The Development of Practical Psychopharmacological Guidelines for the South African Context.

Dissertation submitted to the University of Cape Town Faculty of Health Sciences for the degree of MMed part 3 in Psychiatry

Candidate: Dr Jane Noreen Saunders

MbChB, DCH (SA), FCPsych (SA)

Supervisor: Dr A Robins

Senior Specialist, Department of Clinical Pharmacology,

University of Cape Town and Groote Schuur Hospital

CONTENTS

AIM

To develop practical psychopharmacology guidelines for use by primary care practitioners and non-specialist practitioners working in the field of psychiatry in the state service in South Africa.

INTRODUCTION

This dissertation comprises firstly a literature review of the need for and usefulness of guidelines in psychopharmacology for South African clinicians in primary care or working in psychiatric hospitals with little specialist supervision. The process whereby the guidelines were developed, based on the literature review, is then described. The results of this process, as well as the limitations and areas for improvement, are discussed. This is followed by a conclusion. A copy of the final book in A5 format is included as an addendum.

LITERATURE REVIEW

Mental health morbidity, estimated in 1990 by the World Bank at about 8.1% of disability-adjusted life years lost, is one of the largest causes of lost years of quality life worldwide. Behaviour-related illness, including violence, accounts for another 34% (1). Mental illnesses account for 5 out the top 10 causes of disability world wide with depression alone being second only to heart disease in its impact on loss of productivity in the economically active population (2).

Most public health statistics and evaluations have focused on mortality rather than morbidity and dysfunction. This has led to a gross underestimation of the enormous burden of illness arising from psychiatric and behavioural disorders (1). The consequences of this underestimation are reflected in the inadequate provision of services for mentally ill people and the lack of adequate training of primary health care practitioners in basic psychopharmacology.

There have been dramatic advances in pharmacological and psychosocial treatments of mental illness since the 1960's. The explosion in the number of different psychotropic drugs has resulted in the need for the development of rational guidelines to assist health care providers in providing appropriate quality care. An accurate diagnosis is as central to adequate treatment as matching the patient with treatment options (3).

The South African Situation

In August 1999, there were 473 registered psychiatrists in South Africa, many of whom were not practising or even living in South Africa (4). Flischer et al found that in 1993, 261 out of total of 378 (69%) registered psychiatrists were practising in SA (5). In 1999 approximately 327(69%) psychiatrists were in full time private practice with only 95 (31%) in the state sector. In the 1993 study, there were 6.4 psychiatrists per million South Africans with only 7% spending any time in rural areas and large discrepancies between provinces (5).

The public sector full-time equivalent mental health staff/population ratio in South Africa is 19.5 per 100 000 population (provincial range: 11.3-26.2). This comprises 7 psychiatric nurses, 0.4 occupational therapists, 0.5 social workers, 0.3 psychologists & 0.4 psychiatrists per 100 000 population. This is very low when compared with developed countries (e.g. USA psychiatrists- 16 per 100 000) but generally higher than other African countries (6).

The paucity and maldistribution of psychiatrists in South Africa pose challenges for findings new ways of increasing access to specialist support. This is exacerbated by the experience many people have that they find clinical psychopharmacology confusing because there seem to be as many approaches as there are mental health clinicians (7).

The majority of South Africans depend on health care provision by primary health care providers and non-specialists working at psychiatric hospitals. These professionals are

doctors and nurses who have varying amounts of psychiatric training. Although many practice guidelines for the developed world have been formulated, scarce resources limit applicability to developing countries and lack of infrastructure and stringent budgetary restraints affect the availability and affordability of many interventions.
An urgent need was therefore identified to provide practical guidelines for clinicians to facilitate the practice of a high standard of psychiatry in the local context.

The Rationale behind Guideline Development.

The primary purpose of pharmacological guidelines is to improve the well being of patients. They therefore need to offer guidance without being rigid, particularly in psychiatry where the number of variables in each case is large. (8) Provision of possible options in a given situation while outlining principles of treatment is a useful way to achieve this goal.

It is generally difficult to demonstrate the impact of guidelines on mental health outcomes, and adherence to guidelines is often a problem. (8). The rationale behind guideline development as well as the type of guidelines used, cost, availability, format and size of the book are important in determining their usefulness.

Good guidelines are therefore flexible, practical, comprehensive, concise, accessible and based on the best available evidence. They should be updated and improved without becoming long, complex and therefore impractical. The NIMH Consensus conference

concluded that there is sufficient database evidence and concurrence of expert opinion in psychiatry to produce reasonable practice guidelines. (9) Continual updating and improvement of the recommendations in policies and guidelines are important (9).

Medical practice policy development has undergone a number of changes over the last two decades, representing a change in the intellectual basis of medicine. Changes in the methods used in the formulation of policies have a profound influence on guideline content, thus potentially impacting on hundreds of thousands of clinical decisions (10).

Practice guidelines improve quality of care by anticipating clinical scenarios, synthesising the relevant available information and thus simplifying decisions for clinicians (10). This process therefore involves the identification of outcomes and the comparison of benefits versus harms of each intervention. This, together with other factors such as financial cost of the recommendations, determines the opinion expressed in the guideline (11).

Traditionally accepted medical practices have developed gradually over centuries based in anecdotal accounts and clinical experience (10). This process involves the dissemination of knowledge through lectures, textbooks, opinions by prominent clinicians, journal articles etc. Eddy cites Adam Smith's model of the 18th century marketplace as being the model for this process whereby an "invisible hand" guides the process in a benevolent fashion. The premise is that "Right ideas will thrive, wrong ideas

will wither, and the collective medical consciousness will slowly converge on the correct policy"(10 p1265).

Thus policies have developed without adequate analysis of their efficacy or consequences. The advantage of this approach is that as it is derived from thousands of decisions its inertia prevents any sudden changes based on current fashion. The fundamental problem however remains that policies are dictated by practice the outcomes of which are sensed intuitively. The basis of practice is not clearly defined and outcomes, benefit comparison and costs are not explicitly examined (10).

Objectives of New Approaches to Guidelines:

New approaches to the development of guidelines have developed as a result of the recognition of the problems inherent in traditional approaches and the explosion of medical information. Issues around cost and vigorous marketing by the pharmaceutical industry have left many clinicians overwhelmed and insecure about their prescribing practices. Although various methods are currently used to develop guidelines, good guidelines should share common objectives (12):

- **Accuracy:** the outcome caused by the recommendations should be the intended outcome.
- **Accountability:** the reasoning behind the guidelines should be available for review.

- **Predictability:** the financial and practical consequences should be anticipated.
- **Defensibility:** the rationale recommended should take into account areas of conflicting opinion.
- **Usable:** The recommendations should be practically possible in the target population.

Several new approaches have been developed to try and address the above-mentioned limitations of previous approaches. All have advantages and limitations:

1. **Using global subjective judgement.** Here the policy or guideline is simply announced with no explicit description of evidence or explanation of the rationale behind the document. It is entirely subjective with the potential for lack of inaccuracy being a big concern. There is poor accountability and predictability (12).

2. **Evidence- based approach.** This approach has become extremely popular over the last decade and attempts to overcome many of the problems outlined in 1 above as it describes available evidence and uses it as the basis for policy. Accuracy is much improved and the process is open to scrutiny. Outcome estimation remains subjective as they are not necessarily explicitly measured unless the principles of the outcomes- based approach are incorporated into the process of deriving the guidelines. Because tailoring guidelines to patients' needs

requires information as to how outcomes vary with patients' characteristics, policies derived by means of pure evidence-based principles remain difficult to individualise. Many evidence- based guidelines indicate treatment choices based on levels of scientific certainty (13). The degree of scientific certainty is determined through extensive meta-analysis of as much of the available literature as possible and then scored on the basis of the degree of support for a particular intervention. The estimates upon which recommendations are made are often complex and uncertain (14), requiring a detailed understanding of the process used to arrive at the recommendations.

3. **Outcomes- based approach.** Here the evidence for particular policies is described and possible outcomes are estimated. This allows the policy to be tailored to a variety of clinical scenarios. The accuracy depends largely on the accuracy of the method used to estimate outcomes and begins to fall with an increase in the number of variables needing to be measured as the clinical scenario becomes more complex. The clarity of evidence and rigor of the policymakers are also important. (12)

4. **Preference- based approach.** Here patients' preferences for outcomes are incorporated into the decision-making process. This is useful for opening it to review and individualising the policies (12).

5. **Expert Consensus Guidelines** generally use a combination of global subjective judgement and some evidence- based principles. Rating scales are often used to canvas expert opinion who then rate the intervention. These are then collated and summarised for clinicians' use. (15) Many experts will use evidence-based principles in the process of formulating an opinion but this is not mandatory and there is no standardisation as to how conclusions are reached.

The advantage of some expert guidelines is that they broaden recommendations to clinical scenarios whereas most evidence- based recommendations are made based on clinical trials. Expert guidelines can more easily accommodate multiple variables not accounted for in clinical trials (16). These would include factors such as co-morbidity, psychosocial interventions and drug interactions.

Guidelines or Algorithms?

Although some people use the terms interchangeably, the literature generally distinguishes between guidelines and algorithms. Jobson and Potter (17) suggest that guidelines consider a wide range of possibilities, are multi-faceted and more easily

generalisable whereas algorithms are rule-based with specific inputs, sequences and outputs. Both can give time-linked recommendations and both can be based on deductive reasoning.

Algorithms are meant to enhance rather than limit clinical decision- making but are often criticised for being narrow. If they are too rigid and inflexible and do not take the common variables found in clinical practice into account, they can restrict interventions and run the risk of doing more harm than good (13). Another danger is that clinicians stop thinking about the clinical scenario and act in a mechanistic manner as they follow the flow chart down the page.

The more complex the guideline or algorithm, the more specific training is required to use it (13). This is costly and time consuming. Algorithms that keep referring readers to the text are difficult to use, particularly by clinicians working under time constraints such as in primary care. Algorithms are extremely useful in emergency situations where there are a limited number of crucial steps to be followed (18).

They are also very useful in situations where there are a limited number of variables, (e.g. endocrinological laboratory abnormalities) but become less valuable as the number of variables increases, particularly if these variables are of a differing nature. Most psychiatric clinical scenarios involve psychosocial, laboratory, clinical and pharmacological variables which make the application of algorithmic flow diagrams difficult. The clinician then struggles with a unique patient and recommendations that are designed on the "one size fits all scenario". The simpler the clinical question and the

more evidence available the easier the recommendations are to formulate and follow (10). Algorithms are currently extremely popular but their efficacy has not been well evaluated in the literature.

How to use Guidelines:

Wilson et al have outlined some principles that are useful to consider when implementing guidelines. They include the clinical relevance of the questions posed, the practicality of the suggestions, the strength of the recommendations and their applicability to the current clinical scenario. Recognition of the possible discrepancies that can arise between the objectives of the practising clinicians and those developing the guidelines are important to identify and address (14). Those developing guidelines often do not work in the situation for which the guidelines are developed and many do not fully appreciate the inherent challenges and limitations in those situations.

THE DEVELOPMENT OF THE GUIDELINES

In the second section of this dissertation, the principles discussed above were then applied and guidelines developed. These were then collated into a book that was made available to the target group of practitioners. The references for the review and those for the guidelines were kept separate so that useful references could be included in a book.

Twelve key areas were identified and a chapter devoted to each. Identification of each chapter was done by the recognition of common problems presenting to Valkenberg Hospital in Cape Town and its associated urban and rural community clinics. Primary care nurse and medical practitioners were also consulted. These areas correspond closely to those described in other guidelines (7). They include:

1. General Guidelines when Prescribing Psychotropics
2. Anxiolytics and the Treatment of Anxiety Disorders
3. Treatment of Bipolar Disorder
4. Anti-depressant Treatment
5. Treatment of Psychosis
6. ECT
7. Management of Behavioural Disturbance
8. Psychotropic Prescription in Co- morbid Medical Illness
9. Management of Delirium
10. Management of Psychiatric Illness in Mentally Handicapped Patients
11. Prescription of Psychotropics during Pregnancy and Lactation
12. Prescribing in the Elderly
13. Useful references

The Essential Drug List

The Essential Drug List (EDL) has been developed as part of the Essential Drug Programme in State Health Care in South Africa. The EDL –P indicates essential drugs that should be available at primary care while the EDL-H lists those considered essential in hospitals (19). Drugs on both lists were identified in a specific column in tables and bolded in the text for easy reference. In addition, a list of all psychotropics and anticonvulsants on the EDL-P was provided.

Cost of Medication

The cost of medication was determined by the price of drugs in the public health service in the Western Cape at the time. Because costs may vary a symbol system was used as follows:

Amount	Symbol
< R10.00 /month	-
R11-30/month (still< R1.00/day)	+
R31-90/month (R1-3/ day)	++
R91-210/month (R3-7/day)	+++
> R210/month	++++

The Process of Guideline Development:

There is evidence that practitioners are more likely to use the guidelines if they have a close affiliation to the organization from which the guidelines originate or are involved in the development of these guidelines (8). The development of guidelines is not a static process and regular review and improvement are an integral part of their development. (8) As one person was developing these guidelines, the risk of subjective bias was a potential problem while consistency is an advantage. In order to address these issues, the following steps were taken:

1. A panel of advisory editors was established. These included Prof. B Roberston, Professor and Head of the Department of Psychiatry at the University of Cape Town, Dr Sean Baumann, Senior Specialist Psychiatrist at Valkenberg Hospital, and Dr Ashley Robins, Senior Specialist in the Department of Pharmacology at the University of Cape Town. Dr E Peter, a Senior Specialist psychiatrist and expert in mental handicap and dual diagnosis was an advisory editor for the relevant chapter.

2. All information included in the guidelines was congruent with current thinking as expressed in major peer review journals and publications from professional bodies such as the American Psychiatric Association, the Royal College of Psychiatrists and the Maudsley Guidelines. Major psychiatric textbooks from both the United Kingdom and the United States were consulted and no unsubstantiated anecdotal opinions were included. The review also detailed an appraisal of the cost

effectiveness of special investigations when prescribing certain medication. This involved extensive discussions with the Department of Pharmacology and the Departments of Clinical Pathology and Haematology at Groote Schuur Hospital and the University of Cape Town. In view of the current thinking with regard to guideline development as documented above, no single method was used to formulate the recommendation. Consistency across current international guidelines and major texts formed the basis of the guidelines. All recommendations were contextualised within the local situation and references for each section were supplied at the end of the book.

3. Formal and informal reviews of each chapter were conducted in consultation with the advisory editors, trainees and other colleagues and primary care practitioners. A copy of the book was sent to all academic heads of psychiatric departments in the country and to principal psychiatrists at psychiatric hospitals. Copies were also sent to a number of people in the Department of Health.

4. Ongoing review was invited after the publication of the book and a formal review meeting was held within the Department of Psychiatry at the University of Cape Town with the purpose of improving future editions.

5. In the light of the concerns about clinical algorithms in the literature discussed above, the book was produced as a collection of guidelines. The aim was to provide principles that could be applied in diverse settings ranging from rural

clinics to psychiatric hospitals. The emphasis was therefore on medication available in these settings as opposed to those available only in the private sector.

Two practical issues were raised in early feedback. Firstly, the physical structure of the booklet was seen as very important and recommendations in this regard determined the final choice of layout, size and binding of the book. The second issue was that of cost. To keep the cost down, the author published the book herself with the assistance of *the Printing Press*, a small printing company. This cut down the cost of printing by approximately two thirds, the booklet eventually selling for R25 per copy.

Although a pharmaceutical company did donate some money towards the printing of the first 1000 copies, the booklet was presented to them in its finished form and there was no influence on the content. The books were bought by senior medical students, junior doctors, nurses working in psychiatry and allied professionals. Most books were bought by people working and studying in the Western Province.

