Rapid review of drug management for paediatric seizure termination in the emergency setting

by

JC Stockigt

A thesis submitted in partial fulfillment
of the requirements for the degree

Master of Philosophy (MPhil) in
Emergency Medicine

University of Cape Town

February 2016

DECLARATION

I, Jeannie Claudette Stockigt, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signature: . Signed by candidate

Date: ..... 12 February 2016

Table of Contents

Acknowledgments

The author wishes to express sincere appreciation to Pierre Smit for his assistance in appraising the data, Michael McCaul for his valuable input in tiered approach research and to Dr Cheema, Paediatric Emergency Specialist, for her assistance in the preparation of this submission document.

List of Abbreviations

AGREE II	Appraisal of Guidelines for Research & Evaluation II
AIDS	Acquired Immunodeficiency Syndrome
AMSTAR	Assessing the Methodological Quality of Systematic Reviews
APLS	Advanced Pediatric Life Support
BDZ	Benzodiazepine
CI	Confidence Interval
CNS	Central Nervous System
CPG	Clinical Practice Guideline
CSE	Convulsive Status Epilepticus
CVS	Cardiovascular System
ED	Emergency Department
EMS	Emergency Medical Services
ETAT	Emergency Triage and Treatment
EUCTR	European Union Clinical Trials Registry
GABA	Gamma-aminobutyric Acid
GIN	Guidelines International Network
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HIV	Human Immunodeficiency Virus
HPCSA	Health Professions Council of South Africa
ICTRP	International Clinical Trial Registry Platform
ICU	Intensive Care Unit
IM	Intramuscular
IN	Intranasal
IV	Intravenous
LOS	Length of Stay
mg/kg	milligram per kilogram
MRC	Medical Research Council
NGC	National Guideline Clearinghouse
NICE	National Institute for Healthcare Excellence
OR	Odds Ratio
PACTR	Pan-Africa Clinical Trial Registry
PICU	Pediatric Intensive Care Unit

PR	Per Rectum
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomised Control Trial
RR	Relative Risk
SANCTR	South African National Clinical Trials Registry
SD	Standard Deviation
SIGN	Scottish Intercollegiate Guidelines Network
SL	Sublingual
SR	Systematic Review
WHO	World Health Organisation

PART A – PROTOCOL

As approved by UCT Ethics committee

Table of Contents

Table of Figures & Tables

Rationale for this review

Limited consensus is currently available on the best drug and best route of administration for acute seizure termination in both the prehospital and in-hospital environments. Due to differences between in-hospital (admitted patients in a ward) and prehospital or emergency departments, results and findings in one setting are not necessarily valid or applicable to other environments. In the South African prehospital setting, conflicting information and a lack of clarity exacerbates difficulties in practitioner training and education. Robust evidence-based protocols and evidence-based guidelines have been shown to improve management decisions in emergency situations[1–4]. The prehospital Health Professions Council of South Africa (HPCSA) protocol has not been updated since 2006. In several key areas, including acute seizure management of children, it is in urgent need of revision to incorporate the latest evidence and best practices. This study hopes to provide information that will support an evidence-based revision of the acute seizure management protocol for children in the pre-hospital and emergency department setting.

Literature Review

Paediatric Seizures

What is known about seizures

Terminology

A “seizure” is defined as transient abnormal neurological function caused by excessive abnormal electrical discharge of nerve tissue[5,6]. It may also be referred to as ictus/ictal period with a post-ictal period once the seizure terminates. A “convulsion” is defined as excessive and abnormal motor activity that can be as a result of seizures or other conditions.[5] Therefore, seizures do not equate to convulsions and convulsions do not equate to seizures.

Focal seizures are generally accepted as originating in a network/networks within a single hemisphere and may or may not spread to both hemispheres, referred to as secondary generalisation. Generalised seizure would be a seizure that originates at a point in a network/networks and rapidly encompasses both hemispheres.[7]

Status Epilepticus (SE) used to be defined as seizures lasting more than 30 minutes or multiple seizures in 30 minutes without regaining full consciousness in between each

seizure[1]. As Figure 1 indicates, the longer a seizure continues, the more difficult it will be to terminate[1,8] (either on its own or with medication). For this reason, the newer, more operational definition of SE goes as follows: "Status epilepticus … refers to more than five min of (*i*) continuous seizures or (*ii*) two or more discrete seizures between which there is incomplete recovery of consciousness". [1,9,10]

Convulsive status epilepticus (CSE) refers to repeated tonic-clonic body movements historically expected with seizure activity. As mentioned above, a seizure can be present without convulsions and SE may be present in the absence of any tonic-clonic movements. Non-convulsive SE is more difficult to detect and often left untreated longer than CSE.[11]

Epidemiology of seizures

Worldwide, approximately 50 million people suffer from epilepsy, 2.7 million in the United States (US) alone with 120 000 new onset seizures per year occurring in children less than 18 years of age and 75 000 of these in children less than 5 years (mostly febrile convulsions).[12] North American and European data in 2014 suggested that the incidence of epilepsy is the highest in the first year of life and is reported at 90 – 212 per 100 000 people, declining to 20 – 70 per 100 000 people in later childhood and early adolescence.[13] Approximately 200 000 new seizure presentations occur per year with most seen in the population of <2yr and >65yrs.[12] It is estimated that 11% of all people will have at least one non-pathological seizure in their lifetime while 3% of the population will be diagnosed with epilepsy in their lifetime[14].

In developed world settings, approximately 1% of all adult and 2% of all pediatric emergency department (ED) visits are due to seizures[14] (in 7% of adults and 6% of children the visit is secondary to CSE[8,14]) and 3% of all prehospital transportation occurs because of seizures[14]. In developing countries, the figures are likely to be even higher as there is the added burden of disease such as HIV/AIDS and high rates of serious central nervous system infections including Tuberculosis, meningitis and parasitic diseases (e.g. malaria and neurocysticercosis). According to the World Health Organisation (WHO), in low-income countries, children are 16 times more likely to die before the age of five than those in high-income countries. Six main conditions, of which epilepsy is one, cause this alarming statistics.[15] In Kenya children with CSE are admitted to the hospital 2-6 times more than in London, and many children do not attend hospitals in the Kenyan setting thus potentially increasing this number.[16]

Epidemiology of Convulsive Status Epilepticus

Four to eight per 1000 children will have experienced CSE before the age of 15. In the US and Europe, the estimated incidence of CSE is 6.8 – 41 per 100 000 per year with an associated mortality of 26% (adults)[10,17] and 17-23 per 100 000 children per year[18]. In France, Hubert *et al*.[19] estimate child mortality of 3-5% and that morbidity increases 2 fold when CSE is present. The overall incidence and mortality has increased over the last 30 years according to Logroscino *et al*[17] and elderly patients are two times more likely to suffer death when compared to children. Outcomes related to duration of seizures and mortality is estimated at 15-22% in CSE with 25% of survivors suffering decrease functionality post SE episode.

CSE occurs in 25% - 30% of people with epilepsy with only 36% are receiving treatment for this in sub-Saharan Africa.[20] The data from this survey (Tanzania, Uganda, South Africa, Kenya and Ghana) indicated that 69% of seizures start in childhood and 55% are due to febrile illnesses. During the African Child Neurology Association meeting health summaries from 23 African countries indicate that up to 20% of children admitted to district level hospitals suffer neurological conditions in particular acute seizures.[21] Only seven of these had national guidelines for the treatment of CSE. First line treatment was diazepam (n=21), lorazepam (n=2) or clonazepam (n=1), whilst 2 countries had no intervention beyond diazepam. Only 15 countries have access to pediatric intensive care units or pediatric beds in an adult intensive unit.[21]

Epidemiology of seizures in African settings

In South Africa, 8% of the population will have a seizure at some point in their life and approximately 50% of these will occur in childhood.[22] One in every 100 people will be diagnosed with epilepsy. First-time seizures in children are common[22] and increase the burden of disease in this population. Although true prevalence cannot be estimated, approximately 50% of all epilepsy patients will develop the disease before the age of 15 years[23]. A study in the Northern Province of South Africa indicated an incidence of 6.7 per 1000 children[24]. In the Northeast part of South Africa a crude prevalence of 7.0 per 1000 person years where observed[25] with numbers ranging between 2.9 and 26 per 1000 children on the African continent[24]. A more recent survey, estimates the prevalence at 2.3 per 1000 people in sub-Saharan Africa (survey in South Africa, Uganda and Kenya)[16],with a crude mortality rate of 33.3 per 1000 person years. The rate ratio in the

age group 0-5 years is 4.4 and 22.5 in the 6-12 year age group.[26] This rate is 6 times more than what was generally expected (Kenyan cross-sectional study) in ACE.

Summary of paediatric seizures

In general, seizures are under-appreciated and under-recognised[12]. Seizures are medical emergencies and should be treated promptly[27,10]. Delay in terminating seizures results in worsening neurological outcome, and increases morbidity and mortality[28,29]. Figure 1 (below) indicates the progression of seizures from brief isolated seizures to CSE as seizure duration increases.

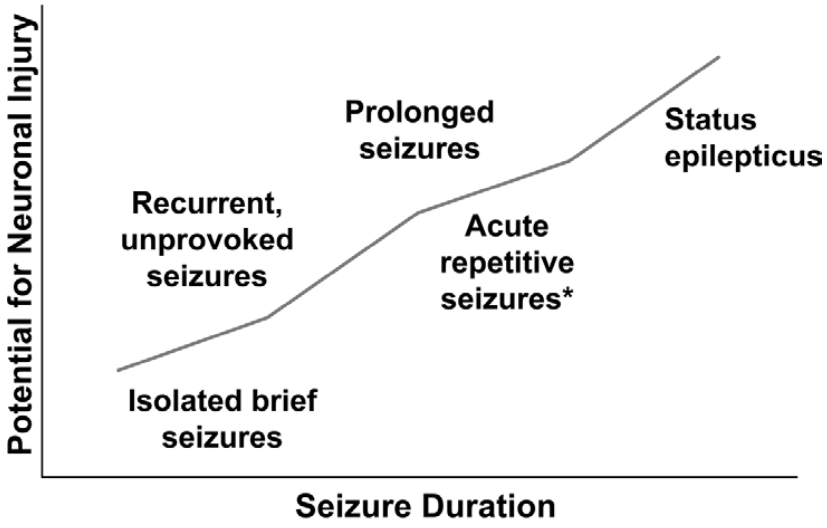
Seizures are the most common neurological emergency in children and may be due to acute or chronic conditions[30,31]. An epidemiology study performed in Richmond, Virginia demonstrated that infections not located in the central nervous system are the most common aetiology for CSE in children younger than two years of age.[31]

Benzodiazepines

History of Benzodiazepines

The first Benzodiazepine (BDZ), chlordiazepoxide (Librium), was identified in 1955 and made commercially available in 1960[32]. Diazepam followed in 1963 and BDZ popularity increased exponentially until researchers linked the mechanism of action to gamma-aminobutyric acid (GABA) and concerns about abuse and dependence increased sufficiently to institute legislation and guidelines for its use. [32]

FIGURE 1: ADOPTED FROM PELLOCK'S OVERVIEW OF SEIZURE AND NEUROLOGICAL INJURY[31]



BDZs have been used in the termination of seizures since 1965, when the first convulsive status epilepticus (CSE) patient was treated with intravenous diazepam. Diazepam is still used today as treatment for the termination of seizures. Midazolam was developed in the 1970s by Hoffman-La Roche and lorazepam followed in 1977. [33]

Benzodiazepine pharmacodynamics and pharmacokinetics

Pharmacokinetics relates to the time or course progression of drug absorption, distribution in the body, metabolism of the given drug and the elimination or excretion thereof. Pharmacodynamics is the relationship between drug concentration and site of action resulting in therapeutic and/or adverse effects. Generally speaking, the higher the concentration of the drug at the site of action (receptor site) the greater the intensity of action. [34]

BDZs act on gamma-aminobutyric acid A ($GABA_A$) receptors in the brain, mainly through ligand-gated chloride ion channels.[35] These receptors are activated when the inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), is released. GABA promotes the opening of the post-synaptic receptor $GABA_A$. Opening of $GABA_A$ receptors increases the polarity of the neural membrane (hyperpolarization) resulting in its inhibitory effects. BDZs increase the affinity between GABA and $GABA_A$ resulting in its potentiating effect on neurotransmission. This property makes it an attractive drug for the use in sedation, hypnosis, anxiolysis, for muscle relaxation and as an anticonvulsant. [35,36]

Some BDZs are longer acting than others (even when using similar routes of administration), depending on the metabolite they are degraded into, the activity and lipid solubility of these metabolites. Metabolites are generated by polymorphic enzymes (CYP3A4, CYP3A5 and CYP2C19) on BDZs. These enzymes affect the rate of absorption and metabolism and because of genetic predisposition some people will take longer to metabolize and eliminate BDZs than others. [37]

Although all BDZs share similarities in their properties, their physiochemical properties differ because of the lipid solubility of the drug. Lipid solubility relates directly to diffusion, absorption and effect of the different subtypes of BDZs because they cross the blood brain barrier to equilibrate within the neural tissue[37]. Ideally, oil-based drugs such as diazepam, should not be administered via the intramuscular (IM) route because of the potential for erratic and delayed absorption.[38] Midazolam and Lorazepam have better solubility and have improved absorption via the IM route.

In a study performed on 8 healthy volunteers, the kinetic parameters of drug distribution were determined by using serial concentration levels.[39] The elimination half-life of diazepam averaged 51.2 hours compared to lorazepam's 15.7 hours, this difference is due to the volume distribution of unbound drug (133 litre/kg diazepam and 12 litre/kg lorazepam). The shorter duration of action (considering the previous mentioned elimination half-life) of diazepam is due to its lipid solubility or octanol/water partition coefficient when compared to the other BDZs.[39]

Diazepam, with a half-life of 20-40 hours, is metabolised into *N*-desmethyldiazepam (nordazepam); the metabolite having a half-life of approximately 60 hours before being excreted in the urine as glucuronide conjugates. Consequently, diazepam is classified as a long acting BDZ.[35,36] Lorazepam, with an estimated half-life of 8-12 hours, is metabolised directly to inactive glucuronide, and thus classified as a short acting BDZ (overall duration of 1-18 hours). Midazolam, with a half-life of 2-4 hours, is metabolised to hydroxylated metabolites (metabolite half-life is 1.9-2 hours[40]) then to inactive glucuronide. Midazolam is therefore classified as an ultra-short-acting BDZ (less than six hour overall duration of action and 22- fold[40] shorter half-life than diazepam). [36]

In healthy neonates, midazolam's onset of action is 3.3- times longer and half-life 3.7- times shorter compared to adults, assuming a drug volume distribution of 1.1 liters/kg in both these groups. Metabolism of CY3A4 and CYP3A5 occurs mostly in the liver and is thus reduced in neonates. Its bioavailability is said to be approximately 50% with either buccal or nasal administration[40] and half-life in neonates is said to vary from 4-6 hours and may be up to 22 hours in premature infants.[40] However, this point is contentious as the GABA receptor involved needs to be taken into account so it is likely that the true situation is even more complex.

Lorazepam is less lipid-soluble than diazepam, resulting in less tissue distribution (other than neural tissue) with a distribution half-life of two to three hours versus 15 minutes for diazepam. Therefore, it should have a longer duration of clinical effect. Lorazepam also binds the GABA receptor more tightly than diazepam, resulting in a longer duration of action.[41] The anticonvulsant effects of lorazepam last six to twelve hours, and the typical dose ranges from 4 to 8 mg. Diazepam enters the brain rapidly because of its high lipid solubility, after 15 to 20 minutes it redistributes to other areas of the body, reducing its clinical effect. Despite its fast distribution half-life, the elimination half-life is extensive. Thus, sedative effects potentially could accumulate with repeated administration.[41,42]

Pharmacological management of seizures in children

Although BDZs have been around for a long time, there is still much controversy around these drugs. Many protocols exist for managing status epilepticus in both the adult and child populations, with little consensus between them[1]. In eleven of the largest pediatric institutions in Australia and New Zealand, a review was performed to determine current practice when managing seizures in the emergency department. It was found that although the APLS guidelines are available, ten sites used seven different clinical practice guidelines and one centre had no set guideline. [43]

In the FEBSTAT study, this non-uniformity in clinical practice was highlighted. The study therefore did not have a standard treatment protocol and allowed individuals to determine own drug choice when attempting to terminate seizures.[44] This non-uniformity impacts the management of pediatrics when they present to prehospital emergency services or emergency departments when having seizures. A few international guidelines exist to streamline clinical management, although even among these inconsistencies exist. Some of these will be briefly discussed below and the drugs compared in Table 3.

Overview of a Selection of International Paediatric Seizure Guidelines

In this overview, the researcher looked at large international organisation known for advancing and improving pediatric medical care. The WHO is commonly referred to when researching high impact treatment in adults and children. Another well-known international organisation dedicated to pediatric emergency care is the Advance Pediatric Life Support group; a group affiliated with both the American college of Emergency Physicians and the American academy of Pediatrics. An organisation intimately involved with seizures and epilepsy, the Neurocritical care society was also searched for current management regimes.

Accepting South Africa as a developing country, looking at another international developing country for how they manage pediatric seizures seemed prudent. In the last few organisations discussed, a national approached is mentioned with the local governing body as the last treatment regime looked at.

The Emergency Triage and Treatment (ETAT)

The ETAT system forms the generic paediatric triage and emergency management guidelines developed by the WHO for hospital care of children. The presence of seizures is an emergency sign during the triage process (pg5) and management includes the

administration of diazepam or paraldehyde (pg14). The dose suggested is based on age or weight and diazepam is given rectally (0.1ml/kg of a 10mg/2ml solution) as an initial dose and second dose if intravenous access is available 10 minutes after the first dose (0.05ml/kg or 0.25mg/kg). If seizures continue after diazepam administration, phenobarbital (20mg/kg of a 200mg/ml solution) is administered.[45]

Advanced Paediatric Life Support (APLS)

In the UK, Australasia, South Africa and many other parts of the world, the APLS guidelines are widely used to manage paediatric emergencies. According to the APLS seizure algorithm, BDZs are first and second line management and administration may occur via IM, intranasal, buccal (midazolam), per rectum (diazepam) or IV (diazepam, midazolam or clonazepam) routes.[46] The drugs and dosages used in the APLS 5th Edition Guidelines are mentioned in Table 3.

Other

Neurocritical Care Society

In a document by Abend & Loddenkemper[47] they acknowledge the lack of evidence-based pathways for management of CSE, but states that a management plan is important to expedite treatment. In 2009 a retrospective, multicentre, observational study indicated that treatment opinions advocate for BDZs to be given as emergent/first line treatment.[48] Lorazepam is used when intravenous (IV) access is available, midazolam for IM or nasal administration and diazepam for rectal administration when IV access not available.[47] Administration may be repeated at 5 -10 minutes if seizures persist.[43] Commonly prescribed drugs and dosages for acute seizure termination in children are compared in Table 3. Lorazepam and diazepam are the most common IV drugs, while midazolam is not approved by the Federal Drug Administration for intranasal or buccal administration. Once the emergent medication has been used, urgent treatment options include Phenytoin, fosphenytoin, phenobarbital, valproic acid, levetiracetam and topiramate.[1,19,47] Midazolam infusion may be considered for refractory CSE treatment (Class IIA, Level B evidence) in bolus or as infusion (Class IV)[47]. A meta-analysis of 111 children showed that midazolam is an effective coma inducing agent with a lower mortality rate when compared to other coma inducing agents and an open label randomised study comparing midazolam and diazepam indicated similar findings.[47]

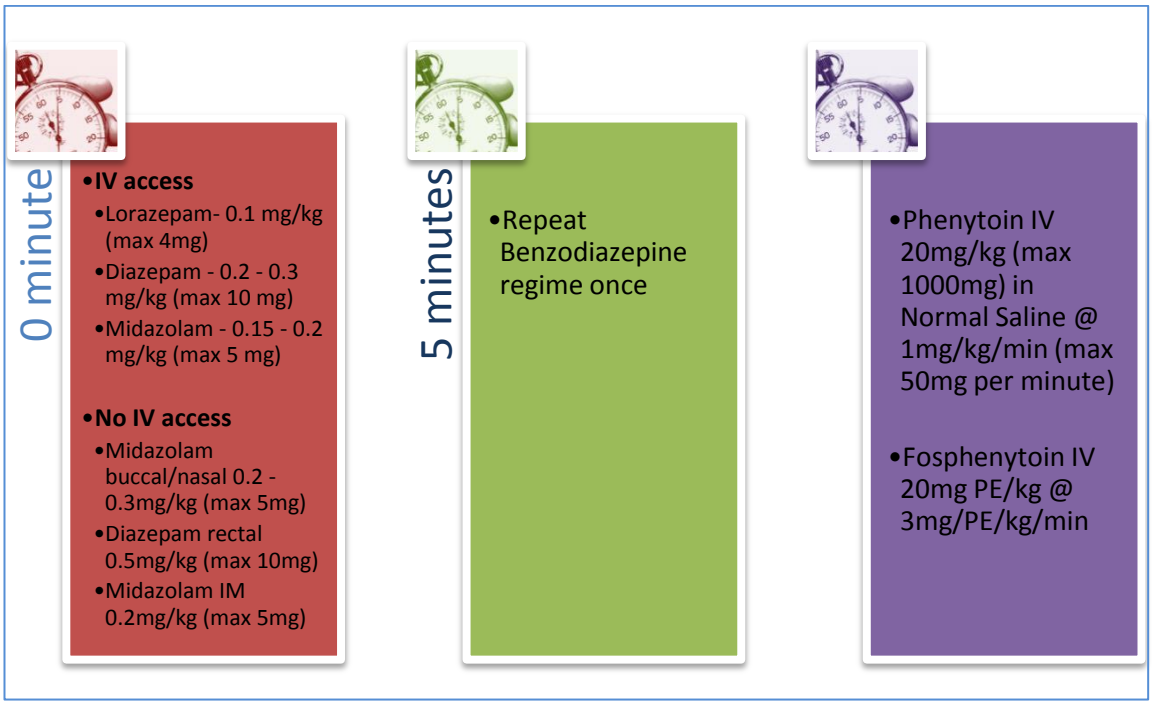
India – consensus guidelines

In Figure 2, an example of a developing country's guideline for CSE management in children is shown. This guideline was developed during a Multi-Disciplinary Consensus Development Workshop on Management of Status Epilepticus in Children in India with experts in neurology, general paediatricians, pediatric intensive care specialists and epileptologists. BDZ are given as first and second line treatment with phenytoin or fosphenytoin as 3rd line after 10 minutes. Dosing contained in this guideline is compared with other guidelines in Table 3. According to this guideline, if a Pediatric Intensive Care Unit (PICU) bed is available, a midazolam infusion can be started. If no PICU bed is available, Valproate or Phenobarbitone should be given and the child must be moved to the PICU as soon as feasible.[1]

Red Cross War Memorial Children's Hospital

Red Cross War Memorial Children's Hospital (RCWMCH) is a specialised tertiary hospital in the Western Cape and receives referrals from healthcare facilities in South Africa as well as other African countries. Because of the national and international reach of this hospital, the author chose to include the seizure management protocol from this facility. This provides a good insight into seizure management in a developing country.[49] The 2004 protocol for managing CSE starts with PR diazepam, then once intravenous (IV) access is gained diazepam is given intravenously. If IV access fails, intranasal midazolam is administered. Phenobarbitone is administered if still convulsing after 2 doses of BDZ, with referral to PICU if this is unsuccessful.[22] An alternative arm at this institution involves commencement of a midazolam infusion if phenobarbitone fails to terminate the seizure and then transfer to PICU. (J. Wilmshurst, 2015 April 23)

FIGURE 2: CONSENSUS GUIDELINES FOR STATUS EPILEPTICUS MANAGEMENT IN CHILDREN (INDIA)[1]



Western Cape Emergency Medicine Guidance

The acute seizure protocol in the Emergency Medicine Guidance for the Western Cape gives a choice of lorazepam, midazolam or diazepam as first line treatment depending on what is available in the EC.[50] The BDZ dose may be repeated once after 10 minutes if convulsions persist. After two doses of BDZ have been given, if the child is still fitting, IV or IM Phenobarbitone is administered. Only if IV Phenobarbitone is not available is IV phenytoin is advised. [50]

Health Professions Council of South Africa (HPCSA)

In the South African prehospital environment, the HPCSA is responsible for creating the protocols and guidelines that guide prehospital providers in their practice. According to the HPCSA seizure protocol IV lorazepam or IV diazepam are first line/ emergent treatments. Lorazepam may be repeated after 10 minutes and diazepam is advised to be administered at “0.2mg/min” with a comment that the dose maybe repeated “every 2-5 minutes”.[51]

Comparison of current protocols for benzodiazepine use for emergency management of paediatric seizures

The dosing variations seen in Table 3 illustrate some of the difficulties faced by prehospital providers when required to perform drug calculations during treatment of pediatric

patients with acute seizures. Variations in the protocols outlining best practice care in this environment are confusing and could potentially lead to under or over dosing children with adverse effects such as respiratory depression or respiratory arrest.[52,53]

Emergency paediatric seizures management – research review

Studies have been done in pre-hospital and in-hospital settings comparing different BDZs, dosages and/or routes to determine if BDZs were safe to administer by prehospital healthcare providers. Alldredge *et al.* performed a study comparing diazepam, lorazepam and placebo for out of hospital seizures. They found that BDZs are safe and effective to administer by prehospital healthcare providers[42,54]. A problem observed by this study was the short shelf life of lorazepam when not stored in a fridge. [42]

A study performed in Sub-Saharan African countries included 436 children between five months to ten years presenting with seizures lasting more than five minutes[47]. Lorazepam 0.1mg/kg sublingual and diazepam 0.5mg/kg intrarectal were compared for effectiveness in cessation of seizures at five, ten and 20 minutes post administration. The lorazepam group achieved cessation in 28% and the diazepam group in 38% at five minutes. At ten minutes the 79% of the diazepam group had stopped seizing compared to 56% of the lorazepam group. These results indicate that sublingual lorazepam is not as effective as intrarectal diazepam in terminating seizures. [55]

Midazolam IV and IM were compared, showing that both routes of administration are safe and effective, however the IV form was slightly faster to show effect [56]. In the emergency setting where minimising distress to the child and speed of administration are paramount, IM administration may have benefit over IV administration, since IM injection requires less skill and time to perform and is less traumatic to the child than finding IV access.

Nasal administration may be another option, but this route may cause mucosal irritation and increase discomfort[27,56]. One study reported 2 participants rejecting nasal

TABLE 1: COMPARISON OF CURRENT PROTOCOLS FOR BENZODIAZEPINE USE FOR EMERGENCY MANAGEMENT OF PAEDIATRIC SEIZURES [1,22,47,50,51]

Drug dose (mg/kg) (max drug)& route	**Diazepam**		**Midazolam**			**Lorazepam**	
Protocol ID	IV	PR	IV	IM	IN/Buccal	IV	Buccal
ETAT WHO[45]		0.1					
APLS[46]		0.5			0.5	0.1	
Abend & Loddenkemper[47]	0.15 - 0.2 (10)			5 (<40kg) 10 (>40kg)	0.2 IN 0.5 buccal	0.1 (4)	
Babl *et al*[43]	0.25	0.5	0.15	0.15			
Mishra *et al*[1]	0.2-0.3 (10)	0.5 (10)	0.15-0.2 (5)	0.2 (5)	0.2-0.3 (5)	0.1 (4)	
Wilmshurst[22]	0.3				0.2 IN 0.5 SL	0.1	
Welzel[50]	0.25	0.5	0.25		0.5 buccal	0.1	0.1
HPCSA[51]	0.2/min (5max <5yr & 10max >5yr/0	0.5 (5max <3yr & 10 max >3yr)	0.15	0.15	0.4 IN & buccal 0.4-1 PR	0.05-0.1	

IV intravenous; PR per rectum; IM intramuscular, IN intranasal; SL sublingual; milligram per minute – no per kilogram dose; mg/kg milligram per kilogram

midazolam; whereas sublingual administration provided the highest plasma levels due to its rapid absorption from the sublingual capillary network.[57]

The RAMPART non-inferiority trial[29] compared IM midazolam and IV lorazepam and found that IM midazolam is at least as effective as IV lorazepam. In this trial, the medication came in pre-packed, shrink-wrapped, pre-filled auto-injectors for the midazolam and pre-filled syringes for intravenous lorazepam. Administration of midazolam took an average of 1.2 minutes compared to lorazepam's 4.8 minutes, with termination of seizures taking 3.3 and 1.6 minutes, respectively. Overall time from opening the instrument box and administration to termination of seizures occurred in 5 minutes with midazolam and 7 minutes with lorazepam. With the IM administration less hospital admissions were observed and more patients were discharged from the ED.

Lorazepam has generally been believed to be superior to diazepam due to a purportedly better safety profile (less respiratory depression and improved, effectiveness in termination[58,59]). However lorazepam IV compared to diazepam IV in a randomised control trial showed that lorazepam did not have improved efficacy or safety compared to diazepam. In the diazepam group 72.1% (101 patients) had termination of seizures after 10 minutes compared with 72.9% (97 patients) in the lorazepam group. Assisted ventilation was required in 26 patients in each group. This study does not support the preferential use of lorazepam over diazepam.[60]

In a small trial (24 enrolled), midazolam IM was compared to diazepam IV. Out of the 13 children in the midazolam group and the 11 in the diazepam group one child from each group required endotracheal intubation and general anaesthesia for CSE. The midazolam group received medication sooner than the diazepam group (3.3 ±2.0 vs 7.8 ±3.2 minutes) with termination of seizures occurring at 7.8 (±4.1) vs 11.2 (±3.6) minutes respectively. [61]

The ideal drug for termination of acute seizures in children in the emergency setting should have a rapid, minimally stressful route of administration, have a short clinical effect without excess tissue accumulation, not require special storage facilities and have minimal adverse effects.[56] Chin[62] suggest that IM route for prehospital administration may be most practical, since it is a quick and safe way to administer medication in a patient that is convulsing (compared to IV access and the danger of needle stick injury with convulsing patients). The data of the RAMPART study indicates statistical superiority of IM route and the trial data supports IM use in the emergency setting.[8]

A study done to determine reasons for admission to PICU found that most children suffered respiratory depression when more than two doses of BDZs were administered in the emergent period.[52] Children who received prehospital treatment with BDZs were more likely to receive more than two doses than those not treated in the prehospital environment, possibly because doctors disregard the treatment given prehospitally[52].

Research Question

In paediatric patients aged 1 month to 18 years with acute seizures lasting more than five minutes, in prehospital or emergency department settings, which BDZ (diazepam, midazolam or lorazepam) provides the easiest administration and which provides the most rapid and sustained termination of seizures with the lowest rate of adverse effects?

