and adolescent psychiatry outpatient group that was not matched for age, general intelligence and educational history. It would have been interesting and valuable to have also had a child and adolescent psychiatry inpatient sample and a pre-operative, elective paediatric surgery inpatient sample as controls for the delirium rating scales.

Methodological weaknesses significantly limit the validity and generalisability of the findings relating to treatment effectiveness and outcome of this sample.

All pharmacological interventions were initiated *in concert* with psychosocial/environmental management and usually initiated concomitant with interventions aimed at addressing the underlying cause, or (more commonly), causes of the delirium. Box 3.1 provides an illustrative example.

In addition, the unblinded clinician who rated the CGI-I (myself), was also the clinician who instituted pharmacotherapy, which may have introduced some expectancy bias.

Lastly, it is uncertain to what extent the findings from this selected subgroup of paediatric delirious inpatients referred to consultation-liaison psychiatry can be generalised to the wider population of children and adolescents experiencing delirium. It may be, for example, that young patients presenting to a casualty department with delirium, or those experiencing a delirium in the inpatient wards who are not referred to psychiatry, are more likely to resolve spontaneously without psychotropic medication.

Box 3.1 An example illustrating the challenges in evaluating antipsychotic treatment efficacy in children with delirium

Patient 7, a 12-year-old boy, developed a delirium in the intensive care unit following a ruptured appendix in the context of sepsis, hypocalcemia, hypertension, acute renal failure, and the abrupt cessation of diazepam 45mg/day.

His treatment plan included intravenous antibiotics, calcium supplementation, antihypertensive medication, and intravenous hydration. In addition, he was prescribed intravenous haloperidol 0.5mg for the treatment of severe agitation and disorganised behaviour which had proven to be unresponsive to aggressive environmental management. He was also recommenced on a lower dose of diazepam to address likely benzodiazepine withdrawal.

In assessing his response to intravenous haloperidol the Clinical Global Impression – Improvement scale was scored as a reflection of sustained improvement for a period of 48 hours after commencing the medication. Clinical judgment in the assessment of the temporal relationship between improvement and the commencement of antipsychotic medication was used in deciding the CGI-I score. In the case of this boy, there was very little improvement other than a slight reduction in agitation over the course of the first 48 hours, and so the CGI-I was scored as ‘minimally improved’.

Over the course of the next 5 days, however, his delirium improved significantly as his clinical and laboratory markers of sepsis improved. To what extent the improvement in his delirium resulted from higher doses of haloperidol, adjunctive diazepam, antibiotics, or environmental manipulation is difficult to ascertain. The emphasis on evidence of *sustained* improvement was to reduce the chance of a partial improvement in symptoms related to natural fluctuation of the disorder being interpreted as a medication effect.

3.9 Strengths of the Case Series

To the best of my knowledge, this case series represents the 4th largest case series of children and adolescents with delirium in the setting of paediatric consultation-liaison psychiatry.

One of the major strengths of the case series is that it reflects the complexities of clinical practice in working with patients with delirium. As such, decisions as to the need for antipsychotic medication, type of antipsychotic, route of administration, adjunctive medication, dosage adjustments etc. were made on a naturalistic, individual case-by-case basis, rather than derived from a protocol.

All assessments, diagnoses, and recommendations for management were made by the same clinician over the 2-year period, and all delirium rating scale scores, including those of the control group, were scored by the same clinician.

To the best of my knowledge, at the time of writing, it is the only case series of children and adolescents, diagnosed with a delirium according to DSM criteria, in which the DRS-R-98 has been employed, and in which an attempt was made to systematically rate response to pharmacological treatment.

Lastly, the phenomenon of delirium in children and adolescents with HIV/AIDS has, until this time, been almost completely unexplored by researchers, with the sole exception of the single case report of Scharko and colleagues (2006).

Chapter 4

Conclusion

4.1 Chapter overview

In this final chapter I will attempt to synthesize the data derived from the systematic review of the literature relating to delirium in children and adolescents, the unsystematic review of the adult delirium literature, and the case series from Red Cross Children's Hospital described in Chapter 3. Whenever a particular conclusion is stated, I will in most instances also indicate whether the evidence for the conclusion has been derived from the systematic review of the child and adolescent literature, the case series, cautious extrapolation from the adult literature, or a combination of the above.

In this chapter I have chosen to focus on what I believe are the most pertinent aspects in this area of research, rather than all aspects of the disorder as it occurs in children and adolescents. Finally, under each subheading I have attempted to highlight the presently unanswered questions and potentially fruitful avenues of research into various aspects of delirium in this age group.

4.2 Conceptual issues

In recent years the conceptual boundaries of delirium have become increasingly eroded. Subsyndromal, 'veiled' and 'emerging' forms of delirium and the existence of *residual* cognitive deficits and functional impairments have blurred the boundaries between both delirium and 'normal' consciousness, and delirium and dementia. There is evidence for this conclusion in all 3 of the data sources utilised in this dissertation. Schieveld and colleagues (2007) have described 'emerging' or 'veiled' delirium in children and adolescents in the paediatric intensive care setting, and Prugh and colleagues (1980) have described 'subclinical delirium' in a 10-year-old boy. Patients with emerging,

partial, or subclinical features of delirium may shift further along the spectrum into full syndromal delirium, and subsequently progress even further into states of stupor and coma. Data from the Red Cross Children's Hospital series suggest that over 20% of children and adolescents with delirium experience a subtle 'prodromal' period lasting days to weeks before the emergence of delirium, and that the distinction between paediatric dementia, delirium, and delirium superimposed on dementia may be far from clear-cut amongst children with advanced HIV/AIDS.

Reconceptualised as a 'spectrum disorder' in recent years, the absence of a 'distress and/or impairment' criterion in current DSM-IV-TR operational diagnostic criteria for delirium has created ambiguity in the delineation of where delirium starts and ends on a continuum of altered consciousness. This has implications for treatment that have not yet been adequately addressed. Pathoplastic effects of normal development and developmental limitations in verbal communication add a further layer of complexity to a disorder that arguably continues to elude adequate definition, even in adults. Prodromal or subtle subclinical manifestations may precede full syndromic delirium by days and even weeks, and subtle residual deficits frequently persist to blur the boundaries of delirium remission.

Schieveld (2006) has argued convincingly the conceptual similarities between delirium and catatonia as nonspecific, final common pathway 'reaction types of the brain' to a variety of 'organic' disturbances. Both catatonia and delirium have multiple medical etiologies, fluctuating and variable courses, diverse manifestations, and both have 'bipolar' hyperactive and hypoactive forms. Like anaemia or fever, these disorders are most commonly evidence of an underlying disease rather than separate disease entities in themselves.

This same author (2008) has postulated the existence of two forms of paediatric delirium – a benign and a malignant form.

