وزارة الصحة
Ministry of Health

MOH Protocols for the Management of Patients with SCHIZOPHRENIA and BIPOLAR Affective Disorder

December 2021 | Version 1

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ACKNOWLEDGEMENT

Since the establishment of Al Amal complex for mental health as a major and teaching hospital our vision is to provide the best services for our patients in mental health field.

We believe such vision to be fulfilled it requires great effort to currently improve and update the medical resources and knowledge of our medical staff.

This book is a humble effort of elite group of consultant psychiatrists in psychiatry department that serve as one of our efforts in the context of our vision.

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- **Introduction**

Schizophrenia and BAD are two major psychiatric disorders, they contribute the great percentage of patients admitted at psychiatric hospitals in KSA & worldwide.

Their chronic disabling symptoms cause considerable burden not only to sufferers but also to their families, and contribute to poorer quality of life and considerable economic burden on society.

In many instances, there is a delay in seeking treatment and in some cases such delay may stretch up to nearly ten years.

This may result from ignorance of the condition, fear of taking medications, and the stigma of receiving a psychiatric diagnosis, and or having to accept psychiatric treatment

There are a lot of schools and guidelines dealing with the treatment of both disorders, in order to find more or less common protocols for treatment of these disorders and our need for national guidelines to deal with this disorder in proper practice way, and also to improve the outcome of such disorders, with an initiative of the Ministry of Health of the Kingdom of Saudi Arabia, a multidisciplinary expert panel of psychiatrists and pharmacists with practice experience in the clinical management of Schizophrenia and BAD disorders where invited to be part of work group to update the previous practical guidelines on biological treatment of these disorders.

Management of Schizophrenia and BAD in daily clinical practice is highly variable as there are many issues that are still debated and not definitely addressed by evidence-based medicine. Biologic therapy is now a well-established strategy for Schizophrenia and BAD.

The recommendations were developed after rigorous evaluation of existing international guidelines as well as the latest emerging evidence.

A. Abbreviations Used

ECG: Electrocardiogram.

SGAs: Second Generation antipsychotic.

FGAs: First Generation antipsychotic.

Eps: Extrapyramidal symptoms.

LAI: Long acting injection.

I.M: Intramuscular.

CBC: Complete Blood Count.

WBC: White Blood Count.

ANC: Absolute Neutrophil Count.

CBT: Cognitive Behavioral Therapy.

NMS: Neuroleptic Malignant Syndrome.

BAD: Bipolar Affective Disorder.

NOS: Not elsewhere classified.

RCT: Randomized Control Trial.

TAU: Treatment as Usual.

IPSRT: Interpersonal and Social Rhythm Therapy.

Li: Lithium.

DVP: Divalproex.

ER, XR: Extended Release.

MAOI: Monoamine Oxidase Inhibitors.

TCA: Tricyclic Antidepressant.

SSRI: Selective Serotonin Reuptake Inhibitors.

STEP-SD: Systematic Treatment Enhancement.

FFT: Family Focus Therapy.

MADRS: Asberg Depression Rating Scale.

NAC: N-Acetyl Cysteine.

PT: Prothrombin Time.

CANMAT: Canadian Clinical Practice Guidelines.

B. Purpose

Our purpose is to improve the outcome in the treatment practice for Schizophrenia and BAD by delivering an update guidelines to the hands of psychiatrists in KSA.

These protocols have been developed to guide medical practitioners for the use of the most effective available treatments for schizophrenia and bipolar disorders in the in-patient and out- patient settings and serve as a framework for clinical decisions and supporting best practices.

The overall aim of these protocols is to establish evidence based recommendations on the use and application of biological therapy for Schizophrenia and BAD, these protocols also address the use of biological therapy in special and problematic medical conditions.

These protocols are developed to provide practical, evidence-based recommendations to primary care physicians and specialists in psychiatry for the management of Schizophrenia and BAD disorders. We have omitted treatments that are currently not available in Saudi Arabia.

There is a clear need for national guidelines due to the extended role and high availability of literature on these agents.

C. Aim & Scope

These protocols are developed to facilitate the assessment of the disorders, and to ensure that their management is appropriate and effective.

These protocols will cover the management of disorders in adults and address the issues of medication use during pregnancy and breastfeeding.

The overall aim of these protocols is to deliver evidence-based recommendations on the use, screening, and monitoring of biologic therapy in patients with Schizophrenia and BAD. These protocols also aim to propose updated decision-making algorithms for practitioners involved in the treatment of these patients and consideration is given to special patient population.

D. PRESCRIBERS OF BIOLOGIC THERAPY

Biologic therapies should be prescribed by psychiatrists with extensive clinical experience in the treatment of schizophrenia and BD with systemic agents, considering that use of these therapies requires appropriate patient selection and follow up.

E. TREATMENT GOALS

Before starting biologic therapy, it is preferable to define treatment goals for each patient. Psychometric assessment tools are recommended for use in daily practice in order to establish and monitor the achievement of treatment goals and guide therapy.

F. Targeted Population

The content of the protocols will be useful for all doctors treating patients with schizophrenia and BD disorders. Efforts have been made to ensure that the guidelines are particularly useful for primary care physicians and specialists in psychiatry, the doctor treating the patient is ultimately responsible for clinical decisions made after reviewing the individual patient's history, clinical presentation and treatment options available.

G. End Users

Psychiatry Consultants, Specialists and Residents, primary care physicians, Psychiatry clinical pharmacists, Pharmacists, Nurses.

Primary Care Physicians Role:

1- initially, primary care physician assess the case for mental health disorders, if he provisionally diagnoses the case with schizophrenia or bipolar disorder he should refer the case to specialized psychiatry clinic.

2- After the case of schizophrenia or bipolar disorder has been stabilized, and proper care was provided by the treating psychiatrist, who can refer back the case to primary care physician for regular follow up and continuing the psychiatric Management plan.

3- During follow up of a Known case schizophrenic or bipolar disorders in the primary care clinic, once the case showed any signs or symptoms of disorder relapse or any safety issues (e.g. suicidality or homicidally), primary care physician should refer the case to specialized psychiatry clinic for stabilization and management.

4- primary care physician should commit to this guideline in regard to all steps of assessment, Management, prescription of psychotropic medications and required routine investigations.

H. Setup

The primary care units, in-patient and outpatient settings and serve as a framework for clinical decisions and supporting best practices.

I. Setting

- Eradah Complex / Hospital and Mental Health.
- Psychiatric clinics in MOH General Hospitals.

J. Methodology

These protocols have been produced by a committee of psychiatrists, a clinical psychologist, pharmacist, patient representative, and family practitioners appointed by the Ministry of Health. They were developed by revising the existing protocols, reviewing relevant literature, including overseas clinical practice guidelines and by expert clinical consensus of professionals with experience in treating patients in the local setting.

The following principles underlie the development of these protocols: Treatment recommendations are supported by scientific evidence whenever possible (randomized controlled clinical trials represent the highest level of evidence) and expert clinical consensus is used when such data are lacking. Treatment should maximize therapeutic benefits and minimize side effects.

We agree on these reviews with more than 75% of the members' votes, In the event of a disagreement, the reviews should be worked on again until an agreement is reached that exceeds this percentage.

Team members reviewed this protocol in several sessions for editing, updating, improving, reviewing, taking expert opinions, and annual updating if any changes or updates released by international/national guidelines.

Policies-procedures and an agreement form should be developed by hospital according to hospital quality standers.

The multidisciplinary work group was made up of expert psychiatrists and pharmacists. Published protocols concerning the treatment of Schizophrenia and BAD were evaluated using the Appraisal of Guidelines, Research and Evaluation II (AGREE II) scale. The guidelines found to meet the criteria for use for our patients are: The NICE Guidelines, American psychiatric Association, The Maudsely Guidelines, the Canadian Guidelines plus a lot of evidence based scientific researches

Formal consensus methodology was adopted to reach consensus on specific items. The consensus statements are based on the best available evidence and their development followed a standardized process. A statement was regarded as consented when agreement was achieved by at least 75% of the voting experts. The strength of recommendation was not expressed.

K. Updating

This edition of the protocols contains updated recommendations based on latest evidence, as well as detailed discussions and recommendations on the management of schizophrenia and BD disorders in adult populations.

Review of protocols Evidence-based clinical practice protocols are only as current as the evidence that supports them. Users must keep in mind that new evidence could supersede recommendations in these protocols. The workgroup advises that these protocols be scheduled for review five years after publication, or when new evidence appears that requires substantive changes to the present recommendations.

Updates of the present protocols will be provided as needed to incorporate new data or agents.

L. Conflict of Interest

This protocol developed based on valid scientific evidence, critical assessment of that evidence, and objective clinical judgment that relates the evidence to the needs of practitioners and patients. No financial relationships with pharmaceutical, medical device, and biotechnology companies.

M. Funding

No fund was provided.

N. Targeted end users

- Psychiatry and Addiction Medicine Consultants, Specialists and Residents
- Nurses
- Psychiatry clinical pharmacists
- Pharmacists

O. DISCLAIMER

Clinical practice Protocols are evidence-based decision-making tools for managing health conditions. They are based on the best information available at the time of writing, and are to be updated regularly. The present guidelines are not meant to serve as strict treatment guidelines. They are also not intended to replace clinical judgement of practicing physicians but are only tools to help manage patients who require biologic treatment for Schizophrenia and BAD. Decisions concerning treatment must always be taken on a case-by-case basis and the prescribing physicians need to personalize care and tailor the treatment regimen to patients' personal circumstances and medical history.

Physicians should also consult the approved product monographs within their institution's formulary for each drug for dosage, special warnings and precautions for use, contraindications, and monitoring of side effects and potential harms. Institution formulary restrictions may also need to be considered when selecting treatment options. Prescribing physicians should refer to their institution's formularies during the decision- making process for choosing specific agents within a recommended specific class.

P. Preface

It is of my great pleasure and honor to present Eradah Psychiatric Complex's first booklet specialized in management protocols of Schizophrenia and Bipolar disorders. And it is of utmost importance to keep it updated with the latest medical treatment protocols for such mental disorders, which form burdens on not only patients but also their families. This booklet comprises comprehensive guidelines of most medical procedures and protocols, which have been collected from a variety of trusted international periodicals, for these conditions.

In addition, we will make sure that this publication gets updated with the latest globally available on the topic in the following copies. We have provided the handbook with the most famous rating scales of Schizophrenia and Bipolar disorders, which concern all of those specializing in Psychiatry in helping to determine the severity of the conditions and the effectiveness of treatment.

Not to forget our endless gratitude to Dr. Khaled Saad Sherra, Dr. Samia Abdulrahman, and Dr. Dalia Mokhtar for their great efforts in elaborating and piecing together this very influential work.