LIMITATIONS AND AREAS FOR IMPROVEMENT

Although a formal request for written feedback was made both in the book itself and in an insert in the book, very few written replies were received. A large number of people have given verbal feedback that has been positive but this has not been formally measured. The impact of guidelines on clinical practice is very difficult to evaluate as this entails measuring outcomes that are very complex, multivariate, and extend beyond the

accuracy of the guidelines themselves. This is beyond the scope of this dissertation (8)(10)(12). In addition to verbal feedback, more written feedback would be useful in improving future editions.

A major limitation in guideline development is that care of patients can only improve if clinicians are able to make accurate diagnoses. Although this is beyond the scope of this book, the importance of training in psychiatry and ongoing CPD for primary care practitioners is central to improving outcomes (12).

As there was one author, the process took a long time and individual bias was a potential problem although the steps taken above minimised this as much as possible. Despite attempts at reducing the cost, many primary care nurse practitioners still found the price prohibitive and more sponsorship will need to be sought for future editions.

CONCLUSIONS:

The book will need ongoing revision. Although outcomes are difficult to determine, a mechanism for assessing the effectiveness of guidelines remains an important research challenge for the future. The involvement of a number of authors and improved distribution to clinicians in rural areas will enhance further editions. The development of practical psychopharmacological guidelines for primary care practitioners working in the state service as opposed to private practise in South Africa is part of a process aimed at the improvement of mental health care delivery in the country.

REFERENCES:

1. Desjarlais R, Eisenberg L, Good B, et al *World Mental Health: Problems and Priorities in Low-income countries.* New York: Oxford University press, 1995.

2. Murray, C, Lopez, A. *The Global Burden of Disease. A Comprehnsive Assessment of Mortality and Disability from Diseases, Injuries and Risk Factors in 1990 and projected.* Harvard University Press, 1996.

3. Kaplan, H , Sadock B, *Kaplan and Sadock's Synopsis of Psychiatry: Behavioural Sciences/ Clinical Psychiatry.* 8th edition. Lippincott, Williams and Wilkins 1998.

4. Health Professions Council of South Africa Statistics 1999. Personal Correspondence.

5. Flischer AJ et al, Riccitelli,G et al. A Survey of Professional Activities of Psychiatrists in South Africa. *Psychiatric Services.* May 1997, 48:5

6. Flischer AJ et al. *Norms and Standards for Psychiatric Care in South Africa. A report submitted to the Department of Health, Republic of South Africa.* (Tender no GES 105/96-97) (3 vols) Cape Town. Department of Psychiatry University of Cape Town 1998.

7. Taylor, D et al. *The Bethlem and Maudsley NHS Trust Prescribing Guidelines.* 5th edition. Martin Dunitz, 1999.

8. Sachs, GS, Gaughan S. Clinical Practice Guidelines: Praises and Problems. *J of Clin Psychiatry* 60:1, January 1999.

9. Kosecoff, J et al. Effects on the National Institutes of Health Consensus Development Programme on physician practice. *JAMA* 1987;258:2708-2713.

10. Eddy, DM. Practice Policies: Where Do They Come From? *JAMA*.1990, 263:1265-1275

11. Eddy, DM. Guidelines for Policy Statements: the Explicit Approach. *JAMA*.1990,263:1839-1841

12. Eddy, DM. Practice Policies- Guidelines for Methods.*JAMA*.1990, 263, 2239-2243

13. Gilbert, DA et al. Texas medication Algorithm Project: Definitions, Rationale, and Methods to Develop Medication Algorithms. *J Clin Psychiatry 1998 59:7,345-351*

14. Wilson, MC et al. Users' Guides to the Medical Literature 8. How to use Clinical Practice Guidelines. B What are the recommendations and how will they help you in caring for your patients? *JAMA* 1995, 274:20,1630-1633

15. American Psychiatric Association Expert Consensus Guidelines for the Treatment of Posttraumatic stress Disorder, *J Clinical Psychiatry*1999;60 suppl 16

16. *American Psychiatric Association Practice Guidelines,* AP Press 1996

17. Jobson KO, Potter WZ, International Psychopharmacology Project Report: introduction. *Psychopharmacol Bull* 1995;31:457-459

18. Cavallaro, D, Grauer, K, *Arrthymia Interpretation: ACLS Preparation and Clinical Approach.* Moby 1996

19. National Essential Drugs List Committee. *South African Standard Treatment Guidelines and Essential Drugs List for Hospital Level 1998.* National Department of Health.

PRACTICAL PSYCHOPHARMACOLOGY FOR SOUTH AFRICA

- Guidelines For The Perplexed

Jane Saunders
Department of Psychiatry
University of Cape Town

PRACTICAL PSYCHOPHARMACOLOGY FOR SOUTH AFRICA -Guidelines for the Perplexed

Jane Saunders
Department of Psychiatry
University of Cape Town

1st Edition 1999

Department of Psychiatry, Faculty of Health Sciences, University of Cape Town, Ansio road, Observatory, 7925. Fax: (021) 448-8158. Phone: (021) 404-2164.Copies of this book can be ordered from the address above.
First edition July 1999

Disclaimer
Every attempt has been made to ensure the accuracy of the information in this publication. Information about drugs is constantly changing and the SAMF and manufacturers information should be consulted should any concerns arise. The author does not accept any liability for any injury, loss or damage howsoever caused.

ISBN 0-620-24959-5

Printed and bound by *The Printing Press.* Durban Rd .Mowbray. Cape Town.

Acknowledgements
I should like to thank the following people for their contributions to this book:
My colleagues at the University of Cape Town, Department of Psychiatry for the references and lengthy discussions.

Advisory Editors:

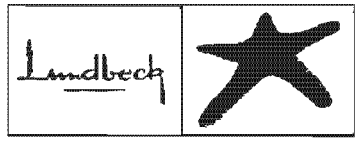
Dr S E Baumann
Dr A Robbins
Prof. B A Roberston
Advisory Editor for the chapter on Patients with Mental Handicap:
Dr E Peter.

Thank you also:
To my husband, Brendan, for his patience and support.
And to my patients from whom I learn every day.

Jane Saunders. July 1999

This book is dedicated to the Patients of Valkenberg Hospital

Printing of this booklet was made possible by the generosity of Lundbeck



CONTENTS

1. PREFACE

The paucity of psychiatrists in South Africa poses challenges for finding new ways of increasing access to specialist support. This is exacerbated by the experience many people have that they find clinical psychopharmacology daunting and confusing. Furthermore, there seem to be as many approaches as there are mental health practitioners. This book arose out of the recognition of this lack of uniformity at Valkenberg Hospital, one of the teaching hospitals of the Department of Psychiatry at the University of Cape Town. It is designed to provide guidance for medical practitioners caring for adult patients with mental illnesses in South Africa, ranging from primary care practitioners to trainee specialists, who frequently have to work without adequate access to specialist advice. It has been specifically designed for use in the public sector and the emphasis of the book is on treatments available in this arena, although virtually all drugs available in South Africa are discussed.

These guidelines have been compiled using the principles of evidence-based medicine and are the result of manual and electronic literature searches and reference to major textbooks as well as lively debate with experienced clinicians. Every attempt has been made to ensure accuracy and to base the guidelines on the latest available information. Major references for each chapter are therefore included at the end of the book. There are no absolute answers in psychopharmacology and this book offers only a considered opinion based on current available evidence.

The intention is to update the book at regular intervals and any comments would be appreciated. Should there be any suggestions with regard to content, please include the reference upon which it is based so that improvements can be made. I hope that this book will assist in demystifying clinical psychopharmacology and in maintaining high standards of patient care.

Dr Jane Saunders
Specialist Psychiatrist and Lecturer
Department of Psychiatry
Faculty of Health Sciences
University of Cape Town
Ansio Road
Observatory
7925
fax: (021) 448-8158
phone: (021) 404-2154

2. GENERAL GUIDELINES WHEN PRESCRIBING PSYCHOTROPICS

1) MAKE A DIAGNOSIS/ES.
2) IDENTIFY COMPLICATING FACTORS:
    - psychiatric, medical, social etc
3) TARGET SYMPTOMS e.g. use a more sedating agent if insomnia a problem
4) REVIEW past successful medication and other interventions.
5) PSYCHOSOCIAL INTERVENTIONS ARE IMPERATIVE
6) BE AWARE OF COST ISSUES.
7) START LOW GO SLOW
8) Weigh up the risks and benefits of any intervention
9) ADEQUATE FINAL DOSE FOR ADEQUATE DURATION
10) AVOID POLYPHARMACY.
11) NEVER SUDDENLY STOP MEDICATION. Taper off slowly. The longer the patient has been on the medication, the more gradual the taper.
12) CONSTANTLY REVIEW the need for medication. Avoid indefinite continuation as a default option.
13) INFORM & INVOLVE THE PATIENT and their family in all decisions around treatment.
14) GET TO KNOW THE DRUGS you prescribe well. NEVER prescribe a drug you know little about.
15) SPECIAL CIRCUMSTANCES:
    - Pregnancy and Lactation
    - Elderly
    - HIV,Renal or Hepatic impairment
    - Drug interactions
16) PHARMACOGENETICS: There is mainly anecdotal evidence that patients whose family members have responded to certain agents are likely to do the same. It's worth a try.
17) CHECK that the medication prescribed is AVAILABLE IN THE PATIENT'S COMMUNITY.
18) IF MONEY IS NO OBJECT: can be more exact in matching the person, the drug and the symptoms.

APPROACH TO FAILURE TO RESPOND TO TREATMENT

1) REVIEW THE DIAGNOSIS.

2) CO- MORBID PSYCHIATRIC DIAGNOSES:
   A] SUBSTANCES
   B] PERSONALITY FACTORS
   C] MENTAL HANDICAP
   D] OTHER AXIS ONE DIAGNOSES

3) CO-MORBID GENERAL MEDICAL PROBLEMS: especially TSH, VDRL,HIV, neurological, metabolic, other endocrine.

4) MEDICATION INDUCED e.g. B Blockers, L DOPA, Thyroxin

5) PROBLEMS WITH THE PSYCHOTROPIC MEDICATION?
   - appropriate dose?
   - appropriate duration?
   - compliance?
   - problems with absorption?
   - drug interactions?
   - side effects? -ask about these directly, especially sexual side effects.
     -NB AKATHISIA in patients on classical neuroleptics

6) PSYCHOSOCIAL FACTORS
   - adequate ongoing psychoeducation for patient and family ?
   - family support?
   - financial stressors?
   - adequate psychotherapy ?

ABBREVIATIONS:
Abbreviations have been defined where possible in the text. Other abbreviations are listed below:

Po	orally
SL	sublingually
Dly	daily
BD	twice a day
Tds	three times per day
Qid	four times a day
Prn	as required
C/I	contraindication
SIADH	Syndrome of Inappropriate ADH Secretion
Na	Sodium

KEYS TO GRAPHS

1. **EDL** = on the Essential Drug List as part of the Essential Drug Programme. Both the primary care (EDL- P) and hospital (EDL-H) lists are included. Drugs on the EDL-P are indicated below and those on the hospital list are indicated in the tables in the text. The availability of drugs may vary. All drugs on the list are indicated with a tick although they may not be specifically listed for that psychiatric indication. All drugs available on both lists are **bolded** in the text for easy identification.
2. **NOTE: The EDL referred to in this text is from the Western Cape and may not be applicable elsewhere**

3. The following drugs are listed on the EDL-P:

PSYCHOTROPICS
Amitriptyline
Chlorpromazine
Fluoxetine
Fluphenazine decanoate
Haloperidal
Lorazepam
Orphenadrine
Zuclopenthixol acetate

ANTICONVULSANTS:
Phenytoin
Carbamazepine
Valproic acid

4. **COST:**

The cost of medication has been indicated as below.
This is because the actual costs vary with different tenders.
The cost is worked out by means of calculating equivalent costs
of drugs at the most commonly prescribed dose in the Western Cape.

Amount	Symbol
< R10.00 /month	-
R11-30/month (still< R1.00/day)	+
R31-90/month (R1-3/ day)	++
R91-210/month (R3-7/day)	+++
> R210/month	++++

3. ANXIOLYTICS AND THE TREATMENT OF ANXIETY DISORDERS

GENERAL PRINCIPLES

- Anxiety is common and often appropriate. A specific diagnosis & assessment should be made and its severity rated
- Medication should only be prescribed for a specific diagnosis.
- Avoid prescribing benzodiazepines for more than 2 weeks.
- **Benzodiazepines have adverse effects:**
  a] sedation
  b] dependence and tolerance
  c] withdrawal
  d] cognitive impairment (especially in the elderly)
  e] delirium (especially in the elderly)
  f] depression
  g] anterograde amnesia

- **Short-acting vrs long -acting agents:**
  Half lives:
  a. Long: **Diazepam** (20-100 hrs)
  b. Intermediate **Lorazepam,** alprazolam, bromazepam (10-20 hrs)
  c. Short: **Oxazepam,** temazepam (6-10 hrs)
  d. Ultra Short Medazolam, triazolam (< 6 hrs)

	Advantages	**Disadvantages**
Long-acting	1. Convenient - ⇓ dosing frequency 2. Minimal inter-dose fluctuation 3. ⇓ withdrawal symptoms	1. Day - time sedation 2. Accumulation 3. ⇑ psycho-motor impairment
Short-acting	1. less accumulation 2. less sedation	1. more frequent dosing 2. withdrawal: can have micro withdrawals between dosing if t ½ very short 3. ⇑ rebound insomnia 4. ⇑ anterograde amnesia

- High potency (i.e. milligram dose required to produce similar therapeutic effects - see chart below) benzodiazepines (e.g. alprazolam) are less likely to cause cognitive dulling the following day, but more likely to cause withdrawal symptoms than the long -acting drugs e.g. diazepam
- When weaning patients off benzodiazepines:
    - convert to an equivalent dose of **diazepam**
    - reduce at NOT MORE than 25% every 2 weeks.
- Always warn patients about adverse effects, particularly advising them:
    - not to drive, operate machinery or engage in other potentially dangerous activities until the effect of the drug has been established.
    - of the dangers of combining alcohol and benzodiazepines.
- Antidepressants are as effective anxiolytics as benzodiazepines.

9) COMMONLY USED BENZODIAZEPINES AND APPROXIMATE EQUIVALENTS TO 5MG DIAZEPAM

Generic	Equiv-Alent Dose	Cost	T1/2	Metabolism	Dose range	EDL
Diazepam	5mg	-	20-100 hrs	hepatic	2-30mg	√
Lorazepam	1mg	-	10 -20 hrs	renal	0.5-5mg	√
Oxazepam	15mg	-	1- 20 hrs	renal	10-30mg	√
Temazepam	15mg	+	6-10 hrs	renal	15-30mg	X
Alprazolam	0.25mg	+++	12-24 hrs	hepatic	0.25-4mg	X
Clonazepam	1mg	++	18-50 hrs	hepatic	0.5-2mg	√

NOTE: LORAZEPAM IMI IS EXPENSIVE

3. ANXIOLYITCS AND THE TREATMENT OF ANXIETY DISORDERS

1) ACUTE DISTRESS

Psychosocial interventions NB

a] **lorazepam** 1-4mg PO / SL BD

b] **diazepam** 2-5mg daily

duration: few days only

2) PANIC DISORDER

- Multi-modal Treatment NB -psychoeducation, Cognitive Behavioural Therapy.
- Exclude physical causes e.g. thyroid disease, cardiac disease, hypoglycaemia,seizures.
- Establish whether these are panic attacks in association with other illnesses e.g. depression, phobias, withdrawal etc
- NB Depression + panic attacks $\Rightarrow$ high risk for suicide

Medication

1. Low starting dose and slow increments.
2. TCA's and SSRI's can exacerbate panic symptoms if started at high dose or increased too rapidly.
3. 1st Line:

   A] **Imipramine** (start @10 mg /day & ↑ by 10mg every 2-3 days & then by 25mg every third day until a dose of 150-200mg is reached over 2-3 weeks. If only 25mg tabs available, give alt days initially

   B] **fluoxetine** 10mg /day for a week(if possible), then 20mg/day. (otherwise give every 2-3 days initially)
4. Full Effect often takes 10 - 12 weeks. Usually start seeing improvement after a few weeks.
5. **Duration:** 1 YEAR - 18 months AFTER REMISSION OF ATTACKS. Panic Disorder is a chronic relapsing illness.