It may be useful at this point to draw an analogy with yet another relatively nonspecific 'reaction type of the brain' – seizures. Seizures in children have both diverse etiologies

and varied manifestations, and yet the same seizure type may occur as a result of a wide array of underlying pathologies. A number of 'benign' seizures occur in children, most notably in the context of febrile convulsions and in the immediate aftermath of a head injury. This is not to say that such seizures are of no consequence. Injury may occur during both the ictal event and the post- ictal phase. However, in the case of febrile convulsions, such seizures can be regarded as relatively benign owing to the fact that they are usually brief, frequently resolved spontaneously or with correction of the precipitating fever, and are of little or no prognostic significance beyond the post-ictal period.

However, paediatric seizures also occur in a 'malignant' form. *Status epilepticus* is probably the most likely candidate as an example of malignant paediatric seizures. In this form, seizures are protracted or continuous, and may not resolve spontaneously. *Status epilepticus* is associated with significant morbidity and mortality. Continuous seizure activity may be "toxic" to the brain and result in residual deficits. Treatment must be directed not only at the underlying cause, but also at terminating the seizures themselves with antiepileptic agents.

Similarly, febrile delirium would seem the most likely candidate for a 'benign paediatric delirium' – brief, resolving spontaneously or rapidly with correction of the precipitating fever with, to the best of our current knowledge, little in the way of prognostic significance beyond the morbidity associated with its immediate behavioural manifestations.

On the other hand, I would like to suggest that 'malignant paediatric delirium' is perhaps the form of delirium most commonly encountered by clinicians in the setting of inpatient paediatric consultation-liaison psychiatry. This subgroup is characterised by delirium which is protracted, frequently poorly responsive to attempts at reversing multiple potential etiologies, and frequently necessitates the use of antipsychotic medications. Paediatric delirium in this context is associated with a mortality rate in excess of 20%. Beyond referral to psychiatric services, the possible correlates of malignant paediatric delirium remain unknown but potentially include:

- Type of precipitant
- Nature of precipitant (complex, multifactorial, difficult to reverse or ameliorate?)
- Delirium superimposed on 'diminished cognitive reserve', such as may occur in children with HIV-associated dementia
- Delirium duration
- Phenomenology or delirium subtype
- EEG correlates
- Functional neuroimaging
- Postulated delirium 'biomarkers'

There is clearly an urgent need for further research in this area.

4.3 Epidemiology

Vulnerability to delirium may well be increased at both ends of the age spectrum, not just amongst the elderly. This increased vulnerability may relate to both the relative immaturity of cholinergic neural networks and of psychological development in children. Unfortunately, no study employing a screening methodology in either clinical or community setting has yet been undertaken that might confirm the anecdotal impressions of a number of authors that young age confers susceptibility to delirium.

However, data obtained from both the case series described above and previous studies identified by the systematic review confirm that the recognition and management of delirium presents a common problem to those working in the area of child and adolescent consultation-liaison psychiatry. Patients with delirium form between 8 and 18% of all referrals to paediatric consultation-liaison psychiatry services, while in the setting of paediatric intensive care such patients comprise 65% of all paediatric consultation-liaison referrals. Other clinical settings in which it delirium is commonly

encountered include paediatric anaesthesia, paediatric burn units, paediatric oncology and emergency units. Although myself and others have suggested that delirium in children is commonly undetected and frequently misdiagnosed, possibly even more so than in adults, the evidence for this statement is currently limited to clinical experience and expert opinion.

4.4 Predisposing, precipitating and protective factors for delirium in children and adolescents

A number of potential predisposing factors were identified through the systematic review of the literature and cautious extrapolation from the literature relating to delirium in adults and the elderly. Of these potential predisposing factors, the existing literature would seem to support the following underlying variables with the greatest weight of evidence: physical ill health, pre-existing psychiatric disorder, caregiver anxiety or caregiver absence, young age, and possibly male gender. Preoperative anxiety in both child and their primary caregiver appears to increase the risk of emergence delirium following anaesthesia. Amongst the elderly, the presence of underlying dementia dramatically increases the relative risk of delirium. My own work in relation to paediatric HIV-associated delirium suggests that the presence of what paediatricians most commonly refer to as 'HIV encephalopathy', but which is probably better described as paediatric HIV-associated subcortical dementia, confers additional risk for superimposed delirium. Unfortunately, no data is currently available in relation to the role of genotype in delirium susceptibility, nor in relation to the impact of underlying mental retardation or pervasive developmental disorder.

The identification of predisposing factors potentially creates the opportunity for screening for delirium amongst high-risk groups, prevention, and early intervention. For example, HIV positive children with markers of possible HIV-associated dementia such as extensive brain atrophy on neuroimaging, focal neurological signs, deteriorating performance on psychometric testing, or in adaptive functioning may well constitute a subgroup of children at greatly elevated risk of delirium. Amongst children admitted to

the paediatric intensive care unit, rating instruments which generically quantify the burden of physical illness such as the PIM and PRISM appear to have utility in identifying those children at increased risk of developing delirium.

Importantly, a number of the predisposing factors listed above are potentially amenable to modification. Amongst hospitalised children, excessive patient anxiety, caregiver anxiety and caregiver absence are good candidates for modification and possible prevention of delirium. The work of Kain and colleagues (2007) suggests that interventions targeting both patient and parental anxiety reduce the incidence of post-anaesthetic delirium. To what extent this finding is applicable to paediatric delirium in other contexts such as paediatric intensive care, paediatric burn units, or in children hospitalised with HIV-associated physical illness is uncertain at present.

In relation to precipitating factors, children appear to be particularly susceptible to delirium in the context of febrile illness, prescribed medications and toxins, anaesthesia, burn injuries, complicated migraine, and abused substances. Importantly, there may be a *more* significant iatrogenic contribution to delirium in this age group than in older patients. These conclusions are drawn from both the systematic literature review of delirium in children and adolescents and data from the Red Cross Children's Hospital case series. Also of note is the fact that a number of medications reported as effective in the *treatment* of delirium in children and adolescents have been reported as precipitating delirium in these patients. In the case series from Red Cross Children's Hospital, described above, the majority of the patients were managed with complex polypharmacy regimens for their physical condition where there was a strong possibility of an iatrogenic contribution to the etiology of the delirium. In fact, in over half of the cases it was felt likely that prescribed medications might have contributed to the development of delirium.

Most medical students would be able to relate that the primary and overarching management strategy for delirium is prompt identification and reversal of the underlying 'cause'. However, data from the Red Cross Children's Hospital case series suggests that in the majority of child and adolescent patients referred to psychiatric services the exact

'cause' of the delirium is uncertain, most likely multifactorial, and often poorly or only partially responsive to attempts at reversing, removing or at least ameliorating a complex and dynamic web of precipitating and predisposing factors.

No research has been conducted to date that has examined the environmental contribution to the development of delirium in children and adolescents. Possible environmental precipitating factors like social isolation, sensory extremes, sensory deprivation or immobility are important, because these factors, relative to other known predisposing and precipitating factors may be more easily correctable. Addressing such factors could potentially play an important and cost-effective role in preventing delirium in young people.

The role of protective factors for the development of delirium has hardly been studied in any age group. A systematic review of the literature was unable to locate any literature addressing the subject of protective factors for delirium in children and adolescents. Potential protective factors that merit study would include intelligence, level of education, adaptive functioning, female gender, caregiver factors and genotype.