Study type:

This study is a tiered approach rapid review of the literature

Specific Objectives

Primary Objectives:

1. To ascertain the time to cessation of seizures post drug administration
2. To establish the speed of BDZ administration as determined by time from decision to treat to administration of medication (includes time to gain access, dose calculation, drawing up and diluting if required)

Secondary Objectives

To determine:

1. The rate of requirement for further anticonvulsant medications within 1 hour of 1st BDZ dose
2. The rate of adverse events/effects as defined by:
    - Respiratory depression – 2 tiers
        - ***Rate of any respiratory depression*** including: decreased respiratory rate, irregular pattern or shallow breathing or hypoxia
        - ***Rate of severe respiratory depression*** – defined as requiring assisted ventilation with bag valve mask and/or intubation within 1 hour of drug administration
    - Cardiovascular (CVS) compromise – 2 tiers

- ***Rate of any CVS compromise*** -indicated by tachycardia and poor perfusion (delayed capillary refill of more than 3 seconds)
- ***Rate of severe CVS compromise*** requiring a fluid bolus within 1 hour of drug administration

3. To determine hospitalisation rates – 3 tiers
    i. Admission to hospital
    ii. Admission to ICU
    iii. Length of stay (LOS)

Methods:

Study design

Rapid reviews are used to inform clinical practice and support policy making when the allocated timeframe is limited.[63] There is currently no standard methodological approach[63,64] for performing rapid reviews, therefore this study will use a methodological approach similar to that of a formal systematic review with the following adaptions: Tiered approach (explained below), searches including English language publications only; no grey literature searches or hand searches will be performed. If one level adequately answers the question, the following tiers will not be necessary.

This "tiered" approach starts with clinical practice guidelines (CPGs) on the top tier. It is accepted that a large collection of researcher worked together to conduct research and produce internationally accepted CPGs. In starting on this tier, the researcher (once the guidelines are appraised) can draw conclusions on a large base of research that was peer reviewed and scrutinised by high quality researchers.

If the researcher is unable to answer the questions set out in the methodology section with information gathered from this tier, the researcher then continues to the second tier. The second tier includes review of reviews. A review of reviews determines a particular topic and a selection of reviews are appraised before inclusion, allowing the reviewer to arrive at a conclusion. Such reviews may include a meta-analysis of the included reviews allowing numerical clarification of the effectiveness of an intervention. Very similar to this is the third tier, including systematic reviews (SR). In SRs, the studies included are appraised and may also include a meta-analysis component. The final tier includes RCTs where the researcher would then look at primary data derived from various RCTs to arrive at conclusions.

The strength of the tiered approach lies in the large amount of good research already available. Although not new information, it is a good way to consolidate information already available by following a systematic process that is repeatable. A weakness of this approach is the lack of new evidence or new conclusions, as well as the inability to report findings other than the conclusions already reported in the various studies.

Inclusion Criteria

Types of Studies

A tiered approach will be followed, thus CPGs will be searched first. If no conclusive answers found, review of reviews then systematic reviews will be considered. If insufficient evidence or lack of high quality information persists, randomised controlled trials will be considered as primary data source.

Participants

Participants in this review will include children between the ages of 1 month and 18 years who present to healthcare providers in the pre-hospital emergency medical services or to emergency departments during an episode of acute generalised seizures.

Interventions

Any comparison of current benzodiazepines in the HPCSA prehospital protocol (diazepam, midazolam and lorazepam) to any other benzodiazepine or placebo for termination of seizures including all accepted emergency routes of benzodiazepine administration (buccal, nasal, intramuscular, intravenous, rectal).

Outcomes

Primary outcomes include the time to termination of seizures post drug administration and the speed of administration of the compared drugs. Secondary outcomes include rate of further anticonvulsant administration and rate of adverse effects within 1 hour of drug administration, hospitalisation and ICU admission rate, hospital length of stay (LOS) and practitioner preference.

Search Strategy

Tier one – Clinical Practice Guidelines

CPGs are good for evidence based information since they result from synthesis of best available research on/in a specific topic/field. Database search for CPGs differ from

searches for SR and RCTs in that they are often broader searches on specific sites/databases.

Databases to search CPGs will include Trip Database (clinical search engine), the National Institute for Healthcare Excellence (NICE), National Guideline Clearinghouse (NGC), Scottish Intercollegiate Guidelines network (SIGN), Guidelines International Network (GIN) and Medical Research Council (MRC). Terminology used:

- Pediatric or paediatric
- Seizure
- Benzodiazepine
- "Emergency treatment" or "emergency management" or "emergency care"

Tier two and lower –Review of Reviews, Systematic Reviews and Randomised Control Trials

The following databases will be searched: MEDLINE (via PubMed), EMBASE (via SCOPUS), Web of Science and CENTRAL. Searches will be performed with the assistance from a search strategy expert using a combination of keywords and relevant medical subject headings (MeSH) listed below. Keywords provided are for MEDLINE search and will be adapted as necessary for other databases.

1. Child* or pediatric* or paediatric*
2. Seizure* or convulsion*
3. Benzodiazepine*

In order to maximise identification of all relevant evidence-based guidelines, reviews and studies, the search will be performed with and without the following combined keyword search terms for setting:

> "Prehospital or pre-hospital" or "emergency medical service" or "emergency department" or "emergency unit" or "emergency centre"

If the search with these yields only minimal results (<50 studies/titles) a wider search using just terms 1-3 will be used as the baseline search.

Additional searches

Reference lists of included studies will be searched for additional studies not yet found with the traditional search. Trial registers will be searched on the fourth tier to ensure most inclusive RCT collection. Trial database such as World Health Organisation International

Clinical Trial Registry Platform (WHO ICTRP), Pan-Africa Clinical Trial Registry (PACTR), European Union Clinical Trials Registry (EUCTR), Clinical Tirals.gov (United States of America National Institutes of Health) and South African National Clinical Trials Register (SANCTR).

Study selection

Screening

Initial screening of titles and abstracts (Appendix B – See Part D) will be independently performed by 2 reviewers (JS & PS)[1] using predetermined criteria (Appendix A – See Part D). Full text articles will be reviewed where sufficient information is not available in abstracts. A list of all excluded articles (with reasons for their exclusion – Appendix C – See Part D) will be recorded. Figure 3 indicates the flow diagram used in conjunction with the PRISMA statement. This flow diagram will be used to guide adequate reporting of all evidence-based guidelines, reviews and studies found during the searches and will be adapted as required depending on search results.

The second round of screening of the remaining CPG, Reviews, SRs and RCTs will be done independently by JS & PS to select studies for inclusion in the review. Standardised, pre-set inclusion and exclusion criteria will be used. If there is disagreement regarding an article's inclusion, JS & PS will discuss between themselves to see if this can be resolved. If unable to agree, BC will act as adjudicator. BC will independently screen 10% of both JS & PS's reviews as a quality control mechanism.

Data Extraction and Quality Assessment

Data will be extracted from full text articles according to the predetermined data extraction sheet. A master list of all studies (Appendix B – See Part D) as well as a list of all excluded studies with reasons (Appendix C – See Part D) is provided.

No study will be excluded based on perceived quality. The quality of the studies included will be formally analysed using set criteria dependent on the type of article. AGREE II (Appendix D – See Part D)[65] is used to determine the quality of CPG using a methodological sound strategy that can be reproduced. CPGs with a score of less than 50% will be considered poor quality and excluded from the document.

Data extraction from the CPGs, RR and SR will be based on the body of evidence matrix (adopted from the Australian Medical Research Council)[66] together with the grade of

[1] Both reviewers completed Clinical Research Methods I & II, complying with University requirements for Master level thesis development

recommendations for each of the relevant recommendations (emergency management in either prehospital or emergency department) extracted from each guideline.

The second and third tiers are similar and will be discussed together. Assessing the Methodological Quality of Systematic Reviews (AMSTAR) uses a set of eleven questions with a rating scale to help determine level of quality. 4-7 is seen as medium quality and 8-11 deemed high quality. Studies with a score of less than 4 will be excluded on the bases of poor quality. The AMSTAR checklist (Appendix E – See Part D) will be used in this document. For the RCT tier, the Jaded Score/Scale will be used to assess quality. This scale uses five basic questions centred on randomisation and blinding. A score of <3 is low range of quality, while a score of ≥3 is seen as high range of quality.

Reporting

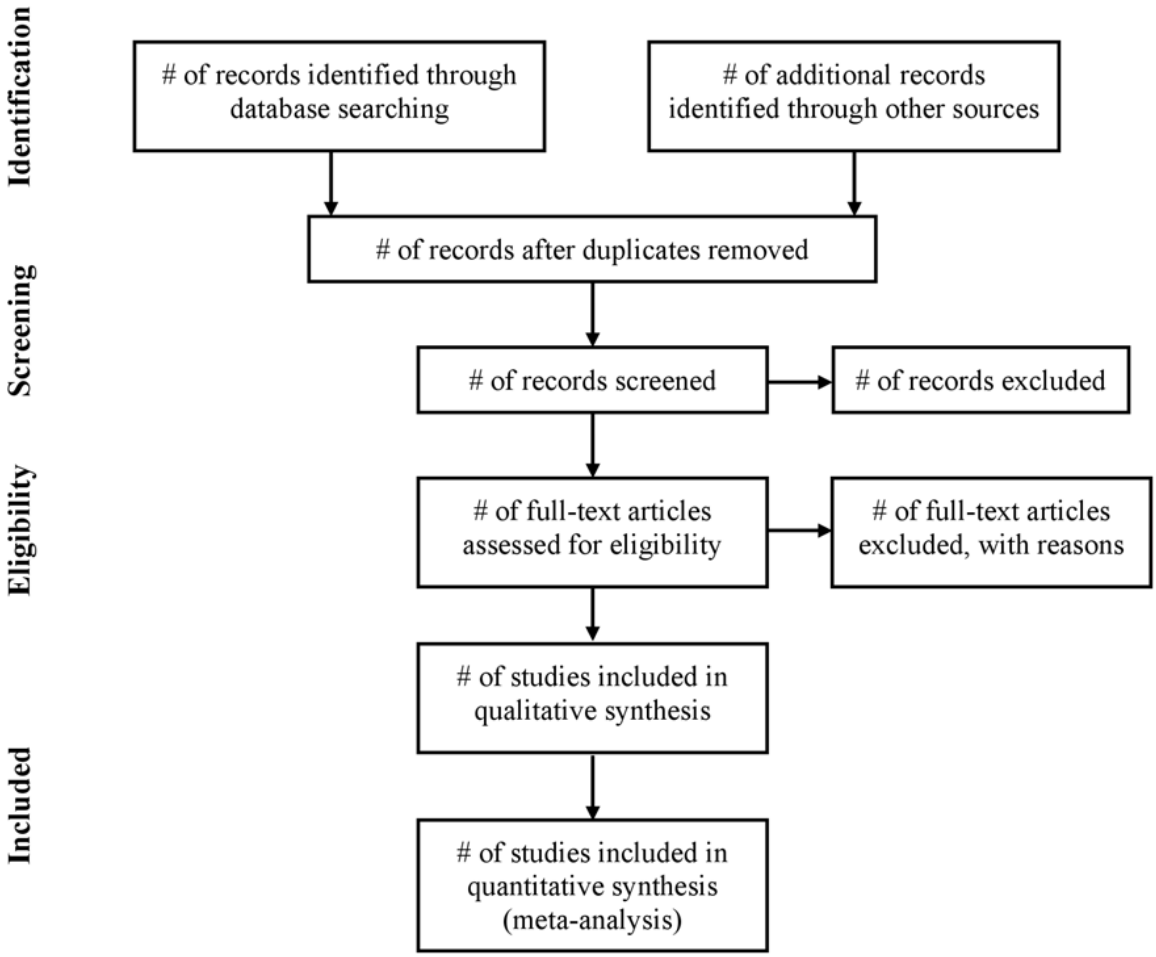
Reporting will indicate results from the highest level of this tiered approach that was able to conclusively answer the question posed in this rapid review. Reporting will be consistent with data being extracted, thus if certain parameters are not available or unreported, this will be clearly documented.

Ethical considerations

Although no participants are involved in this study and as such patient confidentiality cannot be influenced, all electronic data will be kept on a password protected personal computer as well as an external hard drive with daily back up data placed on i-cloud; printed studies will be kept by JS in a locked cupboard in a secure building.

A rigorous process of quality and bias assessment will be followed to ensure valid and reliable conclusions are drawn from studies included in this systematised review. No human subjects, clinical staff or clinical facilities will be directly involved in this study therefore no consent from participants, staff and/or facility managers will be required.

FIGURE 3: INFORMATION FLOW ADAPTED FROM PRISMA STATEMENT



Strengths and limitations

The strength of this rapid review lies in a tiered approach to answering the posed question. The quality of all levels will be thoroughly assessed and recommendations made on good quality information.

Currently, the lack of defined methodology for rapid reviews may act as a limitation. Other limitations are the potentially narrow inclusion and exclusion criteria and limiting searches to the English language, which may cause good, relevant foreign language articles to be missed. Not performing hand or grey literature searches may also result in not finding other potentially relevant studies.

Data dissemination plan

Once the data has been collected, analysed and the final report has been approved, the findings will be published. The findings of this study are relevant to any healthcare provider

who treats children with acute onset seizures. The findings will also be important for policymakers and funders in the prehospital, emergency departments and in-hospital environments. The aim will be to publish the findings in a high-impact, peer-reviewed journal with readership relevant to pre-hospital, emergency and/or paediatric settings. As this review will be done with a high degree of scientific rigour, it is hoped that it will provide a valuable evidence base for updating/revising the HPSCA protocols as well as other local, national and international emergency paediatric seizure protocols.

Conflicts of interest

No conflicts of interest to declare

Timeline and Funding

The projected timeline and funding/budget constraints are illustrated below.

Timeline

Figure 4: *Project timeline*

2015	MAR	APR	MAY	JUN	JUL	AUG	SEPT	OCT	NOV	DEC	JAN
EM-DRC	X	X									
Sx-DRC			X								
Ethics			X	X							
Search & Data Collection					X	X					
Data Analysis							X	X			
Compilation of final report									X	X	
Submission											X

Funding

Figure 5: Resources and budget

This rapid review will be self-funded. Internet access available via eduroam on campus and mobile data system off-campus. Printing access available through printing/copying shop.

February – December 2015				
Item	**Description**	**Unit cost**	**N° of Units**	Total cost
Consumables				
1. materials and supplies	Printing and copying @ R895/1000	895	1	**895**
Research travel				
1. Travel to sites	32km x2 traveling to supervisor @ R2.30p/km	147.20	10	**1472**
2. Parking fees		24	10	**240**
1. Internet access		250	10	**2500**
Total				**5107**

References

1 Mishra D, Sharma S, Sankhyan N, *et al.* Consensus guidelines on management of childhood convulsive status epilepticus. *Indian Pediatr* 2014;**51**:975–90.http://www.ncbi.nlm.nih.gov/pubmed/25560156 (accessed 21 Feb2015).

2 Thuzar M, Malabu UH, Tisdell B, *et al.* Use of a standardised diabetic ketoacidosis management protocol improved clinical outcomes. *Diabetes Res Clin Pract* 2014;**104**:e8–11. doi:10.1016/j.diabres.2014.01.016

3 Fahlstrom K, Boyle C, Makic MBF. Implementation of a nurse-driven burn resuscitation protocol: a quality improvement project. *Crit Care Nurse* 2013;**33**:25–35. doi:10.4037/ccn2013385

4 Scholtes FBJ, Renier WO, Meinardi H. Status epilepticus in children. *Seizure* 1996;**5**:177–84. doi:10.1016/S1059-1311(96)80033-1

5 Cameron P, Jelinek G, Kelly A-M, *et al. Textbook of Adult Emergency Medicine*. 3rd ed. London: : Elsevier Ltd 2009.

6 Fisher RS, Boas WE, Blume W, *et al.* Epileptic Seizures and Epilepsy: Definitions Proposed by the International League Against Epilepsy(ILAE) and the International Bureau for Epilepsy(IBE). *Epilepsia* 2005;**46**:470–2. doi:10.1111/j.1528-1167.2005.00273_1.x

7 Berg AT, Scheffer IE. New concepts in classification of the epilepsies: entering the 21st century. *Epilepsia* 2011;**52**:1058–62. doi:10.1111/j.1528-1167.2011.03101.x

8 Hirsch LJ. Intramuscular versus Intravenous Benzodiazepines for Prehospital Treatment of Status Epilepticus. *N Engl J Med* 2012;**366**:659–60. doi:10.1056/NEJMe1114206

9 Lowenstein DH, Bleck T, Macdonald RL. It's time to revise the definition of status epilepticus. *Epilepsia* 1999;**40**:120–2. doi:10.1111/j.1528-1157.1999.tb02000.x

10 Feen ES, Bershad EM, Suarez JI. Status epilepticus. *South Med J* 2008;**101**:400–6. doi:10.1097/SMJ.0b013e31816852b0

11 Sirven JI, Shafer PO. Status Epilepticus. Epilepsy Found. 2014.http://www.epilepsy.com/learn/impact/seizure-emergencies/status-epilepticus (accessed 26 Apr2016).

12 Smith BJ. Treatment of status epilepticus. *Neurol Clin* 2001;**19**:347–69.http://www.ncbi.nlm.nih.gov/pubmed/11358748 (accessed 3 Apr2015).

13 Wilmshurst JM, Berg AT, Lagae L, *et al.* The challenges and innovations for therapy in children with epilepsy. *Nat Rev Neurol* 2014;**10**:249–60. doi:10.1038/nrneurol.2014.58

14 Martindale JL, Goldstein JN, Pallin DJ. Emergency department seizure epidemiology. *Emerg Med Clin North Am* 2011;**29**:15–27. doi:10.1016/j.emc.2010.08.002

15 Wilmshurst JM. Child Neurology in Africa. *Semin Pediatr Neurol* 2014;**21**:1–2. doi:10.1016/j.spen.2014.02.001

16 Kariuki SM, Kakooza-Mwesige A, Wagner RG, *et al.* Prevalence and factors associated with convulsive status epilepticus in Africans with epilepsy. *Neurology* 2015;**84**:1838–45. doi:10.1212/WNL.0000000000001542

17 Logroscino G, Hesdorffer DC, Cascino G, *et al.* Time trends in incidence, mortality, and case-fatality after first episode of status epilepticus. *Epilepsia* 2001;**42**:1031–5.http://www.ncbi.nlm.nih.gov/pubmed/11554890 (accessed 3 Apr2015).

18 Prins A, Chengo E, Mung'ala Odera V, *et al.* Long-Term Survival and Outcome in Children Admitted to Kilifi District Hospital with Convulsive Status Epilepticus. *Epilepsy Res Treat* 2014;**2014**:1–7. doi:10.1155/2014/643747

19 Hubert P, Parain D, Vallée L. [Management of convulsive status epilepticus in infants and children]. *Rev Neurol (Paris)* 2009;**165**:390–7. doi:10.1016/j.neurol.2008.11.009

20 Kariuki SM, Matuja W, Akpalu A, *et al.* Clinical features, proximate causes, and consequences of active convulsive epilepsy in Africa. *Epilepsia* 2014;**55**:76–85. doi:10.1111/epi.12392

21 Wilmshurst JM, Badoe E, Wammanda RD, *et al.* Child Neurology Services in Africa. *J Child Neurol* 2011;**26**:1555–63. doi:10.1177/0883073811420601

22 Wilmshurst JM. Approach to epilepsy in children. *Contin Med Educ* 2004;**22**:427–33. doi:10.1007/BF02727905

23 Spangenberg J, Lalkhen N. Children with epilepsy and their families. *South African Fam Pract* 2006;**48**:60–3.

24 Ackermann S, Toorn R van. Managing first-time seizures and epilepsy in children.

Contin. Med. Educ. 2012;**30**:16–20.http://www.cmej.org.za/index.php/cmej/article/view/2390/2175 (accessed 6 Apr2015).

25 Wagner RG, Ngugi AK, Twine R, *et al.* Prevalence and risk factors for active convulsive epilepsy in rural northeast South Africa. *Epilepsy Res* 2014;**108**:782–91. doi:10.1016/j.eplepsyres.2014.01.004

26 Ngugi AK, Bottomley C, Fegan G, *et al.* Premature mortality in active convulsive epilepsy in rural Kenya: causes and associated factors. *Neurology* 2014;**82**:582–9. doi:10.1212/WNL.0000000000000123

27 Wermeling DP. Intranasal Delivery of Antiepileptic Medications for Treatment of Seizures. *Neurotherapeutics* 2009;**6**:352–8. doi:10.1016/j.nurt.2009.01.002

28 Chamberlain JM, Okada P, Holsti M, *et al.* Lorazepam vs diazepam for pediatric status epilepticus: a randomized clinical trial. *JAMA* 2014;**311**:1652–60. doi:10.1001/jama.2014.2625

29 Silbergleit R, Lowenstein D, Durkalski V, *et al.* Lessons from the RAMPART study--and which is the best route of administration of benzodiazepines in status epilepticus. *Epilepsia* 2013;**54 Suppl 6**:74–7. doi:10.1111/epi.12284

30 Mitchell WG. Status epilepticus and acute repetitive seizures in children, adolescents, and young adults: etiology, outcome, and treatment. *Epilepsia* 1996;**37 Suppl 1**:S74–80.http://www.ncbi.nlm.nih.gov/pubmed/8647055 (accessed 2 Apr2015).

31 Pellock JM. Overview: definitions and classifications of seizure emergencies. *J Child Neurol* 2007;**22**:9S – 13S. doi:10.1177/0883073807303064

32 Wick JY. The history of benzodiazepines. *Consult Pharm* 2013;**28**:538–48. doi:10.4140/TCP.n.2013.538

33 Lader M. History of benzodiazepine dependence. *J Subst Abuse Treat* 1991;**8**:53–9. doi:10.1016/0740-5472(91)90027-8

34 American Society of Health-System Pharmacists. Introduction to Pharmacokinetics and Pharmacodynamics. *Pharmocokinetics and Pharmcodynamics* 2010;**1**:1–18. doi:10.1007/SpringerReference_184421

35 Rang H, Dale M, Ritter J, *et al. Pharmacology*. 5th ed. Bath: : CHURCHILL &

LIVINGSTONE 2003.

36 Rang H, Dale M, Ritter J, *et al. Rang and Dale's Pharmacology*. 6th ed. Philadelphia: : CHURCHILL & LIVINGSTONE 2007.

37 Oshiro C. Benzodiazepine Pathway, Pharmacokinetics. PharmGKB (US Dep. Helath Hum. Serv. 2015.https://www.pharmgkb.org/pathway/PA165111375 (accessed 31 Mar2015).

38 Blows WT. *The Biological Basis of Nursing: Mental Health*. Routledge 2003. https://books.google.com/books?id=6JmCAgAAQBAJ&pgis=1 (accessed 5 Apr2015).

39 Greenblatt DJ, Divoll M. Diazepam versus lorazepam: relationship of drug distribution to duration of clinical action. *Adv Neurol* 1983;**34**:487–91.http://www.ncbi.nlm.nih.gov/pubmed/6131586 (accessed 23 Jun2015).

40 Pacifici GM. Clinical pharmacology of midazolam in neonates and children: effect of disease-a review. *Int J Pediatr* 2014;**2014**:309342. doi:10.1155/2014/309342

41 Ramsay RE, Hammond EJ, Perchalski RJ, *et al.* Brain Uptake of Phenytoin, Phenobarbital, and Diazepam. *Arch Neurol* 1979;**36**:535–9. doi:10.1001/archneur.1979.00500450029003

42 Alldredge BK, Gelb a M, Isaacs SM, *et al.* A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. *N Engl J Med* 2001;**345**:631–7. doi:10.1056/NEJMoa002141

43 Babl FE, Sheriff N, Borland M, *et al.* Emergency management of paediatric status epilepticus in Australia and New Zealand: Practice patterns in the context of clinical practice guidelines. *J Paediatr Child Health* 2009;**45**:541–6. doi:10.1111/j.1440-1754.2009.01536.x

44 Seinfeld S, Shinnar S, Sun S, *et al.* Emergency management of febrile status epilepticus: Results of the FEBSTAT study. *Epilepsia* 2014;**55**:388–95. doi:10.1111/epi.12526

45 Hales-Tooke a. Improving hospital care for children. *Children*;**15**:116–8.

46 Advanced Life Support Group. *Advanced Paediatric Life Support: The Practical Approach*. 5th ed. Oxford: : Wiley - Balckwell 2011.

47 Abend NS, Loddenkemper T. Management of pediatric status epilepticus. *Curr Treat*

Options Neurol 2014;**16**:301. doi:10.1007/s11940-014-0301-x

48 Cook AM, Castle A, Green A, *et al.* Practice variations in the management of status epilepticus. *Neurocrit Care* 2012;**17**:24–30. doi:10.1007/s12028-012-9711-3

49 Williams N, Nefdt WM, Wilmshurst JM. Epilepsy South Africa: Turning obstacles into true potential. *Epilepsia* 2014;**56**:1–4. doi:10.1111/epi.12641

50 Welzel T, editor. *Emergency Medicine Guideline for the Western Cape*. Cape Town: : Division of Emergency Medicine 2013.

51 Health Professions Council of South Africa. *Advanced Life Support Protocols*. 2006. http://www.hpcsa.co.za/PBEmergencyCare/Guidelines

52 Chin RFM, Verhulst L, Neville BGR, *et al.* Inappropriate emergency management of status epilepticus in children contributes to need for intensive care. *J Neurol Neurosurg Psychiatry* 2004;**75**:1584–8. doi:10.1136/jnnp.2003.032797

53 Thakker A, Shanbag P. A randomized controlled trial of intranasal-midazolam versus intravenous-diazepam for acute childhood seizures. *J Neurol* 2013;**260**:470–4. doi:10.1007/s00415-012-6659-3

54 Pang T, Hirsch LJ. Treatment of Convulsive and Nonconvulsive Status Epilepticus. *Curr Treat Options Neurol* 2005;**7**:247–59.http://www.ncbi.nlm.nih.gov/pubmed/15967088 (accessed 3 Apr2015).

55 Malu CKK, Kahamba DM, Walker TD, *et al.* Efficacy of Sublingual Lorazepam Versus Intrarectal Diazepam for Prolonged Convulsions in Sub-Saharan Africa. *J Child Neurol* 2013;**29**:895–902. doi:10.1177/0883073813493501

56 Ghane M-R, Javadzadeh H-R, Mahmoudi S, *et al.* Intramuscular compared to intravenous midazolam for paediatric sedation: A study on cardiopulmonary safety and effectiveness. *Afr J Paediatr Surg* 2014;**11**:219–24. doi:10.4103/0189-6725.137329

57 Geldner G, Hubmann M, Knoll R, *et al.* Comparison between three transmucosal routes of administration of midazolam in children. *Paediatr Anaesth* 1997;**7**:103–9.http://www.ncbi.nlm.nih.gov/pubmed/9188109 (accessed 2 Apr2015).

58 Qureshi A, Wassmer E, Davies P, *et al.* Comparative audit of intravenous lorazepam and diazepam in the emergency treatment of convulsive status epilepticus in children. *Seizure* 2002;**11**:141–4. doi:10.1053/seiz.2001.0635

59 Chiulli DA, Terndrup TE, Kanter RK. The influence of diazepam or lorazepam on the frequency of endotracheal intubation in childhood status epilepticus. *J Emerg Med*;**9**:13–7.http://www.ncbi.nlm.nih.gov/pubmed/2045642 (accessed 2 Apr2015).

60 Chamberlain JM, Okada P, Holsti M, *et al.* Lorazepam vs Diazepam for Pediatric Status Epilepticus. *Jama* 2014;**311**:1652–60. doi:10.1001/jama.2014.2625

61 Chamberlain JM, Altieri MA, Futterman C, *et al.* A prospective, randomized study comparing intramuscular midazolam with intravenous diazepam for the treatment of seizures in children. *Pediatr Emerg Care* 1997;**13**:92–4.http://www.ncbi.nlm.nih.gov/pubmed/9127414 (accessed 31 Mar2015).

62 Chin RFM. What are the best ways to deliver benzodiazepines in children/patients with prolonged convulsive seizures? *Epileptic Disord* 2014;**16**:S50–8. doi:10.1684/epd.2014.0684

63 Ganann R, Ciliska D, Thomas H. Expediting systematic reviews: methods and implications of rapid reviews. *Implement Sci* 2010;**5**:56. doi:10.1186/1748-5908-5-56

64 Harker J, Kleijnen J. What is a rapid review? A methodological exploration of rapid reviews in Health Technology Assessments. *Int J Evid Based Healthc* 2012;**10**:397–410. doi:10.1111/j.1744-1609.2012.00290.x

65 Brouwers MEA. Appraisal of Guidelines for Research & Evaluation II. *Agree Next Steps Consort* 2009;:1–56.

66 National Health and Medical Research Council. *A guide to the development, implementation and evaluation of clinical practice guidelines*. 1998. http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/cp30.pdf?q=publications/synopses/_files/cp30.pdf

PART B – LITERATURE REVIEW

Total word count: 6735

(Excluding figures, tables & references)

Table of Contents

List of Figures

List of Tables

Objectives of literature review

Internationally, limited consensus is available on the best drug [of the three most commonly used benzodiazepines (BDZs)] and best route of administration for acute seizure termination in children in both the prehospital (EMS) and emergency department environments (ED). Due to differences between in-hospital (patients admitted to a ward) and EMS or ED environment, results and findings in one setting are not necessarily valid or directly applicable to other settings. In the South African prehospital setting, conflicting information and a lack of clarity in protocols exacerbates difficulties in practitioner training and education. Robust evidence-based protocols and evidence-based guidelines have been shown to improve management decisions in emergency situations[2–5]. The prehospital Health Professions Council of South Africa (HPCSA) protocol has not been updated since 2006. In several key areas, including acute seizure management of children, it is in urgent need of revision to incorporate the latest evidence and best practices. This study hopes to provide information that will support an evidence-based revision of the acute seizure management protocol for children in the pre-hospital and emergency department setting.

Literature search strategy

Introduction

In order to prepare this literature review the researcher undertook a limited literature search (as outlined below) and identified a range of relevant and informative studies. However as this literature review has been prepared as the groundwork for the subsequent systematised rapid review, it was beyond its scope to be exhaustive with respect to the comparison of the benzodiazepine (BDZ) drugs themselves (as this is the subject of the main research review). This literature review is therefore presented in sections that are help build the overall background to and rationale for the main study. The initial part deals with evidence regarding the various quality assessment tools available. This is followed by literature and information regarding paediatric seizures, before moving on to the pharmacodynamics of the various BDZ drugs. There follows a comparison of a selection of currently available paediatric seizure emergency guidelines. The last section reports on the literature relating to studies comparing the three commonest BDZ medications used in the emergency environment (i.e. lorazepam, diazepam and midazolam).

Search Strategy for Background Literature Review

The search strategy for this literature review was multifaceted. Background information on seizures, drugs, pharmacodynamics and other related information was obtained from reputable medical and pharmacological textbooks and on-line sources.

Epidemiology statistics and a representative spectrum of research studies were found from broad literature searches on PubMed, Scopus and Web of Science. Key words searched included: “pediatric” AND “seizures”. Reference lists of relevant studies were reviewed for additional studies and informative articles.

For the purposes of the research study itself, the key terms were expanded to include: “benzodiazepine” AND “emergency management” and identified studies were formally screened and quality-assessed as per methodology section.

Since the study methodology is a rapid review (i.e. based on systematic review principles but with a less comprehensive literature search) the guidelines, review of reviews, systematic reviews and randomised control trials included in the rapid review methodology are quality assured in greater detail according to pre-set criteria and validated quality assessment tools (see quality criteria and assessment section below).

Quality criteria and assessment

This rapid review follows a tiered approach to gathering data. The first tier is clinical practice guidelines (CPGs), followed by review of reviews, systematic reviews with the fourth and final tier being randomised control trials.

Quality Assessment of Clinical Practice Guidelines

Clinical Practice Guidelines (CPGs) and was searched exclusively on databases where CPGs will most commonly be found. This included Trip Database (clinical search engine), the National Institute for Healthcare Excellence (NICE), National Guideline Clearinghouse (NGC), Scottish Intercollegiate Guidelines network (SIGN), Guidelines International Network (GIN) and Medical Research Council (MRC). Very broad keyword searches were performed to ensure optimal information.