   Ensure adequate dose for adequate duration. Patients frequently under-treated for too short a period.

6. **Benzodiazepines:**
   a. initially if incapacitated and very rapid control of symptoms NB (max 2-4 weeks)
      - **lorazepam** 1-2mg prn for severe attack. Max 2mg/day
      - 2nd line: **clonazepam** 1-2mg prn. Max 2mg/day - longer t ½ - less withdrawal. Expensive.
      - alprazolam 0.25-0.5mg prn for severe attack. Max 0.5mg/day.(if patient can afford private script)

   b. A few patients: require ongoing benzodiazepines. Avoid if possible.
   c. Dependence does develop, even within one month of initiation of treatment, but tolerance seldom occurs.
   d. Contra-indicated if substance dependence co-morbid.
7. **Treatment Failure:** see guidelines at the front of the book
   a. try another class of antidepressant
   DISCUSS with specialist, Possibilities are:
   b. MAOI's highly effective but food restrictions and risk of hypertensive crisis difficult
   c. Use combinations: medication + CBT.
   d. Combination antidepressants: see chapter on anti-depressants for details
   e. mood stabilisers can be tried to augment

3) SOCIAL PHOBIA

Combination cognitive therapy and exposure.
Often co-morbid with panic attacks, depression and substances
Tricyclics not very effective.

A] **Fluoxetine:** 20mg po daily
B] Moclobemide: starting dose 150mg bd. Max 300mg BD

DURATION : often require long term treatment, depending on severity and duration of symptoms. No clear guidelines.

C] Propranolol: 20-40mg am. For performance anxiety. Initiate treatment PRIOR to the performance in a practice run. Problems: bronchoconstriction, drowsiness, low mood, nightmares.
D] Atenolol: cardioselective 50-100mg/day for performance anxiety.

4) POST TRAUMATIC STRESS DISORDER

- **Psychosocial intervention** most NB. Value of Debriefing controversial.
- Prevent: symptoms developing in the counselor / therapist - need support and supervision

Medication:

- is an adjunct: use for treating specific co-morbid symptoms, or if severe symptoms
- Good response for: intrusive thoughts, hyperarousal, flashbacks, hallucinations and dissociative features
- Poor response for: avoidance, isolation and emotional numbing

a] **Imipramine**. Start at 25mg nocte. Increase by 25mg every 2-3days to max 125-250mg per day
b] **Fluoxetine**: 20-40mg/day
c] Benzodiazepines: if severely distressed - short term only. E.g. lorazepam 1-2mg po prn.

5) OBSESSIVE COMPULSIVE DISORDER

Exposure and Response Prevention and Cognitive Therapy as effective as medication

- high level of commitment from patient necessary
- adjunctive psychosocial measures NB - psycho-education and rehabilitation, patient and family support

Medication:

a] **Fluoxetine:** 20-80mg/day.
High doses often necessary
start low go slow

b] **Clomipramine:** start at 25mg nocte & increase to 250mg/day (max = 300mg/day. Patients should have an ECG with every increase over 250mg/day- reduce dose if QT interval begins to widen)

NOTES:

- Fluoxetine is MUCH CHEAPER than clomipramine
- DURATION: improvement may only occur after 8-12 weeks
  average reduction in symptoms on meds=50%
  treat for at least 1year post recovery / improvement
  may need life-long treatment.

C] **Clonazepam:** 0.5-5mg/day useful in agitation especially. Can be used as monotherapy or adjunct. Expensive

Other possibilities:

D] Neuroleptics: especially for co-morbid tics , Tourette's, or for a small group of patients for whom the symptoms become delusional.
Haloperidol 0.5- 3mg / day.
See chapter on psychosis for details.

E] MAOI'S: dietary restrictions, risk of hypertensive crisis and Serotonin Syndrome a problem

Resistance:

See guidelines at the beginning of the book.

Is difficult to treat and should be referred to a specialist centre if possible

There are many recommended strategies, one is outlined below:

1] 3 trials of different SSRI's, starting with **Fluoxetine** (& CBT). At least 10 weeks each
2] Augment e.g. **clonazepam, haloperidol**
3] Monotherapy: **clonazepam,** MAOI if not tried

6) GENERALISED ANXIETY DISORDER

A controversial entity. Caution with the diagnosis

A] **Imipramine** starting at 10mg-25mg/ day increasing by 10mg/day and the 25mg/day to 125-250mg/day. Rate of increasing dose depends on onset and severity of symptoms.

B] Buspirone: start at 15mg BD and ↑ to 60mg/day

DURATION: 6-12 MONTHS FROM TIME OF RECOVERY

AVOID BENZODIAZEPINES

7) INSOMNIA

BEFORE CONSIDERING MEDICATION:

1) TAKE A THOROUGH SLEEP HISTORY: pattern of sleep/ duration/ psychiatric illness/ medical illness/ medications e.g. fluoxetine, nocturnal anti-cholinergics/ sympathometics, theophylline/ stimulants e.g. caffeine (coffee, energy supplements and drinks, tea)
2) Make a diagnosis: primary or secondary / acute or chronic.-NB depression is a common cause of insomnia.
3) Sleep hygiene and minimisation of aetiological factors is treatment of choice.
4) If hypnotics are to be used: only for short periods, preferably intermittently and for **a maximum of 1-2/52**. Advise re adverse effects.
5) Avoid high potency drugs e.g. **lorazepam.**
6) **Oxazepam** 10 mg po nocte (temazepam is much more expensive)
7) Alternative, although only if desperate= antihistamine **promethazine** 10-25 mg nocte
    - hydroxyzine 50-100mg an alternative
    - all antihistamines have hangover effect and give patients dry mouths
    - avoid the use of amitryptiline or chlorpromazine for insomnia only.

8) CONVERSION DISORDER

SLOW administration of ivi **diazepam** (2-10 mg) useful for abreaction. Only perform this if expert in this procedure.
Must have respiratory resuscitation equipment available for any respiratory depression
Psychosocial interventions imperative

4. TREATMENT OF BIPOLAR DISORDER

PRINCIPLES

1) See general principles
2) LIFE CHARTS are very useful in BPAD to document the nature, frequency and severity of cycling and the relationship with life events.

MANIA

A] ACUTE EPISODE

1) **STOP ANTI-DEPRESSANTS**
2) CHECK for medical complications eg steroids, hyperthyroidism
3) Mood stabiliser levels
4) **ECT** should be considered as a FIRST LINE OPTION in both psychotic & apsychotic acute mania
5) SELECT A **MOOD STABILISER:**
    - Now viewed as 1st line in the treatment of the acute phase
    - DURATION for treatment of acute episode: AT LEAST 1year post acute episode (see below)
    - see chart for details
    - **NOTE- re screening tests and mood stabilizers:** The following measures are cost saving without impacting on patient care: (as advised by the chemical pathology Department at Groote Schuur Hospital)

1.Urea can be used as a screening test for renal function prior to initiating lithium treatment. If it is abnormal or if the patient as renal impairment clinically, a full screen should be done.

2. Alkaline phosphatase (Alk phos), Albumin (Alb), and ALT are sufficient screening tests of liver function. If they are abnormal or if the patient has hepatic Impairment clinically, a full screen should be done.

COMMONLY USED MOOD STABILISERS:

AGENT	PHARMACO-LOGY	DOSE	PROBLEMS	COMMON SIDE EFFECTS	INVESTIGA-TIONS	CO -ST	EDL
LITHIUM Drug Interactions: *especially with renally excreted/acting agents *thiazides, NSAID's, ACE inhib, can cause Li toxicity *alcohol ⇑ 's & Xanthines ⇓ levels	t ½= 20hrs VERY SMALL THERA-PEUTIC INDEX ⇒ TOXICITY A REAL RISK⇒ **TOXIC level: >1.5mmol/l**	start: 400mg bd LEVEL(12hrs post dose) every 5 days, adjusting dose until ≈ **0.8mmol/l** Range: 400-2000mg daily divided:bd. **TOXICITY:** Nystagmus, Coarse Tremor, Ataxia Nausea, diarrhoea→ delirium, seizures → death	*Pregnancy & lactation: see chapter 12 *Nephrotoxic potential 5-10% ⇒ hypothyroidism *NB: small changes in blood level →big effect on side-effect profile *Advise re good hydration (e.g.runners, gastro) ⇒affects levels	*Tremor (Rx propanol) *polydipsia, polyuria * ⇑ weight * acne * GIT symptoms *weakness * cognitive dulling * arrythmias * AVOID IN: • sick sinus syndrome • Thyroid disease • Adjust in renal impairment	PRIOR to starting meds: * Creatinine * TSH * preg test Then Li level after 5d 6 mnthly: Li level Annually: *TSH, T3&T4 * Urea	+	√
CARBAMA-ZEPINE Drug Interactions:	t ½ = 12hrs (after a few days-induces own	start: 200mg bd ⇑ing gradually	*Pregnancy & Lactation: see Chapter 12	* neutropenia - transient in 1st 2 months *agranulocytosis * aplastic anaemia	Prior to starting: • FBC • Alk phos,	++	√

*Lithium, Antipsychotic, nifedipine, - ⇑ CNS effects * ⇓ TCA & neuroleptic levels MAOI: 2/52 washout * <u>Enzyme Inducer</u> ⇓ phenytoin & oral contraceptive levels	metabolism) Metab: both liver & kidney OD: = a tricylic, but not as severe ⇒ seizures, arrythmias respiratory⇓ rare	Range: 400-1600mg divided: tds / bd TOXICITY: Diplopia, dizzy Ataxia Sedation	* mild ⇓ thyroid * Enz inducer: ■ ⇓ oral contracept⇒ pregnancy risk ■ ⇓ folate & vit D deficiency Warn re infections in 1st 2 months→to hospital should they occur	* well tolerated in low doses- ⇑ in high doses: • sedation • cognitive ⇓ • rash-benign • Steven Johnson v rare • GIT s/e • SIADH & ⇓ Na • liver: mild ⇑ enz, serious ⇑ rare	ALT, Alb • TSH • Preg test Then: level as required Annual: FBC,Alb Alk phos, ALT		
SODIUM (Na) VALPROATE Drug Interactions: *May potentiate CNS depressants *phenytoin and carbamazepine *caution aspirin &warfarin	t ½ =8- 12 hrs hepatic metabolism	start: 500mg bd tds required in some patients slow release available on private script ⇑ until levels therapeutic. Usual dose 1.0-1.5g	Generally well tolerated Pregnancy & lactation: see specific section Tremor can ⇑ when prescribed with lithium or neuroleptics	Common: • Sedation • GIT • Tremor • Weight ⇑ Rare: * thrombocytopenia * platelet dysfunction * alopecia * hepatitis & pancreatitis * ataxia & chorea * headache	<u>Prior to starting:</u> • FBC • Alk phos, ALT,Alb • TSH • Preg test <u>Then:</u> Level as required <u>Annual</u>: FBC & Alb, Alk phos, ALT	++	√

TREATMENT OF MANIC SYMPTOMS

a) ACUTE CLASSICAL (EUPHORIC MANIA)

- 1st line: LITHIUM
- 2ndline: carbamazepine or valproate

b) ACUTE MIXED OR DYSPHORIC MANIA

- 1st line: Na Valproate
- 2nd line: Lithium or carbamazepine
- no response: combination mood stabilisers

c) RAPID CYCLING

- 1st line: Na Valproate OR Carbamazepine
- no response: try the other first line
- Then: combination of lithium and carbamazepine OR lithium and valproate - Both effective.

6) **DELAYED ONSET OF ACTION:** Mood stabilisers take 2-3 weeks to work. Physical containment and regulisation of sleep patterns is important but additional measures are often required

7) **ADDITIONAL FACTORS:**

a) If the patient is PSYCHOTIC:

- HALOPERIDOL: 2.5-5MG BD-TDS.
- CHLORPROMAZINE: 100MG - 200MG BD-TDS
- Be alert to symptoms of akathisia.
- NO evidence that higher doses have any advantage.
- >20mg haloperidol /day combined with lithium = theoretical risk of encephalopathy
- DURATION: Discontinue over a month once psychotic symptoms have resolved.

b) IN AGITATION AND BEHAVIOURAL DISTURBANCE:

- LORAZEPAM 1-2MG PO TDS has been shown to be very effective in behavioural control and frequently is neuroleptic sparing. Assists in- patients coping in a less restrictive environment sooner.
- max dose: 4mg/dose or 12mg/day
- duration: usually only required in the 1st few days. Max: 2-3 weeks
- if psychotic, see (a) above
- see specific section on management of acute severely behaviourally disturbed patient

NEUROLEPTICS AND MANIA:

1. See chapter on schizophrenia for details re neuroleptics.
2. Synergistic effect with lithium in classical **psychotic** mania
3. LONG term use (> a few months) should be avoided because:

- they are less effective than mood stabilisers long term
- risk of NMS (see p41) and Tardive Dyskinesia
- can lead to depression long term
- side effects, eg akathisia, EPSE often mistaken for manic symptoms which sets up a vicious cycle
- side effects eg ⇓ facial expression and stiffness often mistaken for depressive symptoms
- if withdrawn too quickly, can lead to the development of a "Supersensitivity Syndrome" and ⇑ in psychosis

RESISTANT MANIA:

- DEFINITION: no strict definition given. Current common definition: failure to respond to combination of at least 2 mood stabilisers and adjunct treatment after at least 4-6 weeks

1. See general principles on approach to treatment resistance
2. AVOID rapid neuroleptisation (admistering large doses of neuroleptics over a short period of time)
3. Check for drug induced akathisia
4. **ECT**
5. Add Clonazepam: see chart in chapter 3 for details. Expensive
6. Atypical antipsychotics:

- CLOZAPINE: after failure of haloperidol and chlorpromazine
  - SAFE WITH Valproate and Lithium
  - NOT with carbamazepine (both can cause agranulocytosis)
  - has acute anti -manic and probably long term mood stabiliser properties
  - good for mixed affective states and rapid cycling.
  - see specific section for regime in chapter 6.