Hoping that Allah may benefit with this work all those working in the Psychiatric field and that it may lay the groundwork for many publications and periodicals to follow from Eradah Complex for Mental Health at Riyadh.

Declaring that Allah's behind our intentions.

Dr. Mohamed M. Al Qahtani

Executive Director of Eradah Complex for Mental Health at Riyadh

Q. Preface

This protocol has been developed after a comprehensive review of the most updated international guidelines to provide the evidence-based recommendation for the most common Psychiatric Disorders for the purpose of improving the quality of services given to our patients.

It is not intended to serve as a Standard of Medical Care. Adherence to it will not ensure successful outcome for every individual, nor should it be interpreted as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. It should not replace the best of the psychiatrist judgment.

The protocol is composed of 3 chapters (Schizophrenia Management, Bipolar Disorder Management and Assessment by Standardized Rating Scales) with the future plan to include more chapters of the most major psychiatric disorders that of clinical importance to the psychiatrist.

Acknowledging the rapid advancement of the scientific knowledge, this protocol will be updated every 2 years.

Committee Monist

• Chapter 1 (Schizophrenia)

A. Introduction

Schizophrenia is a relatively common mental illness with a life time risk approaching one percent, it represents a major psychiatric dis- order in which a person's perception, thought mood and behavior are significantly altered, and symptoms are usually divided into positive symptoms including hallucination and delusions and negative symptoms. Each person will have a unique combination of symptoms and experiences. The first symptoms tend to start in young adulthood, at the time when a person usually make a transition to independent living, but can occur at any age. The symptoms and behavior associated with psychosis can have a distressing impact on the individual, family and friends.

Clinical practice guidelines have been defined as systematically developed statements based on evidence based recommendations for patient management to assist practitioner and patient in decision about appropriate health care for specific situation. The aim of these guidelines is to improve the assessment and treatment of patient with schizophrenia at all stages of the illness.

This management protocol for schizophrenia was prepared after re- viewing the current standard guidelines being followed worldwide. The Algorithm for Pharmacological and Psychosocial treatment is formulated after cross – comparison across four different guidelines. Based on the current status of the evidence some of the recommendation have been combined to form a unified guidelines for management that specify 4 main topics, each of which a physician must consider when seeing a patient. Assessment, pharmacotherapy, psychosocial intervention and delivery of services. Within each of the first 3 topics, 3 phases of the illness are distinguished:

- The Acute Phase, where signs and symptoms worsen, usually bringing the patient to medical attention.
- The Stabilization Phase, where in the illness is subsiding after on a acute episode.
- The Stable or Chronic Phase, wherein acute symptoms may have subsided but functioning is often persistently impaired.

The emphasis of this protocol is on practical issues rather than theoretical knowledge, and pertinent on most important clinical problems that face mental health practitioners who deal with adult schizophrenic patients.

B. GENERAL PSYCHIATRIC MANAGEMENT

Includes the following:

- Assessing symptoms and establishing diagnosis.
- Developing a plan of treatment.
- Developing a therapeutic alliance and promoting treatment adherence.
- Providing patient and family education and therapy.
- Treating comorbid condition.
- Attending to patient social circumstances and functioning.
- Integrating treatment from multiple clinicians.
- Documenting treatment.

Assessment before starting Antipsychotic Medication

- Undertake and record the following baseline investigation.
  - Weight (plotted on chart)
  - Waist circumference
  - Pulse and blood pressure
  - Fasting glucose, glycosylated haemoglobin (HBA1C), blood lipid profile and Prolactin level.
  - Assessment of any movement disorder.
  - Assessment of nutritional status, diet and level of physical activity
  - Electrocardiogram (ECG) if there is history of cardiovascular disease or a physical examination has identified specific cardiovascular risk (Hypotension) or for an inpatient.

Monitoring Throughout Antipsychotic Treatment

- Response to treatment including change in symptoms and behaviour.
- Side effects of treatment.
- The Emergence of movement disorder.
- Weight, weekly for the first 6 weeks, then at 12 weeks, at 1 year and then Annually (Plotted on a chart)

- Waist circumference annually (Plotted on a chart)
- Fasting blood glucose, HbA1c, blood lipid level at 12 weeks and one years and then annually.
- Pulse, blood pressure at 12 weeks at 1 year then Annually
- Adherence.
- Overall Physical Health.

C. ACUTE TREATMENT FOR FIRST PSYCHOTIC EPISODE OF SCHIZOPHRENIA

Treatment Goals

- To prevent harm, control disturbed behaviour, and reduce severity of psychosis associated symptoms (e.g. Agitation, Aggression, Affective Symptoms)
- To determine and address the factors that led to the occurrence of the acute episode
- Rapid return to the best level of functioning.
- To develop alliance with the patient and family.
- To formulate short and long term management plan.
- To connect the patient with appropriate after care in the community.

Acute Phase

- Treatment with Antipsychotic medication is indicated.
- Second Generation (SGAs) / First Generation (FGAs)
- Clinical observation during the first two weeks is vital for the following:
- Efficacy including change in symptoms and behaviour.
- Side effects of treatment, taking into account overlap be-
- Tween certain side effect and clinical features of Schizophrenia, for example the overlap between akathisia and agitation or anxiety.
- Physical Health
- Recognized rating scales should be used to monitor change.
- Titrate and adjust the dose according to response and tolerability
- Assess over 2 – 3 weeks.

- Where there is no response at 2 – 3 weeks treatment should be changed (switch drug or increase the dose).
- Where there is some response, staying, switching and augmenting appear to be equal even though modestly effective.
- Carry on a trial of medication at optimum dosage for 4 -6 weeks.
- Offer Clozapine to people with Schizophrenia.

Whose illness has not responded adequately to treatment despite the sequential use of adequate doses at least two different Antipsychotic drugs. At least one of the drugs should be a non– clozapine second generation antipsychotic.

Stabilization Phase

- Antipsychotic should be continued for 1 – 2 years after the first Episode.
- Those who made functional recovery may be considered candidate for a trial of no medication.
- Withdrawal of Antipsychotic Medications should be done slowly over 6 – 12 months.
- Patient who were ill for an extended period before initial treatment and or have history of violent or suicidal behaviour may require more extended period.
- 80 % of first Episode are at high risk of a second episode within the first 2 – 5 years.

Stable Phase

- Duration of treatment is 2 years for the first episode.
- 5 – 10 years is for 2 or more episodes.
- Life time treatment for multiple episodes or more than two episodes in 5 years.
- A minimum of 5 years of stability without relapse should be
- Observed before slow withdrawal of antipsychotics over 6 – 24 months.

Questions to consider before reducing the dose of maintenance Antipsychotic treatment

- Is the patient symptoms free, and if so for how long? Long standing, non-distressing symptoms which have not previously been responsive to medication maybe excluded.
- What is the severity of the side effects (EPS, Tardive Dyskinesia, obesity, etc.)?
- What is the previous pattern of illness? Consider the speed of
- Onset, duration and severity of episodes and any danger posed to self or others.
- Has dosage reduction been attempted before? If so what was the outcome?
- What are the patient current social circumstances? Is a period of relative stability or are stressful life events anticipated?
- What is the social cost of relapse (e.g. is the patient the sole bread winner for a family)?
- Is the patient able to monitor his/her own symptoms? If so, will he/she seek help?

D. PSYCHOSOCIAL INTERVENTIONS

In the Acute Phase

- Aimed at reducing over stimulating or stressful relationships, life events and promoting relaxation or reduce arousal through simple clear, coherent communication with structured and predictable environment with tolerant non – demanding supportive relationship with the psychiatrist and other member of the treatment team.
- Engagement of the patient and patient's family member in a collaborative treatment relationship.
- Educational meeting to the family members.

In stabilization Phase

- Aimed at sustaining symptoms remission or control, minimize stress on the patient, provide support to minimize the likelihood of relapse, enhance the patient adaptation to live.
- In the community, facilitate the continued reduction in symptoms and consolidation of remission and promote the process of recovery.
- Psychotherapeutic intervention remains supportive but may be less structured and directive than in the acute phase.

In Stable Phase

- For most persons with schizophrenia in the stable phase, treatment program that combine medication with a range of psychosocial services are associated with improved outcomes.
- The selection of appropriate and effective psychosocial treatments needs to be driven by the circumstances of the individual patient's medication and his or her social context.
- Major goals of psychosocial treatment are:
  1. Prevention of relapse and reduction of symptoms severity.
  2. Reduction of negative symptoms.
  3. Improving functional status and quality of life.
  4. Patient and self- help treatment organization.
- A Number of Psychosocial Treatment have Demonstrated effectiveness. The treatment includes:
  1. Family Interventions.
  2. Supported Employment.
  3. Assertive community treatment.
  4. Social skill training.
  5. Cognitive behaviourally oriented psychotherapy.

E. High – dose Antipsychotic: Prescribing and Monitoring

High dose can result from the prescribing of either:

- A single antipsychotic in a dose that is above the recommended maximum or two or more antipsychotics that when expressed as a percentage of

their respective maximum recommended doses and added together result in a cumulative dose of

- More than 100%.
- Regarding efficacy, there is no firm evidence that high doses of antipsychotics are any more effective than standard doses.
- The majority of side-effects associated with antipsychotic treatment are dose related. These include, EPS, sedation, postural hypotension, anticholinergic effects, QTC prolongation and sudden death.

Before using high- dose antipsychotics, ensure that:

- Sufficient time has been allowed for response.
- At last two different antipsychotics have been tried sequentially (one first generation and if possible olanzapine)
- Clozapine has failed or not been tolerated due to agranulocytosis or other serious adverse effect, most other side effects can be managed, a very small proportion of patients may also refuse clozapine outright.
- Compliance is not in doubt.
- Adjunction medication such as antidepressants, or mood stabilizer are not indicated.
- Psychological approaches have failed or are not appropriate.

Process:

- Rule out contraindications (ECG abnormalities, hepatic impairment).
- Consider and minimize any risks by concomitant medication (e.g., potential to cause QTC prolongation, electrolyte disturbance or pharmacokinetic intervention via CYP inhibition).
- Document the decision to prescribe high doses in the clinical notes along with a description to the target symptoms. The use of appropriate scale is advised.
- Physical monitoring should be carried out.
- All patients on high doses should have regular ECGs (baseline, when steady-state serum levels have been reached after each dosage increment, and then every 6-12 months).

- Target symptoms should be assessed after 6 weeks and 3 months if insufficient improvement in these symptoms has occurred, the dose should be decreased to the normal range.