4.5 Comparative phenomenology and delirium subtypes

For the most part, children manifest delirium in much the same way as adults, but developmental influences provide particular challenges in the assessment of certain symptoms and signs of delirium. Certain features like hallucinations (particularly visual hallucinations) and agitation are consistently more frequently reported in delirious children than they are in adults. Visual hallucinations were present in over 50% of the patients in the case series from Red Cross Children's Hospital. In contrast to previous studies, this case series also identified relatively high rates of speech disturbance (52%) and delusions (22%) amongst children and adolescents with delirium. Significantly, over 20% of these patients presented with an apparent delirium prodrome, characterised by apathy, dysphoria, and withdrawal, which appeared to last anywhere between a few days to a week or more prior to the onset of the full delirium syndrome. It is also notable that the two commonest features of delirium in this sample related to *temporal* aspects of the

alteration in mental state, rather than specific symptoms or signs, further underscoring the need for a longitudinal assessment and serial clinical interviews.

Delirium in children may present more subtly than in adults, with less obvious cognitive impairments. In addition, certain relatively unique features of delirium in this age group have been described in the literature, most notably developmental regression with transient loss of skills, and inconsolability by a usual caretaker. In the Red Cross Children's Hospital case series, marked developmental regression with loss of skills was present in 26% of patients, while inconsolability with the usual caregiver was present in 50%.

The same subtypes of delirium as have been described in adults have also been described in children. However, clear delineation between these subtypes may be more problematic in children. The case series described above included only 3 patients with 'pure' hypoactive delirium, but it is worth noting that in all 3 patients the delirium was misdiagnosed as a 'depression', with the referral question centred upon the threshold for antidepressant medication. Subtle, subsyndromal forms of delirium create particular challenges for clinicians. In very young children and infants, subtle disturbances in attachment behaviours, and other acute qualitative disturbances in the mother-child interaction, may provide clues to a possible delirium. This is evident from both my own work with the younger patients described in the Red Cross Children's Hospital series, and the work of other authors identified by the systematic literature review. Thus, although the *range* of symptoms of delirium appears to be similar in all age groups, delirium in childhood may have a particular symptom profile, certain relatively unique features and may also be more difficult to diagnose.

4.6 Morbidity and mortality

Delirium is associated with significant morbidity and mortality in children and adolescents, as it is in adults. Amongst child and adolescent patients with delirium that are referred to consultation-liaison psychiatry services mortality rates have been reported as 12.5% (Schieveld *et al.*, 2007), 20% (Turkel and Tavare, 2003), and as high as 26%

in the series from Red Cross Children's Hospital. However, research has not yet addressed the question, as it has in adults, as to whether these associations hold true after adjusting for physical illness type, severity, and complexity.

Importantly, delirium in children and adolescents has been associated with *residual* cognitive deficits and behavioural problems long after the resolution of the delirium itself, mirroring the data reported in adults that has painted a far from benign picture of delirium's prognosis. The existing literature addressing delirium in children and adolescents provides worrying glimpses of potential continuities with delirium in adults in relation to both morbidity and mortality, and potentially adds weight to the argument for more aggressive management of delirium in this age group. There may exist both 'benign' and 'malignant' forms of paediatric delirium, but at this point in time the correlates of 'malignant paediatric delirium' remain unknown (Schieveld, 2008).

However, evidence for the attenuation of morbidity and mortality with aggressive treatment of delirium, including pharmacotherapy, is lacking in *any* age group. Follow-up studies of delirium in children and adolescents are urgently needed to better characterise both the nature and durability of residual deficits associated with delirium.

4.7 Assessment and diagnosis

Many unanswered questions remain in relation to the assessment and diagnosis of delirium in children and adolescents.

Perhaps the most pressing of these questions for current and future researchers include:

- Are current operational criteria for delirium optimal for making the diagnosis in children?
- Where is the threshold for delirium 'caseness' in children and adolescents?
- Do we need a 'distress and/or impairment' criterion in the diagnosis of delirium in children and adolescents?

Difficulties in the assessment and diagnosis of delirium are far from unique to children, as reflected in the high rates of underrecognition and misdiagnosis amongst adult and geriatric patients with delirium.

As discussed earlier, part of this problem may relate to the way in which delirium is currently operationally defined as a disorder of consciousness. Bhat and Rockwood's (2006) proposals represent an attempt at creating a novel operational definition of delirium as a disorder of disturbed consciousness with high clinical utility in addition to validity and reliability. Although there are clearly more similarities than differences in the manner in which delirium manifests across the lifespan, it is also clear that developmental aspects *do* modify the expression of delirium, particularly in young children. This pathoplastic effect of immaturity on the syndrome of delirium also provides for some relatively unique features of delirium in young children, as described above. Neglecting these maturational aspects may result in an even lower sensitivity and/or specificity of current operational diagnostic criteria when applied to children. At a time when the current operational criteria and syndromic boundaries of delirium are being actively debated, it would seem an opportune time to take a close look at the developmental aspects of the disorder.

As delirium in children appears increasingly more akin to a spectrum disorder than a discrete diagnostic category, I would argue that the absence of both 'distress' and 'impairment' criteria in existing operational definitions of delirium potentially creates a therapeutic dilemma. In this context, where then is the imaginary threshold for pharmacological intervention crossed? This dilemma is particularly evident in the case of hypoactive delirium in children, in which the evidence base for pharmacotherapy is vanishingly thin.

I would like to argue that, in addition to a 'distress and/or impairment' criterion, current operational criteria might benefit from incorporating alternative, modified criteria for use in young children, especially with regards the core criterion of 'disturbance of consciousness'. This could be achieved in the same way that DSM IV-TR currently

offers alternative ways in which children might fulfill the re-experiencing criteria of posttraumatic stress disorder.

Would the current 'core' DSM IV-TR criterion (a 'disturbance of consciousness'; Criterion A) benefit from the addition of alternatives for use in children? The existing literature suggests that two features in particular might be incorporated into current definitions to facilitate diagnosis in children. Both 'transient regression with loss of skills' and 'inconsolability or lack of eye contact with a usual primary caregiver' could potentially serve as substitutes in fulfilling Criterion A in young children. Alternatively, perhaps a greater emphasis on the temporal aspects of the presentation (nocturnal worsening, reversal of sleep-wake cycle, dramatic fluctuation), as is seen in the ICD-10 criteria, would be appropriate in young children.

Current operational criteria for delirium such as those of the DSM-IV-TR were designed for use in adults, and their ability to 'capture' delirium may diminish as we proceed further down the age spectrum. As is the case with the delirium rating instruments, which have been derived from research into adult and geriatric patients with delirium but more recently applied to children and adolescents, their true sensitivity, specificity and reliability in this age group remains unknown.

4.8 Rating instruments

Formal rating instruments are often helpful in the screening and assessment of psychiatric disorders. Delirium rating instruments are, for the most part, derived from DSM operational criteria for delirium. One of these instruments, the DRS, has now been applied to children and adolescents with delirium by 3 separate groups of researchers, including my own study, with similar mean scores and range of scores reported as are generally found in older patients with delirium. Data from the Red Cross Children's Hospital series also suggests that the DRS-R-98 produces similar scores in children and adolescents as have been reported in adults and the elderly.