7. Other interventions are rarely used .

COMBINATION USE OF MOOD STABILISERS:

1. ONLY FOR REFRACTORY BPAD
2. SUPERVISED by a specialist
3. both COMPLEX and potentially DANGEROUS
4. SAFEST & most EFFECTIVE: lithium + valproate

5. TOXIC INTERATIONS can be ⇓ if : add medication in low doses and ⇑ slowly
6. Scrupulous levels advised
7. **COMBINATIONS USED COMMONLY**

COMBINATION	ADVANTAGES	PROBLEMS	SAFETY
Lithium + Valproate	Effective, especially rapid cycling & mixed episode 1st choice	⇑ tremor, weight gain, sedation, GIT problems	✓
Lithium + Carbamazepine	good for rapid cycling lithium may counteract carbamazepine-induced neutropenia	Possible neurotoxicity NO protection against agranulocytosis Watch for carbamazepine's interactions	≈ Avoid in pre-existing CNS pathology
Valproate + Carbamazepine	Effective	Carbamazepine may ⇓ valproate level & valproate may ⇑ carbamazepine level	≈ monitor blood levels closely

MAJOR DEPRESSIVE EPISODE IN BPAD

1. NEVER prescribe an anti- depressant without the patient being on a mood stabiliser
2. CAREFUL: can precipitate MANIC EPISODE or RAPID CYCLING
3. See general guidelines
4. If mild to moderate, use mood stabiliser and psychotherapy. CBT or Interpersonal therapy NB in avoiding the use of antidepressants
5. Anti - depressants should be prescribed for the shortest time possible
6. SSRI's may be less inclined to trigger mania than TCA's.
7. Start anti-depressants at low doses ie 25mg of a TCA for 5 days and increase very gradually
8. Otherwise guidelines as for depression section

MAINTENANCE TREATMENT OF BIPOLAR DISORDER

1. AIM: prevention of relapse (50% will relapse off meds within 6/12 - on meds:<20%)
2. **ALWAYS** use long term treatment:
    - after 2 manic episodes
    - when on antidepressants
    - after 3 hypomanic episodes in <5years
3. **STRONGLY ADVISED** to use long term treatment:
    - if FH of BPAD
    - if episode was SEVERE, RESISTANT OR DESTRUCTIVE
    - if EARLY ONSET (< 20)
    - SUDDEN onset
    - previous SUICIDE ATTEMPT
    - >1 SEVERE DEPRESSED EPISODE
4. DURATION: at **LEAST 3- 4YEARS**
   LIFELONG if multiple severe episodes
6. **MOOD STABILISERS:**
    - continue on the agent effective in the acute phase.
    - see chart for details
7. Ongoing **PSYCHOSOCIAL AND REHABILITATIVE STRATEGIES** essential

5. ANTI-DEPRESSANT TREATMENT

PRINCIPLES

1) See general principles
2) ALWAYS assess SUICIDE RISK prior to any treatment
3) PSYCHOSOCIAL intervention and rehabilitation is imperative
4) DURATION OF TREATMENT: First episode: **6 months- 1 year from time of feeling well**
   2ND OR 3RD : 2-3 YEARS
   >3/VERY SEVERE: probably LIFELONG

The chronicity of depression (akin to Hypertension or diabetes) is increasingly being recognised

5) INVESTIGATIONS:

Depend on situation. Pregnancy test and TSH NB

6) WASHOUTS: (time between discontinuing one drug and starting another)
   Reasons for washouts:
   1] Prevents dangerous interactions eg SEROTONIN SYNDROME
   2] The withdrawal effects from the old agent and side effects of the new agent are not confused
   3] Cross taper when washout not required i.e. decrease 1st agent while gradually starting the second
   3] Recommended washout periods: MAINLY REQUIRED FOR:
      MAOI⇒ OTHER AGENT or visa versa. Also:
      MAOI'S 10 Days before using any other agents
      SSRI'S depends on half life of drug ,(eg fluoxetine @least 4 weeks) if →MAOI, Clomipramine or Venlafaxine
      TCA's if → MAOI or RIMA.4-7 days
      RIMA 2 days before using any other agent
      Venlafaxine 1 week if → MAOI or RIMA cautious with others, cross taper
      Clomipramine Risks as for SSRI's and TCA's

7) COMBINATIONS:

NEVER COMBINE: MAOI + EITHER SSRI or CLOMIPRAMINE
AVOID POLYPHARMACY, especially two SSRI's

8) PRECIPITATION OF MANIA: can occur with all antidepressants

9) Gradually taper dose when stopping treatment unless a serious side effect occurs or the drug has a very long half- life (e.g. Fluoxetine) to avoid discontinuation symptoms.

CHOOSING A DRUG:

A. **TRICYCLIC** UNLESS CONTRAINDICATED
- sedation required ⇒ **amitriptyline**
- less sedation⇒ **imipramine**

SOME CONSIDERATIONS WHEN PRESCRIBING TRICYCLICS:

a] Contra-indications:
- **SUICIDALITY:** - EXTREME CAUTION if previous suicide attempt
  - if acutely suicidal and an in-patient, watch for hoarding and re-evaluate when patient is to be discharged.
  - if suicide a concern in outpatients, use a safer class of drug. If there is no-one available to administer the medication on a daily basis.
  - weekly as opposed to monthly supply can be considered
  - impulsivity a big danger
- MYOCARDIAL INFARCT in the last 6 months
- narrow angle glaucoma
- prostatism
- cardiac conduction abnormalities

b] DOSAGE:
- start: 25mg nocte (50mg if an in-patient) ↑ by 25mg/ every 3rd day
- MINIMUM therapeutic dose for most patients 100- 150mg nocte
- once daily dosing only (nocte)
- ECG to check for Q-T interval lengthening is essential over 250mg/day
- LOFEPRAMINE is different: BD dosing in am and midday because of it's energising capacity. Start at 70mg daily.
- Dothiepin is expensive

c] Unacceptable side effects:

Some patients will not develop tolerance to the alpha blocking, anticholinergic and antihistamic effects by 14 days after last dose adjustment. Tolerance hereafter is unlikely to occur. Change medication after discussion with the patient.

e] Side Effects

These agents have many side-effects. Most patients develop tolerance after about 2 weeks. Adequate explanation and reassurance together with slow dose increases can reduce the impact substantially.

- **Anticholinergic**: blurred vision, dry mouth, constipation, urinary retention, cognitive effects in the elderly
- **Postural Hypotension and dizziness**
- **antihistaminic: weight ⇑ and sedation**
- **sweating**
- **serotonergic side effects** in some agents eg clomipramine and to a lessor extent, **amitriptyline**
- **arrhythmias** in doses over 250mg/day or patients with conduction defects, tachycardia
- **sexual side effects** (tolerance can develop)
- tremor, rashes and blood dyscrasias rare
- **OVERDOSE :**
    1. **a MEDICAL EMERGENCY: potentially fatal.**
    2. Danger: seizures, arrythmias, respiratory depression.
    3. Effects can last up to 72hrs post ingestion even if levels appear safe
    4. Can have seizures at therapeutic levels
    5. Rx: admit, toxicology screen, cardiac monitoring (⇑'d QT interval and widened QRS most common), emesis (**if conscious**) and activated charcoal

B) **SECOND LINE= SSRI'S**

1] **FLUOXETINE** is the only affordable SSRI in the State Service at present. It is on the EDL

t 1/2 = 10 days (metabolites)
Agitation can be a big problem in the first 10 days. If so, use low dose oral lorazepam for this period.
Energising, so give in am.

2] All SSRI's have a similar S/E profile. Generally better tolerated than TCA's but more expensive and not as widely available
Side- effects initially thought to be minimal - increasing adverse drug reports indicate otherwise.

3] The common problems are:

GIT **Headache** **Tremor**
Agitation **Sexual dysfunction** (NB common, tolerance does not develop, seldom volunteered)

SEROTONIN SYNDROME:

- A **medical emergency** - outcome better than NMS
- Cause: drug interactions, most commonly MAOI + SSRI OR SSRI+ SSRI ⇒ ⇑5HT in brainstem and spinal cord
- Clinically: a delirium characterised by: pyrexia, sweating, diarrhoea, hyperreflxia and myocolonus. Eventually rigid with decreased LOC and seizures
- Management: STOP THE DRUGS. HYDRATE. REFER TO GENERAL HOSPITAL STAT.
  (antipyretic, sedative, fluids, clonazepam for myoclonus, nifedipine for hypertension.)

4] CYTOCHROME P450 INHIBITION

This applies to ALL SSRI's. Fluoxetine one of the worst culprits. Different SSRI'S inhibit different iso-enzymes. DRUG INTERACTIONS therefore tricky - can ⇑ toxicity of other drugs metabolised by P450.

5] SSRI DISCONTINUATION SYNDROME:

- Especially in agents with shorter half lives. Dizzy, GIT, fatigue & myalgia, parasthesias, insomnia, dysphoria, depersonalization and derealization. Also: agitation, anxiety and vivid dreams.
- Especially Venlafaxine and Parotexine. (up to 1/3 of patients who stop abruptly) - taper slowly

SPECIFIC SCENARIOS:

1] **DYSTHYMIA:** poor response to TCA's . Use SSRI or RIMA. (MOAI'S very effective, but obviously not first line.) Duration: LONG TIME - years usually

2] **ATYPICAL FEATURES:** (⇑ sleep, "leaden paralysis", mood reactivity, reversed diurnal mood variation)

- <50% response to TCA's
- SSRI's 1st line
- duration as for typical features

3] **CO-MORBID ANXIETY:**

- OCD: SSRI e.g.**Fluoxetine** – see chapter 3
- PANIC: TCA but start very low, go very slow. Assess for suicidality
- Social Phobia: **Fluoxetine** if patient can't afford RIMA or depression severe

4] **CO-MORBID SUBSTANCE USE / ABUSE:**

- Frequently co-morbid, especially alcohol and benzodiazepines. watch also for prescribed drugs
- Substance - induced depression: abstain 2-4 weeks, symptoms should abate dramatically
- SUICIDE A BIG RISK – **fluoxetine**

5] **PSYCHOTIC FEATURES and Agitated Depression:**

- ECT
- OR **amitryptiline** + 2.5mg trifluoperazine (or **haloperidol**) dly or BD if ECT contra-indicated — can try 14 days of this combination prior to ECT
- Tail off & stop anti- psychotic as soon as psychotic symptoms abate. **NO long term antipsychotics.**

6] **CATATONIC DEPRESSION**:

- ECT & diazepam to remove the catatonic shell, then **amitriptyline**
- AVOID NEUROLEPTICS -risk of NMS

7] **BIPOLAR DEPRESSION**:

- See Bipolar notes. 5-20% of patients on antidepressants will become manic.
- SSRI's possibly less likely.

8] **PREGNANCY:** See chapter 12

9] **THE ELDERLY:** See chapter 13

10] **MARKED PERIODICITY TO THE DEPRESSION:**
Add **lithium.**

11] **ACTIVELY SUICIDAL, PROFOUND PSYCHOMOTOR RETARDATION, NOT TAKING IN NUTRIENTS**
ECT

12] **IF MONEY NO OBJECT**: can be more exact in matching the drug, the person and the disease profile.

13] **RESISTANT DEPRESSION:**
= Failure to respond to an adequate dose(equiv 200mg imipramine or 40mg fluoxetine) for an adequate duration (6 weeks) of 2 different classes of antidepressants

1. Establish resistance: most patients NOT really resistant - see general principles
2. ECT

Then: discuss with specialist. Possible approach:

3. MAOI (some authors skip this step)
4. AUGMENTATION – BY SPECIALIST ONLY:
   - Amitryptiline + Fluoxetine (watch serotonin syndrome and TCA toxicity)
   - Amitryptiline + Lithium - level between 0.6 -0.8 mmol/l. Improvement usually in 2 weeks.(will help about 50% non responders).Adding Li to the antidepressant may be more beneficial than starting them together.
   - + thyroxine: 25 -50 micrograms/day - trial of 7-14 days. If respond, continue for 2 months and tail by 12.5 micrograms/ day.
   - NO response? REVIEW PROCESS AGAIN
   - SPECIALIST ONLY AND WITH EXTREME CAUTION: TRY MAOI + TCA ⇒ WASHOUT FIRST
     ⇒ start simultaneously if possible
     ⇒ DOSES initally: 10mg tranylcypramine ⇒ max 30 mg
     50mg amitryptiline ↑ every 3rd day
     ⇒ WATCH BP CAREFULLY - QID MONITORING

CLASSES OF ANTIDEPRESSANTS:

1] TCA: Tricyclic antidepressant
2] Tetracyclic
3] SSRI: Selective Serotonin Reuptake Inhibitor
4] MAOI : Monamine Oxidase Inhibitor (NON REVERSIBLE)
5] RIMA: Reversible Monamine Oxidase Inhibitor
6] SARI: Serotonin 2 Antagonist and Reuptake Inhibitor
7] SNRI: Serotonin-Noradrenaline Reuptake Inhibitor
8] NaSSA: Noradrenergic and Specific Serotonergic Antidepressant

ANTI-DEPRESSANTS AVAILABLE IN MOST STATE HOSPITALS

Name	Starting Dose	Maximum Dose	Comments	Cost	Edl
TRICYCLICS					
Amitriptyline	25mg nocte	250mg nocte	* see A. above. Secondary amine = nortryptiline more limited s/e ⇒ better tolerated * has analgesic properties	-	√
Imipramine	25mg nocte	250mg nocte	See A. above Secondary amine = desipramine more limited s/e ⇒ better tolerated	-	√
Dothiepin	25mg nocte	250mg nocte	See above. Very cardiotoxic.	+	-
TETRACYCLICS					
Mianserin	10mg nocte	90mg nocte	*sedating. * Few anticholinergic properties ⇒ safe in cardiac disease. * safe in OD and porphyria * agranulocytosis: rare	+++	-
MAOI'S					
Tranylcypramine READ PACKAGE INSERT CARE- FULLY	10mg test dose	⇑ to 30mg/day over a week	*monitor LFT's *orthostatic BP⇓ * ⇑ weight * sexual s/e *insomnia – activating * myclonus, muscle pain & parasthesia rare. * **TYRAMINE INDUCED HYPERTENSIVE CRISIS** ⇒ strict dietary restrictions – exclude tyramine rich food –start 2 weeks prior to starting meds. Warning signs: headache, stiff neck, nausea & vomiting, sweating * Avoid in epilepsy, cardiac, renal or thyroid disease * ++	++	-

			drug interactions **OD:** potentially FATAL- agitation, hyperthermia, hypertension, tachycardia, ⇒ coma		
RIMA					
Moclobemide	150mg am	600mg / day tds dosing therapeutic dose @least 300mg/day	* well tolerated. Allegedly devoid of sexual side effects. * S/E: minor GIT, dizziness, insomnia *?? efficacy for severe depression. * promising in phobia's & other anxiety disorders.	+++	-
SSRI'S					
Fluoxetine	20mg am	40mg am	See B. above	+	√
Citalopram	20mg / day	40mg	Poor CYP2D6 inhibitor, so fewer drug interactions. Well tolerated in the elderly. Available in some centres.	++	-
Others Side effects similar for all SSRI's	Varies	Varies Availability in state hospitals vary	Paroxetine (constipation, dry mouth, discontinuation syndrome) Sertraline (GIT s/e, delayed ejaculation), Fluvoxamine (GIT, sedation, headache, dry mouth)	++++	-
SRI/TCA					
Clomipramine	25mg nocte	250mg nocte	Expensive - try fluoxetine first	++	-
SARI					
Trazodone	50 mg nocte	400-600mg/ day ⇑ slowly. BD dosing	* sedation * orthostatic ⇓ BP * headache *dry mouth *mild neutropenia * priapism * arrythmias in vulnerable patients * OD: relatively safe	+++	-

OTHER ANTI-DEPRESSANTS LARGELY UNAVAILABLE IN STATE HOSPITALS

	Dose	Comments
SNRI		
Venlafaxine	37.5mg BD start 375 mg/d max	useful: resistant depression. problems: cost, side effects + especially at high doses. ⇑ BP at high doses. Nausea, sedation, sexual side effects Discontinuation syndrome if stopped abruptly
SARI		
Nefazodone	100mg bd start ⇑ max 200-300mg bd	Usefulness: few sexual side effects generally well tolerated good anxiolytic problems: sedation, dizzy, orthostatic BP⇓, headache, dry mouth, nausea
NaSSA		
mirtazapine	Start 15mg/day ⇑ by 15mg every 2 weeks to a max of 45mg	New s/e: sedation (50%) - give nocte. ⇑ weight, ⇑ LFT's, orthostatic ⇓ BP agranulocytosis and neutropenia rare contra-indicated in pregnancy possible carcinogenicity in massive doses