Prescribing combined antipsychotics

- There is no good objective evidence that combined antipsychotics (That do not include clozapine) offer any efficacy advantage over a single antipsychotic.
- It has been shown that co-prescribed aripiprazole reduces weight in those given clozapine and normalizes proactive in those on haloperidol and risperidone long acting injection (although not amisulpride). But no regulatory trials demonstrating safety.
- There is substantial evidence to support the potential for harm. Therefore, the use of combined antipsychotic should be avoided.
- As minimum requirement, all patients who are on combined antipsychotics drugs should have their side-effects systematically assessed (including ECG monitoring) and any beneficial effect on symptoms carefully documented.

F. Strategies for Inadequate Response

- Review diagnosis.
- Explore adherence.
- Rule out substance abuse.

The 4 main Pharmacological Strategies

- Optimization
- Substitution
- Augmentation
- Combination

20 % of multiple Episodes have no response.

30 % Respond Partially.

G. Switching Antipsychotic Drugs because of Poor Tolerability

General Recommendations for switching antipsychotic drugs

Adverse Effect	Suggested drugs	Alternative
Acute EPS	Aripiprazole Olanzapine Quetiapine	Clozapine
Dyslipidemia	Amisulpride Aripiprazole	
Impaired Glucose Tolerance	Amisulpride Aripiprazole	Risperidone Haloperidol
Hyperprolactinemia	Aripiprazole Quetiapine	Clozapine Olanzapine
Postural hypotension	Amisulpride Aripiprazole	Haloperidol Sulpiride Trifluphenazine
QT Prolongation	Aripiprazole Paliperidone (with ECG monitoring)	Low dose Monotherapy of any drug not formally contra indicated (with ECG monitoring)
Sedation	Amisulpride Aripiprazole Risperidone Sulpiride	Haloperidol Trifluphenazine
Sexual Dysfunction	Aripiprazole Quetiapine	Clozapine
Tardive Dyskinesia	Clozapine	Aripiprazole Olanzapine Quetiapine
Weight Gain	Amisulpride Aripiprazole Haloperidol	Trifluphenazine

* There is evidence that both switching to and co-prescription of aripiprazole are effective in reducing weight, prolactin and dyslipidemia and in reversing impaired glucose tolerance.

ECG, electrocardiogram; EPS, extrapyramidal side-effects.

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H. Equivalent Doses of Conventional Antipsychotic Drugs

Antipsychotic	Equivalent Dose (Consensus)	Range of Values in Literature
Chlorpromazine	100 mg / day	-
Flupenthixol	3 mg / day	2 – 3 mg day
Flupenthixol Depot	10 mg / week	10 – 20 mg / week
Fluphenazine	2 mg / day	2 – 5 mg / week
Fluphenazine Depot	5 mg / week	1 – 12.5 mg / week
Haloperidol	2 mg / day	1.5 – 5 mg / day
Haloperidol Depot	15 mg / week	5 – 25 mg / week
Sulpride	200 mg / day	200 – 300 mg/day
Trifluperazine	5 mg / day	2.5 – 5 mg/ day
Zuclopenthixol	25 mg / day	25 – 60 mg/day
Zuclopenthixol Depot	100 mg / day	40 – 100 mg/week

I. Second Generation Antipsychotics Equivalent Doses

Drug	Approximate equivalent dose (per day, unless stated)
Aripiprazole	10 mg
Olanzapine	7.5-10 mg
Paliperidone palmitate	75 mg/month
Quetiapine	300 mg
Risperidone oral	3 mg
Risperidone LAI	37.5 mg/2 weeks

Comparing potencies of FGAs with SGAs introduces yet more uncertainty in respect to dose equivalence. Very approximately, 100mg chlorpromazine is equivalent to 1.5mg risperidone.

J. Minimum effective Doses

K. Drug	First episode	Multi-episode
FGAs		
Chlorpromazine	200 mg*	300 mg
Haloperidol	2 mg	4 mg
Sulpride	400 mg*	800 mg
Trifluperazine	10 mg*	15 mg
SGAs		
Amisulpride	400 mg*	unclear ?400 mg
Aripiprazole	10 mg	10 mg
Olanzapine	5 mg	7.5 mg
Quetiapine	150 mg*	300 mg
Risperidone	2 mg	3 mg

* Estimate - too few data available.

FGA, first-generation antipsychotic; SGA, second-generation antipsychotic.

L. Antipsychotic Drugs: Licensed Maximum Dose

Antipsychotic Drugs	Maximum dose (mg)
First Generation – Oral	Daily
- Chlorpromazine	1000 mg
- Flupenthixol	18 mg
- Haloperidol	20 mg
- Perphenazine	24 mg
- Pimozide	20 mg
- Sulpride	2400 mg
Trifluperazine	None (suggest 30 mg / day)
- Zuclophenthixol	150 mg / day
Second Generation – Oral	Daily
- Amisulpride	1200 mg
- Aripiprazole	30 mg
- Clozapine	900 mg
- Olanzapine	20 mg
- Paliperidone	12 mg
- Quetiapine	750 – 800 (see BNF)
- Risperidone	16 (see BNF)
Depots	
- Flupenthixol depot	400 mg / month
- Fluphenazine depot	50 mg / week
- Haloperidol depot	300 mg every 4 weeks (see BNF)
- Risperidone	50 mg / 2 week
- Zuclopenthixol depot	600 mg / week
- Paliperidone depot	150 mg / month

M. USE OF ECT IN SCHIZOPHRENIA

In Acute Phase

- ECT in combination with antipsychotic is considered in the following situations:
  1. Severe psychotic symptoms that have not responded to treatment with antipsychotic agents, a trial of clozapine will generally be indicated before acute treatment with E.C.T.
  2. E.C.T. should be considered for patient with prominent catatonic features that have not responded to an acute trial of Lorazepam.
  3. For patient with schizophrenia and co-morbid depression.
  4. ECT may be beneficial if depressive symptoms are resistant to treatment or if features such as suicidal ideation and behaviours or inanition which necessitate a rapid therapeutic response are present.

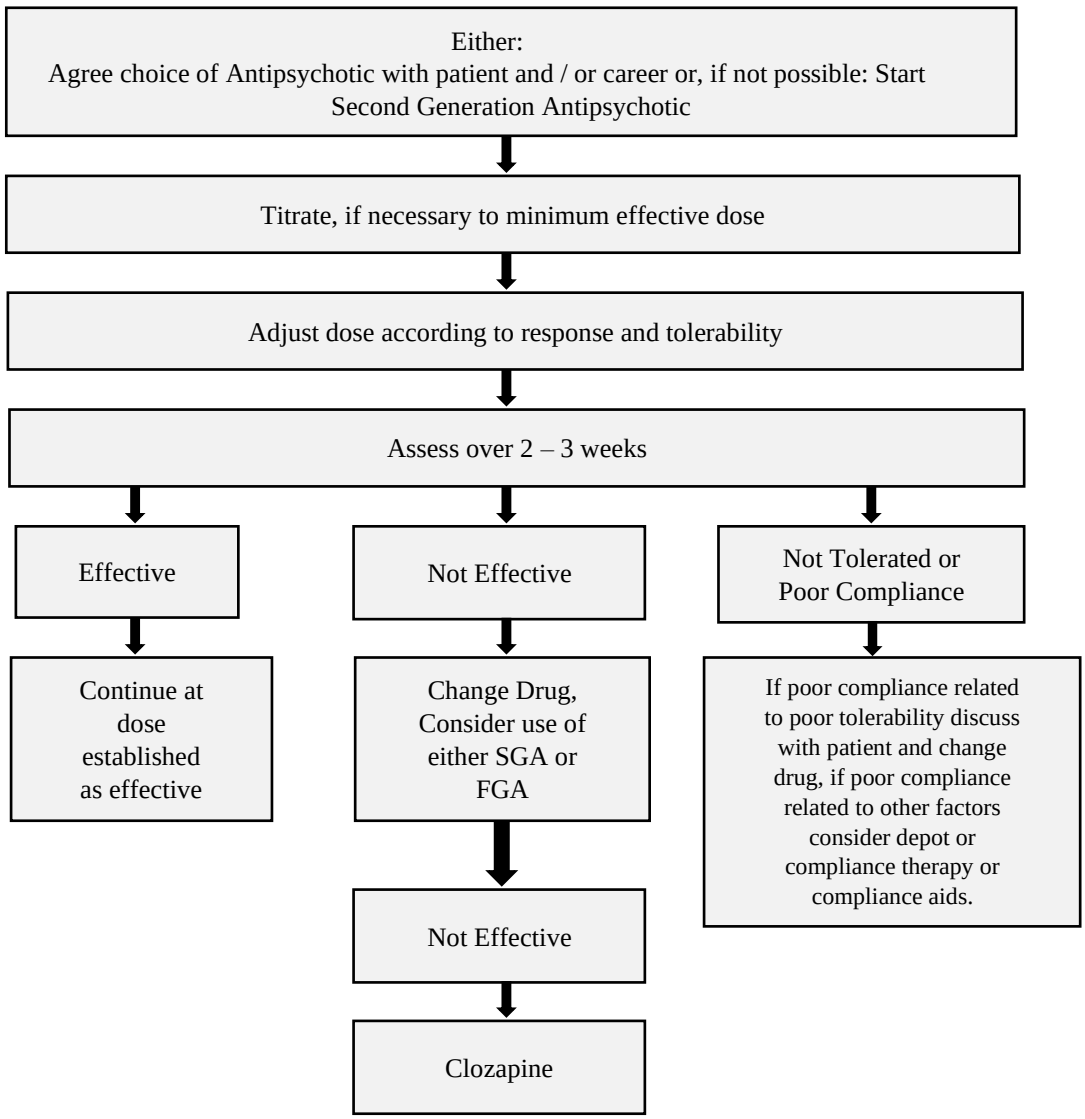
N. RECOMMENDATION FOR THE MANAGEMENT OF NEGATIVE SYMPTOMS OF SCHIZOPHRENIA

- Psychotic illness should be identified and treated as early as possible as this may offer some protection against the development of negative symptoms.
- For any given patients, the antipsychotic that gives the best balance between overall efficacy and side effects should be used.
- Where negative symptoms persist beyond the acute episode of psychosis.
- Ensure EPS (especially Bradykinesia) and depression are detected and treated if present and consider the contribution of the environment to negative symptoms (e.g. Institutionalization, lack of stimulation).
- Consider Augmentation of Antipsychotic treatment with an Antidepressant such as SSRI, ensuring that choice is based on minimizing the potential for compounding side effect through pharmacokinetic or pharmacodynamics drug
- Interactions.
- If clozapine is prescribed, consider augmentation with Lamotrigine or a suitable second antipsychotic.

- There are insufficient data to make recommendation about other pharmacological strategies, but prednisolone, Minocycline, Selegiline, Ginkgo biloba, testosterone and ondansetron may have potential.