However, just because a rating instrument produces similar scores in the child and adolescent population with delirium does not imply that it has a similar sensitivity, specificity and reliability for delirium as in the population in which it was originally validated. It may be that the DRS has in fact a much lower sensitivity, specificity and reliability for delirium in children than in adults or the elderly, owing to the fact that its scale items are not particularly developmentally-sensitive.

Until rating instruments such as the DRS or DRS-R-98 have been formally validated with the use of appropriate control groups in the child and adolescent population, their usefulness in screening, assessment and monitoring of response to treatment may be limited

As a pleomorphic and protean disorder for which the overarching treatment strategy remains reversal or removal of the underlying cause(s), the challenges in the assessment of the efficacy of both pharmacological and environmental adjunctive strategies are considerable but not insurmountable.

A valid and reliable measure of delirium and its severity that can be used for documenting improvement or deterioration in severity by means of repeated measures would clearly be a good start.

Neither the DRS, nor the DRS-R-98 have been fully validated in children and adolescents, and their sensitivity, specificity, positive and negative predictive value for delirium in this age group remains unknown. Similarly, reliability data is currently not available in children and adolescents. The only delirium rating instrument specifically designed for use in children is the PAED scale, which probably only has utility in the post-anaesthetic and possibly PICU setting. One option would be to take an existing instrument like the DRS-R-98, and to apply it to suitable non-delirious child and adolescent control groups, such as psychiatric inpatients and preoperative paediatric surgery inpatients, as well as subjects with delirium in order to establish its discriminant validity and reliability.

Another option, however, would be to follow the example of Sikich and Lerman (2004), who in the absence of a reliable and valid rating scale to measure emergence delirium in children recovering from anaesthesia, set out to develop and evaluate one of their own, the PAED scale. Given the current state of research in this area, a novel instrument specifically designed to evaluate delirium in children and adolescents would perhaps best be developed using a systematic review of the existing literature (as has been described in Chapter 2), and an international, multidisciplinary consensus meeting of experts in the field. Such an instrument would then potentially allow us to screen for delirium in different paediatric settings, provide further clarity with regards high-risk groups, and facilitate preventative interventions in these groups.

If such an instrument included a rating of delirium severity, repeated measures could provide information relating to the natural course and treatment responsiveness of delirium among child and adolescent patients. It is worth considering at this point as to what 'gold standard' such an instrument might be measured against – current DSM IV-TR criteria, or novel, developmentally-sensitive consensus criteria?

In order to measure the effectiveness of adjunctive pharmacological and environmental interventions in delirium in this age group, we also require a valid and reliable measure of physical disease burden and complexity in children and adolescents that is sensitive to relatively rapid changes in physical status. Schieveld *et al.*, (2008) have described the use of the Paediatric Index of Mortality (PIM) and Paediatric Risk of Mortality (PRISM), two widely used instruments for rating generic physical illness severity in predicting delirium in the PICU setting.

In order to validly assess the effectiveness of both pharmacological and environmental interventions in childhood and adolescent delirium, over and above the expected improvements in delirium symptomatology resulting from amelioration or complete reversal of precipitating and perpetuating factor(s), and characteristic fluctuations in delirium symptom severity, it will be necessary to employ in parallel valid repeated measures of both delirium severity and physical illness severity.

If it can be shown in a considerable proportion of young patients with delirium, that despite the burden of physical illness remaining relatively constant, severity of delirium improves in response to pharmacological or environmental interventions, then, at last we might be able to conclude with greater certainty that our interventions are effective. With a reliable and valid instrument for assessing both the presence and severity of paediatric delirium, used in conjunction with a measure such as the PIM or PRISM, we might be in a position to consider a randomised, double-blind, placebo-controlled trial of pharmacotherapy in children with delirium.

4.9 Treatment

The following questions in relation to the treatment of delirium in children and adolescents remain incompletely answered and are arguably amongst the most pertinent for current and future researchers.

- Can, as I have suggested in this study, certain types of delirium in children and adolescents be treated solely with aggressive environmental management, in parallel with attempts at reversing or ameliorating precipitating and/or perpetuating factor(s)?
- Where is threshold for pharmacotherapy? In other words, at what point does the risk: benefit analysis for pharmacotherapy tip in favour of benefit in children and adolescents with delirium?
- Do we, at this point in time, have sufficient empirical evidence relating to the morbidity and mortality associated with paediatric delirium to advocate for aggressive pharmacotherapy in most, if not all cases of delirium?
- How can we best assess treatment effectiveness in paediatric delirium?
- Is predominantly hypoactive delirium in children and adolescents best treated in the same manner as hyperactive delirium?
- Is there a place for psychostimulants in the treatment of hypoactive delirium in children and adolescents?

The existing evidence relating to the treatment of delirium in children and adolescents is based entirely on open and uncontrolled studies, case reports, anecdote, and expert opinion. To a large extent recommendations for management appear to be heavily derived from the evidence base in adults with delirium, which is, as I have taken pains to point out, perilously slim. The situation appears to be particularly fraught in relation to the pharmacological management of hypoactive delirium. Both the characteristically fluctuating nature of delirium and the necessarily multi-component nature of its management present significant challenges to researchers investigating its optimal treatment

Antipsychotics remain the mainstay of delirium pharmacotherapy, although the evidence for efficacy is tenuous and flawed, even in the case of haloperidol, for which there is most evidence. Children and adolescents are especially vulnerable to the side-effects of these medications, and high rates of movement disorders have been reported in some (but by no means all) of the few case series of definite or probable delirium in children or adolescents treated with haloperidol.

The risk: benefit analysis for the use of antipsychotic medications in children and adolescents with delirium thus needs to incorporate an appreciation of:

- A suggestion of serious morbidity and potentially independently increased risk of mortality of delirium in this age group from a number of authors
- The limitations of the existing data relating to the efficacy of antipsychotic medications in *adults* with delirium
- The even more significant limitations of the data relating to efficacy in children and adolescents
- The increased risk of significant side-effects from these medications in children and adolescents
- The potential for distress, impairment and risk of adverse outcomes associated with delirium in individual children and adolescents

In Appendix I (page 396), I have set out my own recommendations for management of delirium in children, with suggestions as to how the imaginary threshold for pharmacotherapy might be demarcated. In essence, the threshold for pharmacotherapy represents the point at which the risk: benefit ratio for the use of antipsychotics tips in favour of benefit. Based on my own clinical experience and a systematic review of the literature I have suggested that the combination of:

- Poor or partial response to environmental management strategies, AND
- Relatively irreversible or persistently elusive precipitating factors, AND
- Distress and/or functional impairment (broadly defined)

identifies a threshold at which, once crossed, the potentially significant risks of antipsychotic medication are outweighed by the potential benefits in this age group.

4.10 Future research

As a common condition of potentially great clinical significance, delirium in children and adolescents clearly warrants further research. In view of the fact that there would currently seem to be only 4 research groups worldwide working on delirium in this age group, an international working group and collaborative research efforts would seem to be the best way forward. Through collaboration, consensus operational criteria for use in children, and a specific, developmentally sensitive delirium rating instrument might become a reality.