31. TREATMENT OF PSYCHOSIS

Principles

1. Target symptoms: such as amount of sedation required and relevant co-morbidity
2. See general principles
3. ESTABLISH THE DIAGNOSIS
4. Review:
   what medication and other interventions have worked previously.
5. Avoid polypharmacy:
   particularly avoid combining depot and oral medication in maintenance treatment and atypical and classical neuroleptics.
6. Titrate the dose carefully.
   MEGADOSING SHOWS NO ADVANTAGE over doses equivalent to **a maximum of** 600-800mg of chlorpromazine and 20 mg of haloperidol per day. Dosing beyond these equivalents should be discussed with a specialist.
7. The onset of antipsychotic activity
   often takes one to two weeks after the initiation of treatment. The other properties of the neuroleptics [e.g. anticholinergic, antihistaminic effects] begin much sooner.
8. Regular benzodiazepines
   e.g. 1-2mg lorazepam 8 hourly or diazepam 5-10mg 12 hourly are highly effective in decreasing aggressive and agitated behavior, thereby acting as neuroleptic sparing agents. These should only given during the initial stages of behavioral disturbance for a maximum of 1-2 weeks. Always include instructions on the prescription chart to omit the dose should the patient be sedated.
9. Beware AKATHISIA
   if the patient suddenly becomes agitated, especially after an initial improvement on neuroleptics. DO NOT automatically increase the dose.
10. Psychosocial interventions are imperative.
    They will depend on the diagnosis, the patient and the social circumstances.
11. See specific headings for treatments appropriate to specific diagnoses.
12. INVESTIGATIONS:
    Depend on the clinical picture and the medication. VDRL, TSH if first episode. Pregnancy test NB if indicated

a. FIRST PRESENTATION OF PSYCHOTIC SYMPTOMS:

- ESTABLISH THE DIAGNOSIS: exclude delirium and other medical emergencies.
- If the patient is not behaviourally disturbed, an observation and assessment period of 3-7 days is recommended, particularly if there is a history of substance abuse.
- If the patient is behaviourally disturbed, see specific section.

b. THE MANAGEMENT OF CANNABIS INTOXICATION:

- Seldom continues beyond seven days post ingestion of cannabis, but can continue until the time of drug elimination, which is often about 21 days.
- The patient usually starts to settle within a few days of admission.
- Neuroleptics are seldom required.Behavioral disturbance can be treated with lorazepam 1- 4mg po/imi p.r.n. 6 hrly or regularly orally for a few days.
- A senior colleague should be consulted before starting neuroleptics.
- Should NOT be treated with long-term neuroleptics.
- NB. Psycho- education and referral for treatment for substance abuse.

c. THE MANAGEMENT OF SCHIZOPHRENIA:

1.Psychosocial interventions
are extremely important in the management of schizophrenia. Psycho- education and rehabilitation are frequently forgotten but play a vital role in the prognosis.

2.Dosing:
1.During the acute episode, doses of neuroleptics are frequently higher than required for maintenance treatment.
2.Outcome in schizophrenia has been linked to the cumulative duration of psychotic periods, especially in the first few years of the illness.
3.The experience the patient has during their first contact with mental health care is extremely important in determining future compliance. Severe side effects incurred by high doses of neuroleptics and negative experiences in acute admission wards play a large role here.
4. Use benzodiazepines as neuroleptic sparing agents in the acute stage.

3.The new Drugs:
- Sometimes referred to as "atypical agents" although this is a confusing term and its definition has not been clarified.
- e.g. Risperidone, Olanzapine and Quetiapine
- They have a lower incidence of EPSE and may be beneficial in the treatment off negative symptoms remains controversial and they are extremely expensive. See separate section for Clozapine, which has specific benefits and generally considered to be a truly atypical agent.

4. **THE DRUGS**

a.) CLASSICAL NEUROLEPTICS:

- *Key for chart below:* - = negligible or absent, + = mild, ++ = moderate, +++ = marked. Note: different texts vary at times by a factor of +. The principle is important.
- Anti-chol=anticholinergic side effects; EPSE= extrapyramidal side-effects.CPZ=chlorpromazine.

Name	Dose Range	Equivalent Dose to 100mg CPZ/day	EPSE	Anti-Chol	Sed-ation	⇓BP	Cost	EL	Comments
High Potency									
1. **Haloperidol**	0.5 - 20mg /day BD dosing	2-3	+++	+	+	+	-	√	
2. **Fluphenazine Decanoate**	6.25 - 25mg imi 2 weekly to monthly up to 50mg/month(this dose is rarely required)	25mg/mth equiv to 300mg/day Chlorpromazine (CPZ)	+++	+	+	+	+	√	
Medium Potency									
1. Trifluoperazine	3 – 20mg /day (1mg tab expensive –2 and 5mg cheap)	5	++/+	+	+	+	-	X	
2. Perphenazine Perphenazine inj	8 - 60mg / day tds dosing 50-200mg imi mthly	8	++/+	+	+	+	++ ++	X X	
Low Potency									
1. **Chlorpromazine**	50 – 800mg / day in BD doses	100	++	++	++	+++	-	√	
2. Thioridazine	10 –75mg/day	100	+	+++	+++	+++	+	X	cheap in geriatric doses NOTE: dangerous arrythmias in doses>100mg/day
3 Zuclopenthixol	100-400mg imi monthly. Dose divided 2 weekly if required.	200 mg/mnth equiv to 300mg CPZ/day	++	++	++	++	-	X	
4. **Flupenthixol**	10 - 60mg imi monthly. Dose divided 2 weekly if required	40 mg/ mnth equiv to 300mg CPZ/day	+	++	++	+	-	√	Possibly some antidepressant properties in low doses

IMPORTANT NOTES re Classical (Older) Neuroleptics:

1. **Daily Dose:** the above are recommended ranges. Higher, or more frequent doses occasionally necessary - discuss with specialist first.

2. **Important Side Effects:**

***Akathisia *Parkinsonism *Dystonia *Tardive Dyskinesia * Neuroleptic Malignant Syndrome *.Anticholinergic effects * Sedation**

Anticholinergic effects include: dry mouth, blurred vision, constipation, urinary retention. Toxicity: central cholinergic effects with a delirium, dilated pupils and seizures

EPSE effects include: ie **Parkinsonism**: stiffness, shuffling gait, drooling, stooped posture, tremor, mask-like facies, akinesia and ataraxia
(indifference towards environment.)

3 **Other Common side-effects:**

1.**Cardiac:** especially low potency eg thioridazine (also assoc with malignant arrythmias in high doses)
-hypotension (see chart)

2.Epilepsy: ALL neuroleptics are epileptogenic
Least: Haloperidol Most: Low potency agents

3. **Sexual**: up to 50% impotence rate. NB cause of non-compliance. Other effects eg retrograde ejaculation(Thioridazine), anorgasmia.
4. **Endocrine:** ⇑ prolactin ⇒ gynaecomastia, galactorrhoea, infertility, amenorrhoea
5. **Weight Gain:** Common. Non-compliance frequently results
6. **Skin:** a. allergic dermatitis (low potency early on)
   b. photosensitivity. (especially chlorpromazine)
   c. blue/gray skin changes in sun exposed areas
   d. Skin -eye syndrome:(Blue/gray + benign pigmentary eye changes)
7. **Eyes:** a. Chlorpromazine: cumulative dose of 1-3kg ⇒benign Pigmentation between lens and cornea
   b. Thioridazine: Irreversible retinal pigmentation⇒night blindness if use over 800mg/day.These doses are no longer used- do not exceed 100mg/day
8. **Jaundice:** benign
9. **Blood:** transient leucopenia common. Agranulocytosis and thrombocytopenia rare.

4. **Frequency of Dosing:** most neuroleptics have a t ½ such that BD or daily dosing is best. BD dosing may be required during the acute phase of treatment.

B.) OTHER AGENTS:

- *Key for chart below:* - = negligible or absent, + = mild, ++ = moderate, +++ = marked. Note: different texts vary at times by a factor of +. The principle is important.
- *None are currently on the EDL*
- Epse= extrapyramidal side effects, Anti-chol=anticholinergic

Name	Pharmacology & Equiv to 100mg/day Chlorpromazine	Epse	Anti-Chol	Sed-ation	⇓ BP	Other s/e	Notes	Cost
Clozapine	See below	-	++	++	++	See below	See below. wcc monitoring must be factored into cost.	++++
Risperidone	2-16mg/day, daily dosing equiv 1-2 av dose:2-4mg/day over 6mg/ day ⇑ing s/e with ⇑ing dose	 + +++	 + +	 + +	 ++ ++	*Agitation *Hypotension *Abdominal pain *Fatigue * anxiety *Nausea *weight ⇑ *rhinitis over 6mg/day: behaves like haloperidol as dose ⇑'s	Well tolerated below 6mg/day which is usually sufficient	++++
Olanzapine	5-20mg/day daily dosing equiv: Unclear ? 2mg	-	+	++	++	*sedation *weight⇑ *hypotension *anticholinergic effects	Mildly abnormal LFT's	++++
Quetiapine	150-750mg/day in BD dosing	-	+	++	++	Weight gain	Monitor LFT's and TFT's	++++
Sulpiride	400-800mg/day. BD dosing equiv dose: 200	+	+	+	+	As for classical neuroleptics	Frequently incorrectly used as anxiolytic, antidepressant and to augment breast-feeding. CROSSES ⇒ breast milk Useful if extrapyramidal symptoms. Possibly safer when re-challenging post NMS	+++
Clothiapine	40-160mg/d equiv dose: 40	+	+++	+++	++	Resp depression, laryngospasm, arrhythmias, seizures & severe sedation a risk when used IVI	40mg Injection ≈ price to 4mg lorazepam IMI	++
Pimozide	1 – 20mg/day equiv: 2	+++	+	+	+	Serious cardiac arrythmias	?? more effective in mono-delusional states	+++

5.FIRST-LINE TREATMENTS:

- **Haloperidol** 2 to 5 mg BD or TDS.
- Trifluoperazine 2-5 mg BD or TDS.
- **Chlorpromazine** 100 to 200 mg once - 2 X daily

- choose the drug depending on previous response, amount of sedation needed, side effect profile etc.
- if one of these drugs does not achieve an adequate response within 4 –6 weeks, try one of the other two.

6.DEPOT PREPARATIONS:

Depot preparations should be considered once an assessment of the diagnosis and appropriate dose of medication has been made where compliance is likely to be a problem, it has been successful in the past, or if the patient chooses it.

Options include: [see table for dosing]

1. **Fluphenazine decanoate** - closest equivalent oral agent = haloperidol
2. **Flupenthixol decanoate** - comes in oral form [expensive]
3. **Zuclopenthixol decanoate**-closest oral equivalent= chlorpromazine.

7.OTHER AVAILABLE ANTIPSYCHOTICS:

One of the above 3 medications should be used wherever possible. See table for alternatives all of which are considerably more expensive

8.CLOZAPINE

- Clozapine is a true atypical neuroleptic. It is expensive and has a dangerous idiosyncratic side effect of agranulocytosis. It should only be prescribed under the supervision of the specialist.
- Should not be used with classical neuroleptics as this will negate many of its benefits.
- Many of its other adverse effects are associated with the rapid increase in dose and are dose dependent. Start low and go very slow to minimize these effects.

Starting dose: **12.5-25 mg nocte.**
Monitor: blood pressure if any symptoms of hypotension occur.
After two days: add 25 mg am

There after:

- increase by **increments of 25 mg** a day until a dose of **300 mg /day** is achieved after approximately three weeks.
- Further increments: should be made cautiously: 50-100 mg per week to a **maximum of 500 mg per day.**
- Doses in excess of this are associated with a **dramatic increase in seizures,** and should only be made under the guidance of a specialist.
- Dosing:
  if sedation is a problem, a larger proportion of the dose can be administered at night.
- If more than a few days are omitted:
  return to starting dose and increase as above.

Duration:

reviewed at 3 months and then again at six months for response. If no response after six months, tail off to stop.
If a response, continue as for guidelines below. Many patients can be maintained at lower doses. Slowly titrate downwards to maintenance dose.

White cell count monitoring:

- the white cell count must be measured **prior to the commencement** of therapy.
- Thereafter must be measured **weekly for 18 weeks and then monthly.**
- Clozapine must be **stopped immediately** if the **neutrophil count drops below 1.5 x 10 to the 9/L.**
- **refer to a physician if the neutrophil count below 0.5.**

Concurrent use of **CARBAMAZEPINE should be avoided.**

8. MANAGEMENT OF TREATMENT RESISTANT PSYCHOSIS

- **Establish Diagnosis:**
  exclude non-psychotic agitation, such as distress in a mentally handicapped patient, temporal lobe status, anger, malingering, Factitious Disorder, substance intoxication or withdrawal, delirium, psychosis due to medical conditions such as syphilis or HIV-positive status, space occupying lesion, AKATHISIA.
  ? bipolar disorder or psychotic depression.
- see general principles for treatment resistance
- **? Compliance**
- **psychosocial factors** such as lack of social support and conflict
- ? Adequate **psycho- education** with family and patient
- **? SUBSTANCES,** most commonly alcohol and cannabis.
- ? **Personality factors**
- **Time: 6-12/52 of treatment**. At least 4-6 weeks of each classical agent.
- Treat **Co-morbidity:**
  - substance abuse
  - benzodiazepines for sedation [short-term only]
  - carbamazepine for aggression or as mood stabilizer
  - lithium responders : more likely to be female with affective symptoms.
  - See notes on akathisia p 40
  - consider a Depot if compliance problem
- **MEGADOSING SHOWS NO BENEFITS**
- **Full review.**
  Establish what psychosocial and pharmacological interventions have been most successful and try these.
- **Clozapine:**
  see specific section p 36.
  If failed to respond to at least two classical agents use strictly alone except in exceptional circumstances.
- **Repeat complete review.**
- **Withdraw** all ineffective drugs
- **Restart** : the previously most effective drug at a low dose

9. PRIOR TO DISCHARGE:

- Try to **reduce the frequency of dosage** to once daily or a maximum of twice daily.
- Try to **reduce the total daily dosage.**
- Maintenance dosing principles: **low steady** dosing. Reduce to low dose gradually. **Avoid intermittent dosing**.
- **Minimize,** preferably avoid, the use of **anti-cholinergics**.
- **Avoid PRN medication.**
- Check that the discharge medication is **available** in the patient' s community.
- Indicate on the discharge summary when the **next IM is due** and what **investigations** have been done.
- **PSYCHO EDUCATION AND REHABILITATION** planning.

10. DURATION OF TREATMENT

- Schizophreniform Disorder: **12 months**
- Schizophrenia-first episode: **12 –24 months**
- Schizophrenia-second and subsequent episodes: **3-5 years.**
- Schizophrenia or Schizophrenia like psychoses with the risk of danger to self or others: **indefinitely.**

11.TREATMENT OF SIDE EFFECTS OF ANTIPSYCHOTIC MEDICATION

1. Parkinsonism:

NOTE: the Parkinsonistic side effects of antipsychotics often mimic negative symptoms. Tremor, rigidity, and bradykinesia are also common.

Treatment:

a. Reduce the dose.

b. And an anticholinergic:

Orphenadrine 50 Mg 2-3x Daily [Maximum Dose: 300 Mg Daily]

c. Change from a high potency to lower potency agent. If still severe, consider an atypical agent.

2. Akathisia:

Very common. **UNDER DIAGNOSED**. Has three components

- a subjective sense of needing to move
- observation that the patient cannot keep still
- dysphoria. Patients often present as being agitated or aggressive.

Treatment:

a. Reduce the dose.
b. Change from a high potency to lower potency agent. If still severe, consider an atypical agent..
c. Propanolol 10-20 mg 2-3x daily.
d. Diazepam 5-10 mg 2-3x daily
e.Orphenadrine 50 mg 2-3x daily [doesn't work as well]

3. Acute Dystonic Reaction

Usually occurs early in treatment or as the dose increased. Painful frightening involuntary muscle spasm, frequently of head and neck. Can include acute laryngeal spasm.