O. TREATMENT ALGORITHMS FOR SCHIZOPHRENIA

Treatment for first episode of Schizophrenia



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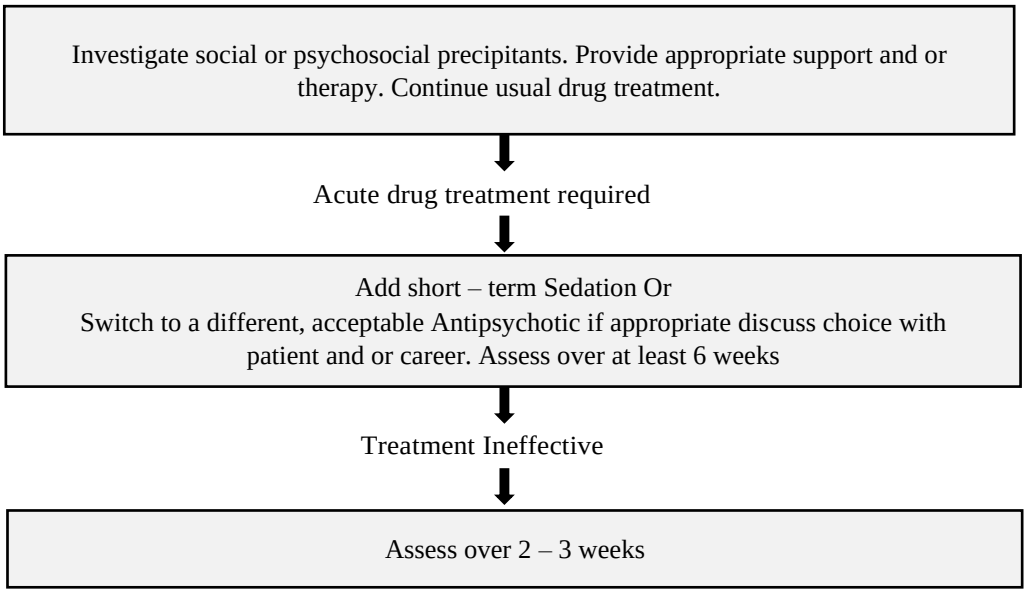
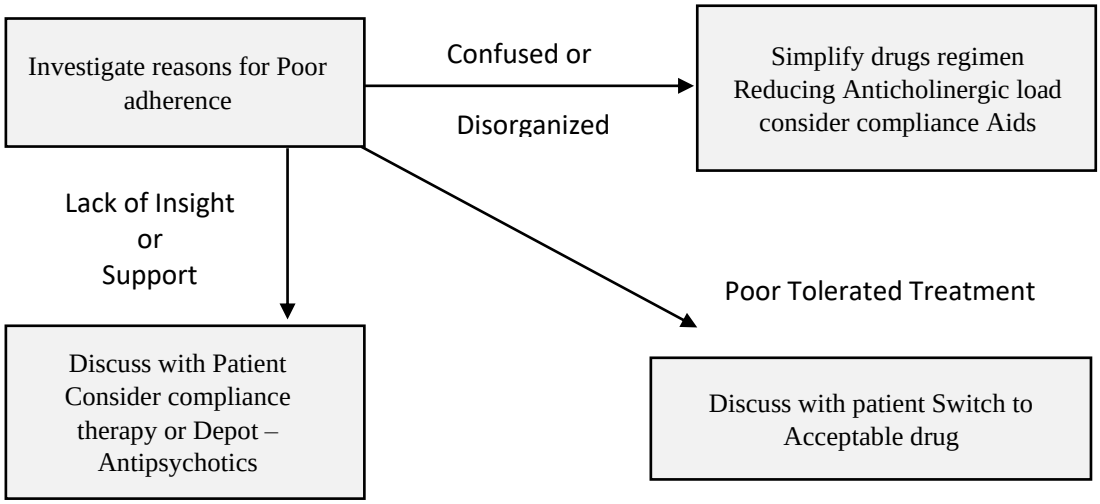
Treatment for Relapse or Acute Exacerbation of Schizophrenia (Full Adherence to Medication Confirmed)



Treatment for Relapse or Acute Exacerbation of Schizophrenia (Adherence Doubtful or Known to be Poor)



P. ADVICE ON PRESCRIBING LONG ACTING INJECTABLE ANTIPSYCHOTICS

- For FGAs, give a test dose – because FGAs are long acting any adverse effect that result from injection are likely to be long – lived. A test dose consisting of a small dose of active drugs in a small volume of oil serves a dual purpose: It is a test of the patient sensitivity to EPS and will reveal any sensitivity to the base oil. For SGAs, test dose is not required.
- Begin with the lowest therapeutic dose.
- Administer at the longest possible licensed interval. All LAIs, can be safely administered at their licensed dosing intervals, bearing in mind the maximum recommended single dose. There is no evidence to suggest that shortening the dose intervals improves efficacy. Moreover, injection is painful, so less frequent administration is desirable. The observation that some patient deteriorate in the days before the next dose is not supported by facts. In trial, relapse seemed to occur 3 – 6 months after withdrawing therapy.
- Adjust doses only after adequate period of assessment
- Depot preparations are not recommended for those who are antipsychotic – naïve.

Antipsychotic LAIs: Suggested doses and frequencies

Drug	Licensed injection site	Test dose (mg)	Dose range (mg/week)	Dose interval (weeks)	comments
Flupentixol decanoate	Buttock or thigh	20	50 mg every 4 weeks to 400mg a week	2-4	Maximum licensed dose is very high relative to other LAIs
Fluphenazine decanoate	Gluteal region	12.5	12.5mg every 2 weeks to 100 mg every 2 weeks	2-5	High EPS
Haloperidol decanoate	Gluteal region	25	50-300 mg every 4 weeks	4	High EPS
Paliperidone Palmitate	Deltoid or gluteal	Not Required	50-150 mg monthly	Monthly	Loading dose required at treatment initiation
Risperidone microspheres	Deltoid or gluteal	Not Required	25-50 mg every 2 weeks	2	Drug release delayed for 2-3 weeks
Zuclopenthixol	Buttock or thigh	100	200 mg every 3 weeks to 600mg a week	2-4	? Slightly better efficacy than some FGAs

Reducing dose of depots

Questions to consider before reducing the dose of maintenance of antipsychotic treatment:

- Are the patient symptoms free and if so, for how long? Long standing, non-distressing symptoms which have not previously been responsive to medication may be excluded.
- What is the severity of the side-effect (EPS – Tardive dyskinesia, obesity, etc…)?
- What is the previous pattern of illness (consider the speed of onset, duration and severity of episodes and any danger posed to self or others)?
- What are the patient's current social circumstances? Is it period of relative stability or are stressful life event anticipated?
- What is the social cost of the relapse (e.g., is the patient the sole breadwinner for a family?)

- Is the patient able to monitor his/her own symptoms? If so, will he/she seek help?
- After consideration of the above, the decision is taken to reduce medication dose, the patient's family should be involved.
- If it has not already been done. Oral antipsychotic medication should be discontinued first.
- The interval between injections should be increased up to 4 weeks before decreasing the dose each time {not with risperidone}.
- The dose should be reduced by no more than a third at any one time {special considerations apply to risperidone}.
- Decrements should, if possible, be made no more frequently than every 3 months preferably every 6 months.
- Discontinuation should be seen as the end point of the above process. Nice (2014) now suggested that intermittent treatment (symptoms triggered) is preferable than no treatment.
- If the patient becomes symptomatic this should be seen not as a failure but rather as an important step in determining the minimum effective dose that the patient requires.
- If the patient becomes symptomatic this should be seen not as a failure but rather as an important step in determining the minimum effective dose that the patient requires.

Q. RISPERIDONE LONG – ACTING INJECTION

- Risperidone depot is not an esterified form of the parent drug; it contains Risperidone coated in Polymer to form microspheres. These microspheres have to be suspended in an aqueous base immediately before use.
- The Injection must be stored in a fridge (consider practicality for community Nurses)
- It is available as doses of 25 mg, 37.5 mg and 50 mg Injection.
- A Test dose is not required or sensible (testing tolerability with oral Risperidone is desirable but not always practical.
- It takes 3 – 4 weeks for the first injection to produce Therapeutic plasma level.
- Patients must be maintained on a full dose of their previous antipsychotic for at least 3 weeks after the administration of the first Risperidone injection.
- Oral antipsychotic cover is sometime required for longer (6 – 8 weeks). If the patient is not already receiving and oral antipsychotic, Oral Risperidone should be prescribed.
- Patients who refuse oral treatment and are acutely ill should not be given Risperidone L.A.I because of the long delay in drug release.
- Risperidone Depot must be administered every 2 weeks, the product License does not allow long interval between doses.
- The most effective way of predicting response to Risperidone L.A.I is to establish dose and response with oral Risperidone.

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Switching to Risperidone Long Acting Injection (R.L.A.I)

Switching From	Recommended Method of Switching	Comments
No treatment (New patient or recently non – compliant)	Start Risperidone Oral at 2 mg tab/ day and titrate to effective dose. If tolerated, prescribe equivalent dose of RLAI. Continue with oral Risperidone for at least 3 weeks then taper over 1 – 2 weeks. Be prepared to continue Oral Risperidone for longer.	Use oral Risperidone before giving the Injection to assure good tolerability. Those responded to 2 mg/day start on 25 mg injection every 2 weeks. Those on higher doses start on 37.5 mg injection every 2 weeks, 50 mg injection every 2 weeks maybe required.
Oral Antipsychotic (Not Risperidone)	Either: - a. Switch to oral Risperidone and titrate to effective dose, If tolerated, prescribe equivalent dose of RLAI – continue with the oral Risperidone as described above. Or, b. Give RLAI then slowly discontinue oral antipsychotics as described above.	Dose assessment is difficult in those switching from another antipsychotic. Broadly speaking those on low oral dose should be switched to 25 mg Injection every 2 weeks. Those of on higher oral dose should receive 37.5 mg Injection or 50 mg Injection every 2 weeks.
Depot Antipsychotics	Give RLAI one week before the last depot injection is given.	For those on low doses start 25 mg injection every 2 weeks and then adjust as necessary. Start 37.5 mg injection every 2 weeks in those previously on doses in the middle or upper range of licensed doses. 50 mg injection every 2 weeks maybe required.
Antipsychotics - Poly pharmacy with Depot	Give RLAI one week before the last depot injection is given, Slowly taper oral Antipsychotics 3-4 weeks later, Be prepared to continue oral Antipsychotic longer.	Aim to treat patient with RLAI as the sole Antipsychotic.