I have already suggested that potentially fruitful avenues for future research in this area include the development and piloting of developmentally-sensitive, modified diagnostic criteria and rating instruments, the screening, prevention and early intervention amongst high-risk groups, follow-up studies to evaluate the frequency, durability and significance of residual deficits, and methodologically rigorous treatment trials. I have also briefly discussed the necessary preconditions for a randomised, double-blind, placebo-controlled trial of pharmacotherapy in children with delirium.

Jan Schieveld (2008) has posed the question as to whether such a trial would be both possible and ethical in paediatric delirium.

I would like to suggest that by employing rating instruments like the PIM or PRISM, in conjunction with either the DRS-R-98 (if it were to be further validated in this population), or the hypothetical, developmentally-sensitive delirium rating instrument outlined above, that such a trial would certainly be *possible*.

The *ethics* of a randomised, double-blind, placebo-controlled trial of pharmacotherapy in children and adolescents with delirium is clearly complex. Just some of the many factors to be considered would include:

- The evidence for morbidity and mortality independently associated with delirium in this age group
- The existing evidence for the effectiveness of adjunctive pharmacotherapy for delirium in adults
- The existing evidence for the effectiveness of adjunctive pharmacotherapy for delirium in children and adolescents
- The evidence relating to the burden of side effects associated with currently recommended pharmacological treatments for delirium in children and adolescents.
- The existence and effectiveness of other, potentially safer, treatments for delirium in children and adolescents

Based on a comprehensive systematic review of the available literature, it would seem that:

- The existing evidence for morbidity and mortality *independently* associated with delirium in children and adolescents, over and above the obvious behavioural concomitants, is very tenuous (although worrying hints and glimpses *are* to be found)

- The current evidence for the effectiveness of adjunctive pharmacotherapy for delirium in *adults* rests largely on open and uncontrolled clinical trials.
- The current evidence for the effectiveness of adjunctive pharmacotherapy for delirium in children and adolescents currently rests on the very lowest rungs of the hierarchical ladder of empirical evidence – case series, case report and expert opinion.
- The evidence relating to the side effect burden of antipsychotic medication in children and adolescents with delirium is decidedly mixed, with some authors reporting high rates of extrapyramidal symptoms and others reporting virtually no side effects. However, there are a number of case reports that document delirium *precipitated* by the use of antipsychotics in young people.

With these factors in mind, I believe that an ethical argument can be put forward for a randomised, controlled trial of aggressive environmental management PLUS antipsychotic medication compared to aggressive environmental management alone in the treatment of delirium in children and adolescents.

An ethical argument for a randomised, *placebo*-controlled trial of adjunctive pharmacotherapy in delirium in this age group is more difficult to formulate, given the current state of the evidence in adult patients with delirium, in which only one placebo-controlled study has been reported to date.

The question of psychostimulants in the management of hypoactive delirium in any age group remains extremely controversial. The demarcation between severe hypoactive delirium and stupor is indistinct, and it is debatable as to whether ‘pure’ hypoactive delirium/stupor should be classified with other forms of delirium at all. The adult literature suggests that hypoactive delirium has both a worse prognosis than other forms of delirium, and a poorer response to antipsychotic medication. Diminished arousal and attention are universal features of hypoactive delirium/stupor, and these features are traditional targets of the psychostimulants. Ameliorating these features would facilitate rehabilitation, self-care and participation in decision-making. The risks of psychostimulants in hypoactive delirium are unclear, but could conceivably include a

worsening of delirium or a 'switch' from hypoactive to hyperactive delirium. It should, however, be recalled that the antipsychotic medications have *also* been implicated in precipitating and exacerbating delirium on occasion, and that the short-acting stimulants have half-lives considerably shorter than the antipsychotic medications. Lastly, if any group is in a position to go forward with a trial of psychostimulants in hypoactive delirium, it would surely be child (neuro)psychiatrists, who are extremely familiar with these medications in the treatment of attention-deficit hyperactivity disorder.

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Appendices

Appendix A

The Delirium Rating Scale (*Trzepacz et al., 1988*)

Item 1: Temporal onset of symptoms

- 0. No significant change from longstanding behaviour
- 1. Gradual onset of symptoms, occurring within a 6-month period
- 2. Acute change in behaviour or personality occurring over a month
- 3. Abrupt change in behaviour, usually occurring over a 1- to 3-day period

Item 2: Perceptual disturbances

- 0. None evident by history or observation
- 1. Feelings of depersonalisation or derealisation
- 2. Visual illusions or misperceptions
- 3. Evidence that the patient is markedly confused about external reality

Item 3: Hallucination type

- 0. Not present
- 1. Auditory hallucinations only
- 2. Visual hallucinations present on history or observation
- 3. Tactile, olfactory, or gustatory hallucinations

Item 4: Delusions

- 0. Not present
- 1. Delusions are systematized i.e. well-organised and persistent
- 2. Delusions are new and not part of a preexisting primary psychiatric disorder

- 3. Delusions are not well circumscribed; are transient, poorly organised , and mostly in response to misperceived environmental cues

Item 5: Psychomotor behaviour

- 0. No significant retardation or agitation
- 1. Mild restlessness, tremulousness, or anxiety evident by observation and a change from patient's usual behaviour
- 2. Moderate agitation with pacing, removing i.v's etc.
- 3. Severe agitation, needs to be restrained, may be combative, or has significant withdrawal from the environment

Item 6: Cognitive status during formal testing

- 0. No cognitive deficits, or deficits which can be alternatively explained by lack of education or prior mental retardation
- 1. Very mild cognitive deficits which might be attributed to inattention due to acute pain, fatigue, depression, or anxiety associated with medical illness
- 2. Cognitive deficit largely in one major area tested ,e.g. memory, but otherwise intact
- 3. Significant cognitive deficits which are diffuse, i.e. affecting many different areas tested, must include periods of disorientation to time or place at least once each 24-hr period; registration and/or recall are abnormal; concentration is reduced
- 4. Severe cognitive deficits, including motor or verbal perseverations, confabulations, disorientation to person, remote and recent memory deficits, and inability to cooperate with formal mental status testing

Item 7: Physical Disorder

- 0. None present or active
- 1. Presence of any physical disorder which might affect mental state
- 2. Specific drug, infection, metabolic, central nervous system lesion, or other medical problem which can be temporally implicated in causing the altered behaviour or mental status

Item 8: Sleep-wake cycle disturbance

- 0. Not present
- 1. Occasional drowsiness during day and mild sleep continuity disturbance at night
- 2. Frequent napping and unable to sleep at night, constituting a significant disruption of or a reversal of the usual sleep-wake cycle
- 3. Drowsiness prominent, difficulty staying alert during interview, loss of self-control over alertness and somnolence
- 4. Drifts into stuporous or comatose periods

Item 9: Lability of mood

- 0. Not present, mood stable
- 1. Affect/mood somewhat altered and changes over the course of hours
- 2. Significant mood changes which are inappropriate to situation, including fear, anger, or tearfulness; rapid shifts of emotion, even over several minutes
- 3. Severe disinhibition of emotions, including temper outbursts, uncontrolled inappropriate laughter, or crying

Item 10: Variability of symptoms

- 0. Symptoms stable and mostly present during daytime
- 2. Symptoms worse at night
- 4. Fluctuating intensity of symptoms, such that they wax and wane during a 24-hr period

Appendix B

The PAED Scale (Sikich *et al.*, 2004)

1. The child makes eye contact with the caregiver
2. The child's actions are purposeful
3. The child is aware of his/her surroundings
4. The child is restless
5. The child is inconsolable

Items 1,2 and 3 are reversed scored as follows: 4 = not at all, 3 = just a little, 2 = quite a bit, 1 = very much, 0 = extremely. Items 4 and 5 are scored as follows: 0 = not at all, 1 = just a little, 2 = quite a bit, 3 = very much, and 4 = extremely.