Treatment:

a. Immediate treatment: **biperidin 5 mg IM stat** or diazepam 5mg-10mg ivi very slowly (resuss equipment available if use IVI diazepam)
b. orphenadrine 50 mg 2-3x daily thereafter for a few days.
c. Reduce the dose.
d. Change medication: Change from a high potency to lower potency agent. If still severe, consider an atypical agent.

4. Anticholinergic Symptoms:

see above for symptoms

Treatment:

a. Reduce dose.
b. Change from a high potency to lower potency agent. If still severe, consider an atypical agent.

5. Tardive Dyskinesia:

Involuntary movements consisting of a complex combination of tics, dystonias and chorea-athetoid movements, most commonly involving the oro- bucco-lingual area.

Usually occur after prolonged treatment

Risk Factors: total antipsychotic dose, female, affective disorder, elderly.

Treatment:

a) **PREVENTION:** the lowest neuroleptic dose for the shortest time necessary.
   Consider the necessity for anticholinergic medication carefully as this may exacerbate.
b) NO DEFINITIVE TREATMENT. Lots of strategies may be tried
c) **Decrease the dose**, or stop the antipsychotic medication.
   Balance risk of relapse against severity of Tardive Dyskinesia.
d) Sulpiride and Clozapine have lower incidence.
   (Clozapine may even treat.)

RESPONSE RATE UNPREDICTABLE. SYMPTOMS MAY INITIALLY GET WORSE.

6. Neuroleptic Malignant Syndrome:

- Potentially fatal medical emergency characterized by rigidity, autonomic instability, and a change in level of consciousness.
- The patients can be mute, catatonic, agitated.
- *Investigations:* ⇑ CPK, [also ⇑ wcc, ⇓Fe.]

Treatment:

a. **STOP ANTIPSYCHOTIC MEDICATION IMMEDIATELY.**
b. Diazepam 5-10 mg 3-4 x orally daily
c. Hydrate
d. Refer to general medical facility
e. EC T.
f. Alternative: dantrolene sodium 1mg/kg orally divided 12hrly. Maximum 50mg/dose

7. Neuroleptic-induced Hyperprolactinaemia:

This is often asymptomatic or symptoms are mild. Can be problematic on rare occasions causing gynaecomastia galactorrhea, amenorrhoea and infertility. Other causes of hyperprolactinemia must be considered.

Treatment:

a. Reduce dose.
b. Switched to clozapine if possible and appropriate.
c. Amantadine or Bromocryptine can be tried, but often leads to worsening psychosis.

Note: prolactin levels fall within days, the rest of the effects such as gynaecomastia take much longer.

12.TREATMENT OF DEPRESSION IN SCHIZOPHRENIA:

- CONTROVERSIAL.
- Be careful not to mistake negative symptoms or drug effects for depression
- If depression is part of acute psychosis, antidepressants can worsen psychosis. Use neuroleptics alone. Resolution is slow.
- If depression occurs when psychosis is in remission, treat with an antidepressant. See depression chapter for details.

13. TREATMENT OF SCHIZO-AFFECTIVE DISORDER:

- Careful not to mistake negative symptoms or drug effects for depression.
- Neuroleptic doses as the schizophrenia.
- If manic, add mood stabilizer. [See BPAD guidelines for details]
- If depressed, follow guidelines for the treatment of depression in schizophrenia. Use of antidepressants in the acute phase is sometimes necessary [see depression guidelines for details]

14. TREATMENT OF CATATONIA:

- Catatonia is a syndrome NOT a diagnosis
- Establish the underlying diagnosis: e.g. Depression, Schizophrenia, NMS, Delirium etc and then treat accordingly
- Avoid neuroleptics- high risk of NMS.
- 1st line: ECT or Benzodiazepines (diazepam 5-10mg po bd-tds.usually used)

7. ECT

GENERAL PRINCIPLES:

1) SAFE, EFFECTIVE AND UNDER-UTILISED
2) Under-utilisation due to misinformation, bias and misconceptions held within psychiatry and by the public
3) Response rate on average >80% ie higher than medication. Patients often respond quite dramatically and much sooner than with medication.

INDICATIONS:

1) MDE: In uni or bipolar disorders, consider as first line in :
   - POST PARTUM mood disorder / psychosis requiring admission
   - with PSYCHOTIC FEATURES
   - RESISTANT depression
   - depressive stupor, not eating or drinking
   - acutely suicidal
   - agitated depression
   - bad melancholia responds well
   - well tolerated in pregnancy and the elderly

2) ACUTE MANIA : consider as a first line option, especially in acute severe mania

3) CATATONIA: Any cause, including Neuroleptic Malignant Syndrome consider as a first line option - removes catatonic shell very effectively.

4) Previous good response and patient preference

FREQUENCY: 3 x a week.(some centres 2X per week)

DURATION: depression- usually 6-12. Mania often longer
catatonia and delirium - often only a few needed
must continue BEYOND CLINICAL IMPROVEMENT. No consensus on how long - at least 2 more. If no response by 6, little chance of response.

DURATION OF EFFECT: ECT only INITIATES REMISSION. **Relapse rates are very high.** Other modalities of treatment must be initiated

MAINTENANCE ECT: only undertaken under exceptional circumstances

CONTRA-INDICATIONS:

- LITHIUM: Caution (studies suggesting ⇑ incidence of: acute confusional state, prolonged apnoea, Li toxicity, NMS type symptoms and worse affect on memory. New studies using sophisticated ECT machines and monitoring has reduced this to a relative C/I in some centres.)
- ANAESTHETIC C/I: A thorough evaluation for fitness for anaethestic is essential
- MI in the last 6 months
- ⇑ intracranial pressure
- Cerebral haemorrhage or aneurysm
- Aortic aneurysm

NOT CONTRA-INDICATED:

- Orthopaedic devices
- Well controlled epilepsy
- Pregnant or geriatric patients

ADVERSE EFFECTS

A) MORTALITY very low: about 0.002% per treatment ≅ any general anaesthetic -generally due to anaesthetic complications, MI or ventricular arrhythmias

B) MOST COMMON:

- Muscle aches
- Headache
- Anaesthetic complications eg aspiration, prolonged apnoea
- Mild post ECT confusion

C) LESS COMMON:

- Nausea & vomiting
- Mania
- Cardiac complications eg MI, arrhythmias
- Ruptured bladder (if not emptied prior to procedure)
- Pulmonary embolus
- Bleeds: subconjunctival, GIT, epistaxis
- CVA
- Prolonged? Tardive status (> 180 seconds) : Treat with IVI diazepam, 10 mg SLOWLY. If no response, proceed as for Status Epilepticus

D) THE MEMORY DEBATE:

- ++++ CONTROVERSIAL
- BOTH anterograde and retrograde problems documented
- VAST MAJORITY: lose memory from just before the procedure to shortly thereafter.
- A few patients may have some barely measurable changes after a few months.
- Virtually no objective changes after 6 months

Preparation for the PROCEDURE:

1) Establish the indication
2) Informed consent. (including pamphlets, a tour of the facility, and discussions with previous recipients).
3) If ECT machine uses bilateral application, assessment for handedness is not required.
4) Pre- anaesthetic physical evaluation. CXR, ECG, FBC and renal function in all patients over 40.
5) Any contra-indications?
6) Assess impact/ advisability of concomitant medication (see below)
7) NPO from midnight the night before
8) EMPTY BLADDER JUST PRIOR TO PROCEDURE
9) GA (with or without atropine/ anticholinergic to ⇓secretions and arrythmias)
10) BIFRONTAL APPLICATION: apply gel for good conduction to the area 4 cm above the line from the angle of the eye to the external auditary meatus. Then apply leads at this point
11) Electrical stimulus ≅ 400mv for 4-5 sec (Remember that there is a 40 fold variablity in seizure thresholds - need ≈ 3X threshold stimulus)
12) Exact technique depends on machine used.

CONCOMITANT MEDICATION

1) Benzodiazepines and Anticonvulsants: reduce to the lowest possible dose of benzodiazepines. Continue anticonvulsants for epilepsy, but may need to use higher stimulus. Anticonvulsant effect ⇓s efficacy of the procedure.
2) SSRI's: no contraindication
3) TCA'S: avoid in cardiac disease. Generally safe.
4) MAOI's: no good data. No need to discontinue but inform anaesthetist
5) Lithium: caution

6) Antipsychotics: ⇓ seizure threshold. Safe use reported for many years. Caution with Clozapine, especially in higher doses.
7) Anticonvulsants: May need to use higher energy stimulus as ⇑ seizure threshold. Continue use though.

NO FIT?

1) Check that machine is plugged in and switched on.
2) Check electrode sites - good conductance and contact
3) ? meds ⇑ing seizure threshold

These 3 will sort out the vast majority of problems.

4) Pure oxygen for 20-30 inhalations - ⇓s seizure threshold
5) ONE off dose of phenothiazines the day before
6) Caffeine augmentation: 200-500mg of caffeine sodium benzoate. Problem ⇑ risk of arrhythmias. Not generally available

8. MANAGEMENT OF BEHAVIOURAL DISTURBANCE:

A. ESTABLISH THE DIAGNOSIS: history, physical and mental state examination.

1. Try and determine whether there is any medical condition, eg hypoglycaemia, head injury, epilepsy etc.
2. Try to examine as thoroughly as possible before sedation. Complete a thorough physical examination, including fundoscopy and blood glucose as soon as possible.
3. **Common medical conditions presenting with aggression:**
   a) *Neurological:* Epilepsy, Meningitis, HIV, Head injuries, stroke, space-occupying lesions
   b) *Other:* hypoxia, metabolic and electrolyte disturbances, infections

3. **Common psychiatric conditions presenting with aggression:** substance intoxication or withdrawal, Schizophrenia and Schizophreniform disorder, any psychosis, Mania, agitated depression, panic disorder, PTSD, Cluster B personalities, distress in a mentally handicapped patient, factitious disorder, malingering.

B. ENSURE SAFETY OF OTHER PATIENTS, STAFF AND YOURSELF.

1) **Keep calm.** One member of the team should take control.
2) DO NOT attempt restraint until you have adequate help. **ALWAYS WORK IN A TEAM**
3) Patients often settle down when confronted with a show of force.
4) Evaluate the patient in a **safe room.**
5) Avoid positioning yourself so that either yourself or the patient feels threatened.
6) Police or security staff should remove any weapons.
7) Ask the police to stay and help if necessary
8) Speak calmly and reassuringly. Don't threaten the patient.

C. RESTRAINT:

- Try non-pharmacological measures first e.g. talking down, distraction, seclusion if necessary.
- Restraint: ensure safety. Administration of medication to a behaviourally disturbed patient is an extremely dangerous time both for the patient and for the staff.
- NEVER attempt to sedate a patient without adequate safe restraint.

D. **MEDICATION:**

1. **Lorazepam** 1-4 mg PO/IMI. Maximum Dose 12 Mg per 24 hrs. Try oral treatment first.

2. If this does not control the disturbed behavior, alternatives are: **lorazepam 2 - 4 mg IM and haloperidol 2-10mg IM.** Repeat after 30 min if this does not achieve control.

3. Once a neuroleptic is introduced into the treatment, **biperidin** must be available. [4mg biperidin IMI prn for acute dystonic reaction or parkinsonism.]

4. If this does not control behavior, or if you need immediate sedation: Ensure that facilities for **cardiac resuscitation and mechanical ventilation** are available before proceeding to the next step. Monitor respiratory status, pulse and BP carefully.A sedated patient should never be unattended.

   Then: **diazepam to 2- 10 mg IV +haloperidol 2-10 mg IV.** Repeat after 10 minutes until sedation is achieved up to a maximum of: 20 mg of haloperidol, 60 mg of diazepam per 24 hours.

5. **Flumazenil** 0.2mg iv over 15 seconds. If no response after 60 seconds, repeat a 0.1mg dose every 60 seconds Maximum dose 1mg. Must be available when using intravenous diazepam.

6. NEVER mix lorazepam or diazepam with other drugs in the same syringe

7. **NEVER give diazepam IMI**

8. Diazepam should be administered very slowly. IV-5 mg per minute.

9. Lorazepam or haloperidol given over two to three minutes.

10. Avoid chlorpromazine in patients with cardiac disease.

11. **If no control, seek advice from senior colleague**.

12. *Alternatives are:*
    zuclopenthixol acetate [Clopixol Acuphase] 100 -- 200 mg IM repeated once daily to once in the three days, not more than 450 mg per course. [Peaks at 24 - 36 hrs, usually effective for 72 hrs.] DO NOT USE: if the patient is neuroleptic naive.

Thereafter:
Treat the underlying diagnosis- see specific sections

9. PSYCHOTROPIC PRESCRIPTION IN CO-MORBID MEDICAL ILLNESS

1. **Brain Injury or Disease:**
   Use geriatric principles

2. **Hepatic impairment:**
   Avoid drugs metabolised by the liver if possible
   Antidepressants:
   Impramine starting at 25mg nocte and ⇑ with weekly or 2 weekly increments
   probably the safest. Aim for 50% of usual dose.
   SSRI's: ⇓ **fluoxetine** by at least 50% . Even more if severe.
   Benzodiazepines: use **Lorazepam** - not metabolised in the liver
   Neuroleptics: **haloperidol** or sulpiride. Start low, go slow
   Mood stabilisers: **Lithium**

3. **Renal Impairment:**
   Calculate the creatinine clearance.
   Antidepressants: all metabolised by the liver. Use low doses and increase carfully
   Neuroleptics: avoid sulpiride. Little data on new agents Low doses
   Mood stabilisers: Avoid lithium. Low doses. Regular levels

5. **HIV / AIDS:**
   Psychiatric illness common in HIV +ve and AIDS
   Psychosocial intervention, adequate pre and post test counseling imperative.
   Depression:
   Very common. Suicide rate 36X average
   If Stage 3 or 4, use geriatric principles
   AZT and other drugs used in treatment can cause depression
   Be careful of drug interactions
   Psychosis:
   May be incidental or AIDS-related
   If AIDS related , often atypical with mixed affective symptoms or mania
   Appears to respond to combination of low dose **haloperidol** and mood stabiliser.
   AZT helpful if available

Neuroleptics:

In stage 3 or 4, geriatric principles - **Haloperidol** low dose best

Highly susceptible to extrapyramidal side-effects

Mood stabilisers:

Lithium - avoid in patients with diarrhoea and dehydration

Carbamazepine: sedation and postural hypotension a problem

Avoid Na Valproate→may accelerate viral replication

AIDS Related Dementia:

Avoid sedating agents

As for any dementia if behaviour/ psychosis a problem

Exclude a delirium

AZT helpful if available

4. **Epilepsy:**

A. Epilepsy and Psychotropics:

1. Neuroleptics: all lower seizure threshold. **Haloperidol** the best.
2. Most anti-convulsants have psychiatric effects, most commonly causing depression, delirium and cognitive dulling.
3. Antidepressants : careful with TCA's. SSRI's probably better.
4. Neuroleptic + Antidepressant: Monitor very carefully.
5. Watch out for drug interactions: complex

B. Treatment of Epilepsy:

Principles:

1. Establish the diagnosis. Epilepsy is a clinical diagnosis. Careful attention to details provided by the patient and bystanders / family very NB
2. Are these focal or generalised, simple or complex?
3. Seizures vrs Psuedoseizures (can co-exist)
4. Start with appropriate drug and gradually increase until effective control or limited by side effects
5. If no control: check compliance. If compliant, switch to another drug
6. If seldom necessary to use more than one agent
7. Levels: if toxicity or non-compliance suspected