AGREE II (Appendix D – See Part D)[6] is used to determine the quality of CPG using a methodological sound strategy that can be reproduced. AGREEII scoring is done per domain (total of six) and per appraiser, after which the scores are counted per domain to achieve a score based on a minimum and maximum score. When a question is deemed not

applicable, the question will not be counted and the final score will be corrected to the actual numbers of questions answered.

The Australian Medical Research Council[7] designed recommendation to assist guideline developers in developing good, clinical applicable guidelines from different types of studies (intervention, diagnosis or screening). They developed an Evidence Statement Form including a body of evidence matrix (Appendix H – see Part D) and four steps on how to use this form to consistently deliver good clinical practice guidelines. Data extracted from the CPGs were appraised using this methodology.

Quality Assessment of Review of Reviews & Systematic Reviews

In a recent publication[8], AMSTAR (Assessing the Methodological Quality of Systematic Reviews), PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and GRADE (Grading of Recommendations, Assessment, Development and Evaluation) were compared. The authors found correlation between AMSTAR and PRISMA, but no correlation between GRADE and AMSTAR or GRADE and PRISMA. AMSTAR uses a set of eleven questions with a rating scale to help determine level of quality. 4-7 is seen as medium quality and 8-11 deemed high quality. The AMSTAR checklist (Appendix E – see Part D) was used to score the one systematic review included in the literature review. No review of reviews or systematic reviews was included into the study, since the research question was answered in the first tier already.

Quality Assessment of Randomised Controlled Trials

The CONSORT[9] statement is well known and extensively used to determine adequate reporting of RCT's, but is not seen as a quality assessment tool per say . To assess quality a checklist or scale is generally used. Many checklists exist to determine the quality of RCT's, but not all of these have been validated[10]. The Jaded Scale (Appendix F – see Part D) has been validated and was used to score the RCT's included in the literature review (new research section). A score ≥3 is seen as a high range of quality.

Available literature

What is known about seizures

Terminology

A "seizure" is defined as transient abnormal neurological function caused by excessive abnormal electrical discharge of nerve tissue[11,12]. It may also be referred to as ictus/ictal period with a post-ictal period once the seizure terminates. A "convulsion" is defined as

excessive and abnormal motor activity that can be as a result of seizures or other conditions.[11] Therefore, seizures do not equate to convulsions and convulsions do not equate to seizures.

Focal seizures are generally accepted as originating in a network/networks within a single hemisphere and may or may not spread to both hemispheres, referred to as secondary generalisation. Generalised seizure would be a seizure that originates at a point in a network/networks and rapidly encompasses both hemispheres.[13]

Status Epilepticus (SE) used to be defined as seizures lasting more than 30 minutes or multiple seizures in 30 minutes without regaining full consciousness in between each seizure[2]. As Figure 1 indicates, the longer a seizure continues, the more difficult it will be to terminate[2,14] (either on its own or with medication). For this reason, the newer, more operational definition of SE goes as follows: “Status epilepticus … refers to more than five min of (*i*) continuous seizures or (*ii*) two or more discrete seizures between which there is incomplete recovery of consciousness”. [2,15,16]

Convulsive status epilepticus (CSE) refers to repeated tonic-clonic body movements historically expected with seizure activity. As mentioned above, a seizure can be present without convulsions and SE may be present in the absence of any tonic-clonic movements. Non-convulsive SE is more difficult to detect and often left untreated longer than CSE.[17]

Epidemiology of seizures

Worldwide, approximately 50 million people suffer from epilepsy, 2.7 million in the United States (US) alone with 120 000 new onset seizures per year occurring in children less than 18 years of age and 75 000 of these in children less than 5 years (mostly febrile convulsions).[18] North American and European data in 2014 suggested that the incidence of epilepsy is the highest in the first year of life and is reported at 90 – 212 per 100 000 people, declining to 20 – 70 per 100 000 people in later childhood and early adolescence.[19] Approximately 200 000 new seizure presentations occur per year with most seen in the population of <2yr and >65yrs.[18] It is estimated that 11% of all people will have at least one non-pathological seizure in their lifetime while 3% of the population will be diagnosed with epilepsy in their lifetime[20].

In developed world settings, approximately 1% of all adult and 2% of all pediatric emergency department (ED) visits are due to seizures[20] (in 7% of adults and 6% of

children the visit is secondary to CSE[14,20]) and 3% of all prehospital transportation occurs because of seizures[20]. In developing countries, the figures are likely to be even higher as there is the added burden of disease such as HIV/AIDS and high rates of serious central nervous system infections including Tuberculosis, meningitis and parasitic diseases (e.g. malaria and neurocysticercosis). According to the World Health Organisation (WHO), in low-income countries, children are 16 times more likely to die before the age of five than those in high-income countries. Six main conditions, of which epilepsy is one, cause this alarming statistics.[21] In Kenya children with CSE are admitted to the hospital 2-6 times more than in London, and many children do not attend hospitals in the Kenyan setting thus potentially underestimating this number.[22]

Epidemiology of Convulsive Status Epilepticus

Four to eight per 1000 children will have experienced Convulsive Status Epilepticus (CSE) before the age of 15. In the US and Europe, the estimated incidence of CSE is 6.8 – 41 per 100 000 per year with an associated mortality of 26% (adults)[16,23] and 17-23 per 100 000 children per year[24]. In France, Hubert et al.[25] estimate child mortality of 3-5% with morbidity increasing 2 fold when CSE is present. The overall incidence and mortality has increased over the last 30 years according to Logroscino et al[23] and elderly patients are two times more likely to suffer death when compared to children. Outcomes related to duration of seizures and mortality is estimated at 15-22% in CSE with 25% of survivors suffering decrease functionality post CSE episode.

CSE occurs in 25% - 30% of people with epilepsy with only 36% are receiving treatment for this in sub-Saharan Africa.[26] The data from this survey (Tanzania, Uganda, South Africa, Kenya and Ghana) indicated that 69% of seizures start in childhood and 55% are due to febrile illnesses. During the African Child Neurology Association meeting, health summaries from 23 African countries indicate that up to 20% of children admitted to district level hospitals suffer neurological conditions in particular acute seizures.[27] Only seven of these 26 countries had national guidelines for the treatment of CSE. First line treatment was diazepam (n=21), lorazepam (n=2) or clonazepam (n=1), whilst 2 countries had no intervention beyond diazepam. Only 15 countries have access to pediatric intensive care units or pediatric beds in an adult intensive unit.[27]

Epidemiology of seizures in the African settings

In South Africa, 8% of the population will have a seizure at some point in their life and approximately 50% of these will occur in childhood.[28] One in every 100 people will be diagnosed with epilepsy. First-time seizures in children are common[28] and increase the burden of disease in this population. Although true prevalence cannot be estimated, approximately 50% of all epilepsy patients will develop the disease before the age of 15 years[29]. A study in the Northern Province of South Africa indicated an active epilepsy prevalence of 6.7 per 1000 children[30]. In the Northeast part of South Africa a crude prevalence of 7.0 per 1000 person years where observed[31] with numbers ranging between 2.9 and 26 per 1000 children on the African continent[30]. A more recent survey, estimates the prevalence at 2.3 per 1000 people in sub-Saharan Africa (survey in South Africa, Uganda and Kenya)[22], with a crude mortality rate of 33.3 per 1000 person years. The rate ratio in the age group 0-5 years is 4.4 and 22.5 in the 6-12 year age group.[32] This rate is 6 times more than what was generally expected (Kenyan cross-sectional study) in ACE.

To allow direct comparison between the US, European and sub-Saharan Africa incidence of CSE, both sets of results have been recalculated to give incidence per 1000 people. In the US and Europe the incidence of CSE is then 0.068 – 0.41 per 1000, compared to the 2.3 per 1000 in sub-Saharan Africa. Mortality rate of CSE in US and Europe is estimated at 0.17 – 0.23 per 1000 and the mortality associated with CSE in sub-Saharan Africa is 33.3 per 1000. *Considering this information, especially in the African setting, it is clear that more should be done to prevent and treat CSE in sub-Sahara. Having explicit, evidence-based guidelines and an easy to use protocol (with readily available medication) where seizures are treated early (at home or in schools) may help to prevent CSE incidences.*

Summary of paediatric seizures

In general, seizures are under-appreciated and under-recognised[18]. Seizures are medical emergencies and should be treated promptly[33,16]. Delay in terminating seizures results in worsening neurological outcome, and increases morbidity and mortality[34,35]. Figure 1 (below) indicates the progression of seizures from brief isolated seizures to CSE as seizure duration increases.

Seizures are the most common neurological emergency in children and may be due to acute or chronic conditions[36,1]. An epidemiological study performed in Richmond,

Virginia demonstrated that febrile seizures secondary to infections not located in the central nervous system are the most common aetiology for CSE in children younger than two years of age.[1]

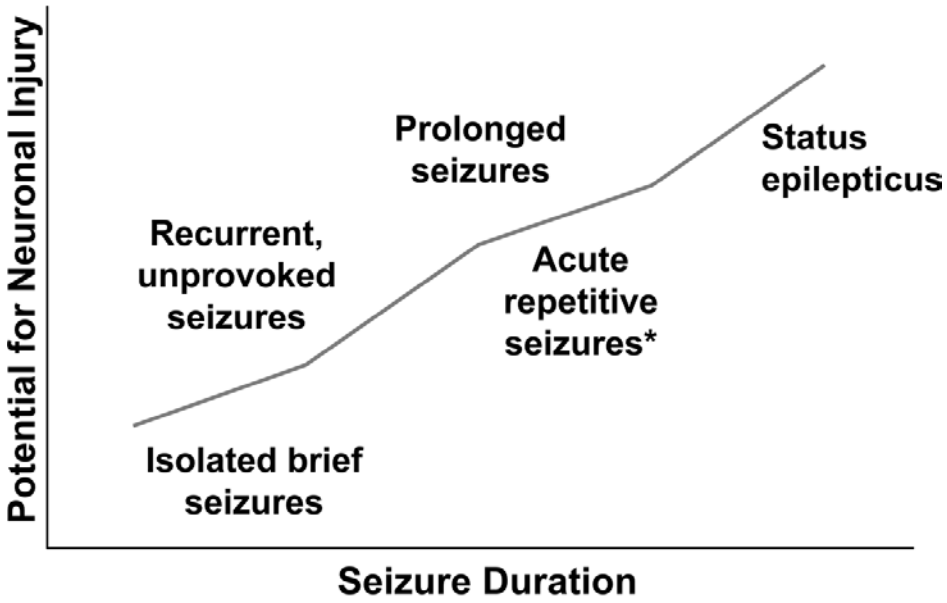
Benzodiazepines

History of Benzodiazepines

The first Benzodiazepine (BDZ), chlordiazepoxide (Librium), was identified in 1955 and made commercially available in 1960[37]. Diazepam followed in 1963 and BDZ popularity increased exponentially until researchers linked the mechanism of action to gamma-aminobutyric acid (GABA) and concerns about abuse and dependence increased sufficiently to institute legislation and guidelines for its use. [37]

BDZs have been used in the termination of seizures since 1965, when the first convulsive status epilepticus (CSE) patient was treated with intravenous diazepam. Diazepam is still used today as treatment for the termination of seizures. Midazolam was developed in the 1970s by Hoffman-La Roche and lorazepam followed in 1977.[38]

FIGURE 1: CORRELATION BETWEEN SEIZURE DURATION AND NEURONAL INJURY. (ADOPTED FROM PELLOCK[1])



Benzodiazepine pharmacodynamics and pharmacokinetics

Pharmacokinetics relates to the time or course progression of drug absorption, distribution in the body, metabolism of the given drug and the elimination or excretion thereof. Pharmacodynamics is the relationship between drug concentration and site of action

resulting in therapeutic and/or adverse effects. Generally speaking, the higher the concentration of the drug at the site of action (receptor site) the greater the intensity of action.[39]

Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the brain (mainly thalamus, limbic and cerebral cortex) with trace amounts found in some other tissues. It is particular abundant in the nigrostriatal system (10 µmol/gram tissue) with lesser concentrations in grey matter (2-5 µmol/gram). The two main receptors are $GABA_A$ and $GABA_B$. $GABA_A$ is a ligand-gated channel that is found postsynaptically and meditates fast postsynaptic inhibition. This is done by increasing the cell's permeability to chloride resulting in a hyperpolarised state which decreases its excitability.[40,41]

BDZs selectively potentiate GABA's effect on the $GABA_A$ receptor by binding to an accessory site, known as the "benzodiazepine receptor" (BZ receptor). Binding to the BZ receptor enhance the agonistic effect on $GABA_A$ by increasing the frequency of chloride ion channel opening, ultimately resulting in a hyperpolarised cell that is slower to send/receive neuronal impulses.[40] This property makes it an attractive drug for the use in sedation, hypnosis and anxiolysis, for muscle relaxation and as an anticonvulsant.[42,41]

Some BDZs are longer acting than others (even when using similar routes of administration), depending on the metabolite they are degraded into, the activity and lipid solubility of these metabolites. Metabolites are generated by polymorphic enzymes (CYP3A4, CYP3A5 and CYP2C19) on BDZs. These enzymes affect the rate of absorption and metabolism and because of genetic predisposition some people will take longer to metabolize and eliminate BDZs than others.[43]

Although all BDZs share similarities in their properties, their physiochemical properties differ because of the lipid solubility of the drug. Lipid solubility relates directly to diffusion, absorption and effect of the different subtypes of BDZs because they cross the blood brain barrier to equilibrate within the neural tissue[43]. Ideally, oil-based drugs such as diazepam, should not be administered via the intramuscular (IM) route because of the potential for erratic and delayed absorption.[44] Midazolam and Lorazepam have better solubility and have improved absorption via the IM route.

In a study performed on eight healthy volunteers, the kinetic parameters of drug distribution were determined by using serial concentration levels.[45] The elimination half-life of diazepam averaged 51.2 hours compared to lorazepam's 15.7 hours, this difference is

due to the volume distribution of unbound drug (133 litre/kg diazepam and 12 litre/kg lorazepam). The shorter duration of action (considering the previous mentioned elimination half-life) of diazepam is due to its lipid solubility or octanol/water partition coefficient when compared to the other BDZs.[45]

Diazepam, with a half-life of 20-40 hours, is metabolised into N-desmethyldiazepam (nordazepam); the metabolite having a half-life of approximately 60 hours before being excreted in the urine as glucuronide conjugates. Consequently, diazepam is classified as a long acting[42,41] Lorazepam, with an estimated half-life of 8-12 hours, is metabolised directly to inactive glucuronide, and thus classified as a short acting BDZ (overall duration of 1-18 hours). Midazolam, with a half-life of 2-4 hours, is metabolised to hydroxylated metabolites (metabolite half-life is 1.9-2 hours[46]) then to inactive glucuronide. Midazolam is therefore classified as an ultra-short-acting BDZ (less than six hour overall duration of action and 22- fold[46] shorter half-life than diazepam). [41]

Lorazepam is less lipid-soluble than diazepam, resulting in less tissue distribution (other than neural tissue) with a distribution half-life of two to three hours versus 15 minutes for diazepam. Therefore, it should have a longer duration of clinical effect. Lorazepam also binds the GABA receptor more tightly than diazepam, resulting in a longer duration of action.[47] The anticonvulsant effects of lorazepam last six to twelve hours, and the typical dose ranges from 4 to 8 mg. Diazepam enters the brain rapidly because of its high lipid solubility, after 15 to 20 minutes it redistributes to other areas of the body, reducing its clinical effect. Despite its fast distribution half-life, the elimination half-life is extensive. Thus, sedative effects potentially could accumulate with repeated administration.[47,48]

Pharmacological management of seizures in children

Although BDZs have been around for a long time, there is still much controversy around these drugs. Many protocols exist for managing status epilepticus in both the adult and child populations, with little consensus between them[2]. In eleven of the largest pediatric institutions in Australia and New Zealand, a review was performed to determine current practice when managing seizures in the emergency department. It was found that although the APLS guidelines are available, ten sites used seven different clinical practice guidelines and one centre had no set guideline. [49]

In the FEBSTAT study, this non-uniformity in clinical practice was highlighted. The study therefore did not have a standard treatment protocol and allowed individuals to determine own drug choice when attempting to terminate seizures.[50] This non-uniformity impacts

the management of pediatrics when they present to prehospital emergency services or emergency departments when having seizures. A few international guidelines exist to streamline clinical management, although even among these inconsistencies exist. Some of these will be briefly discussed below and the drugs

compared in Table 3.

Overview of a Selection of International Paediatric Seizure Guidelines

In this overview, the researcher looked at large international organisation known for advancing and improving pediatric medical care. The WHO is commonly referred to when researching high impact treatment in adults and children. Another well-known international organisation dedicated to pediatric emergency care is the Advance Pediatric Life support group; a group affiliated with both the American college of Emergency Physicians and the American academy of Pediatrics. An organisation intimately involved with seizures and epilepsy, the Neurocritical care society was also searched for current management regimes.

Accepting South Africa as a developing country, looking at another international developing country for how they manage pediatric seizures seemed prudent. In the last few organisations discussed, a national approached is mentioned with the local governing body as the last treatment regime looked at.

The Emergency Triage and Treatment (ETAT)

The ETAT system forms the generic paediatric triage and emergency management guidelines developed by the World Health Organisation (WHO) for hospital care of children. The presence of seizures is an emergency sign during the triage process (pg5) and management includes the administration of diazepam or paraldehyde (pg14). The dose suggested is based on age or weight and diazepam is given rectally (0.1ml/kg of a 10mg/2ml solution) as an initial dose and second dose if intravenous access is available 10 minutes after the first dose (0.05ml/kg or 0.25mg/kg). If seizures continue after diazepam administration, phenobarbital (20mg/kg of a 200mg/ml solution) is administered.[51]

Advanced Paediatric Life Support (APLS)

In the UK, Australasia, South Africa and many other parts of the world, the APLS guidelines are widely used to manage paediatric emergencies. According to the APLS seizure algorithm, BDZs are first and second line management and administration may occur via

intramuscular (IM), intranasal (IN), buccal (midazolam), per rectum (PR) (diazepam) or intravenous (IV) (diazepam, midazolam or clonazepam) routes.[52] The drugs and dosages used in the APLS 5th Edition Guidelines are mentioned in Table 3.

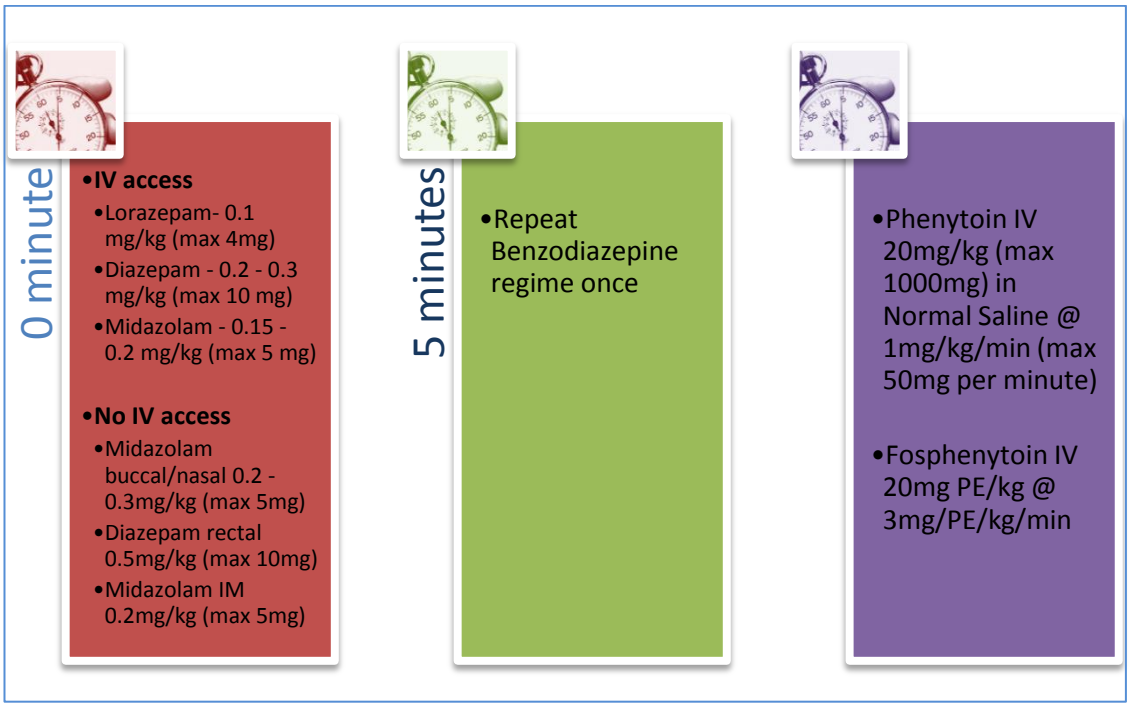
Neurocritical Care Society

In a document by Abend & Loddenkemper[53] they acknowledge the lack of evidence-based pathways for management of CSE, but states that a management plan is important to expedite treatment. In 2009 a retrospective, multicentre, observational study indicated that treatment opinions advocate for BDZs to be given as emergent/first line treatment.[54] Lorazepam is used when IV access is available, midazolam for IM or IN administration and diazepam for rectal administration when IV access not available.[53] Administration may be repeated at 5 -10 minutes if seizures persist.[49] Commonly prescribed drugs and dosages for acute seizure termination in children are compared in Table 3. Lorazepam and diazepam are the most common IV drugs, while midazolam is not approved by the Federal Drug Administration for intranasal or buccal administration. Once the emergent medication has been used, urgent treatment options include Phenytoin, fosphenytoin, phenobarbital, valproic acid, levetiracetam and topiramate.[2,25,53] Midazolam infusion may be considered for refractory CSE treatment (Class IIA, Level B evidence) in bolus or as infusion (Class IV)[53]. A meta-analysis of 111 children showed that midazolam is an effective coma inducing agent with a lower mortality rate when compared to other coma inducing agents and an open label randomised study comparing midazolam and diazepam indicated similar findings.[53]

India – consensus guidelines

In Figure 2, an example of a developing country's guideline for CSE management in children is shown. This guideline was developed during a Multi-Disciplinary Consensus Development Workshop on Management of Status Epilepticus in Children in India with experts in neurology, general paediatricians, pediatric intensive care specialists and epileptologists. BDZ are given as first and second line treatment with phenytoin or fosphenytoin as 3rd line after 10 minutes. Dosing contained in this guideline is compared with other guidelines in Table 3. According to this guideline, if a Pediatric Intensive Care Unit (PICU) bed is available, a midazolam infusion can be started. If no PICU bed is available, Valproate or Phenobarbitone should be given and the child must be moved to the PICU as soon as feasible.[2]

FIGURE 2: CONSENSUS GUIDELINES FOR STATUS EPILEPTICUS MANAGEMENT IN CHILDREN (INDIA)[2]



Overview of a Selection of South Africa Paediatric Seizure Guidelines

Red Cross War Memorial Children's Hospital

Red Cross War Memorial Children's Hospital (RCWMCH) is a specialised tertiary hospital in the Western Cape and receives referrals from healthcare facilities in South Africa as well as other African countries. Because of the national and international reach of this hospital, the author chose to include the seizure management protocol from this facility. This provides a good insight into seizure management in a developing country.[55] The 2004 protocol for managing CSE starts with PR diazepam, then once IV access is gained diazepam is given intravenously. If IV access fails, intranasal midazolam is administered. Phenobarbitone is administered if still convulsing after 2 doses of BDZ, with referral to PICU if this is unsuccessful.[28] An alternative arm at this institution involves commencement of a midazolam infusion if phenobarbitone fails to terminate the seizure and then transfer to PICU. (J. Wilmshurst, 2015 April 23)

Western Cape Emergency Medicine Guidance

The acute seizure protocol in the Emergency Medicine Guidance for the Western Cape gives a choice of lorazepam, midazolam or diazepam as first line treatment depending on what is available in the EC.[56] The BDZ dose may be repeated once after 10 minutes if convulsions persist. After two doses of BDZ have been given, if the child is still fitting, IV or

IM Phenobarbitone is administered. Only if IV Phenobarbitone is not available is IV phenytoin is advised. [56]

Health Professions Council of South Africa

In the South African prehospital environment, the Health Professions Council of South Africa (HPCSA) is responsible for creating the protocols and guidelines that guide prehospital providers in their practice. According to the most recent HPCSA seizure protocol (2006) IV lorazepam or IV diazepam are first line/ emergent treatments. Lorazepam may be repeated after 10 minutes and diazepam is advised to be administered at "0.2mg/min" with a comment that the dose maybe repeated "every 2-5 minutes", although no mg/kg dose is mentioned in the protocol.[57]

The dosing variations seen in Table 3 illustrate some of the difficulties faced by prehospital providers when required to perform drug calculations during treatment of pediatric patients with acute seizures. Variations in the protocols outlining best practice care in this environment are confusing and could potentially lead to under or over dosing children with adverse effects such as respiratory depression or respiratory arrest.[58,59]

Emergency paediatric seizures management – research review

For the purposes of this background literature review and using the limited search strategy outlined above, the researcher found a range of studies comparing benzodiazepines to one another. Some compared lorazepam to diazepam (IV, IN or rectal administration). Lorazepam, midazolam and clonazepam were compared; lorazepam and midazolam as well as various studies comparing diazepam to midazolam. In the following section more detail is provided in an overview of the studies mentioned. They are grouped according to leading study drug.

As discussed earlier, any delay in treatment of seizures can lead to refractory status epilepticus, early treatment is thus paramount.[1,60] Initially uncertainty existed regarding safety and effectiveness of benzodiazepine administration by prehospital providers. In a randomised control trial including 205 adults (high range quality - Jaded score 5), lorazepam, diazepam and placebo were compared.[48]

TABLE 1: COMPARISON OF CURRENT PROTOCOLS FOR BENZODIAZEPINE USE IN EMERGENCY MANAGEMENT OF PAEDIATRIC SEIZURES [2,28,53,56,57]

Drug dose (mg/kg) (max drug) & route	**Diazepam**		**Midazolam**			**Lorazepam**	
Protocol ID	IV	PR	IV	IM	IN/Buccal	IV	Buccal
ETAT WHO[51]		0.1					
APLS[52]		0.5			0.5	0.1	
Abend & Loddenkemper[53]	0.15 - 0.2 (10)			5 (<40kg) 10 (>40kg)	0.2 IN 0.5 buccal	0.1 (4)	
Babl et al[49]	0.25	0.5	0.15	0.15			
Mishra et al[2]	0.2-0.3 (10)	0.5 (10)	0.15-0.2 (5)	0.2 (5)	0.2-0.3 (5)	0.1 (4)	
Wilmshurst[28]	0.3				0.2 IN 0.5 SL	0.1	
Welzel[56]	0.25	0.5	0.25		0.5 buccal	0.1	0.1
HPCSA[57]	0.2 (5max <5yr & 10max >5yr/0	0.5 (5max <3yr & 10 max >3yr)	0.15	0.15	0.4 IN & buccal 0.4-1 PR	0.05-0.1	

IV intravenous; PR per rectum; IM intramuscular, IN intranasal; SL sublingual; mg/kg milligram per kilogram

This study indicated that prehospital treatment of SE with benzodiazepines is safe and effective. They also found that termination of seizures were more likely to occur with lorazepam (OR 5.4; 95%CI2.3-13.2) compared to placebo and diazepam compared to placebo (OR 2.8; 95% CI 1.2-6.7). Overall lorazepam performed better than diazepam but was not statistically significant (OR 1.9 95% CI 0.9-4.3).

Lorazepam

Sublingual lorazepam & rectal diazepam

A randomised control trial performed in two Sub-Saharan African countries (Rwanda and Democratic Republic of Congo) included 436 children at nine hospitals. The children were aged between five months to ten years presenting to the emergency department with seizures lasting more than five minutes.[61] Lorazepam 0.1mg/kg sublingual and diazepam 0.5mg/kg intrarectal were compared for effectiveness in cessation of seizures at five, ten and 20 minutes post administration. The lorazepam group achieved cessation in 28% and the diazepam group in 38% at five minutes. At ten minutes the 79% of the diazepam group had stopped seizing compared to 56% of the lorazepam group. Failure rate when treated with sublingual lorazepam was higher than those in the PR diazepam group (OR 2.95, 95% CI 1.91-4.55). Randomisation was performed with odd and even days of the month and single-blinded resulting in the study scoring zero on the Jaded score, indicating a low range of quality. These results indicate that sublingual lorazepam is not as effective as intrarectal diazepam in terminating seizures. [61]

Intravenous lorazepam & intravenous diazepam

Lorazepam has generally been believed to be superior to diazepam due to a purportedly better safety profile (less respiratory depression and improved, effectiveness in termination[62–64]). However lorazepam IV (n=133) compared to diazepam IV (n=140) in a randomised control trial, published in 2014 (Jaded score of 5 high range quality), showed that lorazepam did not have improved efficacy or safety over diazepam. The study was designed as a superiority trial performed in the ED's of eleven US university hospitals. The trail failed to prove lorazepam's superiority. In the diazepam group 72.1% (101 patients) had termination of seizures after 10 minutes compared with 72.9% (97 patients) in the lorazepam group. Assisted ventilation was required in 26 patients in each group with the lorazepam group having higher rates of sedation (defined as a Riker's score of less than three). These higher rates was the only statistically significant difference between the two groups (absolute risk difference 6.9%; 95% CI 6.1-27.7) as well as favouring the diazepam arm for returning to baseline mental status (Hazard ratio 1.96; 95% 1.35-2.84 P=0.0004). Although the point estimates are similar between the drugs, the confidence interval suggests that one drug may be superior to the other by as much as 10-11%. This study does not support the preferential use of lorazepam over diazepam.[65]

Intravenous lorazepam & intranasal lorazepam

Three other studies performed with Lorazepam showed similar findings. The first study performed in India compared lorazepam IV to lorazepam IN in 141 children age 6-14 years presenting to the ED.[64] This randomised open-label, non-inferiority study showed that in 80% of the IV group and 83% of the IN group seizures terminated after 10 minutes. They concluded that IN lorazepam is not inferior to IV lorazepam (low range of quality; Jaded score 0).

Intravenous lorazepam & intramuscular midazolam

The second study (published 2012; high quality – Jaded score 5) is the Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART) study performed in the prehospital environment by prehospital healthcare providers.[66] They compared IV lorazepam with IM midazolam in double-blind randomised non-inferiority trial. This study included 448 people (adult and children) with seizure cessation prior to hospital arrival as the primary outcome. They found that the IM midazolam group, 73.4% (point estimate 95% CI 0.69-0.78) had better termination of seizures prior to arrival at hospital compared to the 63.4% (point estimate 0.63; 95% CI 0.59-0.68) of the lorazepam group (absolute difference 10 percentage points; 95% CI 4.0-16.1 P<0.001). In the IM group 26.6% failure rate was observed compared to the IV group's 36.6%. The median time from decision to treat and time to seizure cessation were 1.2 minutes and 3.3 minutes respectively in the midazolam group compared to 4.8 minutes and 1.6 minutes respectively in the lorazepam group. Overall time from opening the instrument box (decision to treat) and administration to termination of seizures occurred in ± 5 minutes with midazolam and ±7 minutes with lorazepam. With the IM administration less hospital admissions were observed and more patients were discharged from the ED (hospitalisation and ICU admission - IM group 57.6% & 28.6% vs IV group 65.6% & 36.2%). Both these drugs have a similar safety profile, but the midazolam group were less likely to require rescues treatment (still convulsing) on arrival at hospital.[67]

The last study is a secondary analysis of the RAMPART study (RAMPART study – Jaded score five – high range of quality) mentioned above. In this study they analysed the results of only the 120 patients <18 years of age. The authors found 68.3% seizure cessation in the midazolam group and 71.7% termination in the lorazepam group (risk difference -3.3%; 99% CI -24.9% to 18.2%). They also found that initiating IM midazolam occurred was much faster than initiating IV lorazepam. [66]

Diazepam

In Oregon, a retrospective cohort study (Cochrane's Risk of Bias tool indicates a medium risk of bias) was conducted in the prehospital environment to compare the efficacy and adverse event rate between midazolam to diazepam (multiple routes).[68] The authors found similar safety profiles between the drugs and both showed to be equivalent in terminating seizures.