Appendix C

Delirium Rating Scale–Revised–98 (Trzepacz *et al.*, 2001)

This is a revision of the Delirium Rating Scale (Trzepacz *et al.* 1998). It is used for initial assessment and repeated measurements of delirium symptom severity. The sum of the 13 item scores provides a severity score. All available sources of information are used to rate the items (nurses, family, chart) in addition to examination of the patient. For serial repeated ratings of delirium severity, reasonable time frames should be chosen between ratings to document meaningful changes because delirium symptom severity can fluctuate without interventions.

DRS-R-98 Severity Scale

1. Sleep-wake cycle disturbance

- 0. Not present
- 1. Mild sleep continuity disturbance at night or occasional drowsiness during day
- 2. Moderate disorganisation of sleep-wake cycle (e.g. falling asleep during conversations, napping during the day or several brief awakenings during the night with confusion / behavioural changes or very little nighttime sleep)
- 3. Severe disruption of sleep-wake cycle (e.g. day-night reversal of sleep-wake cycle or severe circadian fragmentation with multiple periods of sleep and wakefulness or severe sleeplessness)

2. Perceptual disturbances and hallucinations

- 0. Not present
- 1. Mild perceptual disturbances (e.g. derealisation or depersonalisation, or patient unable to discriminate dreams from reality)
- 2. Illusions present
- 3. Hallucinations present

3. Delusions

- 0. Not present
- 1. Mildly suspicious, hypervigilant, or preoccupied
- 3. Unusual or overvalued ideation
- 4. Delusional

4. Lability of affect

- 0. Not present
- 1. Affect somewhat altered or incongruent to situation; changes over the course of hours; emotions are mostly under self-control
- 2. Affect is often inappropriate to the situation and intermittently changes over the course of minutes; emotions are not consistently under self-control, though they respond to redirection by others.
- 3. Severe and consistent disinhibition of emotions; affect changes rapidly, is inappropriate to context, and does not respond to redirection by others.

5. Language

- 0. Normal language
- 1. Mild impairment including word-finding difficulty or problems with naming or fluency
- 2. Moderate impairment including comprehension difficulties or deficits in meaningful communication
- 3. Severe impairment including nonsensical semantic content, word salad, muteness, or severely reduced comprehension

6. Thought process abnormalities

- 0. Normal thought processes
- 1. Tangential or circumstantial
- 2. Associations loosely connected occasionally, but largely comprehensible
- 3. Associations loosely connected most of the time

7. Motor agitation

- 0. No restlessness or agitation
- 1. Mild restlessness or gross motor movements or mild fidgetiness
- 2. Moderate motor agitation including dramatic movements of the extremities, pacing, fidgeting, removing intravenous lines, etc.
- 3. Severe motor agitation, such as combativeness or a need for restraints or seclusion

8. Motor retardation

- 0. No slowness of voluntary movements
- 1. Mildly reduced frequency, spontaneity or speed of motor movements, to the degree that may interfere with the assessment
- 2. Moderately reduced frequency, spontaneity or speed of motor movements to the degree that it interferes with participation in activities of self-care
- 3. Severe motor retardation with few spontaneous movements

9. Orientation

- 0. Orientated to person, place and time
- 1. Disorientated to time or to place but not both
- 2. Disorientated to time and place
- 3. Disorientated to person

10. Attention

Attention can be assessed during the interview (e.g. verbal perseverations, distractability, and difficulty with set shifting) and / or through the use of specific tests, e.g. digit span

- 0. Alert and attentive
- 1. Mildly distractible or mild difficulties sustaining attention, but able to refocus with cueing. On formal testing makes only minor errors and is not significantly slow in responses

- 2. Moderate inattention with difficulty focusing and sustaining attention. On formal testing, makes numerous errors and either requires prodding to focus or finish task
- 3. Severe difficulty focusing and/or sustaining attention, with many incorrect or incomplete responses or inability to follow instructions. Distractible by other noises or events in the environment.

11. Short-term memory

Defined as recall of information (e.g. 3 items presented either verbally or visually) after a delay of 2 to 3 minutes

- 0. Short-term memory intact
- 1. Recalls 2/3 items; may recall 3rd after category cueing
- 2. Recalls 1/3 items; may be able to recall other items after category cueing
- 3. Recalls 0/3 items

12. Long-term memory

Can be assessed formally or through interviewing for recall of past personal information. When formally tested, use a verbal and / or visual modality for 3 items recalled after at least 5 minutes.

- 0. No significant long-term memory deficits
- 1. Recalls 2/3 items and/or has minor difficulty recalling details of other long-term information
- 2. Recalls 1/3 items and/or has moderate difficulty recalling other long-term information
- 3. Recalls 0/3 items and/or has severe difficulty recalling other long-term information

13. Visuospatial ability

Consider patient's difficulty navigating their way around environment. Test formally by drawing or copying a design, by arranging puzzle pieces etc.

- 0. No impairment
- 1. Mild impairment such that overall design and most details or pieces are correct; and/or little difficulty navigating in his/her surroundings
- 2. Moderate impairment with distorted appreciation of overall design and/or several errors of details or pieces; and/or needing repeated redirection to keep from getting lost
- 3. Severe impairment on formal testing; and/or repeated wandering or getting lost

DRS-R-98 Optional Diagnostic Items

These 3 items can be used to assist in the differentiation of delirium from other disorders for diagnostic and research purposes. They are added to the severity score for the total scale score, but are NOT included in the severity score.

14. Temporal onset of symptoms

- 0. No significant change from usual or longstanding baseline behaviour
- 1. Gradual onset of symptoms, occurring over a period of several weeks to a month
- 2. Acute change in behaviour or personality occurring over days to a week
- 3. Abrupt change in behaviour occurring over a period of several hours to a day

15. Fluctuation of symptom severity

Rate the waxing and waning of an individual or cluster of symptom(s) over the time frame being rated.

- 0. No symptom fluctuation
- 1. Symptom intensity fluctuates in severity over hours

- 2. Symptom intensity fluctuates in severity over minutes

16. Physical disorder

Rate the degree to which a physiological, medical, or pharmacological problem can be specifically attributed to have caused the symptoms being assessed.