R. Paliperidone Palmitate LAI

It is the major active metabolite of risperidone:

- Following on intra muscular injection, active paliperidone plasma levels are seen within few days, there tone co-administration of oral paliperidone or risperidone during initiation is not required.
- Dosing consists of two initiation doses (deltoid) followed by monthly maintenance doses (deltoid or gluteal)
- Following administration of a single IM dose to the deltoid muscle, on average 28% higher peak concentration compared with IM injection to the gluteal muscle.
- The two muscle injections on day 1 an 8 help quickly to attain therapeutic drug concentrations.
- Paliperidone palmitate IM does not require cold storage.
- No oral supplementation is required on initiation for paliperidone palmitate.
- No test dose is required for paliperidone palmitate but patient should ideally be currently stablished on or have previously responded to oral paliperidone or risperidone.

Paliperidone dose and administration information

	Dose	Route
Initiation		
Day 1	150 mg IM (234 mg)*	Deltoid only
Day 8 (+/-4 days)	100 mg IM (156 mg)*	Deltoid only
Maintenance		
Every month (+/-7 days) thereafter	50-150 mg (78-234 mg)*	Deltoid or gluteal

* Paliperidone palmitate dose can be expressed in terms of active moiety (50-150mg) or weight of compound (78-234 mg).

The maintenance dose is perhaps best judged by consideration of what might be a suitable dose of oral risperidone and then giving paliperidone palmitate it an equivalent dose (see below).

IM, intramuscular

Approximate dose equivalent

Risperidone oral (mg/day) (bioavailability=70%)	Paliperidone oral (mg/day) (bioavailability=28%)	Risperidone LAI (Consta) (mg/2 weeks)	Paliperidone palmitate (mg/monthly)
2	4	25	50
3	6	37.5	75
4	9	50	100
6	12	-	150

Switching to paliperidone palmitate

Switching From	Recommended Method of Switching	Comments
No treatment	Give the two initiation doses: 150 mg IM deltoid on day 1 and 100 mg IM deltoid on day 8 Maintenance dose starts 1 month later.	In general, the lowest most effective maintenance dose should be used the manufacturer recommends of 75 mg monthly for the general adults population. this is approximately equivalent to 3mg/day oral risperidone in practice the modal dose is 100 mg/month Maintenance dose adjustments should be made monthly. however the full effect of the dose adjustment may not be apparent for several months
Oral paliperidone/ risperidone	Give the two initiation doses followed by the maintenance dose and prescribe equivalent dose.	Oral paliperidone/risperidone supplementation during initiation is not necessary.
Oral antipsychotics	Reduce the dose of the oral antipsychotic over 1-2 weeks following the first injection of paliperdone. Give the two initiation doses followed by the maintenance does.	
Depot antipsychotic	For risperidone LAI, begin paliperdone 5-6 weeks after the last injection NB. No initiation doses are required.	Doses of palipridone palmitate IM may be difficult to predict. The manufacturer recommends a dose of 75 mg monthly for general adult population. If switching from RLAI and prescribe equivalent dose maintenance dose adjustments should be made monthly. however the full effect of the dose adjustment may not be apparent for several months
Antipsychotic polypharmacy with depot	Start paliperidon (at the maintenance dose) when the next injection is due NB. No initiation doses are required Reduce the dose of the oral antipsychotic over 1-2 weeks following the first injection of paliperdone	Aim to treat the patient with palipreidone palmitate IM as the sole antipsychotic The maintenance dose should be governed as far as possible by the total dose of oral and injectable antipsychotic.

IM, intramuscular; RLAI, risperidone long-acting injection.

S. REFRACTORY SCHIZOPHRENIA

- For a patient not responding to Antipsychotic therapy, if dose has been optimized, consider watchful waiting.
- Consider increasing Antipsychotic dose according to tolerability.
- If this fails, consider switching to Olanzapine or Risperidone (if not already used).
- If this fails, use Clozapine (Supporting evidence very strong)
- If clozapine fails, use time limited augmentation strategies (Supporting evidence variable)

Implementation of Treatment with Clozapine

- Before initiating treatment with Clozapine a complete blood count (CBC) with differential should be performed.
- The patient general and cardiovascular health status should be evaluated.
- The cardiovascular side effect of clozapine should be considered in planning treatment for patients with pre-existing heart disease.
- Treatment should be initiated at low dose (12.5 – 25 mg once or twice daily) and increased gradually (by no more than
- 25 – 50 mg /day). As tolerated until target dose is reached.
- Because of the risk of marked hypotension, sedation and seizures with rapid escalation, dose titration should not occur more rapidly.
- During dose titration, the patient's cardiovascular status including orthostatic, pulse, blood pressure and subjective complaints of dizziness should be monitored.
- Since side effect of clozapine in the initial and dose adjustment phases maybe severe in some patient, admission to hospital may- be justifiable (e.g., For unstable patients who require rapid dose increase to a therapeutic level. Patient with a limited support sys- tem or patient prone to orthostatic hypotension or seizures)
- The total dose of clozapine should be divided. The larger dose can be given at night.
- Adequate safety monitoring during treatment is important to minimize the risk of adverse events.

- The clozapine package label stated that WBC and neutrophil counts should be evaluated before treatment is initiated, weekly during the first 6 months of treatment and at least every 2 weeks after 6 months of treatment. Then is usually done monthly.
- Clozapine treatment should not be initiated:
  - If the initial WBC count is less than 3500/mm3.
  - If the patient has a history of myeloproliferative disorder.
  - If the patient has a history of clozapine – induced agranulocytosis or granulocytopenia.
- Advised to report any sign of infection immediately (e.g. Sore throat, fever, weakness, lethargy).
- A WBC count less than 2000 /mm3 or absolute neutrophil count (ANC) less than 1000 /mm3 indicating impending or actual agranulocytosis and the clinician should stop Clozapine treatment immediately.
- A WBC of 2000 – 3000 /mm3 or ANC of 1000 – 1500 /mm3 indicates high risk of or impending agranulocytosis, and clinician should stop Clozapine treatment immediately.
- Check the WBC and differential daily and monitor for signs of infection.
- Clozapine may be resumed if no infection is present, the WBC rises to more than 3000/mm3 and ANC is more than 1500/mm3 (resume checking WBC twice a week until it is 3500/mm3).
- If the WBC is 3000 – 3500/mm3, if it falls to 3000/mm3 over 1 – 3 weeks, or if immature WBC form are present, repeat the WBC count with differential count. If the subsequent WBC count is 3000 – 3500/mm3, and the ANC is more than 1500/ mm3, repeat the WBC count with a differential count twice a week until the WBC count is more than 3500/mm3.
- A rechallenge with clozapine should not be undertaken in patient with confirmed cases of a agranulocytosis (ANC less than 500/mm3)
- Rechallenge should be considered only:
  - For patient whose WBC count remained greater than 2000/mm3.
  - For whom trials with multiple other antipsychotic had failed but a good clinical response to Clozapine was shown.

- Myocarditis seems to occur within 6 -8 weeks of starting Clozapine (Median 3 weeks).
- Cardiomyopathy may occur later in treatment (median 9 months) but both may occur at any time.
- Patient should be closely monitored for signs of myocarditis especially in the first few months of treatment.
- Symptoms include: fever, flue- like symptoms, fatigue, and dyspnoea (increased respiratory rate) chest pain.
- Signs include: Tachycardia.
- On radiography / echo. (ECG Changes ST depression) enlarged heart.
- Laboratory investigation: eosinophilia.
- Suggested monitoring.
- Baseline pulse, temperature respiratory rate and C-reactive protein, Troponin, Echo cardiograph (if available).
- Daily if possible pulse, temperature, respiratory rate
- C- reactive protein and troponin on day 7 – 14 – 21 and 28.
- If C- reactive protein is less than 100 mg/L and troponin less than twice upper limit of normal, stop clozapine, and repeat echocardiogram.
- If fever + tachycardia + raised C-reactive protein or troponin (but not as above) do C- reactive protein and troponin daily.

Clozapine Augmentation Strategy

- Clozapine augmentation has become common practice because of inadequate response to Clozapine alone is a frequent clinical events.
- The evidence based on supporting augmentation strategies is growing but is not sufficient to allow the development of any algorithm or schedule of treatment options.
- It is recommended that all augmentation attempts are carefully monitored and, if no clear benefits is forthcoming, abandoned after 3 – 6 months.
- Depending on the type of residual symptoms (e.g. Positive symptoms, Negative, Mood symptoms, Cognitive or Aggressive behaviour).
- Strategies include:

- Adding antipsychotic (e.g. Amisulpride, Aripiprazole, Risperidone, and Haloperidol).
- Anticonvulsant (e.g. Lamotrigine, Topiramate), Lithium, ECT, CBT, Cognitive remediation.

T. Extrapyramidal Side Effects of Antipsychotics Effects

Most common extrapyramidal side-effects

	Dystonia (uncontrolled muscular spasm	Pseudo-parkinsonism (tremor, etc.)	Akathisia (restlessness)[1]	Tardive dyskinesia (abnormal movements)
Signs and symptoms	Muscle spasm in any part of the body, e.g. - eyes rolling upwards (oculogyric crisis) - head and neck twisted to the side (torticollis) - the patient may be unable to swallow or speak clearly in extreme cases, the back may arch or the jaw dislocate Acute dystonia can be both painful and very frightening	Symptoms include: - tremor and/or rigidity - bradykinesia (decreased facial expression, flat monotone voice, slow body movements, inability to initiate movement) - bradyphrenia (slowed thinking) - salivation Pseudo-parkinsonism can be mistaken for depression or the negative symptoms of schizophrenia	A subjectively unpleasant state of inner restlessness where there is a strong desire or compulsion to move, e.g. - foot stamping when seated - constantly crossing/ uncrossing legs - rocking from foot to foot - constantly pacing up and down Akathisia can be mistaken for psychotic agitation and has been linked with suicidal ideation and aggression towards others	A wide variety of movements can occur such as: - lips smacking or chewing tongue protrusion (fly catching) - choreiform hand movements (pill rolling or piano playing) - Pelvic thrusting Severe orofacial movements can lead to difficulty speaking. Movements are worse when under stress
Rating scales	No specific scale. Small component of general EPS scale	Simpson-Angus EPS Rating Scale	Barnes Akathisia Scale	Abnormal Involuntary Movement Scale (AIMS)