Intravenous diazepam & intranasal midazolam

Nasal administration may be another option, but this route may cause mucosal irritation and increase discomfort[33,69]. One study reported 2 participants rejecting nasal midazolam; whereas sublingual administration provided the highest plasma levels due to its rapid absorption from the sublingual capillary network.[70]

IN midazolam (0.2mg/kg) compared to IV diazepam (0.3mg/kg) in 50 children 2 months to 12 years and found them equally effective in terminating seizures.[59] The time from arrival at hospital to treatment initiation was 3.37 minutes (SD 2.46) in the midazolam group and 14.3 minutes (SD 3.39) in the diazepam group with arrival to seizure cessation time 6.67 minutes (SD 3.12) and 17.8 minutes (SD 5.09) for the midazolam and diazepam groups respectively. The study scores 2 on the Jaded score, thus low quality because only the investigator was blinded.

Mahmoudian et al[71] compared IN midazolam (5mg/ml equally divided into each nostril) with IV diazepam (0.2mg/kg) in 70 children aged 2 months – 15 years presenting to the ED with acute seizures. They authors found the mean time from administration to seizure termination were 2.94 minutes (excluding time needed for IV placement; SD 2.62) and 3.58 minutes (SD 1.68) in the diazepam and midazolam groups respectively. Jaded score (3) indicates a high range of quality. The only statistically significant result found was the mean time to seizure control (P=0.007), however, the time required for IV placement was not considered in this time frame. They concluded that both drugs are equally effective with similar safety profile.

Intravenous diazepam & intramuscular midazolam

In a small controlled clinical trial (24 enrolled) performed in the ED, midazolam IM was compared to diazepam IV. Out of the 13 children in the midazolam group and the 11 in the diazepam group one child from each group required endotracheal intubation and general anaesthesia for CSE. The midazolam group received medication sooner than the diazepam

group (3.3 ±2.0 vs 7.8 ±3.2 minutes; P=0.001) with termination of seizures occurring at 7.8 (±4.1) vs 11.2 (±3.6) (P=0.047) minutes respectively. The authors concluded that both treatment modalities are effective in managing seizures, but the midazolam arm received treatment faster and had more rapid termination of seizures. Unable to access the full text of this article and abstract information insufficient to do complete quality assessment, however, the study sample size is too small to have statistical significant results. [72]

Rectal diazepam & intranasal midazolam

In a prospective randomised study including 45 children (1 month to 13 years) whom presented to the ED, midazolam intranasal was compared to diazepam PR for adverse events (Jaded score 0 – randomisation poorly described and blinding not mentioned).[73] The authors found that more children needed rescue treatment (second drug) in the diazepam group compared to the midazolam group (statistically significant P<0.5). In the midazolam group 39% responded within the 1-2 minute range compared to diazepam's 32% in the 2-5minutes range (statistically significant P<0.5) They concluded that midazolam performed better than diazepam as anticonvulsant (statistically significant result P<0.5).

Another study compared IN midazolam [administered with a Mucosal Atomization Device (MAD) at 0.2mg/kg] with PR diazepam (0.3-0.5mg/kg) 18 months before and after the EMS protocol changed. Fifty-seven patients were included in the study of which 39 were treated with midazolam and 18 with diazepam. They found that IN controlled seizures better than the PR route (11 min vs 30 min P=0.003). They also found that with diazepam PR rescue medication was required more often in the ED (OR 8.4; CI 1.6-43.7), higher intubation rates in the ED (OR 12.2 CI 2.0-75.4), more admission to hospital (OR 29.3; CI 3.0-288.6) and longer pediatric ICU stay (OR 53.5; CI 2.7-1046.8). This study score -1 (low range of quality) on the Jaded score since it was not randomised nor blinded and had small study population (outlined by wide CI range)[74]

Rectal diazepam & buccal midazolam

Buccal midazolam and rectal diazepam was compared in a prospective trial (Jaded score -1 – low range of quality)[75] This study included 43 children from two months to twelve years in the emergency department and home care setting. The results showed termination of seizures in 85% of the PR diazepam (0.5mg/kg <5yrs & 0.3mg/kg >6yrs) group and 78% of the buccal midazolam (0.25mg/kg) group. The authors concluded that the difference was not statistically significant and that midazolam is as effective as diazepam (P<0.05).

A single blinded randomised control trial in Uganda (2008) compared the efficacy and safety of rectal diazepam with buccal midazolam (high quality – Jaded score 2).[76] This study enrolled 330 children between the ages of three months and twelve years. Overall treatment failure occurred in 43% of the diazepam group and only 30.3% in the midazolam group (RR 1.42; 95% CI1.06-1.90 P=0.016). In the non-malaria-induced seizures, buccal midazolam was superior to rectal diazepam (failure rate of PR 55.9% vs Buccal 26.5%; RR 2.11; 95% CI 1.26-3.54 P=0.002). Enrolment was stopped at 330 patients (not the initial calculated 352) by the safety monitoring board at the last interim data review due to the significant difference in the two treatments. Secondary outcomes measured the median time for seizure recurrence (20 min vs 25min) and the need for rescue treatment in 46.3% of the rectal and 39.1% in the buccal groups respectively. The authors concluded that buccal midazolam is more beneficial since it is easier to administer, had less recurrence in one hour post administration and a more prolonged anticonvulsive effect.[76]

A systematic review with meta-analysis published in 2010 (AMSTAR score 9/11 – high quality) compared non-intravenous midazolam administration to diazepam by any route for effectiveness.[77] They found midazolam by any route superior to diazepam by any route (RR 1.52; 95% CI1.27-1.82) and non-IV midazolam as effective as IV diazepam (RR 0.79; 95% CI 0.19-3.36), buccal midazolam superior to rectal diazepam (RR 1.54; 95%CI 1.29-1.85). Also that midazolam was administered faster than diazepam (mean difference 2.46min; 95% CI 1.52-3.39min) and respiratory complication were the same (RR 1.49; 95%CI 0.25-8.72) for any route administration.

Diazepam & Midazolam & Lorazepam

A randomised control trial (Jaded score 2; double blinding not mentioned) including 120 children was performed in the ED of an Indian children's hospital.[78] Diazepam (n=40) at 0.3mg/kg, lorazepam (n=40) at 0.1mg/kg and midazolam (n=40) at 0.1mg/kg were compared to evaluate the safety and efficacy for treating acute seizures in children (6 months to 14 years). The results show more seizure recurrence in the diazepam group (10% vs 5% in midazolam and 5.1% in lorazepam groups, although more drowsiness was seen in the diazepam group and one child in the diazepam group requiring ventilation. These results are statistically insignificant and the three drugs are comparable.

A systematic review published in 2009 (6/11 – medium quality) considered the management of SE in childhood.[79] The authors suggested that the choice of benzodiazepine should be made by considering three questions.

1. Most effective drug to terminate and minimise recurrent seizures
2. Fastest and most reliable route
3. Optimal safety profile

According to this systematic review, buccal midazolam was the only drug that had statistically significant results in controlling prolonged seizures. They also found that family and friends prefer the buccal or intranasal routes over rectal administration for reasons of person dignity and social acceptability. IN reach maximum plasma concentration at 10 minutes, whilst buccal achieve the same results at 30 minutes. Intranasal lorazepam may also be a good alternative, especially in seizures due to central nervous system infection because of its extended duration of action. The cost of lorazepam is however, a concern for developing countries.[79]

A study done to determine reasons for admission to PICU found that most children suffered respiratory depression when more than two doses of BDZs were administered in the emergent period.[80] Children who received prehospital treatment with BDZs were more likely to receive more than two doses than those not treated in the prehospital environment, possibly because doctors disregard the treatment given prehospitally[80].

Summary of evidence & further research needs

The ideal drug for termination of acute seizures in children in the emergency setting should have a rapid, minimally stressful route of administration, short time to clinical effect (termination of seizures) without excess tissue accumulation, not require special storage facilities and have minimal adverse effects.[69] Chin[81] suggest that IM route for prehospital administration may be most practical, since it is a quick and safe way to administer medication in a patient that is convulsing (compared to IV access and the danger of needle stick injury with convulsing patients).

In the table below is a summary of the available evidence. Three high range quality RCTs (2, 4 & 8) and one high quality SR (14), together with a medium quality SR (16) indicate that lorazepam IV and midazolam IM is comparable with regards to safety and efficacy. Midazolam has faster termination of seizures due to ease of administration (no time spend

TABLE 2: SUMMARY OF ALL RELEVANT ARTICLES FOUND DURING THE LITERATURE REVIEW

No	Study	Score	Authors' conclusion	Dose
1	RCT: loraz SL vs diaz PR	Jaded 0	Higher failure rate in lorazepam; more rescue treatment needed	Loraz 0.1mg/kg Diaz 0.5mg/kg
2	RCT: loraz IV vs diaz IV	Jaded 5	Loraz not superior to diaz; higher sedation and longer time to return to baseline neurological status in loraz group	Loraz 0.1mg/kg(max 4mg) Diaz 0.2mg/kg(max 8mg)
3	RCT: loraz IV vs loraz IN	Jaded 0	IN not inferior to IV	IN & IV 0.1mg/kg
4	RCT: loraz IV vs midaz IM (RAMPART)	Jaded 5	Similar safety profile, midaz less likely to require rescue treatment; faster termination 5min vs 7min; more ED discharge & less ICU admission	Midaz 13-40kg = 5mg >40kg = 10mg Loraz 13-40kg = 2mg > 40kg = 4mg
No	*Study*	*Score*	*Authors' conclusion*	*Dose*
5	Secondary analysis of RAMPART (pediatrics only)		IM midaz faster action due to faster administration	Midaz 13-40kg = 5mg >40kg = 10mg Loraz 13-40kg = 2mg > 40kg = 4mg
6	Cohort: diaz vs midaz (all routes)	Cochrane risk of bias - medium	Similar safety and equivalent in termination of seizures	Multiple doses and multiple routes
7	Control trial: diaz IV vs midaz IM	Jaded 2	Midaz faster termination of seizures due to faster administration; 6.67 min vs 17.8 min	Midaz 0.2mg/kg Diaz 0.3mg/kg
8	RCT: diaz IV vs midaz IN	Jaded 3	Both drugs equally effective; time for IV placement not considered; termination Diaz2.94 min vs 3.58 min	Midaz 5mg/ml (2.5mg/nostril) Diaz 0.2mg/kg
9	RCT: diaz IV vs Midaz IM	Small study; wide CI	Midaz faster administration & termination; 7.8 min (±4.1) vs 11.2 min (±3.6)	No dose mentioned in abstract
10	RTC: diaz PR vs midaz IN	Jaded 0	Diaz required more rescue therapy; termination diaz 32% in 2-5min vs midaz	Diaz 0.3mg/kg Midaz 0.2mg/kg

			39% in 1-2min	
No	*Study*	*Score*	*Authors' conclusion*	*Dose*
11	RCT: diaz PR vs midaz buccal	Jaded -1	Diaz required more rescue therapy, more hospital & ICU admission	Diaz 0.3 - 0.5mg/kg Midaz 0.2mg/kg
12	RCT: diaz PR vs midaz buccal	Jaded -1	Equally effective; 85% of PR & 78% of buccal terminated with first dose	Diaz ≤5yrs = 0.5mg/kg Diaz ≥6yrs = 0.3mg/kg Midaz 0.25mg/kg
13	RCT: diaz PR vs midaz buccal	Jaded 2	Treatment failure more common in diaz (43% vs 30.3% - RR 1.42; 95% CI 1.06-1.90; P=0.016	Both drugs: 2.5mg – 3-11 months 5mg – 1-4yrs 7.5mg – 5-9yrs 10mg – 10-12yrs
14	SR: diaz (any route) vs midaz (non-IV)	AMSTAR 9/11	Non-IV midaz as effective as diaz	Multiple doses
15	RCT: Diaz vs loarz vs midaz (all IV)	Jaded 2 (n=40 per arm)	All comparable; more recurrence in diaz group	Loraz 0.1mg/kg Midaz 0.1mg/kg Diaz 0.3mg/kg
16	SR: seizure termination	AMSTAR 6/11	Buccal administration only one with statistically significant benefit	Not mentioned

RCT – Randomisded Control Trial; Loraz – lorazepam; Diaz – diazepam; Midaz – midazolam; IV – Intravenous; IM – Intramuscular; IN – Intranasal; PR – Per rectum; CI – Confidence Interval; min – Minutes

obtaining IV access). Midazolam also allow more ED discharge and less hospital and ICU admissions. Midazolam (non IV routes) compared to diazepam (any route) seems to be equally effective in terminating seizures. Lorazepam compared to diazepam (both IV route) are equally effective and lorazepam could not be proven superior. Although most studies indicated similar efficacy, the safety profiles of the three drugs in question are different.

Lorazepam (when compared to diazepam) showed higher rates of sedation with slower return to baseline neurological function.

The high quality evidence provided by these studies seems to favour midazolam (any route) above both lorazepam and diazepam (any route). Further research to confirm this conclusion is required. A wealth of evidence is available, but study populations are small, trials are not randomised adequately or blinding is poorly conducted causing low quality scoring when quality assessed. Information for systematic reviews are available but due to a wide variety in administration routes and drug doses, a meta-analysis of studies may be inappropriate to perform.

Collaboration between various institutions such as Pediatric Emergency Applied Research Network (PECARN) and the Pediatric Emergency Research Network (PERN) can help direct high quality, multicentre RCTs comparing these drugs to one another in a more systematic way. Evidence based answers needs to be found for the most appropriate drug (fastest termination and good safety profile) as well as the best route to administer the drug and the optimal dose for that drug.

Reference

1 Pellock JM. Overview: definitions and classifications of seizure emergencies. *J Child Neurol* 2007;**22**:9S – 13S. doi:10.1177/0883073807303064

2 Mishra D, Sharma S, Sankhyan N, *et al.* Consensus guidelines on management of childhood convulsive status epilepticus. *Indian Pediatr* 2014;**51**:975–90.http://www.ncbi.nlm.nih.gov/pubmed/25560156 (accessed 21 Feb2015).

3 Thuzar M, Malabu UH, Tisdell B, *et al.* Use of a standardised diabetic ketoacidosis management protocol improved clinical outcomes. *Diabetes Res Clin Pract* 2014;**104**:e8–11. doi:10.1016/j.diabres.2014.01.016

4 Fahlstrom K, Boyle C, Makic MBF. Implementation of a nurse-driven burn resuscitation protocol: a quality improvement project. *Crit Care Nurse* 2013;**33**:25–35. doi:10.4037/ccn2013385

5 Scholtes FBJ, Renier WO, Meinardi H. Status epilepticus in children. *Seizure* 1996;**5**:177–84. doi:10.1016/S1059-1311(96)80033-1

6 Brouwers MEA. Appraisal of Guidelines for Research & Evaluation II. *Agree Next Steps Consort* 2009;:1–56.

7 National Health and Medical Research Council. *A guide to the development, implementation and evaluation of clinical practice guidelines*. 1998. http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/cp30.pdf?q=publications/synopses/_files/cp30.pdf

8 Liang Y. The correlation analysis of PRISMA, AMSTAR and GRADE in systematic review | The 21st Cochrane Colloquium. In: *Cochrane Colloquium*. 2013. http://2013.colloquium.cochrane.org/abstracts/correlation-analysis-prisma-amstar-and-grade-systematic-review (accessed 5 Aug2015).

9 Schulz KF, Altman DG, Moher D. WITHDRAWN: CONSORT 2010 statement: Updated guidelines for reporting parallel group randomised trials. *Int J Surg* 2010;**7**. doi:10.1016/j.ijsu.2010.09.006

10 Olivo SA, Macedo LG, Gadotti C, *et al.* Research Report Scales to Assess the Quality of Randomized Controlled Trials : A Systematic Review. *Phys Ther* 2008;**88**:156–75. doi:10.2522/ptj.20070147

11 Cameron P, Jelinek G, Kelly A-M, *et al. Textbook of Adult Emergency Medicine*. 3rd

ed. London: : Elsevier Ltd 2009.

12 Fisher RS, Boas WE, Blume W, *et al.* Epileptic Seizures and Epilepsy: Definitions Proposed by the International League Against Epilepsy(ILAE) and the International Bureau for Epilepsy(IBE). *Epilepsia* 2005;**46**:470–2. doi:10.1111/j.1528-1167.2005.00273_1.x

13 Berg AT, Scheffer IE. New concepts in classification of the epilepsies: entering the 21st century. *Epilepsia* 2011;**52**:1058–62. doi:10.1111/j.1528-1167.2011.03101.x

14 Hirsch LJ. Intramuscular versus Intravenous Benzodiazepines for Prehospital Treatment of Status Epilepticus. *N Engl J Med* 2012;**366**:659–60. doi:10.1056/NEJMe1114206

15 Lowenstein DH, Bleck T, Macdonald RL. It's time to revise the definition of status epilepticus. *Epilepsia* 1999;**40**:120–2. doi:10.1111/j.1528-1157.1999.tb02000.x

16 Feen ES, Bershad EM, Suarez JI. Status epilepticus. *South Med J* 2008;**101**:400–6. doi:10.1097/SMJ.0b013e31816852b0

17 Sirven JI, Shafer PO. Status Epilepticus. Epilepsy Found. 2014.http://www.epilepsy.com/learn/impact/seizure-emergencies/status-epilepticus (accessed 26 Apr2016).

18 Smith BJ. Treatment of status epilepticus. *Neurol Clin* 2001;**19**:347–69.http://www.ncbi.nlm.nih.gov/pubmed/11358748 (accessed 3 Apr2015).

19 Wilmshurst JM, Berg AT, Lagae L, *et al.* The challenges and innovations for therapy in children with epilepsy. *Nat Rev Neurol* 2014;**10**:249–60. doi:10.1038/nrneurol.2014.58

20 Martindale JL, Goldstein JN, Pallin DJ. Emergency department seizure epidemiology. *Emerg Med Clin North Am* 2011;**29**:15–27. doi:10.1016/j.emc.2010.08.002

21 Wilmshurst JM. Child Neurology in Africa. *Semin Pediatr Neurol* 2014;**21**:1–2. doi:10.1016/j.spen.2014.02.001

22 Kariuki SM, Kakooza-Mwesige A, Wagner RG, *et al.* Prevalence and factors associated with convulsive status epilepticus in Africans with epilepsy. *Neurology* 2015;**84**:1838–45. doi:10.1212/WNL.0000000000001542

23 Logroscino G, Hesdorffer DC, Cascino G, *et al.* Time trends in incidence, mortality,

and case-fatality after first episode of status epilepticus. *Epilepsia* 2001;**42**:1031–5.http://www.ncbi.nlm.nih.gov/pubmed/11554890 (accessed 3 Apr2015).

24 Prins A, Chengo E, Mung'ala Odera V, *et al.* Long-Term Survival and Outcome in Children Admitted to Kilifi District Hospital with Convulsive Status Epilepticus. *Epilepsy Res Treat* 2014;**2014**:1–7. doi:10.1155/2014/643747

25 Hubert P, Parain D, Vallée L. [Management of convulsive status epilepticus in infants and children]. *Rev Neurol (Paris)* 2009;**165**:390–7. doi:10.1016/j.neurol.2008.11.009

26 Kariuki SM, Matuja W, Akpalu A, *et al.* Clinical features, proximate causes, and consequences of active convulsive epilepsy in Africa. *Epilepsia* 2014;**55**:76–85. doi:10.1111/epi.12392

27 Wilmshurst JM, Badoe E, Wammanda RD, *et al.* Child Neurology Services in Africa. *J Child Neurol* 2011;**26**:1555–63. doi:10.1177/0883073811420601

28 Wilmshurst JM. Approach to epilepsy in children. *Contin Med Educ* 2004;**22**:427–33. doi:10.1007/BF02727905

29 Spangenberg J, Lalkhen N. Children with epilepsy and their families. *South African Fam Pract* 2006;**48**:60–3.

30 Ackermann S, Toorn R van. Managing first-time seizures and epilepsy in children. Contin. Med. Educ. 2012;**30**:16–20.http://www.cmej.org.za/index.php/cmej/article/view/2390/2175 (accessed 6 Apr2015).

31 Wagner RG, Ngugi AK, Twine R, *et al.* Prevalence and risk factors for active convulsive epilepsy in rural northeast South Africa. *Epilepsy Res* 2014;**108**:782–91. doi:10.1016/j.eplepsyres.2014.01.004

32 Ngugi AK, Bottomley C, Fegan G, *et al.* Premature mortality in active convulsive epilepsy in rural Kenya: causes and associated factors. *Neurology* 2014;**82**:582–9. doi:10.1212/WNL.0000000000000123

33 Wermeling DP. Intranasal Delivery of Antiepileptic Medications for Treatment of Seizures. *Neurotherapeutics* 2009;**6**:352–8. doi:10.1016/j.nurt.2009.01.002

34 Chamberlain JM, Okada P, Holsti M, *et al.* Lorazepam vs diazepam for pediatric status epilepticus: a randomized clinical trial. *JAMA* 2014;**311**:1652–60. doi:10.1001/jama.2014.2625

35 Silbergleit R, Lowenstein D, Durkalski V, *et al.* Lessons from the RAMPART study--and which is the best route of administration of benzodiazepines in status epilepticus. *Epilepsia* 2013;**54 Suppl 6**:74–7. doi:10.1111/epi.12284

36 Mitchell WG. Status epilepticus and acute repetitive seizures in children, adolescents, and young adults: etiology, outcome, and treatment. *Epilepsia* 1996;**37 Suppl 1**:S74–80.http://www.ncbi.nlm.nih.gov/pubmed/8647055 (accessed 2 Apr2015).

37 Wick JY. The history of benzodiazepines. *Consult Pharm* 2013;**28**:538–48. doi:10.4140/TCP.n.2013.538

38 Lader M. History of benzodiazepine dependence. *J Subst Abuse Treat* 1991;**8**:53–9. doi:10.1016/0740-5472(91)90027-8

39 American Society of Health-System Pharmacists. Introduction to Pharmacokinetics and Pharmacodynamics. *Pharmocokinetics and Pharmcodynamics* 2010;**1**:1–18. doi:10.1007/SpringerReference_184421

40 Katzung BG, Trevor AJ. *Examination & Board Review Pharmacology*. 5th ed. Stamford: : Appelton & Lange 1998.

41 Rang H, Dale M, Ritter J, *et al. Rang and Dale's Pharmacology*. 6th ed. Philadelphia: : CHURCHILL & LIVINGSTONE 2007.

42 Rang H, Dale M, Ritter J, *et al. Pharmacology*. 5th ed. Bath: : CHURCHILL & LIVINGSTONE 2003.

43 Oshiro C. Benzodiazepine Pathway, Pharmacokinetics. PharmGKB (US Dep. Helath Hum. Serv. 2015.https://www.pharmgkb.org/pathway/PA165111375 (accessed 31 Mar2015).

44 Blows WT. *The Biological Basis of Nursing: Mental Health*. Routledge 2003. https://books.google.com/books?id=6JmCAgAAQBAJ&pgis=1 (accessed 5 Apr2015).

45 Greenblatt DJ, Divoll M. Diazepam versus lorazepam: relationship of drug distribution to duration of clinical action. *Adv Neurol* 1983;**34**:487–91.http://www.ncbi.nlm.nih.gov/pubmed/6131586 (accessed 23 Jun2015).

46 Pacifici GM. Clinical pharmacology of midazolam in neonates and children: effect of disease-a review. *Int J Pediatr* 2014;**2014**:309342. doi:10.1155/2014/309342

47 Ramsay RE, Hammond EJ, Perchalski RJ, *et al.* Brain Uptake of Phenytoin, Phenobarbital, and Diazepam. *Arch Neurol* 1979;**36**:535–9. doi:10.1001/archneur.1979.00500450029003

48 Alldredge BK, Gelb a M, Isaacs SM, *et al.* A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. *N Engl J Med* 2001;**345**:631–7. doi:10.1056/NEJMoa002141

49 Babl FE, Sheriff N, Borland M, *et al.* Emergency management of paediatric status epilepticus in Australia and New Zealand: Practice patterns in the context of clinical practice guidelines. *J Paediatr Child Health* 2009;**45**:541–6. doi:10.1111/j.1440-1754.2009.01536.x

50 Seinfeld S, Shinnar S, Sun S, *et al.* Emergency management of febrile status epilepticus: Results of the FEBSTAT study. *Epilepsia* 2014;**55**:388–95. doi:10.1111/epi.12526

51 Hales-Tooke a. Improving hospital care for children. *Children*;**15**:116–8.

52 Advanced Life Support Group. *Advanced Paediatric Life Support: The Practical Approach*. 5th ed. Oxford: : Wiley - Balckwell 2011.

53 Abend NS, Loddenkemper T. Management of pediatric status epilepticus. *Curr Treat Options Neurol* 2014;**16**:301. doi:10.1007/s11940-014-0301-x

54 Cook AM, Castle A, Green A, *et al.* Practice variations in the management of status epilepticus. *Neurocrit Care* 2012;**17**:24–30. doi:10.1007/s12028-012-9711-3

55 Williams N, Nefdt WM, Wilmshurst JM. Epilepsy South Africa: Turning obstacles into true potential. *Epilepsia* 2014;**56**:1–4. doi:10.1111/epi.12641

56 Welzel T, editor. *Emergency Medicine Guideline for the Western Cape*. Cape Town: : Division of Emergency Medicine 2013.

57 Health Professions Council of South Africa. *Advanced Life Support Protocols*. 2006. http://www.hpcsa.co.za/PBEmergencyCare/Guidelines

58 Chin RFM, Verhulst L, Neville BGR, *et al.* Inappropriate emergency management of status epilepticus in children contributes to need for intensive care. *J Neurol Neurosurg Psychiatry* 2004;**75**:1584–8. doi:10.1136/jnnp.2003.032797

59 Thakker A, Shanbag P. A randomized controlled trial of intranasal-midazolam versus

intravenous-diazepam for acute childhood seizures. *J Neurol* 2013;**260**:470–4. doi:10.1007/s00415-012-6659-3

60 Pang T, Hirsch LJ. Treatment of Convulsive and Nonconvulsive Status Epilepticus. *Curr Treat Options Neurol* 2005;**7**:247–59.http://www.ncbi.nlm.nih.gov/pubmed/15967088 (accessed 3 Apr2015).

61 Malu CKK, Kahamba DM, Walker TD, *et al.* Efficacy of Sublingual Lorazepam Versus Intrarectal Diazepam for Prolonged Convulsions in Sub-Saharan Africa. *J Child Neurol* 2013;**29**:895–902. doi:10.1177/0883073813493501

62 Qureshi A, Wassmer E, Davies P, *et al.* Comparative audit of intravenous lorazepam and diazepam in the emergency treatment of convulsive status epilepticus in children. *Seizure* 2002;**11**:141–4. doi:10.1053/seiz.2001.0635

63 Chiulli DA, Terndrup TE, Kanter RK. The influence of diazepam or lorazepam on the frequency of endotracheal intubation in childhood status epilepticus. *J Emerg Med*;**9**:13–7.http://www.ncbi.nlm.nih.gov/pubmed/2045642 (accessed 2 Apr2015).

64 Arya R, Gulati S, Kabra M, *et al.* Intranasal versus intravenous lorazepam for control of acute seizures in children: a randomized open-label study. *Epilepsia* 2011;**52**:788–93. doi:10.1111/j.1528-1167.2010.02949.x

65 Chamberlain JM, Okada P, Holsti M, *et al.* Lorazepam vs Diazepam for Pediatric Status Epilepticus. *Jama* 2014;**311**:1652–60. doi:10.1001/jama.2014.2625

66 Welch RD, Nicholas K, Durkalski-Mauldin VL, *et al.* Intramuscular midazolam versus intravenous lorazepam for the prehospital treatment of status epilepticus in the pediatric population. *Epilepsia* 2015;**56**:254–62. doi:10.1111/epi.12905

67 Silbergleit R, Durkalski V, Lowenstein D, *et al.* Intramuscular versus intravenous therapy for prehospital status epilepticus. *N Engl J Med* 2012;**366**:591–600. doi:10.1056/NEJMoa1107494

68 Warden CR, Frederick C. Midazolam and diazepam for pediatric seizures in the prehospital setting. *Prehosp Emerg Care* 2009;**10**:463–7. doi:10.1080/10903120600885126

69 Ghane M-R, Javadzadeh H-R, Mahmoudi S, *et al.* Intramuscular compared to intravenous midazolam for paediatric sedation: A study on cardiopulmonary safety and effectiveness. *Afr J Paediatr Surg* 2014;**11**:219–24. doi:10.4103/0189-

6725.137329

70 Geldner G, Hubmann M, Knoll R, *et al.* Comparison between three transmucosal routes of administration of midazolam in children. *Paediatr Anaesth* 1997;**7**:103–9.http://www.ncbi.nlm.nih.gov/pubmed/9188109 (accessed 2 Apr2015).

71 Mahmoudian T, Zadeh MM. Comparison of intranasal midazolam with intravenous diazepam for treating acute seizures in children. *Epilepsy Behav* 2004;**5**:253–5. doi:10.1016/j.yebeh.2004.01.003

72 Chamberlain JM, Altieri MA, Futterman C, *et al.* A prospective, randomized study comparing intramuscular midazolam with intravenous diazepam for the treatment of seizures in children. *Pediatr Emerg Care* 1997;**13**:92–4.http://www.ncbi.nlm.nih.gov/pubmed/9127414 (accessed 31 Mar2015).

73 Fişgin, TunçGurer, YavuzTezic, TahsinSenbil, NesrinZorlu, PelinOkuyaz, CetinAkgün D. Effects of Intranasal Midazolam and Rectal Diazepam on Acute Convulsions in Children: Prospective Randomized Study. *J Child Neurol* 2002;**17**:123–36.

74 Holsti M, Sill BL, Firth SD, *et al.* Prehospital Intranasal Midazolam for the Treatment of Pediatric Seizures. *Pediatr Emerg Care* 2007;**23**:148–53. doi:10.1097/PEC.0b013e3180328c92

75 Baysun S, Aydin OF, Atmaca E, *et al.* A comparison of buccal midazolam and rectal diazepam for the acute treatment of seizures. *Clin Pediatr (Phila)* 2005;**44**:771–6.http://www.ncbi.nlm.nih.gov/pubmed/16327963 (accessed 29 Oct2015).