7. Agents to be Used:

Focal and generalised tonic clonic seizures	Primary generalised Absence Seizures
Phenytoin Carbamazepine Valproate	Valproate Ethosuximide

8. Doses:
   a. **Phenytoin:** Start at 300mg nocte. Usual maintenance dose:200mg-500mg/day
   b. **Carbamazepine:** Start at 100mg tds. ⇑ to 200mg tds over 2 weeks.
      Usual maintenance dose 600-1400 mg/ day divided in BD or tds dosing.
   c. **Valproate:** start at 200mg tds. Max: 2500mg/day. Divided bd or tds.
   d. Ethosuximide: start at 250mg BD and ⇑ to 1500mg/day in bd doses

9. The drugs:

a. Carbamazepine: see Bipolar notes

b. Na Valproate: see Bipolar notes

c. Phenytoin

- t ½ = 22 hrs ⇒ level after 7/7.
- Narrow therapeutic index: toxicity easy
  enzyme inducer
- S/E: Gingival hyperplasia, gum hypertrophy, hirsutes, folate deficiency , peripheral neuropathy tremor, confusion, ataxia and headache, Depression & mild cognitive dulling
  Pregnancy: teratogenic- neural tube defects (give 5mg/day folate from 3 months pre-conception)
  ++ drug interactions

d. Ethosuximide:

- t ½ = 50 -60 hrs
- S/E:GIT common, CNS: headache, ataxia, dizziness, depression, Haematological disorders rare, Steven's Johnson rare

e. The New Agents:

- *Gabapentin:* may have mood stabilising effects.
- *Lamotrigine:* may have mood stabilising effects
- *Vigabatrin:* depression and psychosis can occur
- *Topiramate:* depression, confusion and tremor may occur

C. Management of Status Epilepticus:

1. = a seizure that persists so that recovery between attacks does not occur *or* seizures persisting beyond 20 -30 mins
2. Mortality 20%
3. Clue to possible underlying structural abnormality
4. Clinical manifestations become subtle with time.
5. Management:

Refer to a medical hospital but start the following: (both phenobarb and phenytoin ivi are cardiotoxic and the patient needs monitoring in a general hospital. Accompany the patient)

a. **ABC:** secure airway, monitor vital signs, including airway, cardiac and respiratory monitoring ASAP
b. Take blood for the following while starting infusion: glucose, electrolytes, renal and hepatic function, FBC, toxicology gases, levels
c. **History and exam:** ? trauma, epilepsy, focal signs, infection, medical illness, substances, OD etc
d. **start IV infusion:** 100mg thiamine and 50ml of 50 % dextrose
e. **Start anticonvulsant therapy:**

0 -10 min: **diazepam ivi slowly up to 20 mg**
still fitting ?
10-40 min: **phenytoin ivi 20mg/kg @ 150mg/min**
still fitting ?
Phenytoin - additional 5-10mg/kg
still fitting ? ⇒ **ICU**
Phenobarbital -20mg/kg . give 200mg ivi bolus and the rest at 50 -75mg/min
still fitting ?
Phenobarbital - 5-10mg/kg additional
still fitting after 60 -90min?
anaethesia with midazolam or propofol.

10. MANAGEMENT OF DELIRIUM

1. Always be alert to the possibility of a delirium, especially in a patient with a sudden change in behaviour.
2. Delirium is characterised by a change in level of consciousness and poor attention- onset is usually acute.
3. Delirium is associated with a high mortality rate
4. Manage delirious patients in a medical hospital (except mild DT's).
5. Do not assume that all disordered behaviour is psychosis
6. **Delirium in a medical ill patient:**
   a) Treat the underlying cause.

   b) **Haloperidol:**
   - tailor the dose to the individual situation.
   - generally: 0.5 (elderly) to max 20mg/day
   - po/imi/ivi- well tolerated ivi
   - oral takes 4-6 hrs to peak & imi 20 -40 min
   - if situation urgent, use ivi - need much lower dose than oral , fewer EPSE when given ivi contra-indicated in: benzodiazepine or alcohol withdrawal & hepatic failure

   c) **Benzodiazepines:**
   - for benzodiazepine withdrawal: convert usage to diazepam - see benzodiazepine notes p 8
   - hepatic impairment - lorazepam 1-4 mg po/imi/ivi tds rather than diazepam.

   d) **Delirium Tremens:**
   1. <u>Exclude other or exacerbating causes, e.g.:</u>
   - infections: chest and urine
   - Hypoglycaemia and other metabolic dysregulation
   - Hepatic failure
   - Stroke or subdural haematoma: look for focal signs
   - Withdrawal from other substances

   Investigations if appropriate: visidex, FBC, electrolytes, LFT's, CXR, urine analysis etc

   2. <u>If uncomplicated: physically well patient with mild tremor and sweating. May be anxious</u>
   - adequate nutrition, no factors as in 1 above.

   Then: **diazepam** 5-10mg bd / tds for up to 5 days.
   Advise patient to tail dose as symptoms abate
   Thiamine 100mg Daily for 1 month
   Vitamin B Co 1 tablet BD for 2 weeks

3. Admit to a general hospital if more severe, no social support, malnourished or complications:

a) Titrate dose against symptoms
b) Rehydrate cautiously: **ALWAYS** add 100mg thiamine to the glucose solution
c) **diazepam** po 5-20mg tds - 4 hrly. Tail as symptoms abate.
d) **Lorazepam** 2-4mg imi can be given if very restless. (max 8mg/day)
e) 2nd Line: carbamazepine starting at 200mg tds, propranolol (rarely required)
f) Maximum benzodiazepine dose/day should not exceed the equivalent of 80mg of diazepam (eg 60mg diazepam and 8mg lorazepam/day)
g) **Wernicke's Encephalopathy** : treat **all patients** prophylactically:
   - **thiamine** 100mg ivi stat (if a drip is up- anaphylaxis rarely occurs-adrenaline must be available) or 100mg po/ imi stat **and** 100mg Daily for at least 3 months.
   - **+ vit B co** 1 tab BD X 1 month
   - **Signs of Wernicke's:** ataxia, confusion, memory ⇓, ⇓ LOC, ophthalmoplegia or nystagmus, hypothermia or hypotension.

Rx: IVI thiamine bolus if possible (see above), **then** thiamine 100 mg BD or tds for at least 6 months

h) DO NOT GIVE NEUROLEPTICS TO PATIENTS IN DT'S (lowers seizure threshold)
i) **Withdrawal Seizures:** start with ivi diazepam up to 20mg SLOWLY
If still fitting, consider another cause (eg subdural) and proceed as for status epilepticus
j) **Monitoring:** continued careful monitoring for complications. Avoid restraint. Keep patient calm
k) **Post Treatment:** motivational counseling and referral.

11. MANAGEMENT OF PSYCHIATRIC ILLNESS IN PATIENTS WITH MENTAL HANDICAP

Principles:

1. These patients are known as **Dually Diagnosed Patients**.
2. Mental handicap is not a mental illness.
3. DSM is NOT mental handicap friendly: many patients not easily categorised and defined as atypical
4. See general guidelines. In addition: make an accurate diagnosis, both physical and psychiatric, including a thorough mental state examination.
5. Identify specific problems e.g. aggression, withdrawal
6. Do **not assume that behavioural disturbance = psychosis.** It usually doesn't.
7. Atypical presentation: concrete thinking & poor communication skills, impoverished social skills, distress presenting as behavioural disturbance.
8. Very vulnerable to drug effects: both administration and withdrawal.
9. Collateral NB
10. Possible reasons for aggression / apparent psychosis:
    - recent stressor: e.g. abuse, loss of support, routine
    - learned maladaptive behaviour
    - physical illness or pain
    - medication: overmedicated or withdrawal
    - bereavement
    - Non- psychotic psychiatric illness e.g. depression, anxiety, PTSD
    - related to seizures (can include psychotic behaviour)
11. Psychoeducation and rehabilitation- patient and family
12. Psychosocial interventions very important
13. Behaviour Therapy
14. Multidisciplinary team ideal
15. Track treatment progress by defining objective index behaviours and quality of life outcomes

MEDICATION:

- Often inappropriately prescribed without a diagnosis
- Overdosing a big problem - geriatric principles: start very low, go very slow
- Only change one drug at a time
- Patients with mental handicap may have difficulty understanding and complaining about side effects.

SOME SUGGESTIONS:

Neuroleptics

1. Haloperidol: Avoid – akathisia very common
2. Chlorpromazine and Thioridazine may precipitate seizures
3. Clozapine: wcc monitoring may be a problem
4. Risperidone and Olanzapine possibilities on private script

BEWARE SIDE - EFFECTS, espec AKATHISIA

Anti -convulsants:

AVOID: 1.phenobarb: ⇑'s aggression & cognitive dulling
2.Clonazepam: can worsen aggression and disinhibition

Antidepressants:

UNDER USED
TCA's watch s/e and ⇓ing seizure threshold
Fluoxetine: avoid if poor appetite a problem
watch for agitation and akathisia

Benzodiazepines:

AVOID - withdrawal and paradoxical reaction common
Lorazepam can be useful in acute aggressive situation, provided that paradoxical reaction dose not occur

Propanolol: helpful in aggression. Watch for depression long term

If possible, AVOID:

1. **PRN benzodiazepines**
2. **Anticholinergics (- lowest possible dose)**

57. GUIDELINES FOR THE PRESCRIPTION OF PSYCHOTROPICS DURING PREGNANCY AND LACTATION

A. Pregnancy -General Principles

1. MENSTRUAL HISTORY and **L. M. P** vital **prior** to prescription
2. **Preconception counseling is ideal**. Some adverse effects can be prevented [through decreasing dose, stopping or switching medication] or the risks reduced dramatically [administration of folate with carbamazepine and valproate]
3. **There are now 2 patients**. This applies to both pharmacological and psychosocial interventions.
4. **Support, education and ongoing assessment** of the patient and her family is important.
5. Taking medication during pregnancy is a **balance between the risks** and the advantages to both mother and child.
6. The **ideal** for the infant is to avoid all drugs, especially in the first trimester
7. Metabolism changes during pregnancy - doses may need to be reviewed
8. Address **co-morbidity** - especially **substance use.**
9. The **newer the agent the less is generally known about safety**
10. Use the lowest possible dose.

B. Lactation - General Principles:

1. **ALL psychotropics cross** into breast milk, but usually in small amounts
2. There are now **2 patients**
3. Maternal **support and education** important
4. Breast feeding should be **encouraged and facilitated** if at all possible
5. If medication used in pregnancy, try to continue with it unless contraindicated
6. **First 3 months most critical time:** Infant's liver has reduced metabolising capacity for 1st 10-12 weeks.
7. **Risks** much higher in **premature** infants
8. **Avoid** drugs in infants with **organ impairment**
9. Try **nocte** doses to avoid daytime sedation and avoid sedating agents
10. **Lowest** possible dose

PREGNANCY	LACTATION
Antidepressants	
1. **TCA's:** safest **Imipramine** or less sedating agent better.	Safest Watch for sedation
2. **SSRI's:** less data and what is available is variable Most data about **Fluoxetine:** probably safe Long-term behavioral and learning effects unknown	**Fluoxetine:** Jitteriness & diarrhoea in the newborn. Sertraline may be the best
3. **MAOI:** contra- indicated	Contra-indicated
4. **New agents:** little data. Mirtazepine contra-indicated → possible teratogenicity	Little data
Benzodiazepines	
Avoid, especially in the first trimester. initial data suggested an association with cleft lip and palate.- not subsequently supported. High doses peri-partum ⇒ " Floppy Infant Syndrome". Sustained use ⇒ withdrawal symptoms in the newborn.	Sedation and withdrawal potential problems
Mood Stabilisers and Common Anti-Convulsants	
NONE ARE SAFE. Weigh up risks of the drug vs. risk of relapse. *More regular monitoring of levels required* *High resolution ultrasound at 18 weeks preferable*	
1. Lithium: increased incidence of Ebstein's anomaly, but risks less than previously thought. Other adverse effects such as neonatal hypothyroidism and hypotonicity occur rarely. Monthly levels, electrolytes & TSH. More regularly in last trimester. Beware toxicity peripartum. Avoid in first trimester particularly	Avoid in breast feeding & Neonatal renal impairment
2. **Na Valproate**: Avoid. Bad neural tube defects in 1st trimester⇒ folate 5mg/day starting 3 months pre-conception helps prevent.	Safest in breast feeding. Little crosses into breast milk
3. **Carbamazepine:** Avoid. Craniofacial abnormalities and fingernail hypoplasia. Neural tube defects ⇒ 5mg/day folate starting 3 months preconception helps prevent.If used in last 6 weeks of pregnancy, add vit K to avoid bleeding Vitamin K to newborn. Developmental delay.	Careful: about 60% crosses into breast milk
4. **Phenytoin:** Avoid Increased risk of neural tube defects ⇒ 5mg/day folate starting 3months preconception helps prevent. Vitamin K during last 6 weeks. Vitamin K to newborn. Pharmacokinetics may change in pregnancy	Excreted in breast milk but risks are small
Neuroleptics	
Classical agents: Generally safe. No effects on cognition in infant Watch for postural hypotension with low potency	Watch for sedation
New agents: too little data to recommend safely	Too little data to recommend safely

13. GUIDELINES FOR PRESCRIBING IN THE ELDERLY

Principles:

1. Complete Assessment: History, drugs (prescribed, over the counter, alcohol etc), MSE, Mini Mental State Examination, physical examination
2. Beware the 3 D's: Dementia, Depression and Delirium. May occur independently or simultaneously. Often difficult to differentiate.
3. Psychosocial assessment and assessment of activities of daily living are imperative.
4. **The care- giver:** High levels of psychiatric and physical morbidity in caregivers , especially in those of demented patients
5. Presentation often **atypical** : distinguish depression from dementia
6. High completed suicide rate.
7. **Identify losses:** relative or friend, function, occupation.
8. Be alert for signs of elderly abuse.
9. **START VERY LOW, GO VERY SLOW, TITRATE CAREFULLY -** ⇑ ' d sensitivity
10. Co-morbidity: medical illness, substance and OTC drug abuse.
11. Asses level of Renal and Hepatic impairment
12. Medications may be causing, exacerbating the problem
13. Remember **reversible factors** - medical eg thyroid, vitamins, anaemia, insulin dysregulation,constipation, UTI etc
    - psychosocial eg isolation, broken glasses, poor lighting, etc.
14. Careful with drugs causing dizziness and postural hypotension which can cause **falls**.
15. Pre-existing medication: requirements will ⇓ with ⇑ing age
    Never stop benzodiazepines abruptly
16. Watch for toxicity.

a) Depression:
Often presents with somatic symptoms or psuedodementia
Often take longer to respond
Psychotic symptoms common in the elderly

TCA's
Cardiac, anticholinergic, postural side effects and sedation a problem
Secondary amines eg nortryptiline preferable in terms of anticholinergic effects, but expensive
Imipramine 25 mg nocte. Start alternative days if s/e a concern. Increase by 25mg every 5-7 days.
Lofepramine can be tried if imipramine not tolerated

SSRI's:
Most better tolerated but much more expensive
Fluoxetine - agitation, long half life and anorexia can be problems. Start 10mg / day or 20mg every 2-3 days initially.
Citalopram well tolerated - 20mg/day

ECT:
Safe and effective

b) Mood stabilisers:
Avoid carbamazepine.
Lithium or **Valproate** depending on renal and hepatic function. Monitor levels closely. Often need 50% of expected lithium dose.
Both can ⇑ tremor (especially lithium)

c.) Neuroleptics:
1st choice: Very Low dose **haloperidol**. 0.5 -3mg/day - very sensitive to EPSE
Avoid drugs with strong anticholinergic and sedative properties
Others:
Risperidone: 0.5-2mg/day
Olanzapine: 5mg/day in BD dose. Hypotension a problem

d.) Benzodiazepines :
Try and avoid. - confusion, sedation, ⇓short term memory ⇑ falls
If unavoidable, use lowest dose for shortest time possible
Avoid diazepam - long half life
Assess hepatic and renal function
Useful in demented patients who are agitated only 1-2/ month - lorazepam 1mg. NOT REGULARLY
DO NOT write up geriatric patients for prn benzodiazepines

e)Dementia:

1.Assessment in Dementia:

See above guidelines. In addition:

1. Assess: violence and suicide potential
2. Analyse behaviour: **ABC**
   Antecedents
   Behaviour (the nature of the problem)
   Consequences (? inadvertently being reinforced)
3. ? adequate supervision - needs ⇑ as dementia worsens
4. ? driving
5. ? wandering - safety
6. Educate and support caregivers eg ARDA
7. **R's**: Routine (keep things simple), Reassure, Repeat, Remind, Redirect if agitated or upset (avoid confrontation)
8. Attend to legal and financial matters: make a will while still competent. Curators and Power of Attorney
9. Avoid medications for behavioural disturbance if possible. Use above interventions first

2 Behavioural disturbance/ psychotic symptoms:

During the day: **Haloperidol** starting at **0.5mg** daily or BD. ⇑ by 0.5mg increments max 3mg/day
At night: **Thioridazine** 10-25mg nocte is effective and well tolerated

3. Treating cognitive impairment in Alzheimers Disease (not other forms of dementia as yet):

Medication:

Anticholinesterase inhibitors

e.g. **Donepezil:** 5mg daily for 1/12 ⇑ing to 10mg daily.
Rivastigmine: 1.5 – 6mg po BD

- Private script only
- Only effective in some patients with Alzheimers. Regular review of efficacy therefore important. discontinue if no improvement or stabilization after 12-24 weeks
- Very expensive, but may be cost – effective.
- Duration of effect unknown - studies beyond 6 months awaited
- Well- tolerated: flushing, GIT symptoms most common.