Prevalence (with older drugs)	Approximately 10% but more common: - in young males in the neuroleptic naive - with high potency drugs (e.g. haloperidol) Dystonic reactions are rare in the elderly	Approximately 20% but more common in: - elderly females - Those with pre-existing neurological damage (head injury, stroke, etc.)	Approximately 25% less with SGAs: in decreasing order: aripiprazole, lurasidone, risperidone, olanzapine, quetiapine and clozapine	5% of patients per year of antipsychotic exposure. More common in: - elderly women - those with affective illness - those who have had acute EPS early in treatment Tardive dyskinesia may be associated with neurocognitive deficits.
Time taken to develop	Acute dystonia can occur within hours of starting antipsychotics (minutes if the IM or IV route is used) Tardive dystonia occurs after months to years of antipsychotic treatment	Days to weeks after antipsychotic drugs are started or the dose is increased	Acute akathisia occurs within hours to weeks of starting antipsychotics or increasing the dose. Tardive akathisia takes longer to develop and can persist after antipsychotics have been withdrawn	Months to years Approximately 50% of cases are reversible

Treatment	Anticholinergic drugs given orally, IM or IV depending on the severity of symptoms: remember the patient may be unable to swallow response to IV administration will be seen within 5 minutes response to IM administration takes around 20 minutes tardive dystonia may respond to ECT where symptoms do not respond to simpler measures including switching to an antipsychotics with a low propensity for EPD, botulinum toxin may be effective	Several options are available depending on the clinical circumstances: reduce the antipsychotic dose change to an antipsychotic with lower propensity for pseudo-parkinsonism prescribe an anticholinergic. The majority of patients do not require long-term anticholinergics. Use should be reviewed at least every 3 months. Do not prescribe at night (symptoms usually absent during sleep)	Several options are available depending on the clinical circumstances: reduce the antipsychotic dose change to an antipsychotic drug with lower propensity for akathisia a reduction in symptoms may be seen with: propranolol 30-80 mg/ day (evidence poor), clonazepam (low dose 5HT antagonists such as: cyproheptadine, mirtazapine, trazodone, mianserin, and cyproheptadine may help, as may diphenhydramine All are unlicensed for this indication Anticholinergics are generally unhelpful	Several options are available depending on the clinical circumstances: stop anticholinergic if prescribed reduced dose of antipsychotic change to a lower propensity with lower propensity for tardive dyskinesia; note data are conflicting clozapine is the antipsychotics most likely to be associated with resolution of symptoms. Quetiapine may also be useful in this regard.

Neuroleptic malignant syndrome (NMS)

- It is rare, but potentially or even fatal condition
- The incidence and mortality rate of NMS are difficult to establish
- It has been estimated that less than 1% of all patients treated with conventional antipsychotics will experience NMS.
- Mortality is probably lower with SGAs. Symptoms are the same as those seen with FGAs except that rigidity is less common.
- NMS is also sometimes seen with other drugs such as antidepressants and lithium.
- NMS is also sometimes seen with other drugs such as antidepressants and lithium.
- Combination of antipsychotic with SSRIs, or cholinesterase inhibitors may increase the risk.
- NMSs type syndromes induced by SGA/SSRI combinations may share their symptoms and pathogenesis with serotonin syndrome.
- The use of benzodiazepines has been linked to an important increase in the risk of NMS.

Diagnosis and management of NMS

Signs and symptoms (presentation varies considerably)	Fever, diaphoresis, rigidity, confusion, fluctuating consciousness Fluctuating blood pressure, tachycardia Elevated creatine kinase, leukocytosis, altered liver function tests
Risk factors	Highly potency typical drugs, recent or rapid dose increase, rapid dose reduction, abrupt withdrawal of anticholinergics, antipsychotic polypharmacy Psychosis, organic brain disease, alcoholism, Parkinson's disease, hyperthyroidism, psychomotor agitation, mental retardation Agitation, dehydration
Treatments	**In the psychiatric unit** Withdraw antipsychotics, monitor temperature, pulse, blood pressure. Consider benzodiazepine if not already prescribed-IM lorazepam has been used **In the medical / A&E unit:** Rehydration, bromocriptine+dantrolene, sedation with benzodiazepines, artificial ventilation if required L-dopa, apomorphine, and carbamazepine have also been used, among many other drugs. Consider ECT for treatment of psychosis
Restarting antipsychotics	Antipsychotic treatment will be required in most instances and re-challenge is associated with acceptable risk Stop antipsychotic for at least 5 days, preferably longer. Allow time for symptoms and signs of NMS to resolve completely Begin with very small dose and increase very slowly with close monitoring of temperature, pulse and blood pressure. Creatine kinase monitoring may be used. but is controversial. Close monitoring of physical and biochemical parameters is effective in reducing progression to full-blown NMS. Consider using an antipsychotic structurally unrelated to that previously associated with NMS. or a drug with low dopamine affinity (quetiapine or clozapine). Aripiprazole may also be considered but it has a long plasma half-life and has been linked to an increased risk of NMS. Avoid depots (of any kind) and high potency conventional antipsychotics.

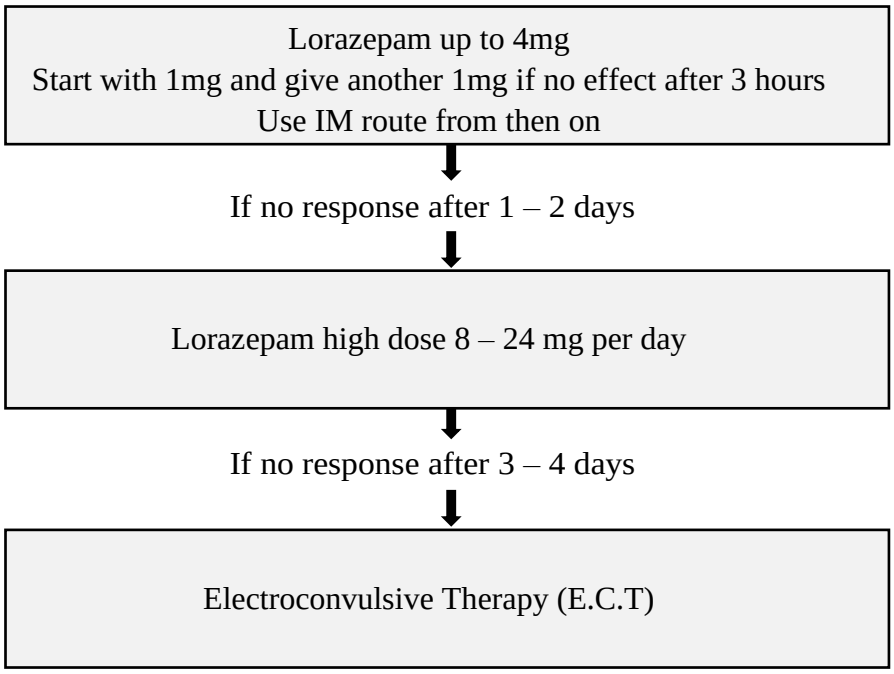
U. CATATONIA

- Is associated with Schizophrenia, Mood Disorder and less frequently in general medical conditions
- A number of neurological disorders, endocrine and metabolic disorders, infections, drug withdrawal and toxic drug states can precipitate catatonic symptoms
- Prompt treatment of catatonia is crucial and may prevent complications such as dehydration, venous thrombosis, pulmonary embolism and pneumonia
- Benzodiazepines are rapidly effective and regarded as first line treatment
- There is most experience with Lorazepam up to 4mg daily, but repeated and higher doses (8 – 24mg per day) may be needed
- Patients with Schizophrenia are less likely to respond to Benzodiazepine; ECT treatment is indicated

USE OF ANTIPSYCHOTICS IN CATATONIA

- The use of antipsychotic in patient with catatonic symptoms is controversial
- Some authors recommend that it should be avoided
- Case reports of successful treatment with Aripiprazole, Risperidone, Olanzapine, Ziprasidone and Clozapine
- During the acute phase of Catatonia, antipsychotic should be avoided
- Antipsychotic use in malignant Catatonia is catastrophically harmful
- In patients with chronic persistent catatonic symptoms, treatment of the underlying cause is necessary.
- SGAs may be used in those patients with Schizophrenia who have predisposition to Catatonia.
- Quetiapine is cautiously recommended in those patients.

Algorithm for Treating Catatonia



V. Cardiovascular effects of antipsychotic drugs treatment

- Many psychotropic drugs are associated with ECG changes and some are causally linked to serious ventricular arrhythmia and sudden death.
- Specifically, some antipsychotics block cardiac potassium channels and are linked to prolongation of the cardiac QT interval, a risk factor for the ventricular arrhythmia torsade pointes.
- Other reported antipsychotics-induced ECG changes include at rail fibrillation, giant p waves, T-wave change and heart block.
- A number of physiological/pathological factors are associated with an increased risk of QT changes and of arrhythmia i.e. cardiac, metabolic and others.
- Many non-psychotropic drugs are linked to QT prolongation i.e. antibiotics, antimalarial, antiarrhythmic and others.
- Other cardiovascular risk factors such as smoking, obesity and impaired glucose tolerance.
- In the absence of conclusive data, assume all antipsychotics are linked to sudden cardiac death.
- Prescribe the lowest dose possible and avoid polypharmacy/ metabolic interaction.
- Perform E.C.G on admission, and, if previous abnormality or additional risk factor, at yearly check-up.
- Consider measuring QTC within a week of achieving a therapeutic dose of a moderate/high risk antipsychotics of QT prolongation or of newly prescribed combined antipsychotics.
- The effect of drugs on QTC interval is usually plasma level dependent. Drug interaction are therefore important, especially when using metabolic inhibitor drugs such as fluvoxamine, fluoxetine, paroxetine and valproate.

Effect of Antipsychotics on QTC

No Effect	Low Effect	Moderate Effect	High effect	Unknown Effect
- Aripiprazole	- Clozapine - Flupenthixol - Fluphenazine - Perphenazine - Olanzapine - Paliperidone - Risperidone - Sulpiride	- Amisulpiride - Chlorpromazine - Haloperidol - Quetiapine	- Any intravenous antipsychotic - Pimozide - Any drug or combination of drug used in doses exceeding recommended maximum	Trifluoperazine Zuclopenthixol

Management of QT prolongation in patients receiving antipsychotic drug

OTc	Action	Refer to cardiologist
< 440 msec (men) or < 470 msec (women)	None unless abnormal T-wave morphology	Consider if in doubt
< 440 msec (men) or < 470 msec (women) but < 500 msec	Consider reducing dose or Switching to drug of lower effect. Repeat ECG	Consider
< 500 msec	Repeat ECG. Stop susceptive causative drug(s) and switch to drug of lower effect	Immediately
Abnormal T-wave morphology	Review treatment. Consider reducing dose or switch to drug of lower effect	Immediately

W. ANTIPSYCHOTIC DRUGS ON HYPERPROLACTINEMIA

- All antipsychotics cause measurable changes in Prolactin, but some do not increase Prolactin above the normal range of standard doses.
- These drugs are Clozapine, Olanzapine, Quetiapine, Aripiprazole and Ziprasidone.
- The degree of Prolactin elevation is probably dose related.