76 Mpimbaza A, Ndeezi G, Staedke S, *et al.* Comparison of buccal midazolam with rectal diazepam in the treatment of prolonged seizures in Ugandan children: a randomized clinical trial. *Pediatrics* 2008;**121**:e58–64. doi:10.1542/peds.2007-0930

77 McMullan J, Sasson C, Pancioli A, *et al.* Midazolam versus diazepam for the treatment of status epilepticus in children and young adults: a meta-analysis. *Acad Emerg Med* 2010;**17**:575–82. doi:10.1111/j.1553-2712.2010.00751.x

78 Gathwala G, Goel M, Singh J, *et al.* Intravenous diazepam, midazolam and lorazepam in acute seizure control. *Indian J Pediatr* 2012;**79**:327–32. doi:10.1007/s12098-011-0505-y

79 Sofou K, Kristjánsdóttir R, Papachatzakis NE, *et al.* Management of Prolonged Seizures and Status Epilepticus in Childhood: A Systematic Review. *J Child Neurol*

2009;**24**:918–26. doi:10.1177/0883073809332768

80 Chin RFM, Verhulst L, Neville BGR, *et al.* Inappropriate emergency management of status epilepticus in children contributes to need for intensive care. *J Neurol Neurosurg Psychiatry* 2004;**75**:1584–8. doi:10.1136/jnnp.2003.032797

81 Chin RFM. What are the best ways to deliver benzodiazepines in children/patients with prolonged convulsive seizures? *Epileptic Disord* 2014;**16**:S50–8. doi:10.1684/epd.2014.0684

PART C – ARTICLE

This article was written for future publication in Emergency Medicine Journal. As such the Instructions for Authors was followed (Appendix H – Part D) during the writing of this article.

The following deviations from the journal's instructions where made:

- More references included than the allocated 25 references. This was done to allow the examiner better insight into the background and reasons for choosing this particular topic and methodology.
- Figures are within the text and not as separate attachments. This allows better flow and ease of reading. Tables should be place where first cited, however the results tables are grouped together to allow comparing of results with greater ease.
- Headings and subheadings in the text are done in colour for aesthetic value and ease of reading

Rapid Review of Drug Management for Paediatric Seizure Termination in the Emergency Setting

Jeannie Stockigt

University of Cape Town

Faculty of Health

Division of Emergency Medicine

jeanniestock@gmail.com

PO Box 4509
Tyger Valley
7536

0027 734453970

Word count: 2997

(Excluding title page, abstract, references, figures and tables)

Keywords: acute, paediatric, seizure, benzodiazepine, emergency, management

Table of Contents

Table of Figures

Table of Tables

Abstract

Rapid review of drug management for paediatric seizure termination in the emergency setting

JC Stockigt, B Cheema

Background

Prolonged seizures are a medical emergency and require immediate treatment to prevent complications. Benzodiazepines (BDZ's) are integral to acute seizure management. The most commonly used BDZs are Lorazepam, Diazepam and Midazolam. Lorazepam is often perceived as the superior choice, however recent studies have challenged this practice but results appear inconclusive and contradictory. This study aims to consolidate the available literature and formulate recommendations for the use of BDZs as emergent treatment for paediatrics.

Methods

A tiered rapid review was performed. In August 2015 a search including TRIP (clinical search engine), the National Institute for Healthcare Excellence (NICE), National Guideline Clearinghouse (NGC), Scottish Intercollegiate Guidelines network (SIGN), Guidelines International Network (GIN) as well as the South African and European Medical Research Councils were searched for the first tier. A second updated search was performed in January 2016 including EMBASE and Medline. Clinical practice guidelines (CPGs) were included if they covered emergency treatment of acute seizures in paediatrics using benzodiazepines (BDZ). Data was obtained by two independent reviewers using FORM framework.

What is known on this subject?

Benzodiazepines (BDZ) play a central role in acute seizure management. Despite decades of research, the most ideal BDZ for emergency seizure termination in children remains unclear.

What might this study add?

Current evidence appears to support Midazolam as first line treatment for acute seizure management in

Results

Midazolam performed better than both Lorazepam and Diazepam with faster seizure termination, more discharges and shorter ICU stays. Lorazepam was not superior to Diazepam and had higher sedation rates with slower return to baseline function.

Conclusion

Midazolam is gaining favour as first-line treatment due to ease and speed of administration. Lorazepam is not superior to Diazepam. The rectal route should only be used if no other option available.

Introduction

Prolonged seizures (lasting more than five minutes)[1] are a medical emergency and should be treated promptly[2,3] to avoid neurological damage.[4,5] Convulsive status epilepticus was defined as seizures lasting more than 30 minutes or multiple seizures without regaining full consciousness between seizures, however, the newer definition: “more than five min of (i) continuous seizures or (ii) two or more discrete seizures between which there is incomplete recovery of consciousness”[6–8], has been adopted internationally to prevent treatment delays and associated morbidity with prolonged seizures.[4,9,10]

Benzodiazepine (BDZs) use for terminating acute seizures started in 1965.[11] It is still accepted as emergency drug of choice for acute seizure management.[12–18] This study therefore considered BDZs as drug management for acute seizures in the emergency setting.

Currently there is limited consensus with regards to the best drug to use as first-line treatment.[6,19,20] Numerous studies have been done to determine the superiority of any of the three most commonly used benzodiazepines (BDZ),[19,21–25] which are Diazepam, Lorazepam and Midazolam. In the emergency setting, prompt treatment requires an easily accessible administration route and sustained termination with minimal adverse events. Lorazepam is perceived to be the drug of choice due to lower rates of adverse events.[26–28] Lorazepam requires refrigeration and intravenous (IV) access for optimum efficacy and longevity.[9,21,29,30] Diazepam is often used as first line when Lorazepam is unavailable or IV access not present, since it can be administered IV or rectally (PR) and doesn’t require refrigeration.[9,31–34] Recently, newer evidence challenged the practice described above. Thud creating an on-going debate as to which BDZ is best for the use in acute seizure termination.

This tiered rapid review addresses the question: “In paediatric patients aged 1 month to 18 years with acute seizures lasting more than five minutes, in prehospital or emergency department settings, which BDZ (diazepam, midazolam or lorazepam) provides the easiest administration and which provides the most rapid and sustained termination of seizures with the lowest rate of adverse effects?” The aim is to consolidate the available evidence and provide clearer direction for policy makers in prehospital and emergency department settings as well as the healthcare providers attending to children with seizures.

Objectives

Primary objectives included ascertaining time to cessation of seizures post drug administration and establishing speed of BDZ administration [determined by time from decision to treat to administration of medication (includes time to gain access, dose calculation, drawing up and diluting if required]. Secondary objectives focused on adverse event rates including rescue treatment (2nd dose) within 1 hour of 1st BDZ dose, respiratory depression (decreased respiratory rate or assisted ventilation required) or cardiovascular compromise (poor perfusion and/or fluid bolus required) as well as hospitalisation rates (admission to hospital and/or admission to ICU).

Methods

Ethics approval (Appendix N, Part D) was obtained before this tiered, rapid review was performed. This approach aimed to identify high quality clinical practice guidelines (CPGs) as the first tier for evidence collection. If unable to answer the research question in full on this tier, the lower tiers would be used. The lower tiers include review of reviews, systematic reviews and randomised control trials. An updated search was performed prior to publication to ensure most recent articles are included.

Criteria for included studies

Types of Studies

Guidelines, review of reviews and systematic reviews included if they discussed acute seizures management (specifically BDZs) of children in the emergency setting. The fourth tier considered only randomised control trials (no quasi-random or non-random trials). The second, updated search included only systematic reviews and randomised control trials.

Types of Population

Articles were included if acute seizure management in paediatric populations (>28 days to 18 yrs) or acute seizure management in mixed (adults and children) populations were discussed.

Types of Interventions

Any dose and route of benzodiazepine (Lorazepam, Diazepam and Midazolam) were accepted. Articles were excluded if compared to drugs other than the three mentioned.

Types of Outcomes

Outcomes considered included time from arrival of healthcare providers to decision to treat, from decision to treat to drug administration and time from administration to seizure cessation. Secondary outcomes included the need for a second BDZ dose, respiratory depression or assisted ventilation required, cardiovascular compromise (delayed capillary refill time or fluid bolus required) and hospital admission to either a normal ward or Intensive Care Unit (ICU).

Search strategy

Electronic search

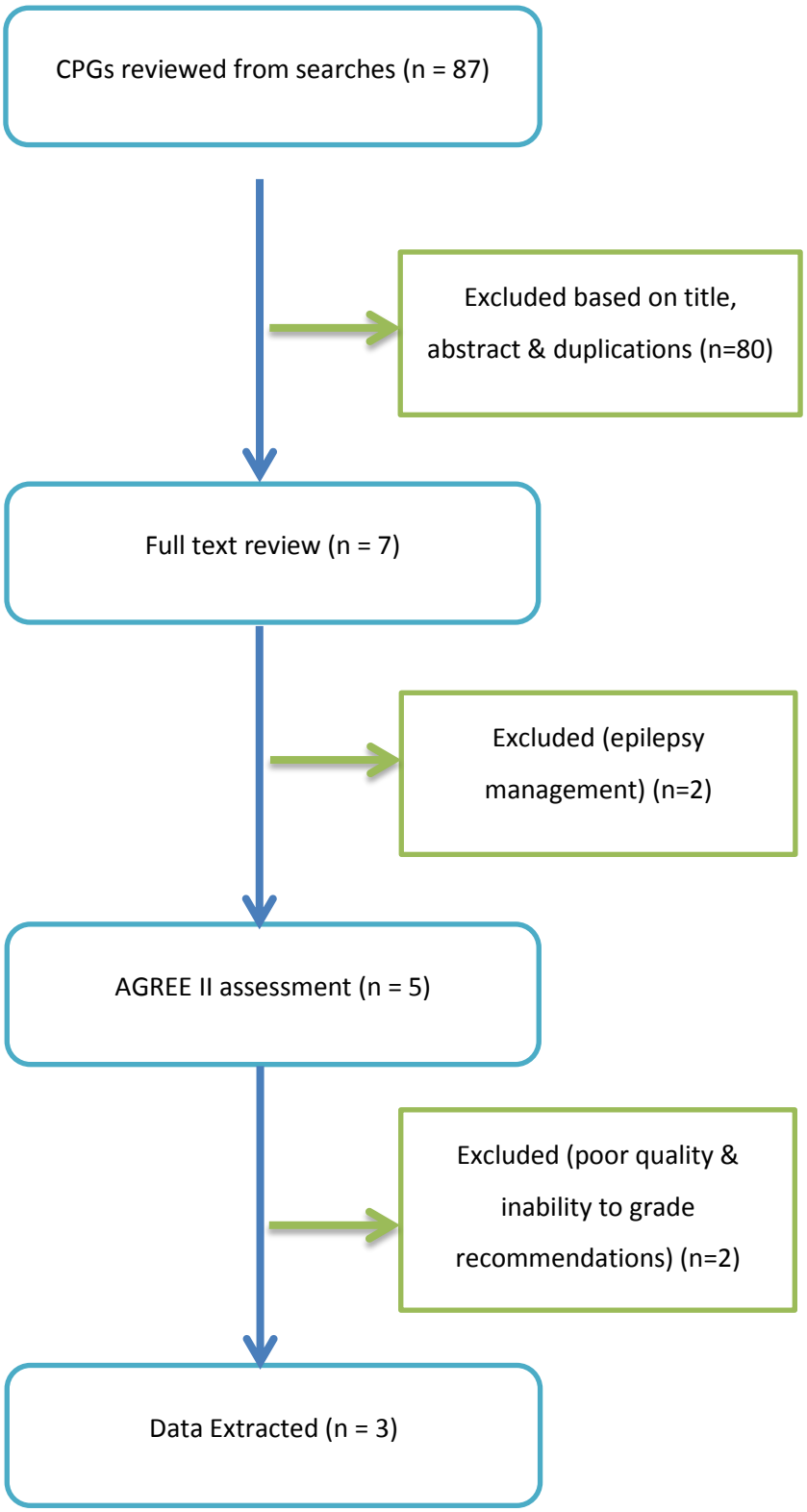
Databases including TRIP (clinical search engine), the National Institute for Healthcare Excellence (NICE), National Guideline Clearinghouse (NGC), Scottish Intercollegiate Guidelines network (SIGN), Guidelines International Network (GIN) as well as the South African and European Medical Research Councils were searched on the first tier. Searches were done using the keywords “paediatric”, “seizure”, “benzodiazepine” and “emergency treatment” or “emergency management” or “emergency care”. The first tier was searched without language or date limitation and grey literature was not searched (Figure 1). A list of all articles (Appendix B) and excluded articles with reasons (Appendix C) is available in Part D.

All objectives were answered with data collected from this tier and the lower tiers were not used and therefore no searches performed for them.

Secondary search

The most recent CPG, published in 2014, includes studies published up until 2012, an additional search was therefore performed on MEDLINE (via PubMed) and EMBASE (via SCOPUS) to ensure relevant newer articles are included prior to formulating recommendations. Search strategy and key terms as for guideline search, date limitation (January 2012 to January 2016) and study type (RCT & SR only) were included: The search results are shown in Figure 2.

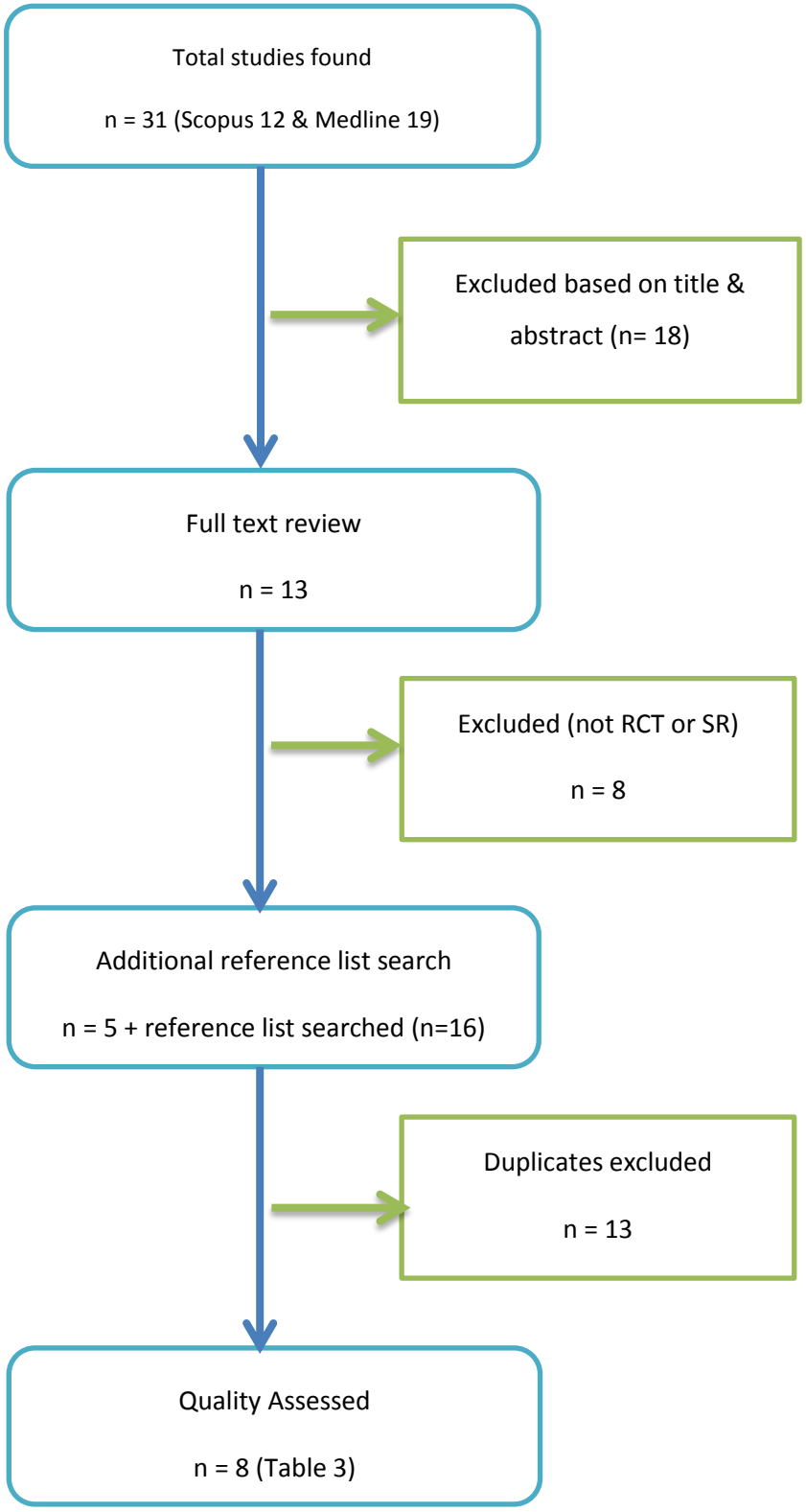
Figure 1: Results from clinical practice guideline search



[2]

[2] Only 1st tier done – primary and secondary outcomes answered on this tier

Figure 2: Additional search results from January 2012 to January 2016



[3]

[3] Table 3 show results, quality assessment documents in Part D, Appendix F and Appendix G

Data collection and analysis

Two independent reviewers (JS & PS) assessed articles for eligibility using pre-determined inclusion and exclusion criteria (Appendix A – Part D)[4]. Five guidelines were included and quality assessed using the Appraisal of Guidelines for Research & Evaluation (AGREE) Instrument (Updated in 2010 to AGREE II) [12] checklist by JS and PS independently, disagreements were adjudicated by BC[5]. Guidelines scoring below 50% were excluded.

(AGREE II assessments available in Part D, Appendix D1-D5)

Data Extraction

Guideline recommendations pertaining to acute seizures were collected independently by JS and PS using a predetermined data collection tool (Appendix M, Part D). The FORM framework[35], using a Body of Evidence (BoE) Matrix and Grades of Recommendations, was developed for the Australian National Health Medical Research Council (NHMRC). This framework was specifically designed for quality assessment of recommendations prior to guideline development.[36] Although still a novel method, the design and production of this FORM framework (Appendix I, Part D) was published in 2011. Some examples of how this is done in practice are listed in Part D (Appendix J - tiered approach for data collection and Appendix K - using guidelines to inform recommendations).

The NHMRC FORM framework uses five key components to assess the evidence with regards to its internal validity [(1) evidence base and (2) consistency of included studies], the overall (3) clinical impact of the intervention and external factors that may influence the effectiveness [(4) generalizability and (5) applicability] of the recommendation (Appendix L, Part D). Once the BoE is rated in each of the five components, an evidence statement matrix is prepared. From this a recommendation is formulated and finally a grade for the recommendation is determined. Overall “A” or “B” grading (see Table 1) can only be achieved if both the evidence base and consistency scored an “A” or “B” rating. Table 1 illustrates the NHMRC BoE Matrix used to rate individual recommendations.

Once the recommendation is rated, it is then either adopted (accepted without change), adapted (accepted with adjustments) or contextualised. In the results section, this adapt, adopt or contextualise process was performed for each recommendations.

[4] Jeannie Stockigt & Pierre Smit
[5] Baljit Cheema

Table 1: NHMRC Body of evidence matrix and grade of recommendations

Component	A (Excellent)	B (Good)	C (Satisfactory)	D (Poor)
Evidence Base[6]	One of more level I studies with a low risk of bias or several level II studies with a low risk of bias	One or two level II studies with a low risk of bias or an SR/several level III studies with a low risk of bias	One or two level III studies with a low risk of bias , or level I or II studies with a moderate risk of bias	Level IV studies, or level I or II studies/SR with a high risk of bias
Consistency[7]	All studies consistent	Most studies consistent and inconsistency may be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical impact	Very large	Substantial	Moderate	Slight or restricted
Generalizability	Population/s studied in body of evidence are the same as target population in the	Population/s studied in the body of evidence are similar to the target population for the	Population/s studied in the body of evidence differ to the target population guideline but is clinically sensible to apply	Population/s studied in the body of evidence differ to the target population and hard to judge whether it is sensible to

[6] Level of evidence determined from the NHMRC Evidence Hierarchy
[7] If only one study – this component is ranked "not applicable"

	guideline	guideline	this evidence to the target population[8]	generalise to the target population
Applicability	Directly applicable to healthcare context	Applicable to healthcare context with some caveats	Probably applicable to healthcare context with some caveats	Not applicable to healthcare context
Grade of Recommendation		Description		
A		BoE can be trusted to guide practice		
B		BoE can be trusted to guide practice in most situations		
C		BoE provides some support for recommendation but care should be taken in its application		
D		BoE is weak and recommendations must be applied with caution		

Table taken from FORM Framework[35]

[8] For example: results in adults that are clinically sensible to apply to children OR psychosocial outcomes for one cancer that may be applicable to patients with another cancer

Results

Description of included CPGs

Background

National Institute for Health and Care Excellence (NICE) is a collection of guidelines developed for the National Institute of Health in the United Kingdom and other public health settings. The CPG used from the NICE collection: *The diagnosis and management of the epilepsies in adults and children in primary and secondary care,*[37] was partially updated in 2012.

National Guideline Clearinghouse (NGC) is a searchable database maintained by the Agency for Healthcare Research and Quality in partnership with American Medical Association and the National Health Insurance Plans. The CPG used from NGC collection is: *Guidelines for the evaluation and management of status epilepticus*.[38]

Guidelines International Network (GIN) is an international network of 99 organisations and 139 individual members (representing 49 countries) which supports evidence-based healthcare. *Evidence-based guideline for paediatric seizure management using GRADE methodology*[39] was the guideline used from this network.

(More information available in Part D, Appendix E)

Included Studies and Population

NICE

Recommendations based on eight studies. Population and setting includes community, emergency department and admitted patients of adults (>18 yrs), young adults (11 to 17 yrs) and children (>28 days to 11yrs).

NGC

Recommendations based on sixteen Lorazepam studies, eleven Midazolam studies and 20 studies including Diazepam. Studies include adults and children (age not specified) in the emergency and admitted patient setting.

GIN

Recommendations based on 20 studies in the prehospital, emergency department and admitted patient population including both adults and children (>28 days).

Included interventions and comparisons

Interventions in CPGs include lorazepam, diazepam and midazolam compared to one another through various routes.

Included outcomes

Outcomes included were time from administration to seizure cessation at five, ten or 15 minutes, from decision to treat to seizure termination as well as the rate of rescue drugs administered (second dose of BDZs) Other outcomes included safety profile (least amount of adverse events), fastest seizure cessation, shortest hospital stay and least ICU days.

Findings

CPG results

Ten recommendations were collected (Table 2). Midazolam is gaining favour as first-line therapy in emergency situations, especially where IV access is not available. Time from decision to treat to drug administration as well as time from decision to treat to seizure termination is quickest with midazolam (non-IV route) when compared to lorazepam and diazepam. NICE and NGC still recommend lorazepam as first choice when IV access is available, however GIN suggest that all three are equivalent when used IV. All three CPGs agree that diazepam PR should only be used if no other option is available due to low social acceptability, difficulty administering it correctly and lower efficacy when compared to other BDZs and other routes. No direct data found on rate of rescue BDZs required in the CPGs, but the additional studies have some results (discussed below).

Updated search results (including reference list search)

The additional update search resulted in eight studies (Table 3) included to ensure a comprehensive view of the current available evidence. The higher quality studies are printed in bold and results are listed in the table, some results are discussed below with relation to the objectives.

Time to initiation and time to cessation

Study 2 shows time from arrival to treatment occurred faster in midazolam IM group (3.37 ± 2.46 min vs 14.13 ± 3.39 min) compared to diazepam IV. Time from drug administration to cessation was similar (3.01 ±2.79 min vs 2.67 ± 2.31) and time from arrival to cessation was faster in the midazolam group (6.67 ± 3.12 vs 17.18 ± 5.09 min). Study 6 indicates that seizure termination prior to hospital arrival was lower in the midazolam group (68.3% vs 71.6%) compared to lorazepam IV group, but the wide CI (-24.9% to 18.2%) indicates a large margin of error. Although midazolam seems to be favoured, no definitive answers are available comparing all three BDZs for time from arrival to seizure cessation.

Speed of administration

Three studies (2, 5 & 8) indicate midazolam as fastest drug to administer due to its various non-IV routes. Time to administer midazolam via non-IV route ranged from 2.46 minutes to 3.37 minutes. In a systematic review (study 7), buccal midazolam was the only drug/route combination with statistically significant efficacy and speed over PR diazepam. Study 8 concludes that non-IV midazolam is superior to diazepam via any route (RR 1.52; 95%CI 1.27-1.82) for seizure cessation. Recurrence appears lower when midazolam is used, while efficacy appears similar between the three drugs.

Rate of rescue benzodiazepines required

Only two high quality studies (4 and 6) mentioned rate of rescue treatment required as an measurable outcome. In study 4 lorazepam IV is compared to diazepam IV. The outcomes indicated that the lorazepam group had less seizure recurrence (requiring less rescue therapy) than the diazepam group at 1hr post initial intervention, but the Diazepam group required less rescue therapy at 4 hrs post initial intervention. The second study (6) compared midazolam IM to lorazepam IV and concluded that the midazolam group required less rescue treatment than the lorazepam group.

Adverse Events

Most studies indicated a similar adverse event rate between the three BDZs; however lorazepam appears to induce deeper sedation. Study 1 shows diazepam to have excessive sedation and longer return to baseline neurological function when compared to lorazepam IV. Another study (4) performed in 2014, found lorazepam to have higher rates of sedation when compared to diazepam (Absolute risk difference 16.9%; 95% CI 6.1-27.7). Improved

randomisation and blinding with a larger study population (n=273 vs n=120) allowed Study 4 a better quality assessment score than Study 1.

Respiratory compromise is similar when comparing non-IV midazolam to IV diazepam (Study 8). Cardiovascular compromise is not specifically mentioned in the CPG's or in the additional search results.

In Study 6, hospitalisation was required in 285/445 patients in IM midazolam group and 292/445 in the IV lorazepam group (RR 0.88, 95% CI 0.79-0.98) with ICU admission in 128/445 of the IM group and 161/445 of the lorazepam IV group (RR 0.79; 95% CI 0.65-0.95). Midazolam appears to have less seizure recurrence, allows more ED discharges thus resulting in less hospital and ICU admissions.

Discussion

The primary objectives of this study were to ascertain the time to cessation of seizures post drug administration and to establish the speed of BDZ administration as determined by time from decision to treat to administration of medication (includes time to gain access, dose calculation, drawing up and diluting if required).

Time to seizure cessation is influenced by drug choice and route of administration, especially the time required to achieve the administration route (IV access in paediatrics require skill). Time from healthcare provider's arrival to decision to treat is more difficult to ascertain since diagnosing seizures is required before treatment can be initiated.

The objectives of this article are quantitative in nature and although CPGs base their recommendations on studies with such exact times, guideline recommendations do not necessarily report them.

Midazolam is recommended by all three CPG's as 1st line treatment (IM - Grade A, Buccal - Grade B and IN - Grade B) when IV is unavailable. When IV access is present Lorazepam is recommended (Grade A and Grade B). A newer study (Table 3, study 4) shows lorazepam to be more sedative than diazepam. With this in mind, lorazepam as first choice when IV access is present must be revised. The available evidence considers lorazepam, diazepam and midazolam to be equally effective via the IV route (Table 3, Study 1 and GIN CPG), suggesting any of the three BDZs that is readily available is acceptable as first-line.