- 0. None present or active
- 1. Presence of any physical disorder that might affect mental state
- 2. Drug, infection, metabolic disorder, CNS lesion or other medical problem that specifically can be implicated in causing the altered behaviour or mental state.

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Appendix D

Oxford Centre for Evidence-based Medicine Levels of Evidence (Therapy/Prevention)

- Level 1a:** Systematic review of randomised controlled trials (with homogeneity*)
- Level 1b:** Individual randomised controlled trial (with narrow Confidence Interval)
- Level 1c:** All or none §
- Level 2a:** Systematic review (with homogeneity*) of cohort studies
- Level 2b:** Individual cohort study (including low quality RCT; e.g., <80% follow-up)
- Level 2c:** "Outcomes" Research; Ecological studies
- Level 3a:** Systematic review (with homogeneity*) of case-control studies
- Level 3b:** Individual Case-Control Study
- Level 4:** Case-series (and poor quality cohort and case-control studies §§
- Level 5:** Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998.

Notes

* By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level.

§ Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it.

Grades of Recommendation

A: consistent level 1 studies

B: consistent level 2 or 3 studies *or* extrapolations from level 1 studies

C: level 4 studies *or* extrapolations from level 2 or 3 studies

D: level 5 evidence *or* troublingly inconsistent or inconclusive studies of any level

("Extrapolations" are where data is used in a situation which has potentially clinically important differences than the original study situation)

Appendix E Case series: Delirium Rating Scale (DRS), Delirium Rating Scale –Revised- 98 (DRS-R-98), and Paediatric Anaesthesia Emergence Delirium (PAED) scale in 23 children and adolescents diagnosed with delirium (N=23)

No.	DRS score (max =32; missing items omitted) %	DRS score (max =32; missing items scored midway) %	DRS-98-R Total (max = 46; missing items omitted) %	DRS-98-R Total (max = 46; missing items scored midway) %	DRS-98-R Severity (max = 39; missing items omitted) %	DRS-98-R Severity (max = 39; missing items scored midway) %	PAED score (max = 20; missing items omitted) %	PAED score (max = 20; missing items scored midway %
1	21/32 (65.5)	21/32 (65.5)	20/43 (46.5)	21.5/46 (47.0)	14/36 (39.0)	15.5/39 (40.0)	14 (70.0)	14 (70.0)
2	21/32 (65.5)	21/32 (65.5)	20/46 (43.5)	20/46 (43.5)	14/39 (36.0)	14/39 (36.0)	13 (65.0)	13 (65.0)
3	19/32 (59.5)	19/32 (59.5)	18/46 (39.0)	18/46 (39.0)	12/39 (31.0)	12/39 (31.0)	6/16 (37.5)	8 (40.0)
4	21/32 (65.5)	21/32 (65.5)	22/31 (71.0)	29.5/46 (64.0)	16/24 (67.0)	23.5/39 (60.0)	16 (80.0)	16 (80.0)
5	25/32 (78.0)	25/32 (78.0)	26/37 (70.0)	30.5/46 (66.5)	20/30 (67.0)	24.5/39 (63.0)	15 (75.0)	15 (75.0)

Appendix E (continued) Case series: Delirium Rating Scale (DRS), Delirium Rating Scale –Revised- 98 (DRS-R-98), and Paediatric Anaesthesia Emergence Delirium (PAED) scale in 23 children and adolescents diagnosed with delirium (N=23)

No.	DRS score (max =32; missing items omitted) %	DRS score (max =32; missing items scored midway) %	DRS-98-R Total (max = 46; missing items omitted) %	DRS-98-R Total (max = 46; missing items scored midway) %	DRS-98-R Severity (max = 39; missing items omitted) %	DRS-98-R Severity (max = 39; missing items scored midway) %	PAED score (max = 20; missing items omitted) %	PAED score (max = 20; missing items scored midway %
6	24/32 (75.0)	24/32 (75.0)	25/37 (67.5)	29.5/46 (64.0)	19/30 (63.5)	23.5/39 (60.5)	13 (65.0)	13 (65.0)
7	22/32 (69.0)	22/32 (69.0)	25/37 (67.5)	29.5/46 (64.0)	19/30 (63.5)	23.5/39 (60.5)	16 (80.0)	16 (80.0)
8	16/28 (57.0)	18/32 (56.0)	17/37 (46.0)	21.5/46 (47.0)	11/30 (36.5)	15.5/39 (40.0)	11 (55.0)	11 (55.0)
9	20/32 (62.5)	20/32 (62.5)	20/43 (46.5)	21.5/46 (47.0)	13/36 (36.0)	14.5/39 (37.0)	15 (75.0)	15 (75.0)
10	27/32 (84.5)	27/32 (84.5)	29/43 (67.0)	30.5/46 (66.5)	23/36 (64.0)	24.5/39 (63.0)	9 (45.0)	9 (45.0)

Appendix E (continued) Case series: Delirium Rating Scale (DRS), Delirium Rating Scale –Revised- 98 (DRS-R-98), and Paediatric Anaesthesia Emergence Delirium (PAED) scale in 23 children and adolescents diagnosed with delirium (N=23)

No.	DRS score (max =32; missing items omitted) %	DRS score (max =32; missing items scored midway) %	DRS-98-R Total (max = 46; missing items omitted) %	DRS-98-R Total (max = 46; missing items scored midway) %	DRS-98-R Severity (max = 39; missing items omitted) %	DRS-98-R Severity (max = 39; missing items scored midway) %	PAED score (max = 20; missing items omitted) %	PAED score (max = 20; missing items scored midway %
11	21/32 (65.5)	21/32 (65.5)	13/25 (52.0)	23.5/46 (51.0)	8/18 (44.5)	18.5/39 (47.5)	7 (35.0)	7 (35.0)
12	14/32 (44.0)	14/32 (44.0)	16/37 (43.0)	20.5/46 (44.5)	12/30 (40.0)	16.5/39 (42.5)	6 (30.0)	6 (30.0)
13	23/30 (76.5)	24/32 (75.0)	19/22 (86.0)	31/46 (67.5)	12/15 (80.0)	24/39 (61.5)	16 (80.0)	16 (80.0)
14	23/32 (73.0)	23/32 (73.0)	24/37 (65.0)	28.5/46 (62.0)	18/30 (60.0)	22.5/39 (58.0)	12/16 (75.0)	14 (70.0)
15	28/32 (87.5)	28/32 (87.5)	30/46 (65.0)	30/46 (65.0)	23/39 (59.0)	23/39 (56.5)	12/16 (75.0)	14 (70.0)

Appendix E (continued) Case series: Delirium Rating Scale (DRS), Delirium Rating Scale –Revised- 98 (DRS-R-98), and Paediatric Anaesthesia Emergence Delirium (PAED) scale in 23 children and adolescents diagnosed with delirium (N=23)