Monitoring

- All patients should have their Prolactin concentration measured before starting an antipsychotic.
- After 3 months, all patients should be asked about Prolactin related symptoms (sexual dysfunction, amenorrhea, etc.); if Hyperprolactinemia is suspected, Prolactin concentration should be measured.
- After this, yearly monitoring is suggested unless symptoms arise.
- Prolactin elevating drugs (Amisulpride, Sulpiride, Risperidone, FGAs) should if possible be avoided in the following:
  - Patients under 25 years of age (i.e. before peak bone mass).
  - Patients with Osteoporosis.
  - Patients with history of hormone-dependent breast cancer
- Long term use of Prolactin elevating drugs should be probably avoided in young women, given the possible increased risk of breast cancer and risk of decreased bone mineral density.

Measurement and Interpretation of Prolactin Concentration

- Take blood sample at least 1 hour after waking or eating
- Minimize stress during venepuncture (stress elevates plasma prolactin)
- Re-test if Prolactin concentration (530 – 2500 mIU/L)
- Refer for further tests to rule out Prolactinoma if Prolactin concentration is >2500 mIU/L

Treatment of Antipsychotic Induced Hyperprolactinemia

- For most patients with symptomatic Hyperprolactinemia, switch to non-Prolactin elevating drug
- An alternative is to add Aripiprazole to existing treatment; higher doses appear unnecessary
- For patients who need to remain on Prolactin elevating antipsychotics, Dopamine agonist may be effective
- Amantadine, Carbergoline and Bromocriptine have all been used, but each has the potential to worsen psychosis (this has not been reported in trials)

Antipsychotics not usually associated with Hyperprolactinemia

- Aripiprazole
- Clozapine
- Olanzapine
- Quetiapine
- Ziprasidone

X. ANTIPSYCHOTIC INDUCED WEIGHT GAIN

- Suggested mechanisms include 5-HT2c antagonism, H1 antagonism, Hyperprolactinemia and increased serum Leptin (leading to Leptin desensitization)
- Weight gain seems to result from food intake and in some cases reduced energy expenditure.
- All available antipsychotics have been associated with weight gain, although mean weight gained varies substantially between drugs.

Relative Risk of Weight Gain and Mean Weight Gain of Antipsychotic Drugs

Drug	Risk/Extent of Weight Gain
- Clozapine - Olanzapine	**HIGH**
- Chlorpromazine - Quetiapine - Risperidone - Paliperidone	**MODERATE**
- Amisulpride - Aripiprazole - Haloperidol - Sulpiride - Ziprasidone	**LOW**

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Treatment of Drug Induced Weight Gain

- Weight gain is an important side-effect with obvious consequences for self-image, morbidity and mortality.
- Prevention and treatment are of clinical urgency.
- Patients should be weighed and their weight clearly recorded when starting or changing antipsychotic drug.
- Estimates of Body Mass Index and waist circumference should, ideally, also be made at baseline and later at least every 6 months.
- Weekly monitoring of weight is recommended in early treatment for the first 3 months at least.
- When weight gain occurs, initial options involve switching drugs or instituting behavioural programs or both.
- Switching always presents a risk of relapse and treatment discontinuation; there is strong support for switching to Aripiprazole or Ziprasidone (when available).
- Switching to other drug with a low propensity for weight gain is also beneficial.
- Add Aripiprazole to existing treatment.
- A variety of behavioural methods has been proposed and evaluated with fairly good results; methods include:
  - Calorie restriction, low glycaemic index diet, weight watcher and diet/exercise programs
- Pharmacological methods should be considered only when behavioural methods or switching have failed or where obesity presents clear, immediate physical risk to the patient.
- Metformin is probably considered the drug of choice for antipsychotic induced weight gain.

Y. Substance Use Disorder and Schizophrenia (Dual Diagnosis)

- Nearly one half of patients with schizophrenia have co – morbid substance use disorder.
- The goals of treatment of patient with Schizophrenia who also have a substance use disorder is the same as those without comorbidity but with the addition of the goals for the treatment of substance use disorder, (e. g. Harm reduction, abstinence, Relapse Prevention and Rehabilitation).
- The optimal intervention is integrated treatment for both schizophrenia and substance use in a single program.

Z. LONG TERM HOSPITALIZATION

- 10 – 20 % of patient with Schizophrenia remained severely psychotic with grossly impaired functioning despite optimal pharmacological and conventional care.
- Group of patients require long term supervised hospitalization for their safety and protection, as well for the protection of the family and the community.
- Studies suggested that, patients with resistant schizophrenia who require long term hospitalization profit most from treatment program that emphasize highly structured behavioural technique.

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Review Sheet for Inpatient Schizophrenics whose Admission Exceeds 8 weeks

Patient Name:	File No:
Ward:	Date of admission:
Treating Consultant:	Duration of admission in weeks ( )
Psychiatric diagnosis:	Medical Conference (if present)

Fill the correct circle:

1. Initial titration to therapeutic dose:
   - Within a week.
   - More than a week, justify:

2. Time of assessment of response to the therapeutic dose: Objects
   - 2 – 3 weeks.
   - More than 3 weeks, justify:

3. Number of antipsychotic trials:
   - 2 trails.
   - More than 2, justify:

4. Time to switch to the second antipsychotic:
   - 2 trails.
   - More than 2, justify:

5. When two different antipsychotic were ineffective, clozapine therapy is:
   - Considered.
   - Not considered, justify:

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May Al Harbi

References (Chapter 1)

- The Maudsley Prescribing Guidelines 12th Edition
- American Psychiatric Association Practice Guideline (Copyright 2010)
- Nice Guideline February 2014
- Canadian Clinical Practice Guidelines for Schizophrenia

• Chapter 2 (Bipolar Disorder)

A. Introduction

- Bipolar disorder is a life long illness that is complicated by high comorbidity and risk of poor health outcomes.
- It is characterized by dramatic shift in mood, behaviour and energy.
- The management of bipolar disorder is based on patient safety, and begins with evidence based treatment and long term management should focus on maintaining euthymic and requires ongoing medication and be benefit from adjunctive psychotherapy.

Aim of the protocol

- The focus of interest is bipolar disorder (BD)
- The aim of protocol is management of the disorder with attention to special population and situation including acute and maintenance treatment of bipolar disorder with safety and monitoring procedures.

Foundations of management Epidemiology

- Most frequently diagnosed before age 30 years, bipolar disorder includes bipolar I disorder, characterized by manic or mixed episodes (nearly always alternating with depressive episodes) and bipolar II disorder, which marked by recurrent episodes of depression and less severe or briefer hypomanic episodes.
- Related are cyclothymia, characterized by hypomania and subthreshold depression and bipolar disorder not otherwise specified, a “catch-all” diagnosis for conditions that do not fit neatly into bipolar disorder but that are felt to be properly classified with the bipolar spectrum.
- Some experts argue that up to 50% of recurrent depressions might be so classified, but others have disagreed with this widening of the diagnosis.
- Lifetime prevalence of bipolar I disorder is 1% to 2% in both men and women; prevalence of bipolar II disorder is at least 2% and may be underestimated due to the likelihood of recall bias in reporting hypomania.

- Estimates of the prevalence of bipolar disorder not otherwise specified vary widely, but the total lifetime prevalence of these 3 disorders is at least 2.4% to 6%.

Table 1.1. Evidence criteria

1. Meta-analysis is or replicated double-blind (DB). Randomized controlled trial (ACT) that includes a placebo condition. 2. At least one DB-RCT with placebo or active comparison condition. 3. Prospective uncontrolled trial with at least ten or more subjects. 4. Anecdotal reports or expert opinion.

Table 1.1. Evidence criteria

First line	Level 1 or level 2 evidence plus clinical support for efficacy and safety.
Second line	Level 3 evidence or higher plus clinical support for efficacy and safety.
Third line	Level 4 evidence or higher plus clinical support for efficacy and safety.
Not recommended	Level 1 or level 2 evidence for lack of efficacy

Diagnostic Assessment:

DSM 5 has separate chapters for Bipolar disorders and related conditions as well as depressive disorders. The old name of Bipolar Dis- order Not Otherwise Specified (BD-NOS), has been replaced with (Bipolar Disorders Not Elsewhere Classified).

BD associated with general medical condition and substance induced BD has been added as well.

In manic episode criteria, “abnormally and persistently increased activity or energy” has been added to criterion A, which previously referred only to distinct period of abnormally and persistently elevated, expansive or irritable mood.

During antidepressant treatment, a manic episode might emerge which can qualify as a manic episode of BD, provided that the symptoms persisted beyond the physiological effects of the treatment.

Diagnosis of "mixed episode" has been replaced with a "mixed features" specifier, requiring 3 symptoms of the opposite pole, which would apply to manic, hypomanic and depressive episodes.

Chronic Disease Management:

Bipolar disorder is a chronic illness at which the patients require long term management. A small, cluster-randomized trial (RCT) examined the effect of community mental health teams (n=23) who received enhanced training in relapse prevention vs. treatment-as-usual (TAU) in 96 patients with BD.

The median survival time of patients treated by the trained teams was prolonged by 8.5 weeks compared to those receiving TAU. A combined care model including clinician support through the use of simplified guidelines was found to result in significantly greater guideline-concordant therapy over a 3 year follow up period compared to TAU in patients with BD. (CANMAT 2013).

Symptoms checklist method can significantly increase the recognition of early warning signs for manic or depressive relapse. There was a positive correlation between the social/occupational functioning and the frequency of monitoring.

Psychosocial interventions

Psychosocial interventions such as group psycho-education, cognitive behavioral therapy (CBT) and interpersonal & social rhythm therapy (IPSRT) have demonstrated significant benefits when used combined with pharmacotherapy, both in the treatment of acute depressive episodes and also long-term maintenance treatment, including decreased relapse rates, mood fluctuation, the need for medications and hospitalization as well as increased functioning and medication adherence.

That's why, providing psychological treatment and in particular, brief psycho-education -which has been demonstrated to be as effective as CBT at much lower cost- is an essential aspect in BD patient's management.

A family-focused treatment approach designed to help caregivers improve illness management skills and their own self-care was shown to effectively reduce depressive symptoms and health-risk behavior among caregivers and family members and on the other hand reduce depressive symptoms in patients.