Vitamin E: CONTROVERSIAL. Improves function. ? if improves cognition. Adequate versus toxic doses not yet established
Hormone Replacement Therapy: should be advised to all women if no contraindications. Protective for Alzheimers (- at least delays onset), osteoporosis, atherosclerotic disease.

14. USEFUL REFERENCES

1. GENERAL TEXTS

a. American Psychiatric Association Practise Guidelines, AP Press 1996, Washington DC

b. Bazire S. GP Psychotropic Handbook. Second ed. Quay Books, 1998

c. Feldman RS, Meyer JS, Quenzer LT. Principles of Neuropsychopharmocology. Sinauer Assoc 1996.

d. Gary S et al. Clinical Practise Guidelines: Praise and Problems. Journal of Clinical Psychiatry. January 1999, vol 60 no 1.

e. Gibbon, C (ed.): South African Medicines Formulary, Medical Association of South Africa. 1997

f. Isselbacher, K J et al. Harrison's Principles of Internal Medicine, Thirteenth edition. 1994, McGraw-Hill, inc. ISBN 0079111696.

g. Kaplan HI, Sadock BJ: Kaplan and Sadock's Synopsis of Psychiatry: Behavioural Sciences/Clinical Psychiatry. Eighth edn. Lippincott, Williams and Wilkins1998

h. Leonard BE. Fundamentals of Psychopharmocolgy. John Wiley and Sons.1992

i. National Essential Drugs List Committee. South African Standard Treatment Guidelines and Essential Drugs List for Hospital Level 1998. National Department of Health.

j. National Essential Drugs List Committee. South African Standard Treatment Guidelines and Essential Drug List for Primary Health Care 1998. National Department of Health.

k. Perry P J, Alexander B, Liskow BI. Psychotropic Drug Handbook. American Psychiatric Press. 1997.

l. Peter, E M, Talmud J, Informed Prescriber of Psychotropic Medication 1998-1999.

m. Stahl, SM: Essential Psychopharmocology. Neuroscientific Basis and Practical Applications. Cambridge University Press.1996.

n. Taylor D, McConnell D, McConnell H, Kerwin R. The Bethlem & Maudsley NHS Trust 1999 Prescribing Guidelines. Martin Dunitz 1999.

o. Yudofsky SC, Hales RE (eds) American Psychiatric Textbook of Psychiatry. AP Press 1997. Washington DC.

2. ANXIETY DISORDERS

a. American Psychiatric Association Practise Guidelines for the Treatment of Patients with Panic Disorder

b. Barlow DH, Wineze J. DSM Four and Beyond: what is generalised anxiety disorder? Acta Psychiatrica Scandanavia. Suppl 1998.393:23-9

c. Goodman WK. OCD Diagnosis and Treatment. Journal of Clinical Psychiatry 1999, 60 .Suppl 18c, 27-32

d. March JS, Frances A, carpenter D, Kahn D. Expert Consensus Guidelines Series. Treatment of Obsessive-Compulsive Disorder. Journal of Clinical Psychiatry 1997.58 1-80

e. Lader M. Treatment of Anxiety. British Medical Journal, 1994.309: 321-324.

f. Lader, MH. Brand AJ. Interaction of Pharmacological & Psychological Treatment of Anxiety. British Journal of Psychiatry, 1998:34, 42-8

g. Sutherland SM, Davidson JRT. Pharmacotherapy for Post-Traumatic Stress Disorder. Psychiatric clinics of North America 1994.17:409-423

h. Van Vliet IM, Den Boer JA, westenberg HGM: Psychopharmacological Treatment of Social Phobia: a double blind placebo controlled study with fluvoxamine. Psychopharmocolgy 1994.55:517-522.

i. Versiani M, Nardi AE, Mundim FD, et al. Pharmacotherapy of Social Phobia: a controlled study with moclobemide and phenelzine. British Journal of Psychiatry 1992. 161:353-360.

3. **BIPOLAR DISORDER**

a. American Psychiatric Association. Expert Consensus Guideline Series: Treatment of Bipolar Disorder. Journal of Clinical Psychiatry.1996.57:3-88

b. American Psychiatric Association. Practise Guidelines for the Treatment of Patients with Bipolar Disorder. American Journal Of Psychiatry 1994.151.Supplement.

c. Bowden CL. Role of Newer Medications for Bipolar Disorder. Journal of Clinical Psychopharmocology.1996.16:48s-55s

d. Freeman MP, Stoll AL. Mood Stabilizer Combinations: A Review of Safety and Efficacy.American Journal of Psychiatry.1998. 155:12-21

e. Gelenberg AJ, Hopkins HS. Antipsychotics in Bipolar Disorder. Journal of Clinical Psychiatry. 1996 57:49-52.

f. Gershon S, Soares J: Current Therapeutic Profile of Lithium. Archives of General Psychiatry. 1997.54:16-19.

g. Schou M. Forty years of Lithium Treatment. Archives of General Psychiatry 1997.54:9-13.

h. Swann AC. Mixed or Dysphoric Manic States: psychopathology and treatment. Journal of Clinical Psychiatry.1995.56:6-10.

i. Taylor D, Duncan D. Treatment Options for Rapid Cycling Bipolar Affective Disorder. Psychiatric Bulletin.1996.20.601-603

4. **DEPRESSION**

a. American Psychiatric Association. Practise Guidelines for the Treatment for Major Depressive Disorder in Adults. American Journal of Psychiatry.1993.150:1-21

b. Austin MP, Souza FG, Goodwin GM. Lithium Augmentation in Antidepressant-resistant Patients-A Quantitative Analysis. British Journal of Psychiatry.1991, 159:510-514.

c. Gram LF. Drug Therapy: Fluoxetine. New England Journal of Medicine 1994.331:1354-1361.

d. Guscott R, Grof P: The Clinical Meaning of Refractory Depression- A Review for the Clinician. American Journal of Psychiatry. 1991 148:695-704.

e. Haddad P. Newer antidepressants and the Discontinuation Syndrome. Journal of Clinical Psychiatry, 1997, vol 58 (Suppl 7).17-22.

f. Hoptopf M, Lewis G, Normand C. Are SSRI's more Cost- Effective than Tricyclics? British Journal of Psychiatry 1996. 168:404-409

g. Kupfer DJ. Management of Recurrent Depression. Journal of Clinical Psychiatry.1993.54:51-58.

h. Leonard BE. SSRI Differentiation: Pharmacology and Pharmacokinetics. Human Psychopharmocolgy. 1995. 10:s149-s158.

i. Nemeroff CB. Evolutionary Trends in the Pharmacotherapeutic Management of Depression. Journal of Clinical Psychiatry 1994. 55:3-15

j. Taylor DP, Carter R et al. Cytochrome and Psychotropic Drug Interactions. British Journal of Psychiatry 1996. 168: 529-532

k. Zanardi R. Franchini L, Mitchell, S. Discontinuation Symptoms after Treatment with Serotonin re-uptake Inhibitors. Journal of Clinical Psychiatry, 1997, 58, 291-297.

5. SCHIZOPHRENIA

a. Buchanan RW, Buckley PF, Tamminga CA, Schultz SC. Schizophrenia Research: a Biennium of Progress. Proceedings from the Sixth International Congress on Schizophrenia Research. April 12-16 1997. Schizophrenia Bulletin 1998.24:501-518

b. Casey DE. Side-effect profiles of the new antipsychotic agents. Journal of Clinical Psychiatry, 1996, 6: suppl 3,17

c. Conley RR, Tamminga CA, Bartko JJ. et al. Olanzapine compared with Chlorpromazine in Treatment -Resistant schizophrenia. American Journal of Psychiatry, 1996,57:suppl 11

d. Frances A, Doherty J, Kahn D: Treatment of Schizophrenia. The Expert Guideline Series. The Journal of Clinical Psychiatry. 1996.57.supplement.

e. Gerlach J, Peacock L. New antipsychotics: the present status. International Clinical Psychopharmacology. 1995;10: Suppl 3, 39-48.

f. Keith S. Pharmacological Advances in the Treatment of Schizophrenia. New England Journal of Medicine. 1997.337:851-852.

g. Kornhuber MD. Wellner M. Neuroleptic Malignant Syndrome. Current Opinion in Neurology.1994.7:353-357

h. Merder, SR. Management of Treatment Resistant patients with Schizophrenia. Journal of Clinical Psychiatry 1996,6: suppl 3,17.

i. Mojtabai R. Nichlson RA. Carpenter BN. Role of Psychosocial Treatments in the Management of Schizophrenia. A Meta-analytic Review of Controlled Outcome Studies. Schizophrenia Bulletin.1998.24: 569-587.

j. Pacia SV. Devinsky O. Clozapine-Related Seizures: Experience with 5629 patients. Neurology 1994. 44: 2247-2249

k. Penn D. Mueser K. Research Update on the Psychosocial Treatment of Schizophrenia.American Journal of Psychiatry. 1996.169:555-562

l. Rosenheck R et al. Impact of Clozapine on Negative Symptoms and on the Deficit Syndrome in Refractory Schizophrenia. American Journal of Psychiatry 1999.156:88-93.

m. Rosenheck R. Cramer J. Xu W.et al. A comparison of Clozapine and Haloperidol in Hospitalised Patients with Refractory Schizophrenia. The New England Journal of Medicine.1997.337: 809-815.

n. Thompson C. The Use of High Dose Antipsychotic Medication. British Journal of Psychiatry.1994.164.448-458.

o. Weiden P, Aquilla R, Standard J, Atypical antipsychotic drugs and Long-term outcome in Schizophrenia. Journal of Clinical Psychiatry 1996; 57,53060

6. ECT

a. Freeman CP. (ed). The ECT Handbook. The Second Report of the Royal College of Psychiatrists Special Committee on ECT.1995

b. Kellner CH. Nixon DW. Bernstein HJ. ECT-Drug Interactions: a Review. Psychopharmocology Bulletin.1991.27: 595-609.

c. Mukherjee S. Sackheim HA, Schnur DB. Electroconvulsive Therapy of Acute Manic Episodes: A Review of 50 years' Experience. British Journal of Psychiatry 1994. 151:169-176.

7. THE ELDERLY

a. American Psychiatric Association. Practise Guidelines for the Treatment of Patients with Alzheimer's Disease and other Dementias of Late Life. American Journal of Psychiatry.1997.154:May Supplement

b. Cummings JF. Current Perspectives in Alheimer's Disease. Neurology.1998.51:s1-s17.

c. Crossberg GT, Manepalli J. the Older Patient with Psychotic Symptoms. Psychiatric Services.1995.46:55-59

d. McCall WV. Management of Primary Sleep Disorders among Elderly Persons. Psychiatric Services.1995.46.49-54

e. Leibowitz BD et al. Diagnosis and Treatment of Depression in Late Life. Consensus Statement Update. Journal of the American Medical Association, Oct 1997.278:14,1186-90.

f. Small, G W et al. Diagnosis and Treatment of Alzheimers and Related Disorders. Consensus Statement of the American Association of the Geriatric Psychiatry, the Alzheimers Association and the American Geriatric Society. Journal of the American Medical Association, Oct 1997,278:16,1363-71.

g. Smith SL, Sherrill KA, Colenda C. Assessing and Treating Anxiety in Elderly Persons. Psychiatric Services. 1995.46:36-42

7. PREGNANCY AND LACTATION

a. Cohen LS. Rosenbaum JF. (1998). Psychotropic Drug Use During Pregnancy: Weighing the risks. Journal of clinical Psychiatry 1998. 59(Suppl 2) 18-28.

b. Cooper PJ, Murray L. Post Natal Depression. British Medical Journal. 1998.316:1884-1886.

c. Dewi B, Harris P. Harris B. Aspects of Perinatal Psychiatric Illness. British Journal of Psychiatry.1996.169:555-562

d. Weinberg MK. Tronick EZ. The Impact of Maternal Psychiatric Illness on Infant Development. Journal of Clinical Psychiatry. 59 (suppl 2). 53-61.

e. Wisner KL. James MP. Findling RL. Antidepressant Treatment during Breast-Feeding. American Journal of Psychiatry, September 1996. 1132-1136

8. CO-MORBID MEDICAL ILLNESS

1. GENERAL TEXTS

a. Yudofsky SC. Hales RE (eds) American Psychiatric press Textbook of Neuropsychiatry. 1997 AP Press. Washington DC.

2. HIV/AIDS

a. APA Commission on AIDS. Policy Guidelines on the Recognition and Management of HIV-related Neuropsychiatric Findings and Associated Impairments

b. Kieburtz K, Zettlemaier AE et al. Manic Syndrome in AIDS. American Journal of Psychiatry.1991.148.1068-1070

c. Levy JK. Fernandez F. Neuropsychiatric Aspects of HIV infection of the Central Nervous System. In APA press Textbook of Neuropsychiatry 1997. (Yudofsky, SC and Hales RE eds)

d. Jefferson JW. Possible Risks associated with Valproate Treatment of AIDS-related Mania. Journal of Clinical Psychiatry. June 1998

3. EPILEPSY

a. Lowenstein DH. Alldredge BK: Status Epilepticus. New England Journal of Psychiatry. 1998. 338:970-977

b. Mattson, RH. Medical Management of Epilepsy in adults. Neurology. Nov 1998,51:5. Suppl4,s15-20

9. PATIENTS WITH MENTAL HANDICAP

a. Kalachnik VE et al. Guidelines for the Use of Psychotropic Medication in: Psychotropic Medications and Developmental Disabilities. The International consensus Handbook. Reiss A, Amon MG (eds) Ohio State University Press.1998.45-72

b. Baumaiester AA, Servin JA, King BH. Neuroleptics in Psychotropic Medications and Developmental Disabilities. The International consensus Handbook. Reiss A, Amon MG (eds) Ohio State University Press.1998.45-72