No.	DRS score (max =32; missing items omitted) %	DRS score (max =32; missing items scored midway) %	DRS-98-R Total (max = 46; missing items omitted) %	DRS-98-R Total (max = 46; missing items scored midway) %	DRS-98-R Severity (max = 39; missing items omitted) %	DRS-98-R Severity (max = 39; missing items scored midway) %	PAED score (max = 20; missing items omitted) %	PAED score (max = 20; missing items scored midway %
16	20/28 (71.5)	22/32 (69.0)	15/25 (60.0)	20.5/46 (45.0)	10/18 (55.5)	20.5/39 (52.5)	11/16 (69.0)	13 (65.0)
17	22/32 (69.0)	22/32 (69.0)	23/34 (68.0)	29/46 (63.0)	18/27 (67.0)	24/39 (61.5)	16 (80.0)	16 (80.0)
18	23/32 (72.0)	23/32 (72.0)	25/37 (67.5)	29.5/46 (64.0)	20/30 (67.0)	24.5/39 (63.0)	12 (60.0)	12 (60.0)
19	19/32 (59.5)	19/32 (59.5)	22/43 (51.0)	23.5/46 (51.0)	17/36 (47.0)	18.5/39 (47.5)	7/16 (44.0)	9 (45.0)
20	25/32 (78.0)	25/32 (78.0)	26/46 (56.5)	26/46 (56.5)	19/39 (41.5)	19/39 (41.5)	10 (50.0)	10 (50.0)

Appendix E (continued) Case series: Delirium Rating Scale (DRS), Delirium Rating Scale –Revised- 98 (DRS-R-98), and Paediatric Anaesthesia Emergence Delirium (PAED) scale in 23 children and adolescents diagnosed with delirium (N=23)

No.	DRS score (max =32; missing items omitted) %	DRS score (max =32; missing items scored midway) %	DRS-98-R Total (max = 46; missing items omitted) %	DRS-98-R Total (max = 46; missing items scored midway) %	DRS-98-R Severity (max = 39; missing items omitted) %	DRS-98-R Severity (max = 39; missing items scored midway) %	PAED score (max = 20; missing items omitted) %	PAED score (max = 20; missing items scored midway) %
21	17/32 (53.0)	17/32 (53.0)	17/40 (42.5)	20/46 (43.5)	11/33 (33.5)	14/39 (36.0)	10 (50.0)	10 (50.0)
22	26/32 (81.0)	26/32 (81.0)	28/34 (82.0)	34/46 (74.0)	22/27 (81.5)	28/39 (72.0)	12/16 (75.0)	14 (70.0)
23	27/32 (84.5)	27/32 (84.5)	23/34 (68.0)	29/46 (63.0)	17/27 (63.0)	23/39 (59.0)	11/16 (69.0)	13 (65.0)
Mean	22.2 (69.4)	22.1 (69.2)	27.4 (59.6)	26 (56.5)	21 (54.0)	20.2 (51.7)	12.5 (62.6)	12.3 (61.7)

Appendix F Delirium Rating Scale (DRS) scores in a non-delirious child and adolescent psychiatry outpatient sample (N=25)

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
1 Temporal onset	0	0	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
2 Percepts	0	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3 Hallucinations	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4 Delusions	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5 Psychomotor	1	1	1	3	1	1	1	1	1	1	2	1	1	1	2	0	1	2	2	1	1	0	1	1	1
6 Cognitive	0	1	1	3	1	2	1	2	0	2	3	1	1	2	3	0	0	1	1	0	1	1	1	1	2
7 Physical	2	0	0	2	1	0	0	0	0	1	2	2	2	2	2	0	1	0	0	0	2	0	0	0	0
8 Sleep-wake	0	0	1	1	0	1	2	0	1	1	1	1	0	0	1	0	0	0	0	0	0	0	0	1	0
9 Mood lability	1	1	1	0	0	1	1	0	0	2	1	1	1	0	1	1	1	2	1	0	1	1	0	1	2
10 Variability	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1
Total	5	5	10	10	3	5	5	3	3	7	9	6	5	5	9	1	3	6	4	1	6	3	3	5	6

Appendix G Delirium Rating Scale-Revised-98 (DRS-R-98) scores in a non-delirious child and adolescent psychiatry outpatient sample (N=25)

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
1 Sleep-wake	1	1	1	1	0	1	1	0	1	1	1	0	1	0	1	0	0	0	0	0	0	0	0	1	0
2 Perceptual	0	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3 Delusions	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4 Affect lability	2	1	1	0	0	1	1	0	0	2	1	0	1	1	1	1	1	2	1	0	1	1	0	1	2
5 Language	1	1	1	1	1	1	1	0	0	1	1	1	1	2	1	0	0	2	0	0	1	0	0	0	1
6 Thought	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0
7 Agitation	1	1	1	0	0	2	1	1	0	1	1	1	1	0	2	0	0	2	2	0	1	0	1	1	1

Appendix G (continued) Delirium Rating Scale-Revised-98 (DRS-R-98) scores in a non-delirious child and adolescent psychiatry outpatient sample (N=25)

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25		
8	0	0	0	2	1	0	0	0	2	0	0	0	0	1	0	1	2	0	0	1	0	0	0	0	0	0	
Retardation																											
9 Orientation	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	1	0	0	0	0	0	0
10 Attention	0	2	1	2	1	2	1	2	0	2	2	1	1	1	2	0	1	2	1	0	1	1	1	1	1	2	2
11 STM	0	1	0	1	0	0	0	1	0	1	0	0	0	0	2	0	0	0	0	0	0	0	0	1	0	0	0
12 LTM	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
13	1	0	0	0	0	0	1	0	0	1	0	0	1	0	2	0	0	1	0	0	0	0	0	0	0	0	0
Visuospatial																											

Appendix G (continued) Delirium Rating Scale-Revised-98 (DRS-R-98) scores in a non-delirious child and adolescent psychiatry outpatient sample (N=25)

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Severity	6	7	8	8	3	7	6	4	3	9	6	3	6	5	13	2	5	11	5	1	5	3	3	4	6
14 Temporal onset	0	0	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
15	1	1	1	0	0	0	0	0	0	1	1	1	0	1	0	0	0	0	0	0	1	1	1	1	1
Fluctuation																									
16 Physical	2	0	0	2	1	0	0	0	0	2	2	2	2	2	2	1	1	0	0	0	2	0	0	0	0
Total	9	8	10	11	4	7	6	4	4	12	9	6	8	8	15	3	6	11	5	1	8	4	4	5	7

Appendix II Paediatric Anaesthesia Emergence Delirium (PAED) scale scores in a non-delirious child and adolescent psychiatry outpatient sample (N=25)

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	
1 Eye contact	3	2	2	3	1	2	2	2	2	2	2	2	1	3	2	4	3	3	1	1	1	1	1	1	1	0
2 Actions purposeful	1	1	1	1	1	1	1	1	0	1	1	1	1	1	2	1	1	2	1	1	1	1	0	0	0	1
3 Aware of surroundings	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	0	1	0	0	0	0	1
4 Restless	2	1	1	0	1	3	2	1	0	0	3	1	2	0	3	0	0	3	2	0	1	0	0	1	1	2
5 Inconsoleable	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	7	5	6	5	4	7	6	5	2	4	7	5	5	5	8	6	5	9	5	2	4	2	1	2	4	

Appendix I. Algorithm for the treatment of paediatric delirium