Table 2: Clinical Practice Guideline results and recommendation grading

NICE - THE DIAGNOSIS AND MANAGEMENT OF EPILEPSIES IN ADULTS AND CHILDREN IN PRIMARY AND SECONDARY CARE		
	Community	Emergency Department
Recommendation quoted from NICE guideline **AGREE II score:** • **Domain 1 – 97.2%** • **Domain 2 – 91.7%** • **Domain 3 – 89.6%** • **Domain 4 – 100%** • **Domain 5 – 89.6%** • **Domain 6 – 95%**	"Administer buccal midazolam as first-line treatment in children, young people and adults with prolonged or repeated seizures in the community. Administer rectal diazepam if preferred or if buccal midazolam is not available. If intravenous access is already established and resuscitation facilities are available, administer intravenous lorazepam."[37]	"Administer intravenous lorazepam as first-line treatment in hospital in children, young people and adults with ongoing generalised tonic–clonic seizures (convulsive status epilepticus). Administer intravenous diazepam if intravenous lorazepam is unavailable, or use buccal midazolam if unable to secure immediate intravenous access. Administer a maximum of two doses of the first-line treatment (including pre-hospital treatment)."[37]
Quality of evidence[9]	Moderate – buccal vs IV diazepam Moderate – buccal vs rectal diazepam (less recurrence with buccal)	Moderate - IV lorazepam and IV diazepam similar Moderate – buccal vs IV diazepam
Author's summary	1st line, no patent IV: Midazolam Buccal 2nd line, no patent IV: Diazepam rectal 1st line with patent IV: Lorazepam	1st line: no patent IV – Midazolam buccal 1st line: with patent IV – Lorazepam 2nd line: with patent IV – Diazepam
NHMRC Body of Evidence grading	Grade B (Good)	Grade C (Satisfactory)
Recommendation implementation	Adapted (after newer studies incorporated)	Adapted (after newer studies incorporated)

[9] Strength of recommendation not mentioned in guidelines – GRADE not used

NGC - GUIDELINES FOR THE EVALUATION AND MANAGEMENT OF STATUS EPILEPTICUS			
	Emergent treatment	Emergent treatment	Emergent treatment
Recommendation quoted from NGC guideline **AGREE II score:** • **Domain 1 – 66.7%** • **Domain 2 – 52.8%** • **Domain 3 – 83.3%** • **Domain 4 – 88.9%** • **Domain 5 – 70.8%** • **Domain 6 – 62.5%**	"Lorazepam is the drug of choice for intravenous (IV) administration."[38]	"Midazolam is the drug of choice for intramuscular (IM) administration."[38]	"Rectal diazepam can be given when there is no IV access and IM administration of midazolam is contraindicated."[38]
Quality of evidence (GRADE methodology)	Moderate	Moderate	Moderate
Strength of recommendation (GRADE methodology)	Strong	Strong	Strong
Author's summary	1st line: with patent IV – Lorazepam	1st line: with no patent IV – Midazolam IM	Diazepam rectal – only if no patent IV and Midazolam IM is contra-indicated
NHMRC Body of Evidence grading	Grade B (Good)	Grade A (Excellent)	Grade B (Good)
Recommendation implementation	Adapted (after newer studies incorporated)	Adopted	Adopted

GIN - AN EVIDENCE-BASED GUIDELINE FOR PAEDIATRIC PREHOSPITAL SEIZURE MANAGEMENT USING GRADE METHODOLOGY					
Recommendation quoted from GIN **AGREE II score:** • **Domain 1 – 91.7%** • **Domain 2 – 83.3%** • **Domain 3 – 77%** • **Domain 4 – 88.9%** • **Domain 5 – 62.5%** • **Domain 6 – 91.6%**	"We recommend that prehospital protocols for seizure management in children utilize alternative (non-IV) routes of drug administration as first-line therapy for treating children with status epilepticus"[39]	"We recommend buccal midazolam over rectal (PR) diazepam for prehospital seizure cessation and control"[39]	"We suggest IM midazolam over PR diazepam for prehospital seizure cessation and control."[39]	"We suggest intranasal (IN) midazolam over PR diazepam for prehospital seizure cessation and control."[39]	"We suggest IV diazepam, midazolam, or lorazepam as equivalent therapeutic options when IV benzodiazepines are administered"[39]
Quality of evidence (GRADE methodology)	Moderate	Low	Very low	Very low	Very low
Strength of recommendation (GRADE methodology)	Strong	Strong	Weak	Weak	Weak
Author's summary	IV access not necessary when close proximity to hospital. Consider IV placement when prolonged transportation time	Buccal Midazolam over rectal Diazepam	IM Midazolam over rectal Diazepam	IN Midazolam over rectal diazepam	Lorazepam, Midazolam and Diazepam deemed equivalent when used IV
NHMRC Body of Evidence grading for each recommendation	Grade B (Good)	Grade B (Good)	Grade C (Satisfactory)	Grade C (Satisfactory)	Grade C (Satisfactory)
Recommendation implementation	Adapted (transportation time a factor)	Adopted	Adopted	Adopted	Adopted

Recommendations drawn from the NICE, NGC and GIN guidelines[37–39]

Table 3: Additional search results from January 2012 to January 2016

RESULTS – RANDOMISED CONTROL TRIALS (RCT)							
No	Author & Date	Publication date	Type	Outcome	Intervention	Results	Quality Score
1	Gathwala, *et al.*[23]	2012	RCT (n=120)	1. Safety 2. Efficacy	Loraz IV (0.1mg/kg), diaz IV (0.3mg/kg) & midaz IV (0.1mg/kg)	1. Excessive somnolence & sedation with diaz compared to other two 2. Equally effective (loraz 91.12 sec; midaz 92.69 sec & diaz 83.94 sec)	Jaded score 2 (low rang quality)
2	**Thakker, *et al.*** [40]	**2013**	**RCT (n=50)**	**1. Time from arrival to treatment** **2. Time from drug admin to cessation** **3. Time from arrival to cessation**	**Midaz IN (0.2mg/kg) vs diaz IV (0.3mg/kg)**	**1. Midaz faster initiation (3.37 ± 2.46 vs 14.13 ± 3.39 min)** **2. Similar duration (3.01 ±2.79 vs 2.67 ± 2.31)** **3. Shorter in midaz group (6.67 ± 3.12 vs 17.18 ± 5.09 min)**	**Jaded score 5 (high range quality)**
3	Malu, *et al.* [31]	2014	RCT (n=436)	Seizure termination 1. 5min 2. 10 min 3. 20min	Standard (PR diaz – 0.5mg/kg)) vs Loraz SL (0.1mg/kg)	1. PR 38% vs SL 28% 2. PR 79% vs SL 56% 3. PR 91% vs SL 83% (P0.012) statistically significant results favouring diaz	Jaded score 0 (low range quality)

RESULTS – RANDOMISED CONTROL TRIALS (RCT)							
No	Author & Date	Publication date	Type	Outcome	Intervention	Results	Quality Score
4	**Chamberlain, *et al.*[19]**	**2014**	**RCT (n=273)**	**Superiority trial** **1. Efficacy** **2. Safety** **3. Recurrence in 1h & recurrence at 4hrs post admin**	**Loraz IV (0.1mg/kg) compared to Diaz IV (0.2mg/kg**	**1. Similar efficacy (72.1% in diaz group vs 72.9% in loraz group)** **2. Higher rate of sedation in loraz group (50% vs 66.9% - Absolute risk difference 16.9%; 95% CI 6.1-27.7)** **3. Loraz group less recurrence 10.9% vs 10.3% at 1 hr; with diaz less recurrence at 4hrs (38.6% vs 39.2%)**	**Jaded score 5 (high range quality)**
5	Portela, *et al*.[41]	2015	RCT (n=36)	Seizure termination 5 minutes post drug administration 1. Time to administration 2. Time from administration to cessation	Diaz IV (0.5mg/kg) vs Midaz IM (0.5mg/kg)	Equal effective for termination 1. Time to administration in midaz group faster (2.8 vs 7.4min) 2. Time to cessation faster in Midaz group (7.3 vs 10.6 min)	Jaded Score 2 (low range quality)

RESULTS – RANDOMISED CONTROL TRIALS (RCT)							
No	Author & Date	Publication date	Type	Outcome	Intervention	Results	Quality Score
6	**Welch, *et al*** [25]	**2015**	**Secondary analysis of RCT: RAMPART study – paediatrics only (n=120)**	**Non-inferiority of midaz compared to loraz for prehospital SE termination** **1. Seizure cessation prior to hospital arrival** **2. Rate of recurring seizures** **3. Hospitalisation & ICU admittance (requiring intubation)**	**Midaz IM (10mg when >40kg; 5mg when 13-40kg) vs loraz IV (4mg when >40kg; 2mg when 13-40kg)**	**1. Midaz group 68.3% vs 71.6% in loraz group** **2. Fewer in the midaz group** **3. Fewer in midaz group were hospitalised, intubated and admitted to ICU than loraz group**	**Jaded score 5 (high quality) [original study]**
RESULTS – SYSTEMATIC REVIEWS (SR) FROM REFERENCE SEARCHES							
7	Sofou, *et al.* [24]	2009	SR (8 studies included n=694)	Therapeutic management of SE	Midaz IV, IM, IN & Buccal compared to Diaz (PR & IV) and to Loraz IN & IV [various doses]	Buccal midaz safe and efficacious – may serve as first-line	AMSTAR 3/11 (low quality)

RESULTS – SYSTEMATIC REVIEWS (SR) FROM REFERENCE SEARCHES							
No	Author & Date	Publication date	Type	Outcome	Intervention	Results	Quality Score
8	**McMullan, *et al*[9]**	**2010**	**SR (6 studies included n=774)**	**If non-IV midaz is as effective as diaz by any route?**	**Diaz compared to midaz via any route**	• **Midaz via any rote is superior to diaz via any route (RR 1.52; 95%CI 1.27-1.82) for cessation** • **Buccal midaz superior to PR diaz (RR 1.54; 95% CI 1.29-1.85)** • **Midaz administer faster diaz (mean difference 2.46min; 95% CI 1.52-3.39)** • **Respiratory compromise similar between the two (RR 1.49; 95% CI 0.25-8.27**	**AMSTAR 9/11 (high quality)**

AMSTAR – A measurement Tool to Assess Systematic Reviews; CI – Confidence Interval; Diaz – diazepam; GRACE – Good Research for Comparative Effectiveness; ICU – Intensive Care Unit; IM – Intramuscular; IN – Intranasal; IV – Intravenous; Jaded score – or Oxford quality scoring system: a quality assessment for RCTs; Loraz – lorazepam; Midaz – midazolam; min – Minutes; n – sample size; PR – Per rectum; RCT – Randomisded Control Trial; RR – risk ratio; SE – Status Epilepticus; sec – seconds; SR – Systematic review

In the updated search, exact times are given in some studies. Study 1 compares time from drug administration to seizure cessation. IV lorazepam and IV diazepam compared to IV midazolam (92.69) shows lorazepam (91.12sec) and diazepam (83.94sec) to have a marginally quicker onset of action. However, when measuring time form decision to treat to seizure cessation midazolam performs better.

Study 2 shows midazolam IN initiated faster (arrival to treatment 3.37 vs 14.13min) and terminated seizures faster (arrival to cessation 6.67 vs 17.18 min) than diazepam IV. Midazolam IM is faster to administer (2.8 vs 7.4min) and faster from administration to seizure termination (7.3 vs 10.6min) than IV diazepam (Study 5).[41] Intra-nasal administration is performed with a mucosal atomiser device or when not available, by slowly dripping undiluted drug into the nostrils. (Half dose in each nostril). Buccal administration is performed in a similar manner.

Conclusion

The research question aimed to determine the BDZ which is the easiest to administer, has most rapid and sustained seizure termination with lowest adverse events. The available evidence points to midazolam as the easiest to administer, producing rapid cessation with low recurrence and comparable adverse event rate. Midazolam terminate seizures faster due to speed/ease of non-IV routes and should be used as first-line treatment in the emergency setting.

Recommendations

The recommendations for the optimal management of acute seizures in both the prehospital and emergency department aim to be as inclusive and complete as the current evidence allows. Although this evidence directly influences emergency management, the recommendations are aimed at both the frontline (first contact) healthcare workers as well as the policy makers in both the prehospital and emergency department.

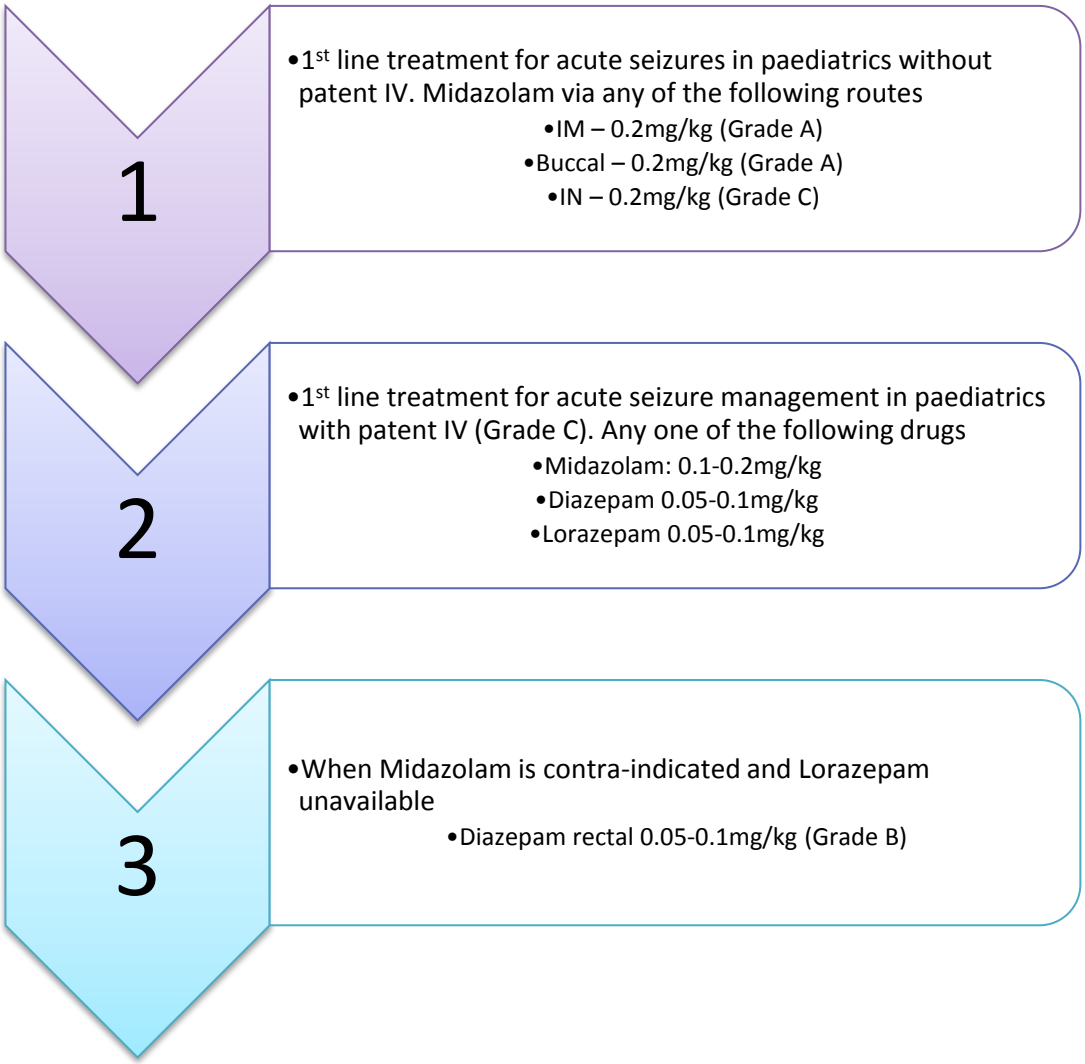
In the prehospital environment, IV access is not a priority where transport time is short. During longer transportation IV access should be considered when safe to perform by a skilled provider. (Grade B recommendation). Less adverse events occurred with IM over IV administration and non-IV routes achieve quicker seizure cessation, especially if IV access must still be obtained. The recommendations are listed below.

Implications for practice

Lorazepam requires refrigeration (impractical in the prehospital setting) and is better suited for an emergency department where refrigeration is possible. Diazepam is an oil based drug and precipitate when diluted, making it unsuitable for smaller doses in low weight children. Midazolam is often used in the emergency setting (as sedative and anxiolytic) and most practitioners are comfortable using it. It can be used in smaller doses for low weight children since dilution is unproblematic. Midazolam is already widely used and using IM, IN or buccal administration for seizure termination is an attractive option.

The Emergency Care Technicians in the prehospital environment only carry Diazepam for seizure treatment. This would have to be reconsidered in the light of new available evidence.

Figure 3: Recommendations



Implications for research

Most studies compare one drug to another via various routes, but few of the available studies directly compare the three BDZs with regards to ease, effectiveness, rate of failed terminations and rate of adverse events. None of the three benzodiazepines in question have unequivocally been proven superior and future research, especially a direct comparison between the three most common BDZ's (route, dose, time to administration, time to cessation, etc.), in a large, multicentre, high quality RCT type study would be best suited to settle this debate.

Limitations

The tiered approach in this rapid review is both strength and limitation. Its limitation lies in the novelty of this method (first published in 2011) as well as the uncertainty surrounding the methodological rigidity of rapid reviews in general. The strength however lies in the process of "standing on the shoulders of giants". International guideline review of reviews and systematic reviews are generally developed by well-defined groups of people and/or organisations, including researchers, experts in the studied field and academia with research methodology background lending them greater authority than a single author.

Acknowledgements

The authors acknowledge Pierre Smit and Michael McCaul for their valuable assistance.

Declarations

No conflict of interest. No funding received.

References

1 NICE. Treating prolonged or repeated seizures and convulsive status epilepticus. Published Online First: 2013.http://pathways.nice.org.uk/pathways/epilepsy#path=view:/pathways/epilepsy/treating-prolonged-or-repeated-seizures-and-convulsive-status-epilepticus.xml&content=view-node:nodes-treating-ongoing-generalised-tonicclonic-seizures-convulsive-status-epilepticu

2 Wermeling DP. Intranasal Delivery of Antiepileptic Medications for Treatment of Seizures. *Neurotherapeutics* 2009;**6**:352–8. doi:10.1016/j.nurt.2009.01.002

3 Feen ES, Bershad EM, Suarez JI. Status epilepticus. *South Med J* 2008;**101**:400–6. doi:10.1097/SMJ.0b013e31816852b0

4 Hubert P, Parain D, Vallée L. [Management of convulsive status epilepticus in infants and children]. *Rev Neurol (Paris)* 2009;**165**:390–7. doi:10.1016/j.neurol.2008.11.009

5 Pellock JM. Overview: definitions and classifications of seizure emergencies. *J Child Neurol* 2007;**22**:9S – 13S. doi:10.1177/0883073807303064

6 Mishra D, Sharma S, Sankhyan N, *et al.* Consensus guidelines on management of childhood convulsive status epilepticus. *Indian Pediatr* 2014;**51**:975–90.http://www.ncbi.nlm.nih.gov/pubmed/25560156 (accessed 21 Feb2015).

7 Lowenstein DH, Bleck T, Macdonald RL. It's time to revise the definition of status epilepticus. *Epilepsia* 1999;**40**:120–2. doi:10.1111/j.1528-1157.1999.tb02000.x

8 Wilkes R, Tasker RC. Pediatric intensive care treatment of uncontrolled status epilepticus. *Crit Care Clin* 2013;**29**:239–57. doi:10.1016/j.ccc.2012.11.007

9 McMullan J, Sasson C, Pancioli A, *et al.* Midazolam versus diazepam for the treatment of status epilepticus in children and young adults: a meta-analysis. *Acad Emerg Med* 2010;**17**:575–82. doi:10.1111/j.1553-2712.2010.00751.x

10 Prasad M, Krishnan PR, Sequeira R, *et al.* Anticonvulsant therapy for status epilepticus. *Cochrane database Syst Rev* 2014;**9**:CD003723. doi:10.1002/14651858.CD003723.pub3

11 Lader M. History of benzodiazepine dependence. *J Subst Abuse Treat* 1991;**8**:53–9.

doi:10.1016/0740-5472(91)90027-8

12 Friedman J. Emergency management of the paediatric patient with generalized convulsive status epilepticus. *Paediatr Child Health* 2011;**16**:91–104.http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3043041&tool=pmcentrez&rendertype=abstract (accessed 9 Sep2015).

13 Tasker RC. Emergency treatment of acute seizures and status epilepticus. *Arch Dis Child* 1998;**79**:78–83. doi:10.1136/adc.79.1.78

14 Bassan H, Barzilay M, Shinnar S, *et al.* Prolonged febrile seizures, clinical characteristics, and acute management. *Epilepsia* 2013;**54**:1092–8. doi:10.1111/epi.12164

15 Abend NS, Loddenkemper T. Management of pediatric status epilepticus. *Curr Treat Options Neurol* 2014;**16**:301. doi:10.1007/s11940-014-0301-x

16 Chin RFM, Verhulst L, Neville BGR, *et al.* Inappropriate emergency management of status epilepticus in children contributes to need for intensive care. *J Neurol Neurosurg Psychiatry* 2004;**75**:1584–8. doi:10.1136/jnnp.2003.032797

17 Seinfeld S, Shinnar S, Sun S, *et al.* Emergency management of febrile status epilepticus: results of the FEBSTAT study. *Epilepsia* 2014;**55**:388–95. doi:10.1111/epi.12526

18 Babl FE, Sheriff N, Borland M, *et al.* Emergency management of paediatric status epilepticus in Australia and New Zealand: Practice patterns in the context of clinical practice guidelines. *J Paediatr Child Health* 2009;**45**:541–6. doi:10.1111/j.1440-1754.2009.01536.x

19 Chamberlain JM, Okada P, Holsti M, *et al.* Lorazepam vs Diazepam for Pediatric Status Epilepticus. *Jama* 2014;**311**:1652–60. doi:10.1001/jama.2014.2625

20 Raj D, Gulati S, Lodha R. Status epilepticus. *Indian J Pediatr* 2011;**78**:219–26. doi:10.1007/s12098-010-0291-y

21 Silbergleit R, Durkalski V, Lowenstein D, *et al.* Intramuscular versus intravenous therapy for prehospital status epilepticus. *N Engl J Med* 2012;**366**:591–600. doi:10.1056/NEJMoa1107494

22 Hirsch LJ. Intramuscular versus Intravenous Benzodiazepines for Prehospital Treatment of Status Epilepticus. *N Engl J Med* 2012;**366**:659–60. doi:10.1056/NEJMe1114206

23 Gathwala G, Goel M, Singh J, *et al.* Intravenous diazepam, midazolam and lorazepam in acute seizure control. *Indian J Pediatr* 2012;**79**:327–32. doi:10.1007/s12098-011-0505-y

24 Sofou K, Kristjánsdóttir R, Papachatzakis NE, *et al.* Management of Prolonged Seizures and Status Epilepticus in Childhood: A Systematic Review. *J Child Neurol* 2009;**24**:918–26. doi:10.1177/0883073809332768

25 Welch RD, Nicholas K, Durkalski-Mauldin VL, *et al.* Intramuscular midazolam versus intravenous lorazepam for the prehospital treatment of status epilepticus in the pediatric population. *Epilepsia* 2015;**56**:254–62. doi:10.1111/epi.12905

26 Arya R, Gulati S, Kabra M, *et al.* Intranasal versus intravenous lorazepam for control of acute seizures in children: a randomized open-label study. *Epilepsia* 2011;**52**:788–93. doi:10.1111/j.1528-1167.2010.02949.x

27 Henry JC, Holloway R. Review: lorazepam provides the best control for status epilepticus. *Evid Based Med* 2006;**11**:54. doi:10.1136/ebm.11.2.54

28 Cock HR. A comparison of lorazepam and diazepam as initial therapy in convulsive status epilepticus. *QJM* 2002;**95**:225–31. doi:10.1093/qjmed/95.4.225

29 Leppik IE, Patel SI. Intramuscular and rectal therapies of acute seizures. *Epilepsy Behav* 2015;**49**:307–12. doi:10.1016/j.yebeh.2015.05.001

30 Drife JO. New England journal. *BMJ Br Med J* 1999;**318**:1565. doi:10.1056/NEJMoa1005372

31 Malu CKK, Kahamba DM, Walker TD, *et al.* Efficacy of Sublingual Lorazepam Versus Intrarectal Diazepam for Prolonged Convulsions in Sub-Saharan Africa. *J Child Neurol* 2013;**29**:895–902. doi:10.1177/0883073813493501

32 Verrotti A, Milioni M, Zaccara G. Safety and efficacy of diazepam autoinjector for the management of epilepsy. *Expert Rev Neurother* 2015;**15**:127–33. doi:10.1586/14737175.2015.1003043

33 Albano A, Reisdorff EJ, Wiegenstein JG. Rectal diazepam in pediatric status epilepticus. *Am J Emerg Med* 1989;**7**:168–72. doi:10.1016/0735-6757(89)90131-9

34 Qureshi A, Wassmer E, Davies P, *et al.* Comparative audit of intravenous lorazepam and diazepam in the emergency treatment of convulsive status epilepticus in children. *Seizure* 2002;**11**:141–4. doi:10.1053/seiz.2001.0635

35 Hillier S, Grimmer-Somers K, Merlin T, *et al.* FORM: an Australian method for formulating and grading recommendations in evidence-based clinical guidelines. *BMC Med Res Methodol* 2011;**11**:23. doi:10.1186/1471-2288-11-23

36 NHMRC GAR. NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. *Natl Heal Med Res Counc* 2009;:1–23.

37 The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care | Guidance and guidelines | NICE. https://www.nice.org.uk/guidance/cg137 (accessed 13 Aug2015).

38 Brophy GM, Bell R, Claassen J, *et al.* Guidelines for the evaluation and management of status epilepticus. *Neurocrit Care* 2012;**17**:3–23. doi:10.1007/s12028-012-9695-z

39 Shah MI, Macias CG, Dayan PS, *et al.* An Evidence-based Guideline for Pediatric Prehospital Seizure Management Using GRADE Methodology. *Prehosp Emerg Care* 2014;**18 Suppl 1**:15–24. doi:10.3109/10903127.2013.844874

40 Thakker A, Shanbag P. A randomized controlled trial of intranasal-midazolam versus intravenous-diazepam for acute childhood seizures. *J Neurol* 2013;**260**:470–4. doi:10.1007/s00415-012-6659-3

41 Portela JL, Garcia PCR, Piva JP, *et al.* Intramuscular midazolam versus intravenous diazepam for treatment of seizures in the pediatric emergency department: A randomized clinical trial. *Med Intensiva* Published Online First: 10 June 2014. doi:10.1016/j.medin.2014.04.003

PART D – SUPPORTING DOCUMENTS

Table of Contents

Appendix A: Inclusion & Exclusion criteria

Inclusion criteria

- Prehospital and/or emergency department studies
- Includes Pediatrics > 1 month and ≤18 years
- Seizures lasting > 5minutes
- Benzodiazepine (diazepam, midazolam or lorazepam) compared to one another or placebo
- Emergency management by trained provider (doctor, nurse, pre-hospital provider or trained family member)

Exclusion criteria

- Non-human studies
- Studies solely of admitted patients or ward studies
- Studies solely of adult patients >18 years or infants <1 month
- Seizures in patients with known traumatic injury
- Studies solely comparing drugs other than included benzodiazepines
- Clinical Practice Guidelines published before 1 January 2010 with no subsequent updates
- Review of Reviews and Systematic Reviews published before 1 January 2010
- Duplication
- Irrelevance due to other reason

Appendix B: Master list of all articles found in search

NICE database search

Terms used: “pediatric” AND “seizures” – 46 results

1. Retigabine for the adjunctive treatment of partial onset seizures in epilepsy (/guidance/ta232), Technology appraisals, Published July 2011
2. Epilepsy (http://pathways.nice.org.uk/pathways/epilepsy), NICE pathway
3. Specialist Reporting of Paediatric Neuroimaging, (https://www.nice.org.uk/savingsAndProductivityAndLocalPracticeResource?ci=http%3a%2f%2fsearch.nice.org.uk%2fsl_657), Published February 2013
4. Paediatric Urgent Care Pathways, (https://www.nice.org.uk/savingsAndProductivityAndLocalPracticeResource?ci=http%3a%2f%2fsearch.nice.org.uk%2fsl_776), Published May 2014
5. Diabetes (type 1 and type 2) in children and young people: diagnosis and management (NG18) (/guidance/ng18), Guidelines, Published August 2015
6. The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care (CG137) (/guidance/cg137), Guidelines, Published January 2012
7. The epilepsies in children and young people (QS27) (/guidance/qs27), Quality standards, Published February 2013
8. The epilepsies in adults (QS26) (/guidance/qs26), Quality standards, Published February 2013
9. Vagus nerve stimulation for refractory epilepsy in children (IPG50) (/guidance/ipg50), Interventional procedure guidance, Published March 2004
10. Gastro-oesophageal reflux disease: recognition, diagnosis and management in children and young people (NG1) (/guidance/ng1), Guidelines, Published January 2015
11. Head injury (CG176) (/guidance/cg176), Guidelines, Published January 2014
12. Transient loss of consciousness ('blackouts') management in adults and young people (CG109) (/guidance/cg109), Guidelines, Published August 2010
13. Bacterial meningitis and meningococcal septicaemia (http://pathways.nice.org.uk/pathways/bacterial-meningitis-and-meningococcalsepticaemia), NICE Pathway

14. Feverish illness in children (http://pathways.nice.org.uk/pathways/feverish-illnessin-children), NICE Pathway
15. Antibiotics for early-onset neonatal infection (http://pathways.nice.org.uk/pathways/antibiotics-for-early-onset-neonatal-infection), NICE Pathway
16. Alcohol-use disorders (http://pathways.nice.org.uk/pathways/alcohol-use-disorders), NICE Pathway
17. Head injury (http://pathways.nice.org.uk/pathways/head-injury), NICE Pathway
18. Attention deficit hyperactivity disorder (http://pathways.nice.org.uk/pathways/attention-deficit-hyperactivity-disorder), NICE Pathway
19. Transient loss of consciousness (http://pathways.nice.org.uk/pathways/transientloss-of-consciousness), NICE Pathway
20. When to suspect child maltreatment http://pathways.nice.org.uk/pathways/whento-suspect-child-maltreatment), NICE Pathway
21. Diabetes (type 1 and type 2) in children and young people: diagnosis and management (NG18) (/guidance/ng18), Published August 2015
22. Alcohol-use disorders: Diagnosis and clinical management of alcohol-related physical complications (CG100) (/guidance/cg100), Guidelines, Published June 2010
23. Bacterial meningitis and meningococcal septicaemia (CG102) (/guidance/cg102), Guidelines, Published June 2010
24. Feverish illness in children (CG160) (/guidance/cg160), Guidelines, Published May 2013
25. Gastro-oesophageal reflux disease: recognition, diagnosis and management in children and young people (NG1) (/guidance/ng1), Published January 2015
26. Depression in children and young people: Identification and management in primary, community and secondary care (CG28) (/guidance/cg28), Guidelines, Published September 2005
27. Bacterial meningitis and meningococcal septicaemia in children and young people (QS19) (/guidance/qs19), Quality standards, Published June 2012
28. Head injury (QS74) (/guidance/qs74), Quality standards, Published October 2014
29. Attention deficit hyperactivity disorder (CG72) (/guidance/cg72), Guidelines, Published September 2008
30. Antibiotics for neonatal infection (QS75) (/guidance/qs75), Quality standards, Published December 2014

31. Alcohol-use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence (CG115) (/guidance/cg115), Guidelines, Published February 2011
32. Long-acting reversible contraception (update) (CG30) (/guidance/cg30), Guidelines, Published October 2005
33. ESUOM34: Management of vomiting in children and young people with gastroenteritis: ondansetron (/advice/esuom34), ESUOM, Published October 2014
34. Pharmalgen for the treatment of bee and wasp venom allergy (TA246) (/guidance/ta246), Technology appraisals, Published February 2012
35. Antibiotics for early-onset neonatal infection (CG149) (/guidance/cg149), Guidelines, Published August 2012
36. Hypertension in pregnancy (CG107) (/guidance/cg107), Guidelines, Published August 2010
37. Carmustine implants and temozolomide for the treatment of newly diagnosed high-gradeglioma (TA121) (/guidance/ta121), Technology appraisals, Published June 2007
38. ESUOM2: Sleep disorders in children and young people with attention deficit hyperactivity disorder: melatonin (/advice/esuom2), ESUOM, Published January 2013
39. Improving the quality of care for children with epilepsy (https://www.nice.org.uk/savingsAndProductivityAndLocalPracticeResource?ci=http%3a%2f%2fsearch.nice.org.uk%2fsl_615), Published November 2012
40. Advice from NICE aims to improve commissioning of care for people with epilepsy (/news/press-and-media/advice-from-nice-aims-to-improve-commissioning-of-care-forpeople-with-epilepsy), Published February 2013
41. ESUOM15: Hypersalivation: oral glycopyrronium bromide (/advice/esuom15), ESUOM Published July 2013
42. Healthy start vitamins: special report on cost effectiveness (/article/pmg25), Published August 2015
43. Helping children and adults manage diabetes: NICE publishes updated suite of guidelines (/news/press-and-media/helping-children-and-adults-manage-diabetes-nice-ublishesupdated-suite-of-guidelines), Published August 2015
44. ESUOM28: Rapid tranquillisation in mental health settings: promethazine hydrochloride (/advice/esuom28), ESUOM, Published March 2014
45. MIB31: Peptest for diagnosing gastro-oesophageal reflux (/advice/mib31) MIB, Published May 2015
46. The guidelines manual (/article/pmg6), Published November 2012

Scottish Intercollegiate Guidelines Network (SIGN)

Searched "Guidelines" by "Subject – Child health"

47. Management of attention deficit and hyperkinetic disorders in children and young people, October 2009
48. Management of invasive meningococcal disease in children and young people, May 2008
49. Assessment, diagnosis and clinical interventions for children and young people with autism spectrum disorders, July 2007 (recommendations being updated)
50. Bronchiolitis in children, November 2006 (recommendations older than 7 years)
51. Prevention and management of dental decay in the pre-school child, November 2005 (recommendations being updated)
52. Diagnosis and management of epilepsies in children and young people, March 2005 (Older than 10 years - Withdrawn February 2015)
53. Diagnosis and management of childhood otitis media in primary care, February 2003 (recommendations older than 7 years)
54. Safe sedation of children undergoing diagnostic and therapeutic procedures, (Withdrawn - Revised May 2004)
55. Attention deficit and hyperkinetic disorders in children and young people, June 2001 (Updated October 2009 - Superseded by SIGN 112)
56. Preventing dental caries in children at high caries risk: Targeted prevention of dental caries in the permanent teeth of 6-16 year olds presenting for dental care, December 2000 (Superseded by SIGN 138)

Guidelines International Network (GIN)

Searched "pediatric AND seizure" – 1 result

57. An Evidence-based Guideline for Pediatric Prehospital Seizure Management Using GRADE Methodology, Published in Prehospital Emergency Care, 2014

National Guideline Clearinghouse (NGC)

Searched "pediatrics AND seizures AND benzodiazepines" – 13 results

58. Guidelines for the evaluation and management of status epilepticus. 2012 Apr 24. NGC:009114
59. Alcohol-use disorders. Diagnosis, assessment and management of harmful drinking and alcohol dependence. 2011 Feb. NGC:008761
60. Consensus-based clinical practice guideline for the management of volatile substance use in Australia. 2011 Sep. NGC:009737
61. Evidence-based guideline update: medical treatment of infantile spasms: report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. 2004 May 25 (revised 2012 Jun 12). NGC:009161
62. Autism spectrum disorders in pre-school children. 2010 Mar. NGC:009535
63. The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. 2004 Oct (revised 2012 Jan). NGC:008985
64. Guidelines for the identification and management of substance use and substance use disorders in pregnancy. 2014. NGC:010619
65. Practice parameter for the assessment and treatment of children and adolescents with schizophrenia. 1994 Jun (revised 2013 Sep). NGC:010492
66. Nursing care of the woman receiving regional analgesia/anesthesia in labor. Second edition. Evidence-based clinical practice guideline. 2001 Jan (revised 2011). NGC:009001
67. Practice guideline for the treatment of patients with eating disorders. 1993 (revised 2006 Jun; reaffirmed 2011). NGC:004987
68. Analgesia and anesthesia for the breastfeeding mother, revised 2012. 2006 (revised 2012 Dec). NGC:009516
69. Adapting your practice: general recommendations for the care of homeless patients. 2004 (revised 2010). NGC:007876
70. Assessment and management of chronic pain. 2005 Nov (revised 2013 Nov). NGC:010140

Trip Database

Searched “pediatric AND seizures AND benzodiazepine AND “emergency treatment” and filtered by “guidelines” – 17 results

71. Benzodiazepines: Risks and benefits. A reconsideration, British Association for Psychopharmacology 2014, Uk Guidelines

72. Children and infants with seizures - acute management, Clinical Practice Guidelines Portal 2009, Aus & NZ Guidelines

73. Summary of recommendations for the diagnosis and treatment of malaria by the Committee to Advise on Tropical Medicine and Travel (CATMAT), CMA Infobase (Canada) 2014, Canada Guidelines

74. The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care, National Institute for Health and Clinical Excellence - Clinical Guidelines 2012, Uk Guidelines

75. Australian guidelines for the treatment of acute stress disorder and posttraumatic stress disorder, Clinical Practice Guidelines Portal 2013, Aus & NZ Guidelines

76. Emergency management of the paediatric patient with generalized convulsive status epilepticus, Canadian Paediatric Society 2011, Canada Guidelines

77. Vertigo, NICE Clinical Knowledge Summaries 2010, Uk Guidelines

78. Adult trauma clinical practice guidelines. Initial management of closed head injury in adults (2nd edition), Clinical Practice Guidelines Portal 2011, Aus & NZ Guidelines

79. Pharmacotherapies for relapse prevention in alcohol dependence (2nd edition), Clinical Practice Guidelines Portal 2011, Aus & NZ Guidelines

80. Pharmacological treatment of bipolar disorder in primary care, Clinical Practice Guidelines Portal 2010, Aus & NZ Guidelines

81. Guideline Summary: The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. [National Collaborating Centre for Primary Care], info@guideline.gov (NGC) 2013, USA Guidelines

82. Clinical practice guidelines for the management of gliomas - astrocytomas and oligodendrogliomas, Clinical Practice Guidelines Portal 2009, Aus & NZ Guidelines

83. Management of cannabis use disorder and related issues - a clinician's guide, Clinical Practice Guidelines Portal 2009, Aus & NZ Guidelines

84. Canadian clinical practice guidelines on the management and prevention of obesity in adults and children, CMA Infobase (Canada) 2007, Canada Guidelines

85. The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. [National Collaborating Centre for Primary Care], info@guidelines.gov (NGC) 2012, USA Guidelines

86. Clinical practice guideline: Violence: The short-term management of disturbed/violent behaviour in in-patient psychiatric settings and emergency departments, Royal College of Nursing 2007, Uk Guidelines

87. Non-convulsive status epilepticus, Tuberous Sclerosis Association 2007, Uk Guidelines

South African Medical Research Council

No results

European Science Foundation (formerly European Medical Research Council)

No results

Appendix C: Excluded articles with reasons

NICE database search

Terms used: “pediatric” AND “seizures” – 46 results

1. Retigabine for the adjunctive treatment of partial onset seizures in epilepsy (/guidance/ta232), Technology appraisals, Published July 2011
    - Excluded – not benzodiazepine
2. Epilepsy (http://pathways.nice.org.uk/pathways/epilepsy), NICE pathway
    - Excluded – long term epilepsy management
3. Specialist Reporting of Paediatric Neuroimaging, (https://www.nice.org.uk/savingsAndProductivityAndLocalPracticeResource?http%3a%2f%2fsearch.nice.org.uk%2fsl_657), Published February 2013
    - Excluded – irrelevant
4. Paediatric Urgent Care Pathways, (https://www.nice.org.uk/savingsAndProductivityAndLocalPracticeResource?ci=http%3a%2f%2fsearch.nice.org.uk%2fsl_776), Published May 2014
    - Excluded – pathway only
5. Diabetes (type 1 and type 2) in children and young people: diagnosis and management
(NG18) (/guidance/ng18), Guidelines, Published August 2015
    - Excluded – Irrelevant
6. The epilepsies in children and young people (QS27) (/guidance/qs27), Quality standards, Published February 2013
    - Excluded – full text review – long term antiepileptic treatment
7. Vagus nerve stimulation for refractory epilepsy in children (IPG50) (/guidance/ipg50), Interventional procedure guidance, Published March 2004
    - Excluded – Irrelevant
8. Gastro-oesophageal reflux disease: recognition, diagnosis and management in children and young people (NG1) (/guidance/ng1), Guidelines, Published January 2015
    - Excluded – Irrelevant
9. Head injury (CG176) (/guidance/cg176), Guidelines, Published January 2014
    - Excluded – Irrelevant

10. Transient loss of consciousness ('blackouts') management in adults and young people (CG109) (/guidance/cg109), Guidelines, Published August 2010
    - Excluded – Irrelevant
11. Bacterial meningitis and meningococcal septicaemia (http://pathways.nice.org.uk/pathways/bacterial-meningitis-and-meningococcalsepticaemia), NICE Pathway
    - Excluded – Irrelevant
12. Feverish illness in children (http://pathways.nice.org.uk/pathways/feverish-illnessin-children), NICE Pathway
    - Excluded – Irrelevant
13. Antibiotics for early-onset neonatal infection (http://pathways.nice.org.uk/pathways/antibiotics-for-early-onset-neonatal-infection), NICE Pathway
    - Excluded – Irrelevant
14. Alcohol-use disorders (http://pathways.nice.org.uk/pathways/alcohol-use-disorders), NICE Pathway
    - Excluded – Irrelevant
15. Head injury (http://pathways.nice.org.uk/pathways/head-injury), NICE Pathway
    - Excluded – Irrelevant
16. Attention deficit hyperactivity disorder (http://pathways.nice.org.uk/pathways/attention-deficit-hyperactivity-disorder), NICE Pathway
    - Excluded – Irrelevant
17. Transient loss of consciousness (http://pathways.nice.org.uk/pathways/transientloss-of-consciousness), NICE Pathway
    - Excluded – Irrelevant
18. When to suspect child maltreatment http://pathways.nice.org.uk/pathways/whento-suspect-child-maltreatment), NICE Pathway
    - Excluded – Irrelevant
19. Diabetes (type 1 and type 2) in children and young people: diagnosis and management (NG18) (/guidance/ng18), Published August 2015

- Excluded – Irrelevant

20. Alcohol-use disorders: Diagnosis and clinical management of alcohol-related physical complications (CG100) (/guidance/cg100), Guidelines, Published June 2010
    - Excluded – Irrelevant
21. Bacterial meningitis and meningococcal septicaemia (CG102) (/guidance/cg102), Guidelines, Published June 2010
    - Excluded – Irrelevant
22. Feverish illness in children (CG160) (/guidance/cg160), Guidelines, Published May 2013
    - Excluded – Irrelevant
23. Gastro-oesophageal reflux disease: recognition, diagnosis and management in children and young people (NG1) (/guidance/ng1), Published January 2015
    - Excluded – Irrelevant
24. Depression in children and young people: Identification and management in primary, community and secondary care (CG28) (/guidance/cg28), Guidelines, Published September 2005
    - Excluded – Irrelevant
25. Bacterial meningitis and meningococcal septicaemia in children and young people (QS19) (/guidance/qs19), Quality standards, Published June 2012
    - Excluded – Irrelevant
26. Head injury (QS74) (/guidance/qs74), Quality standards, Published October 2014
    - Excluded – Irrelevant
27. Attention deficit hyperactivity disorder (CG72) (/guidance/cg72), Guidelines, Published September 2008
    - Excluded – Irrelevant
28. Antibiotics for neonatal infection (QS75) (/guidance/qs75), Quality standards, Published December 2014
    - Excluded – Irrelevant
29. Alcohol-use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence (CG115) (/guidance/cg115), Guidelines, Published February 2011
    - Excluded – Irrelevant
30. Long-acting reversible contraception (update) (CG30) (/guidance/cg30), Guidelines, Published October 2005

- Excluded – Irrelevant

31. ESUOM34: Management of vomiting in children and young people with gastroenteritis: ondansetron (/advice/esuom34), ESUOM, Published October 2014
    - Excluded – Irrelevant
32. Pharmalgen for the treatment of bee and wasp venom allergy (TA246) (/guidance/ta246), Technology appraisals, Published February 2012
    - Excluded – Irrelevant
33. Antibiotics for early-onset neonatal infection (CG149) (/guidance/cg149), Guidelines, Published August 2012
    - Excluded – Irrelevant
34. Hypertension in pregnancy (CG107) (/guidance/cg107), Guidelines, Published August 2010
    - Excluded – Irrelevant
35. Carmustine implants and temozolomide for the treatment of newly diagnosed high-gradeglioma (TA121) (/guidance/ta121), Technology appraisals, Published June 2007
    - Excluded – Irrelevant
36. ESUOM2: Sleep disorders in children and young people with attention deficit hyperactivity disorder: melatonin (/advice/esuom2), ESUOM, Published January 2013
    - Excluded – Irrelevant
37. Improving the quality of care for children with epilepsy (https://www.nice.org.uk/savingsAndProductivityAndLocalPracticeResource?ci=http%3a%2f%2fsearch.nice.org.uk%2fsl_615), Published November 2012
    - Excluded – Irrelevant
38. Advice from NICE aims to improve commissioning of care for people with epilepsy (/news/press-and-media/advice-from-nice-aims-to-improve-commissioning-of-care-forpeople-with-epilepsy), Published February 2013
    - Excluded – Irrelevant
39. ESUOM15: Hypersalivation: oral glycopyrronium bromide (/advice/esuom15), ESUOM Published July 2013
    - Excluded – Irrelevant
40. Healthy start vitamins: special report on cost effectiveness (/article/pmg25), Published August 2015

- Excluded – Irrelevant

41. Helping children and adults manage diabetes: NICE publishes updated suite of guidelines (/news/press-and-media/helping-children-and-adults-manage-diabetes-nice-ublishesupdated-suite-of-guidelines), Published August 2015
    - Excluded – Irrelevant
42. ESUOM28: Rapid tranquillisation in mental health settings: promethazine hydrochloride (/advice/esuom28), ESUOM, Published March 2014
    - Excluded – Irrelevant
43. MIB31: Peptest for diagnosing gastro-oesophageal reflux (/advice/mib31) MIB, Published May 2015
    - Excluded – Irrelevant
44. The guidelines manual (/article/pmg6), Published November 2012

Scottish Intercollegiate Guidelines Network (SIGN)

Searched "Guidelines" by "Subject – Child health"

45. Management of attention deficit and hyperkinetic disorders in children and young people, October 2009
    - Excluded – Irrelevant
46. Management of invasive meningococcal disease in children and young people, May 2008
    - Excluded – Irrelevant
47. Assessment, diagnosis and clinical interventions for children and young people with autism spectrum disorders, July 2007 (recommendations being updated)
    - Excluded – Irrelevant
48. Bronchiolitis in children, November 2006 (recommendations older than 7 years)
    - Excluded – Irrelevant
49. Prevention and management of dental decay in the pre-school child, November 2005 (recommendations being updated)
    - Excluded – Irrelevant
50. Diagnosis and management of childhood otitis media in primary care, February 2003 (recommendations older than 7 years)
    - Excluded – Irrelevant

51. Safe sedation of children undergoing diagnostic and therapeutic procedures, (Withdrawn - Revised May 2004)
    - Excluded – Irrelevant
52. Attention deficit and hyperkinetic disorders in children and young people, June 2001 (Updated October 2009 - Superseded by SIGN 112)
    - Excluded – Irrelevant
53. Preventing dental caries in children at high caries risk: Targeted prevention of dental caries in the permanent teeth of 6-16 year olds presenting for dental care, December 2000 (Superseded by SIGN 138)

National Guideline Clearinghouse (NGC)

Searched "pediatrics AND seizures AND benzodiazepines" – 13 results

54. Alcohol-use disorders. Diagnosis, assessment and management of harmful drinking and alcohol dependence. 2011 Feb. NGC:008761
    - Excluded – Irrelevant
55. Consensus-based clinical practice guideline for the management of volatile substance use in Australia. 2011 Sep. NGC:009737
    - Excluded – Irrelevant
56. Evidence-based guideline update: medical treatment of infantile spasms: report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. 2004 May 25 (revised 2012 Jun 12). NGC:009161
    - Excluded – Not seizures, not emergency treatment
57. Autism spectrum disorders in pre-school children. 2010 Mar. NGC:009535
    - Excluded – Irrelevant
58. The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. 2004 Oct (revised 2012 Jan). NGC:008985
    - Excluded – Duplication
59. Guidelines for the identification and management of substance use and substance use disorders in pregnancy. 2014. NGC:010619
    - Excluded – Irrelevant
60. Practice parameter for the assessment and treatment of children and adolescents with schizophrenia. 1994 Jun (revised 2013 Sep). NGC:010492

- Excluded – Irrelevant

61. Nursing care of the woman receiving regional analgesia/anesthesia in labor. Second edition. Evidence-based clinical practice guideline. 2001 Jan (revised 2011). NGC:009001
    - Excluded – Irrelevant
62. Practice guideline for the treatment of patients with eating disorders. 1993 (revised 2006 Jun; reaffirmed 2011). NGC:004987
    - Excluded – Irrelevant
63. Analgesia and anesthesia for the breastfeeding mother, revised 2012. 2006 (revised 2012 Dec). NGC:009516
    - Excluded – Irrelevant
64. Adapting your practice: general recommendations for the care of homeless patients. 2004 (revised 2010). NGC:007876
    - Excluded – Irrelevant
65. Assessment and management of chronic pain. 2005 Nov (revised 2013 Nov). NGC:010140

Trip Database

Searched “pediatric AND seizures AND benzodiazepine AND “emergency treatment” and filtered by “guidelines” – 17 results

66. Benzodiazepines: Risks and benefits. A reconsideration, British Association for Psychopharmacology 2014, Uk Guidelines
    - Excluded – Irrelevant
67. Summary of recommendations for the diagnosis and treatment of malaria by the Committee to Advise on Tropical Medicine and Travel (CATMAT), CMA Infobase (Canada) 2014, Canada Guidelines
    - Excluded – Irrelevant
68. The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care, National Institute for Health and Clinical Excellence - Clinical Guidelines 2012, Uk Guidelines
    - Excluded – Duplication
69. Australian guidelines for the treatment of acute stress disorder and posttraumatic stress disorder, Clinical Practice Guidelines Portal 2013, Aus & NZ Guidelines

- Excluded – Irrelevant

70. Vertigo, NICE Clinical Knowledge Summaries 2010, Uk Guidelines
    - Excluded – Irrelevant
71. Adult trauma clinical practice guidelines. Initial management of closed head injury in adults (2nd edition), Clinical Practice Guidelines Portal 2011, Aus & NZ Guidelines
    - Excluded – Irrelevant
72. Pharmacotherapies for relapse prevention in alcohol dependence (2nd edition), Clinical Practice Guidelines Portal 2011, Aus & NZ Guidelines
    - Excluded – Irrelevant
73. Pharmacological treatment of bipolar disorder in primary care, Clinical Practice Guidelines Portal 2010, Aus & NZ Guidelines
    - Excluded – Irrelevant
74. Guideline Summary: The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. [National Collaborating Centre for Primary Care], info@guideline.gov (NGC) 2013, USA Guidelines
    - Excluded – Duplication
75. Clinical practice guidelines for the management of gliomas - astrocytomas and oligodendrogliomas, Clinical Practice Guidelines Portal 2009, Aus & NZ Guidelines
    - Excluded – Irrelevant
76. Management of cannabis use disorder and related issues - a clinician's guide, Clinical Practice Guidelines Portal 2009, Aus & NZ Guidelines
    - Excluded – Irrelevant
77. Canadian clinical practice guidelines on the management and prevention of obesity in adults and children, CMA Infobase (Canada) 2007, Canada Guidelines
    - Excluded – Irrelevant
78. The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. [National Collaborating Centre for Primary Care], info@guidelines.gov (NGC) 2012, USA Guidelines
    - Excluded – Duplication
79. Clinical practice guideline: Violence: The short-term management of disturbed/violent behaviour in in-patient psychiatric settings and emergency departments, Royal College of Nursing 2007, Uk Guidelines
    - Excluded – Irrelevant

80. Non-convulsive status epilepticus, Tuberous Sclerosis Association 2007, Uk Guidelines
    - Excluded – Full text assessment – non-convulsive long term management

Appendix D: AGREE II

	Domain 1. Scope and Purpose	Score (between 1-7)
1	The overall objective(s) of the guideline is (are) specifically described.	
2	The health question(s) covered by the guideline is (are) specifically described.	
3	The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	
	Domain 2. Stakeholder Involvement	
4	The guideline development group includes individuals from all the relevant professional groups.	
5	The views and preferences of the target population (patients, public, etc.) have been sought.	
6	The target users of the guideline are clearly defined.	
	Domain 3. Rigour of Development	
7	Systematic methods were used to search for evidence.	
8	The criteria for selecting the evidence are clearly described.	
9	The strengths and limitations of the body of evidence are clearly described.	
10	The methods for formulating the recommendations are clearly described.	
11	The health benefits, side effects, and risks have been considered in formulating the recommendations.	
12	There is an explicit link between the recommendations and the supporting evidence.	
13	The guideline has been externally reviewed by experts prior to its publication.	

14	A procedure for updating the guideline is provided.	
	Domain 4. Clarity of Presentation	
15	The recommendations are specific and unambiguous.	
16	The different options for management of the condition or health issue are clearly presented.	
17	Key recommendations are easily identifiable.	
	Domain 5. Applicability	
18	The guideline describes facilitators and barriers to its application.	
19	The guideline provides advice and/or tools on how the recommendations can be put into practice.	
20	The potential resource implications of applying the recommendations have been considered.	
21	The guideline presents monitoring and/ or auditing criteria.	
	Domain 6. Editorial Independence	
22	The views of the funding body have not influenced the content of the guideline.	
23	Competing interests of guideline development group members have been recorded and addressed.	

http://www.agreetrust.org/wp-content/uploads/2013/10/AGREE-II-Users-Manual-and-23-item-Instrument_2009_UPDATE_2013.pdf

Appendix D.1: AGREE II score for "The diagnosis and management of epilepsies in adults and children in primary and secondary care" – NICE

Combined results of reviewers' appraisal

Domain 1									**Totals**
	Item 1	Item 2	Item 3						41
Appraiser 1	7	7	7						21
Appraiser 2	7	7	6						20
Max: 7 x 3 x 2 = 42; Min: 1 x 3 x 2 = 6									
41 - 6 / 42 - 6 = 97.2 %									

Domain 2									**Totals**
	Item 1	Item 2	Item 3						39
Appraiser 1	6	7	7						20
Appraiser 2	6	6	7						19
Max: 7 x 3 x 2 = 42; Min: 1 x 3 x 2 = 6									
39 - 6 / 42 - 6 = 91.7 %									

Domain 3									**Totals**
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	102
Appraiser 1	6	6	6	7	6	7	7	6	51
Appraiser 2	7	5	6	7	6	6	7	7	51

Max: 7 x 8 x 2 = 112; Min: 1 x 8 x 2 = 16					
102 - 16 /112 - 16 = 89.6%					
Domain 4					**Totals**
	Item 1	Item 2	Item 3		42
Appraiser 1	7	7	7		21
Appraiser 2	7	7	7		21
Max: 7 x 3 x 2 = 42; Min: 1 x 3 x 2 = 6					
42 - 6 / 42 - 6 = 100 %					
Domain 5					**Totals**
	Item 1	Item 2	Item 3	Item 4	51
Appraiser 1	7	6	6	7	26
Appraiser 2	7	6	6	6	25
Max: 7 x 4 x 2 = 56; Min: 1 x 4 x 2 = 8					
51 - 8 / 56 - 8 = 89.6 %					
Domain 6					**Totals**
	Item 1	Item 2			23
Appraiser 1	6	6			12

Appraiser 2	6	5	11
Max: 7 x 2 x 2 = 28; Min: 1 x 2 x 2 = 4			
23 - 4 / 28 - 4 = 95%			

Appendix D.2: AGREE II score for Guidelines for the evaluation and management of status epilepticus - NGC

Combined results of reviewers' appraisal

Domain 1									**Totals**
	Item 1	Item 2	Item 3						30
Appraiser 1	4	4	4						12
Appraiser 2	6	6	6						18
Max: 7 x 3 x 2 = 42; Min: 1 x 3 x 2 = 6									
30 - 6 / 42 - 6 = 66.7%									

Domain 2									**Totals**
	Item 1	Item 2	Item 3						25
Appraiser 1	4	3	4						11
Appraiser 2	6	2	6						14
Max: 7 x 3 x 2 = 42; Min: 1 x 3 x 2 = 6									
25 - 6 / 42 - 6 = 52.8%									

Domain 3									**Totals**
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	96
Appraiser 1	7	7	3	6	6	6	6	3	44
Appraiser 2	7	7	6	7	6	7	6	6	52

Max: 7 x 8 x 2 = 112; Min: 1 x 8 x 2 = 16					
96 - 16 /112 - 16 = 83.3%					
Domain 4					**Totals**
	Item 1	Item 2	Item 3		38
Appraiser 1	6	6	5		17
Appraiser 2	7	7	7		21
Max: 7 x 3 x 2 = 42; Min: 1 x 3 x 2 = 6					
38 - 6 / 42 - 6 = 88.9%					
Domain 5					**Totals**
	Item 1	Item 2	Item 3	Item 4	42
Appraiser 1	4	5	5	5	19
Appraiser 2	6	5	6	6	23
Max: 7 x 4 x 2 = 56; Min: 1 x 4 x 2 = 8					
42 - 8 / 56 - 8 = 70.8%					
Domain 6					**Totals**
	Item 1	Item 2			19
Appraiser 1	5	5			10

Appraiser 2	5	4		9
Max: 7 x 2 x 2 = 28; Min: 1 x 2 x 2 = 4				
19 - 4 / 28 - 4 = 62.5%				

Appendix D.3: AGREE II score: Evidence-based guideline for pediatric prehospital seizure management using GRADE methodology - GIN

Combined results of reviewers' appraisal

Domain 1				**Totals**
	Item 1	Item 2	Item 3	39
Appraiser 1	7	7	6	20
Appraiser 2	6	6	7	19
Max: 7 x 3 x 2 = 42; Min: 1 x 3 x 2 = 6				
39 – 6 / 42 - 6 = 91.7%				

Domain 2				**Totals**
	Item 1	Item 2	Item 3	36
Appraiser 1	6	4	4	14
Appraiser 2	5	1	6	12
Max: 7 x 3 x 2 = 42; Min: 1 x 3 x 2 = 6				
36 – 6 / 42 - 6 = 83.3%				
Domain 3				**Totals**

	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	90
Appraiser 1	5	4	6	7	7	7	6	3	45
Appraiser 2	4	3	6	6	6	6	5	3	45
Max: 7 x 8 x 2 = 112; Min: 1 x 8 x 2 = 16									
90 - 16 /112 - 16 = 77%									

Domain 4				**Totals**
	Item 1	Item 2	Item 3	38
Appraiser 1	6	6	6	18
Appraiser 2	7	6	7	20
Max: 7 x 3 x 2 = 42; Min: 1 x 3 x 2 = 6				
38 - 6 / 42 - 6 = 88.9%				

Domain 5					**Totals**
	Item 1	Item 2	Item 3	Item 4	38
Appraiser 1	5	6	6	3	20
Appraiser 2	6	5	4	3	18
Max: 7 x 4 x 2 = 56; Min: 1 x 4 x 2 = 8					
38 - 8 / 56 - 8 = 62.5%					

Domain 6				**Totals**
	Item 1	Item 2	Item 3	26
Appraiser 1	6	7		13
Appraiser 2	6	7		13
Max: 7 x 2 x 2 = 28; Min: 1 x 2 x 2 = 4				
26 - 4 / 28 - 4 = 91.6%				

Appendix D.4: AGREE II score: Emergency management of paediatric patients with generalised convulsive status epilepticus

Combined results of reviewers' appraisal

Domain 1				**Totals**
	Item 1	Item 2	Item 3	28
Appraiser 1	5	5	5	15
Appraiser 2	5	4	4	13
Max: 7 x 3 x 2 = 42; Min: 1 x 3 x 2 = 6				
28 - 6 / 42 - 6 = 61.1 %				

Domain 2				**Totals**
	Item 1	Item 2	Item 3	18
Appraiser 1	3	3	3	9
Appraiser 2	6	1	2	9

Max: 7 x 3 x 2 = 42; Min: 1 x 3 x 2 = 6									
18 - 6 / 42 - 6 = 33.3 %									
Domain 3									**Totals**
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	28
Appraiser 1	1	1	1	1	4	5	1	1	15
Appraiser 2	1	1	1	1	4	4	1	1	14
Max: 7 x 8 x 2 = 112; Min: 1 x 8 x 2 = 16									
28 - 16 /112 - 16 = 12.5 %									

Domain 4				**Totals**
	Item 1	Item 2	Item 3	29
Appraiser 1	5	6	4	15
Appraiser 2	5	5	4	14
Max: 7 x 3 x 2 = 42; Min: 1 x 3 x 2 = 6				
29 - 6 / 42 - 6 = 63.9%				
Domain 5				**Totals**
	Item 1	Item 2	Item 3	Item 4	33

Appraiser 1	5	5	6	1	17
Appraiser 2	4	5	6	1	16
Max: 7 x 4 x 2 = 56; Min: 1 x 4 x 2 = 8					
33 - 8 / 56 - 8 = 52.1%					

Domain 6			**Totals**
	Item 1	Item 2	
Appraiser 1	n/a	n/a	n/a
Appraiser 2	n/a	n/a	n/a
Max: 7 x 2 x 2 = 28; Min: 1 x 2 x 2 = 4			
- 4 / 28 - 4 = %			

Appendix D.5: AGREE II score: Children and Infants with Seizures – Acute Management

Combined results of reviewers' appraisal

Domain 1				**Totals**
	Item 1	Item 2	Item 3	35
Appraiser 1	7	4	5	16
Appraiser 2	7	6	6	19
Max: 7 x 3 x 2 = 42; Min: 1 x 3 x 2 = 6				
35 - 6 / 42 - 6 = 80.6%				

Domain 2	**Totals**

	Item 1	Item 2	Item 3						29
Appraiser 1	5	3	6						14
Appraiser 2	6	2	7						15
Max: 7 x 3 x 2 = 42; Min: 1 x 3 x 2 = 6									
29 - 6 / 42 - 6 = 63.9%									
Domain 3									**Totals**
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	70
Appraiser 1	2	2	3	3	6	6	7	7	36
Appraiser 2	2	1	3	2	6	6	7	7	34
Max: 7 x 8 x 2 = 112; Min: 1 x 8 x 2 = 16									
70 - 16 /112 - 16 = 56.3%									
Domain 4									**Totals**
	Item 1	Item 2	Item 3						37
Appraiser 1	6	6	4						16
Appraiser 2	7	7	7						21
Max: 7 x 3 x 2 = 42; Min: 1 x 3 x 2 = 6									
37 - 6 / 42 - 6 = 86.1%									

Domain 5					**Totals**
	Item 1	Item 2	Item 3	Item 4	37
Appraiser 1	4	6	4	4	18
Appraiser 2	5	6	6	2	19
Max: 7 x 4 x 2 = 56; Min: 1 x 4 x 2 = 8					
37 - 8 / 56 - 8 = 60.4%					

Domain 6			**Totals**
	Item 1	Item 2	
Appraiser 1	n/a	n/a	n/a
Appraiser 2	n/a	n/a	n/a
Max: 7 x 2 x 2 = 28; Min: 1 x 2 x 2 = 4			
- 4 / 28 - 4 = %			

Appendix E: Background information of included Clinical Practice Guidelines

National Institute for Health and Care Excellence – NICE

NICE is a collection of guidelines developed for the National Institute of Health in the United Kingdom and other public health settings. Since 1999 NICE has been producing, developing and providing guidance on a range of topics. Generally guidelines are updated every four years with the reviewing beginning two years prior to publication.

Developers involved include the National Collaboration Centre for Primary Care (NCC-PC), National Clinical Guidelines Centre, a methodology team (healthcare professionals, academics and a patient perspective was incorporated) and a guideline development group. Key clinical questions are developed and answers found with full literature searches, critical appraisals and evidence reviews.

Recommendations are made based on relevant evidence (databases searched included Embase, Medline, Cinahl & Cohcrane library for studies published in English) and expert consensus. The group made 285 recommendations in total.

National Guideline Clearinghouse – NGC

National Guideline Clearinghouse (NGC) is a searchable database maintained by the Agency for Healthcare Research and Quality in partnership with American Medical Association and the National Health Insurance Plans. It forms part of the Department of Health in the United States of America and consists of an editorial team (healthcare professionals with experience in CPG quality) together with an expert panel (clinical, academia, administration and informatics) that assess guidelines submitted to NGC.

The CPG used from NGC collection: *Guidelines for the evaluation and management of status epilepticus* was developed by the Neurocritical Care Society Status Epilepticus Guideline Writing Committee.

Recommendations are made using Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology and based on available evidence (Medline and hand searches up until August 2011, published in English) and expert consensus.

Guidelines International Network – GIN

GIN is an international network of 99 organisations and 139 individual members (representing 49 countries) which supports evidence-based healthcare. They provide

partnerships (partners include AGREE research group, GRADE working group, International Federation for Emergency Medicine, the World Medical Association and the International Network of Agencies for Health Technologies Assessment) for guideline development and hosts a large international guideline library.

The CPG used from GIN: *Evidence-based guideline for pediatric seizure management using GRADE methodology* was developed by a multidisciplinary panel. Questions were developed by a work group (National Highway Traffic Safety Administration, Emergency Medical Services for Children, National EMS Advisory Council and the Evidence-based Guideline Steering Committee) using a Delphi technique to arrive at consensus-based recommendations.

A panel of experts in pediatric emergency medicine, emergency medicine and evidence based guideline development & research specialists used the National Evidence-based Guideline Model with a Delphi technique to reach consensus and develop recommendations.

Appendix F: Jaded cores for additional search (Jan 2012 – Jan 2016)

1. Was the study described as random?

- Yes
- No

2. Was the randomization scheme described and appropriate?

- Yes
- No

3. Was the study described as double-blind?

- Yes
- No

4. Was the method of double blinding appropriate?

- Yes
- No

5. Was there a description of dropouts and withdrawals?

- Yes
- No

The randomised control trials were scored using this online scoring system.

Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary?. Control Clin Trials. 1996;17(1):1-12. PMID: 8721797

http://www.pmidcalc.org/?sid=8721797&newtest=Y

Appendix F.1: Gathwala

1. Was the study described as random?	: Yes [1]
2. Was the randomization scheme described and appropriate?	: Yes [1]
3. Was the study described as double-blind?	: No [0]
4. Was the method of double blinding appropriate?	: No [-1]
5. Was there a description of dropouts and withdrawals?	: Yes [1]

Score: 2
LOW range of quality score

Gathwala G, Goel M, Singh J, *et al.* Intravenous diazepam, midazolam and lorazepam in acute seizure control. *Indian J Pediatr* 2012;**79**:327–32. doi:10.1007/s12098-011-0505-y

Appendix F.2: Thakker

1. Was the study described as random?	: Yes [1]
2. Was the randomization scheme described and appropriate?	: Yes [1]
3. Was the study described as double-blind?	: Yes [1]
4. Was the method of double blinding appropriate?	: Yes [1]
5. Was there a description of dropouts and withdrawals?	: Yes [1]

Score: 5
HIGH range of quality score

Thakker A, Shanbag P. A randomized controlled trial of intranasal-midazolam versus intravenous-diazepam for acute childhood seizures. *J Neurol* 2013;**260**:470–4. doi:10.1007/s00415-012-6659-3

Appendix F.3: Malu

1. Was the study described as random?	: Yes [1]
2. Was the randomization scheme described and appropriate?	: No [-1]
3. Was the study described as double-blind?	: No [0]
4. Was the method of double blinding appropriate?	: No [-1]
5. Was there a description of dropouts and withdrawals?	: Yes [1]

Score: 0
LOW range of quality score

Malu CKK, Kahamba DM, Walker TD, *et al.* Efficacy of Sublingual Lorazepam Versus Intrarectal Diazepam for Prolonged Convulsions in Sub-Saharan Africa. *J Child Neurol* 2013;**29**:895–902. doi:10.1177/0883073813493501

Appendix F.4: Chamberlain

1. Was the study described as random?	: Yes [1]
2. Was the randomization scheme described and appropriate?	: Yes [1]
3. Was the study described as double-blind?	: Yes [1]
4. Was the method of double blinding appropriate?	: Yes [1]
5. Was there a description of dropouts and withdrawals?	: Yes [1]

Score: 5
HIGH range of quality score

Chamberlain JM, Okada P, Holsti M, *et al.* Lorazepam vs Diazepam for Pediatric Status Epilepticus. *Jama* 2014;**311**:1652–60. doi:10.1001/jama.2014.2625

Appendix F.5: Portela

1. Was the study described as random?	: Yes [1]
2. Was the randomization scheme described and appropriate?	: Yes [1]
3. Was the study described as double-blind?	: No [0]
4. Was the method of double blinding appropriate?	: No [-1]
5. Was there a description of dropouts and withdrawals?	: Yes [1]

Score: 2
LOW range of quality score

Portela JL, Garcia PCR, Piva JP, *et al.* Intramuscular midazolam versus intravenous diazepam for treatment of seizures in the pediatric emergency department: A randomized clinical trial. *Med Intensiva* Published Online First: 10 June 2014. doi:10.1016/j.medin.2014.04.003

Appendix F.6: Welch

1. Was the study described as random?	: Yes [1]
2. Was the randomization scheme described and appropriate?	: Yes [1]
3. Was the study described as double-blind?	: Yes [1]
4. Was the method of double blinding appropriate?	: Yes [1]
5. Was there a description of dropouts and withdrawals?	: Yes [1]

Score: 5
HIGH range of quality score

Welch RD, Nicholas K, Durkalski-Mauldin VL, *et al.* Intramuscular midazolam versus intravenous lorazepam for the prehospital treatment of status epilepticus in the pediatric population. *Epilepsia* 2015;**56**:254–62. doi:10.1111/epi.12905

Appendix G: AMSTAR

1. Was an 'a priori' design provided?

The research question and inclusion criteria should be established before the conduct of the review.

Note: Need to refer to a protocol, ethics approval, or pre-determined/a priori published research objectives to score a "yes."

2. Was there duplicate study selection and data extraction?

There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.

Note: 2 people do study selection, 2 people do data extraction, consensus process or one person checks the other's work.

3. Was a comprehensive literature search performed?

At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.

Note: If at least 2 sources + one supplementary strategy used, select "yes" (Cochrane register/Central counts as 2 sources; a grey literature search counts as supplementary).

4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?

The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.

Note: If review indicates that there was a search for "grey literature" or "unpublished literature," indicate "yes." SIGLE database, dissertations, conference proceedings, and trial registries are all considered grey for this purpose. If searching a source that contains both grey and non-grey, must specify that they were searching for grey/unpublished lit.

5. Was a list of studies (included and excluded) provided?

A list of included and excluded studies should be provided.

Note: Acceptable if the excluded studies are referenced. If there is an electronic link to the list but the link is dead, select "no."

6. Were the characteristics of the included studies provided?

In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.

Note: Acceptable if not in table format as long as they are described as above.

7. Was the scientific quality of the included studies assessed and documented?

'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.

Note: Can include use of a quality scoring tool or checklist, e.g., Jadad scale, risk of bias, sensitivity analysis, etc., or a description of quality items, with some kind of result for EACH study (“low” or “high” is fine, as long as it is clear which studies scored “low” and which scored “high”; a summary score/range for all studies is not acceptable).

8. Was the scientific quality of the included studies used appropriately in formulating conclusions?

The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.

Note: Might say something such as “the results should be interpreted with caution due to poor quality of included studies.” Cannot score “yes” for this question if scored “no” for question 7.

9. Were the methods used to combine the findings of studies appropriate?

For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?).

Note: Indicate “yes” if they mention or describe heterogeneity, i.e., if they explain that they cannot pool because of heterogeneity/variability between interventions.

10. Was the likelihood of publication bias assessed?

An assessment of publication bias should include a combination of graphical aids (e.g. funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken).

Note: If no test values or funnel plot included, score “no”. Score “yes” if mentions that publication bias could not be assessed because there were fewer than 10 included studies.

11. Was the conflict of interest included?

Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.

Note: To get a “yes,” must indicate source of funding or support for the systematic review AND for each of the included studies.

http://amstar.ca/Amstar_Checklist.php

Appendix G.1: AMSTAR Sofou

AMSTAR Checklist **Printer Friendly Version**

Article Name:
Sofou

1. Was an 'a priori' design provided?
The research question and inclusion criteria should be established before the conduct of the review.

Note: Need to refer to a protocol, ethics approval, or pre-determined/a priori published research objectives to score a "yes."

- ☐ Yes
- ☐ No
- ☑ Can't answer
- ☐ Not applicable

---

2. Was there duplicate study selection and data extraction?
There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.

Note: 2 people do study selection, 2 people do data extraction, consensus process or one person checks the other's work.

- ☑ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable

---

3. Was a comprehensive literature search performed?
At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.

Note: If at least 2 sources + one supplementary strategy used, select "yes" (Cochrane register/Central counts as 2 sources; a grey literature search counts as supplementary).

- ☐ Yes
- ☑ No
- ☐ Can't answer
- ☐ Not applicable

---

4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?
The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.

Note: If review indicates that there was a search for "grey literature" or "unpublished literature," indicate "yes." SINGLE database, dissertations, conference proceedings, and trial registries are all considered grey for this purpose. If searching a source that contains both grey and non-grey, must specify that they were searching for grey/unpublished lit.

- ☐ Yes
- ☑ No
- ☐ Can't answer
- ☐ Not applicable

5. Was a list of studies (included and excluded) provided?
A list of included and excluded studies should be provided.

Note: Acceptable if the excluded studies are referenced. If there is an electronic link to the list but the link is dead, select "no."

- [ ] Yes
- [ ] No
- [x] Can't answer
- [ ] Not applicable

---

6. Were the characteristics of the included studies provided?
In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.

Note: Acceptable if not in table format as long as they are described as above.

- [x] Yes
- [ ] No
- [ ] Can't answer
- [ ] Not applicable

---

7. Was the scientific quality of the included studies assessed and documented?
'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.

Note: Can include use of a quality scoring tool or checklist, e.g., Jadad scale, risk of bias, sensitivity analysis, etc., or a description of quality items, with some kind of result for EACH study ("low" or "high" is fine, as long as it is clear which studies scored "low" and which scored "high"; a summary score/range for all studies is not acceptable).

- [x] Yes
- [ ] No
- [ ] Can't answer
- [ ] Not applicable

---

8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.

Note: Might say something such as "the results should be interpreted with caution due to poor quality of included studies." Cannot score "yes" for this question if scored "no" for question 7.

- [ ] Yes
- [ ] No
- [x] Can't answer
- [ ] Not applicable

---

9. Were the methods used to combine the findings of studies appropriate?
For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?).

Note: Indicate "yes" if they mention or describe heterogeneity, i.e., if they explain that they cannot pool because of heterogeneity/variability between interventions.

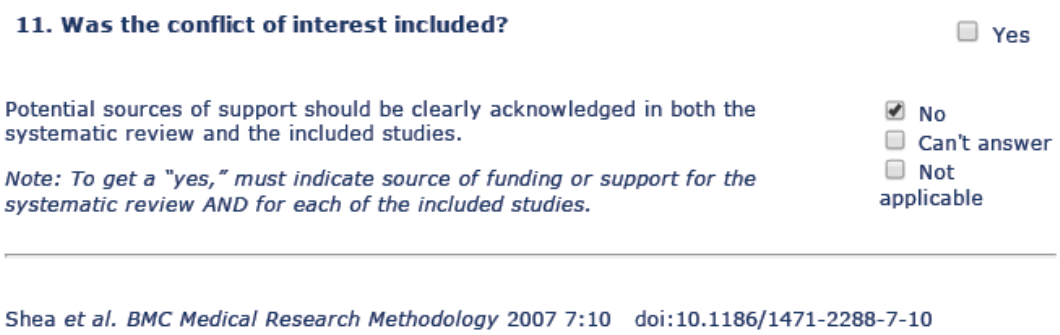
- [ ] Yes
- [x] No
- [ ] Can't answer
- [ ] Not applicable

---

10. Was the likelihood of publication bias assessed?
An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken).

Note: If no test values or funnel plot included, score "no". Score "yes" if mentions that publication bias could not be assessed because there were fewer than 10 included studies.

- [ ] Yes
- [x] No
- [ ] Can't answer
- [ ] Not applicable



Sofou K, Kristjánsdóttir R, Papachatzakis NE, *et al.* Management of Prolonged Seizures and Status Epilepticus in Childhood: A Systematic Review. *J Child Neurol* 2009;**24**:918–26. doi:10.1177/0883073809332768

Appendix G.2: AMSTAR McMullan

AMSTAR Checklist **Printer Friendly Version**

Article Name:
McMullan

1. Was an 'a priori' design provided?
The research question and inclusion criteria should be established before the conduct of the review.

Note: Need to refer to a protocol, ethics approval, or pre-determined/a priori published research objectives to score a "yes."

☑ Yes ☐ No ☐ Can't answer ☐ Not applicable

---

2. Was there duplicate study selection and data extraction?
There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.

Note: 2 people do study selection, 2 people do data extraction, consensus process or one person checks the other's work.

☑ Yes ☐ No ☐ Can't answer ☐ Not applicable

---

3. Was a comprehensive literature search performed?
At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.

Note: If at least 2 sources + one supplementary strategy used, select "yes" (Cochrane register/Central counts as 2 sources; a grey literature search counts as supplementary).

☑ Yes ☐ No ☐ Can't answer ☐ Not applicable

---

4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?
The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.

Note: If review indicates that there was a search for "grey literature" or "unpublished literature," indicate "yes." SINGLE database, dissertations, conference proceedings, and trial registries are all considered grey for this purpose. If searching a source that contains both grey and non-grey, must specify that they were searching for grey/unpublished lit.

☑ Yes ☐ No ☐ Can't answer ☐ Not applicable

---

5. Was a list of studies (included and excluded) provided?
A list of included and excluded studies should be provided.

Note: Acceptable if the excluded studies are referenced. If there is an electronic link to the list but the link is dead, select "no."

- [ ] Yes
- [x] No
- [ ] Can't answer
- [ ] Not applicable

---

6. Were the characteristics of the included studies provided?
In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.

Note: Acceptable if not in table format as long as they are described as above.

- [x] Yes
- [ ] No
- [ ] Can't answer
- [ ] Not applicable

---

7. Was the scientific quality of the included studies assessed and documented?
'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.

Note: Can include use of a quality scoring tool or checklist, e.g., Jadad scale, risk of bias, sensitivity analysis, etc., or a description of quality items, with some kind of result for EACH study ("low" or "high" is fine, as long as it is clear which studies scored "low" and which scored "high"; a summary score/range for all studies is not acceptable).

- [x] Yes
- [ ] No
- [ ] Can't answer
- [ ] Not applicable

---

8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.

Note: Might say something such as "the results should be interpreted with caution due to poor quality of included studies." Cannot score "yes" for this question if scored "no" for question 7.

- [x] Yes
- [ ] No
- [ ] Can't answer
- [ ] Not applicable

---

9. Were the methods used to combine the findings of studies appropriate?
For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?).

Note: Indicate "yes" if they mention or describe heterogeneity, i.e., if they explain that they cannot pool because of heterogeneity/variability between interventions.

- [x] Yes
- [ ] No
- [ ] Can't answer
- [ ] Not applicable

---

10. Was the likelihood of publication bias assessed?
An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken).

Note: If no test values or funnel plot included, score "no". Score "yes" if mentions that publication bias could not be assessed because there were fewer than 10 included studies.

- [x] Yes
- [ ] No
- [ ] Can't answer
- [ ] Not applicable

---

11. Was the conflict of interest included? ☐ Yes

Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.

Note: To get a "yes," must indicate source of funding or support for the systematic review AND for each of the included studies.

☑ No
☐ Can't answer
☐ Not applicable

Shea *et al. BMC Medical Research Methodology* 2007 7:10 doi:10.1186/1471-2288-7-10

McMullan J, Sasson C, Pancioli A, *et al.* Midazolam versus diazepam for the treatment of status epilepticus in children and young adults: a meta-analysis. *Acad Emerg Med* 2010;**17**:575–82. doi:10.1111/j.1553-2712.2010.00751.x

Appendix H: EMJ Instructions to Authors

Title page

The title page must contain the following information:

- Title of the article.
- Full name, postal address, e-mail and telephone number of the corresponding author.
- Full name, department, institution, city and country of all co-authors.
- Up to five keywords relevant to the content of your manuscript. This will enable us to identify the most suitable reviewers for your manuscript.
- Word count, excluding title page, abstract, references, figures and tables.

Manuscript format

The manuscript must be submitted as a Word document. PDF is not accepted.

The manuscript should be presented in the following order:

- Title page.
- Abstract, or a summary for case reports (Note: references should not be included in abstracts or summaries).
- Main text separated under appropriate headings and subheadings using the following hierarchy: BOLD CAPS, bold lower case, Plain text, Italics.
- Tables should be in Word format and placed in the main text where the table is first cited.
- Tables must be cited in the main text in numerical order.
- Acknowledgments, Competing Interests, Funding and all other required statements. Reference list.

Images must be uploaded as separate files (view further details under the Figures/illustrations section). All images must be cited within the main text in numerical order and legends should be provided at the end of the manuscript.

Appendices should be uploaded using the File Designation "Supplementary File" and cited in the main text. Please remove any hidden text headers or footers from your file before submission.

Style

Abbreviations and symbols must be standard. SI units should be used throughout, except for blood pressure values which should be reported in mm Hg.

Whenever possible, drugs should be given their approved generic name. Where a proprietary (brand) name is used, it should begin with a capital letter.

Acronyms should be used sparingly and fully explained when first used.

Figures/illustrations

Images must be uploaded as separate files. All images must be cited within the main text in numerical order and legends should be provided at the end of the manuscript.

Video: How to improve your graphs and tables >>

Colour images and charges

For certain journals, authors of unsolicited manuscripts that wish to publish colour figures in print will be charged a fee to cover the cost of printing. Refer to the specific journal's instructions for authors for more information.

Alternatively, authors are encouraged to supply colour illustrations for online publication and black and white versions for print publication. Colour publication online is offered at no charge, but the figure legend must not refer to the use of colours.

Detailed guidance on figure preparation >>

File types

Figures should be submitted in TIFF or EPS format. JPEG files are acceptable in some cases. A minimum resolution of 300 dpi is required, except for line art which should be 1200 dpi. Histograms should be presented in a simple, two-dimensional format, with no background grid.

During submission, ensure that the figure files are labelled with the correct File Designation of "Mono Image" for black and white figures and "Colour Image" for colour figures.

Figures are checked using automated quality control and if they are below the minimum standard you will be alerted and asked to resupply them.

Please ensure that any specific patient/hospital details are removed or blacked out (e.g. X-rays, MRI scans, etc). Figures that use a black bar to obscure a patient's identity are NOT accepted.

Tables

Tables should be in Word format and placed in the main text where the table is first cited. Tables must be cited in the main text in numerical order. Please note that tables embedded as Excel files within the manuscript are NOT accepted. Tables in Excel should be copied and pasted into the manuscript Word file.

Tables should be self-explanatory and the data they contain must not be duplicated in the text or figures. Any tables submitted that are longer/larger than 2 pages will be published as online only supplementary material.

Video: How to improve your graphs and tables >>

Multimedia files

You may submit multimedia files to enhance your article. Video files are preferred in .WMF or .AVI formats, but can also be supplied as .FLV, .Mov, and .MP4. When submitting, please ensure you upload them using the File Designation "Supplementary File - Video".

References

Authors are responsible for the accuracy of cited references and these should be checked before the manuscript is submitted.

Citing in the text

References must be numbered sequentially as they appear in the text. References cited in figures or tables (or in their legends and footnotes) should be numbered according to the place in the text where that table or figure is first cited. Reference numbers in the text should be inserted immediately after punctuation (with no word spacing)—for example,[6] not [6].

Where more than one reference is cited, these should be separated by a comma, for example,[1, 4, 39]. For sequences of consecutive numbers, give the first and last number of the sequence separated by a hyphen, for example,[22-25]. References provided in this format are translated during the production process to superscript type, and act as hyperlinks from the text to the quoted references in electronic forms of the article.

Please note that if references are not cited in order the manuscript may be returned for amendment before it is passed on to the Editor for review.

Preparing the reference list

References must be numbered consecutively in the order in which they are mentioned in the text.

Only papers published or in press should be included in the reference list. Personal communications or unpublished data must be cited in parentheses in the text with the name(s) of the source(s) and the year. Authors should request permission from the source to cite unpublished data.

Journals from BMJ use a slightly modified version of Vancouver referencing style (see example below). The style template is available via Endnote. Note that The BMJ uses a different style.

BMJ reference style

List the names and initials of all authors if there are 3 or fewer; otherwise list the first 3 and add 'et al.' (The exception is the Journal of Medical Genetics, which lists all authors). Use one space only between words up to the year and then no spaces. The journal title should be in italic and abbreviated according to the style of Medline. If the journal is not listed in Medline then it should be written out in full.

Check journal abbreviations using PubMed >>

Check citation information using PubMed >>

Permissions

If you are using any material e.g. figures, tables or videos that have already been published elsewhere, you must obtain permission to reuse them from the copyright holder (this may be the publisher rather than the author) and include any required permission statements in the figure legends. This includes your own previously published material, if you are not the copyright holder.

It is the author's responsibility to secure all permissions prior to publication.

Online only supplementary material

Additional figures and tables, methodology, raw data, etc may be published online only as supplementary material. If your paper exceeds the word count you should consider if any

parts of the article could be published online only. Please note that these files will not be copyedited or typeset and will be published as supplied, therefore PDF files are preferred.

All supplementary files should be uploaded using the File Designation "Supplementary File". Please ensure that any supplementary files are cited within the main text of the article.

Some journals also encourage authors to submit translated versions of their abstracts in their local language, which are published online only alongside the English version. These should be uploaded using the File Designation “Abstract in local language”.

Statistics

Statistical analyses must explain the methods used.

Guidelines on presenting statistics >>

Research reporting guidelines

Authors are encouraged to use the relevant research reporting guidelines for the study type provided by the EQUATOR Network. This will ensure that you provide enough information for editors, peer reviewers and readers to understand how the research was performed and to judge whether the findings are likely to be reliable.

The key reporting guidelines are:

- Randomised controlled trials (RCTs): CONSORT guidelines
- Systematic reviews and meta-analyses: PRISMA guidelines and MOOSE guidelines
- Observational studies in epidemiology: STROBE guidelines and MOOSE guidelines
- Diagnostic accuracy studies: STARD guidelines
- Quality improvement studies: SQUIRE guidelines

Research checklists should be uploaded using the File Designation “Research Checklist”.

Pre-submission checklist

In order to reduce the chance of your manuscript being returned to you, please check:

Author information: Have you provided details of all of your co-authors? Is the information that you have entered into ScholarOne the same as the information on the manuscript title page?

Manuscript length and formatting: Have you checked that your manuscript doesn't exceed the requirements for word count, number of tables and/or figures, and number of references? Have you provided your abstract in the correct format? Have you supplied any required additional information for your article type, such as key messages?

- **Tables**: Have you embedded any tables into the main text? Have they been cited in the text? Have you provided appropriate table legends? Have you uploaded any lengthy tables as supplementary files for online publication?
- **Figures**: Have you uploaded any figures separately from the text? Have they been supplied in an acceptable format and are they of sufficient quality? Are they suitable for black and white reproduction (unless you intend to pay any required fees for colour printing)? Have the files been labelled appropriately? Have the figures been cited in the text? Have you provided appropriate figure legends?
- **References**: Have all of the references been cited in the text?
- **Supplementary files and appendices**: Have you supplied these in an acceptable format? Have they been cited in the main text?
- **Statements**: Have you included the necessary statements relating to contributorship, competing interests, data sharing and ethical approval?
- **Research reporting checklists**: Have you either provided the appropriate statement for your study type, or explained why a checklist isn't required?
- **Permissions**: Have you obtained from the copyright holder to re-use any previously published material? Has the source been acknowledged?
- **Reviewers**: Have you provided the names of any preferred and non-preferred reviewers?
- **Revised manuscripts**: Have you supplied both a marked copy and a clean copy of your manuscript? Have you provided a point by point response to the reviewer and editor comments?

Information required for all authors submitting a manuscript to any BMJ journal:

- Manuscript files in the appropriate format, including a cover letter and title page
- Details of any co-authors (name, institution, city, country and email address)

- Details of preferred reviewers (name and email address)
- Word count, number of figures, number of tables, number of references and number of supplementary files for online only publication
- Competing interest statement
- Contributorship statement

Additional information that can be provided or may be required when submitting certain article types to certain journals:

- Name of the research funder(s)
- ORCID number(s) for all authors
- Names of any collaborators
- Details of non-preferred reviewers (name and email address)
- Clinical trial registration number
- Patient consent form
- Details of ethical approval
- Research reporting checklist (or a reason why one has not been provided)
- Data sharing statement
- Permission from the copyright holder to re-use previously published material
- Title of an alternate BMJ journal to which your manuscript can be automatically submitted if rejected from your first choice journal

Original Articles

Full length articles reporting research. Authors of original articles are required to comply with one of the appropriate reporting guidelines endorsed by the EQUATOR Network. More information can be found here.

Checklist Choices

BMJ requires compliance with the following reporting guidelines; please upload your completed checklist with your submission and label it "Research Checklist". Below is a list of the most commonly used research checklists which should be selected based on the type of study you are reporting. If your study's methodology does not have a suitable research checklist you may submit the paper, but must state in the cover letter why no checklist is attached.

CONSORT statement - Required for all randomised controlled trials

PRISMA statement - Required for all systematic reviews

EVEREST statement - Required for all economic evaluations

STARD statement - Required for all diagnostic research papers

STROBE statement - Required for all observational studies

MOOSE statement - Required for all meta-analyses of observational studies

Guidance and forms are available here.

Abstract: 250 words

Word count: up to 3000 words

Illustrations and tables: up to 6

References: 25

Additional information (such as data collection tools, surveys, etc) may be placed on the web site as a data supplement. In some cases, we may ask to publish the abstract in print and the full-length article on the website only.

You also have the option to publish the abstract of your paper in your local language. If you wish to do this, please upload a Word copy of your abstract to your manuscript on Scholar One and save it as 'supplementary material'.

Recommended Sections:

Introduction: The article should include a brief introduction explaining why you chose to do the study – this would include a description of the importance of the topic, a summary of what is already known and why the study was needed, and the goal of the study. Three to four paragraphs should be sufficient.

Methods: Guidelines exist for the reporting of methodology and results for randomized trials, observational studies and retrospective chart review. Please see above or refer to the EQUATOR website for guidelines according to the specific type of study. The Methodology section must include a statement about ethics approval before it can be reviewed. Clinical trials must be previously registered and the registration number given.

Results: Please follow the standardized guidelines (as in Methods) for reporting of results. For statistics, confidence intervals are preferred to p values.

Discussion: The discussion should begin with a brief summary of the findings (no more than one paragraph) followed by the following (in whatever order works best in the flow of the article): how this study is similar or different from prior studies with regards to methods and results; limitations of this study; implications of the results for practice or policy. If you wish to offer a conclusion, this should be done in the last paragraph of the Discussion rather than as a separate subsection.

Tables should be placed in the main text where they are first cited while figures should be provided as supplementary files.

"What this paper adds" Box

Please produce a box offering a thumbnail sketch of what your article adds to the literature, for readers who would like an overview without reading the whole article It should be divided into two short sections, each with 1-3 short sentences.

Section 1: What is already known on this subject

In two or three single sentence bullet points please summarise the state of scientific knowledge on this subject before you did your study and why this study needed to be done. Be clear and specific, not vague.

For example you might say: "Numerous observational studies have suggested that tea drinking may be effective in treating depression, but until now evidence from randomised controlled trials has been lacking/the only randomised controlled trial to date was underpowered/was carried out in an unusual population/did not use internationally accepted outcome measures/used too low a dose of tea."

Or: "Evidence from trials of tea therapy in depression have given conflicting results. Although Sjogren and Smith conducted a systematic review in 1995, a further 15 trials have been carried out since then…"

Section 2: What this study adds

In one or two single sentence bullet points give a simple answer to the question "What do we now know as a result of this study that we did not know before?" Be brief, succinct,

specific, and accurate. For example: “Our study suggests that tea drinking has no overall benefit in depression”.

You might use the last sentence to summarise any implications for practice, research, policy, or public health. For example, your study might have: asked and answered a new question (one whose relevance has only recently become clear) contradicted a belief, dogma, or previous evidence provided a new perspective on something that is already known in general provided evidence of higher methodological quality for a message which is already known.

Appendix I: Origin of the Australian National Health and Medical Research Council's FORM framework

Hillier S, Grimmer-Somers K, Merlin T, *et al.* FORM: an Australian method for formulating and grading recommendations in evidence-based clinical guidelines. *BMC Med Res Methodol* 2011;**11**:23. doi:10.1186/1471-2288-11-23

Appendix J: Example of rapid review using a tiered approach

The Centre for Allied HEalth Evidence. Effectiveness of mass media interventions: A rapid review. *Public Health* 2009;:1–66.https://www2.health.vic.gov.au/Api/downloadmedia/%7B8D2B56DE-0133-4562-97B1-9D82E731ABAC%7D

Appendix K: Example of rapid review using guidelines to formulate recommendations

Gambito ED V., Gonzalez-Suarez CB, Grimmer KA, *et al.* Updating contextualized clinical practice guidelines on stroke rehabilitation and low back pain management using a novel assessment framework that standardizes decisions. *BMC Res Notes* 2015;**8**:643. doi:10.1186/s13104-015-1588-8

Appendix L: National Health and Medical Research Council recommendations for guideline developers

1. Evidence base (number of studies, level of evidence and risk of bias in the included studies)		
	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency (if only one study was available, rank this component as 'not applicable')		
	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
3. Clinical impact (Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)		
	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
4. Generalizability (how well does the body of evidence match the population and clinical setting in question)		

	A	Evidence directly generalizable to target population
	B	Evidence directly generalizable to target population with some caveats
	C	Evidence not directly generalizable to the target population but could be sensibly applied
	D	Evidence not directly generalizable to target population and hard to judge whether it is sensible to apply
5. Applicability (Is the body of evidence relevant to the review question's population)		
	A	Evidence directly applicable to South African healthcare context
	B	Evidence applicable to South African healthcare context with few caveats
	C	Evidence probably applicable to South African healthcare context with some caveats
	D	Evidence not applicable to South African healthcare context
Other factors (Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)		
EVIDENCE STATEMENT MATRIX		
Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.		
Component	Rating	Description
1. Evidence base		
2. Consistency		
3. Clinical impact		

4. Generalizability		
5. Applicability		
Evidence Statement		
Recommendation and the grade of the recommendation (what recommendation can be drawn from the evidence)		
Implementation of recommendation (indicate with yes/no and provide explanations about the answers)		
Will this recommendation result in changes in usual care?		
Are there any resource implications associated with implementing this recommendation?		
Will the implementation of this recommendation require changes in the way care is currently organised?		
Are the guideline development group aware of any barriers to the implementation of this recommendation?		

https://www.nhmrc.gov.au/guidelines-publications/cp65

http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/cp30.pdf?q=publications/synopses/_files/cp30.pdf

Appendix M: Clinical Practice Guideline data extraction sheet

Name					
Publication date					
Country of Origin					
Population age range					
Quality assessment performed on studies (yes; no; unclear)					
Studies/ populations excluded **(yes; no; unclear)** **Reasons for exclusion**					
Quality of CPG (AGREEII score)					
Recommendations from the guideline **(eg. Setting, Drug, Route of administration, Timing)**					
Using the matrix and grading below, what is the evidence rating for each recommendation (relevant to review question)? **Eg: Component & A - D**					

Body of Evidence Matrix evaluation

Component	A	B	C	D
	Excellent	Good	Satisfactory	Poor
Evidence Base	≥ 1 level I studies with a low ROB or Several level II studies with a los ROB	1 or 2 level II studies with low ROB or SR/several level III studies with a low ROB	1 or 2 level III studies with a low ROB or Level I or II studies with a moderate ROB	Level IV studies or Level I – III studies/SR with a high ROB
Consistency	All studies consistent	Most studies consistent and inconsistency may be explained	Some inconsistency reflecting genuine uncertainty around a clinical question	Evidence is inconsistent
Clinical Impact	Very large	Substantial	Moderate	Slight or restricted
Generalizability	Population/s studied in BOE are the same as the target population for the guideline	Population/s studied in the BOE are similar to the target population for the guideline	Population/s studied in the BOE differ to target population for guideline but is clinically sensible to apply this evidence to target population	Population/s studied in the BOE differ to target population and hard to judge whether it is sensible to generalise to target population
Applicability	Directly applicable to the healthcare context	Applicable to healthcare context with few caveats	Probably applicable to the healthcare context with some caveats	Not applicable to the healthcare context

Recommended Grade	Description
A	BOE can be trusted to guide practice
B	BOE can be trusted to guide practice in most situations
C	BOE provides some support for the recommendations but care should be taken in its application
D	BOE is weak and recommendations must be

	applied with caution

Evidence Matrix Hierarchy

Level	Intervention studies
I	A systematic review of level II studies
II	A randomised control trial
III-1	A pseudo-randomised controlled trial (alternating allocation or some other method)
III-2	A comparative study with concurrent controls: • Non-randomised experimental trial • Cohort study • Case-control study • Interrupted time series with a control group
III-3	A comparative study without concurrent controls: • Historical control study • Two or more single arm study • Interrupted time series without a parallel control group
IV	Case series with either post-test or pre-test/post-test outcomes

Appendix N: Ethics Approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

14 September 2015

HREC REF: 669/2015

Dr B Cheema
Paediatric Emergency Medicine
E52, Room 25
OMB

Dear Dr Cheema

PROJECT TITLE: RAPID REVIEW OF DRUG MANAGEMENT FOR PAEDIATRIC SEIZURE TERMINATION IN THE EMERGENCY SETTING (Masters candidate- Ms J Stockigt)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th September 2016.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

We acknowledge that the student, Ms Jeanine Stockigt will also be involved in this study.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH

HREC 669/2015

2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI),and Declaration of Helsinki (2013) guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC 669/2015