B. ACUTE MANAGEMENT OF BIPOLAR MANIA AS ADOPTED FROM CANMAT

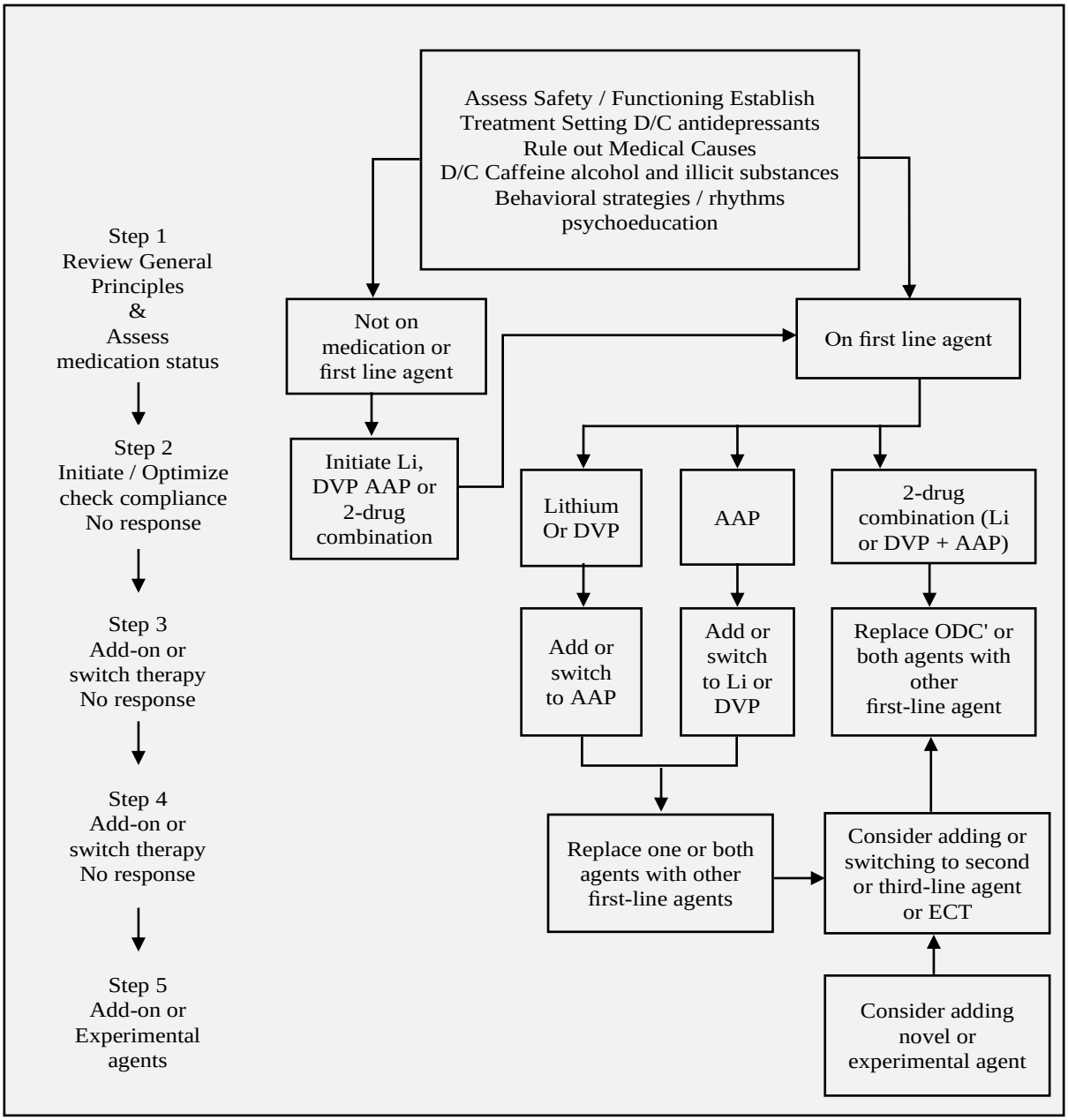

Fig. treatment algorithm for Acute Mania. Novel ⁄ experimental agents:

Zotepine, Levetiracetam, Phenytoin, Mexiletine, Omega-3- fatty acids, Calcitonin, rapid Tryptophan depletion, Allopurinol, Amisulpride, Folic acid, Memantine. D ⁄C = discontinue; Li = Lithium; DVP = Divalproex; AAP = atypical antipsychotic agent.

Emergency management of acute mania

The acutely manic bipolar patient may present in an agitated state that acts as a barrier to therapy, interrupts the physician–patient alliance, and creates a disruptive, even hazardous, environment.

Recommendation for Agitation Management

Oral therapy should be offered first, as evidence suggests that oral agents can be as effective as IM agents

- Risperidone (level 2)
- Olanzapine (level 2)
- Quetiapine (level 3)
- Divalproex ER (level 3)
- Patients who refused oral atypical anti psychotics:
- IM Olanzapine (level 2)
- Combination of intramuscular haloperidol and a benzodiazepine should be considered (level 2)

In general, benzodiazepines should not be used as monotherapy, but are useful adjuncts to sedate acutely agitated patients.

Pharmacological Treatment of Manic Episodes

Step 1: Review general principles and assess medication status

When the patient presented with manic episode the patient should be immediately assessed for:

- Risk of aggressive behaviour/violence to others,
- Suicide and degree of insight and the ability to adhere to treatment.
- A physical examination with appropriate lab investigations but may be deferred until the patient is more cooperative.
- Based on the overall assessment the type of treatment setting (e.g. ambulatory or inpatient) should be established.
- Antidepressants should be discontinued
- Rule out factors that may be perpetuating manic symptoms, such as prescribed medication, illicit-drug use/abuse or an endocrine disorder,

stimulants such as caffeine and alcohol and gradually discontinue nicotine.

- When patients are stabilized, behavioural and educational strategies should be applied in order to direct subsequent therapeutic choices, current therapy should be assessed including the dose.

The decision to treat manic patient influenced by:

a) Current and prior medication use.
b) Patient factors that may influence prognosis or safety.
c) Untreated manic patients or those receiving a medication other than a first-line agent, therapy should be initiated with one or more of the first-line agents.
d) For patients who are uncontrolled on monotherapy with a first-line medication, the first option before adding or switching therapies is to optimize the dose of current medication and to identify issues of non-adherence that is frequent cause of recurrence, which is often associated with hospitalization or suicide.

Table of Recommendation for Pharmacological Treatment of Acute Mania

First line	Monotherapy Lithium, divalproex, divalproex ER", olanzapine, risperidone, quetiapine, aripiprazole Adjunctive therapy with lithium or divalproex: Risperidone, quetiapine, olanzapine, aripiprazole.
Second Line	Monotherapy Carbamazepine, carbamazepine ER, ECT, Haloperidol Combination therapy Lithium + divalproex
Third Line	Monotherapy Chlorpromazine, clozapine. Combination therapy Lithium or divalproex + haloperidol, lithium + carbamazepine
Not recommended	Monotherapy Gabapentin, topiramate, lamotrigine, verapamil, tiagabine Combination therapy

	Risperidone + carbamazepine, olanzapine · + carbamazepine

ECT; electroconvulsive therapy; XR or ER =extended release. New or change to recommendation.

Given the metabolic side effects, use should be carefully monitored. Recommendations for pharmacological treatment of acute mania

Table of Recommendation for Pharmacological Treatment of Acute Mania

Table of Predictors of response in acute mania

Agent	Predictors of response	Predictors of non-response
Lithium	Elated mania (184,185) Previous response to lithium (184, 185) Mania-depression-euthymia course (103) No neurological impairment (184, 185) No psychotic symptoms (184, 185) No substance abuse (8, 184, 1 85) Few episodes of illness (103, 184, 185)	Mixed state (8, 103, 186, 194) Rapid cycling (8, 1 03) Depression-Mania-euthymia course (8, 1 03) Presence of depressive symptoms (184, 187) Multiple episodes (8) No family history (8)
Divalproex	Rapid cycling (103, 187, 189, 195) Mixed state (103, 186, 187, 189) Multiple prior mood episodes (187, 188) Irritable dysphoric subtype (1 96) Secondary mania (103) Comorbid substance abuse (189)	Comorbid personality disorders (189) More severe mania (189)
Carbamazepine	Mixed state (1 03, 189) Increased severity of acute mania (189) No family history of mood disorders (189) Early age of onset (189) Course dominated by manic episodes (189)	Rapid cycling (103, 197) >10 years illness (197)
Atypical antipsychotics	Early age of onset (190) No prior substance abuse (190)	

	No prior antipsychotic treatment (190) Rapid Cycling (3. 127, 191)	

Step 2:

First Line:

- Lithium/Divalproex monotherapy: Lithium, Divalproex, Divalproex ER
- Atypical antipsychotic monotherapy: Olanzapine, Risperidone, Quetiapine, Aripiprazole, Paliperidone ER.
- Atypical antipsychotic combination therapy: Risperidone, Quetiapine, Olanzapine, Aripiprazole.

New clinical trial data, and the availability of several agents, justify some changes to the recommendations. Monotherapy with Paliperidone ER and Divalproex ER, as first line options for evidence (CANMA T 2013 P. 4-6).

Step 3:

Add-on or switch therapy (alternate first-line therapies):

If therapy with one of the first-line agents at optimal dose is inadequate or not tolerated, the next step should involve:

- Switching to or adding-on an alternate first-line agent. Based on the efficacy and relative safety of first-line agents,
- The use of second- and third-line agents is only recommended after these classes of agents have been tried alone or in combination.

Step 4:

Add-on or switch therapy (second- and third line therapies):

Second line:

Monotherapy: Carbamazepine, Carbamazepine ER, ECT, haloperidol Combination therapy: Lithium + Divalproex.

While electroconvulsive therapy (ECT) can be an effective option, research studies have not been rigorous and therefore it continues to be recommended as a second-line therapy (level 3).

Given the strong data for efficacy, haloperidol has been upgraded to a second-line option.

However, haloperidol should only be used on a short-term basis to treat acute mania as continuation of haloperidol may increase the risk of a depressive episode (CANMAT 2013).

Third line:

Monotherapy: Chlorpromazine, Clozapine.

Combination therapy: Lithium or Divalproex + Haloperidol, Lithium + Carbamazepine, Divalproex, adjunctive Folic acid was significantly better than placebo in improving mania scores (level 2) 50% of patients responded to doses of Memantine ranging from 20 mg to 40 mg (level3) (CANMAT 2013).

Given the limited data, at this time, these agents can only be recommended as add-on therapies after failure of standard therapies Adjunctive therapies with negative data requiring further study:

1) Adjunctive flexible-dose Paliperidone in patients with manic or mixed episodes who had not responded to Lithium or Divalproex, (level 2, negative).
2) BD mania / mixed episodes found no significant benefits with adjunctive at high or low dose.

In mania with psychotic features: Evidence support Aripiprazole use, during the acute manic and maintenance phases of BD.

In mixed states: adjunctive Olanzapine compared demonstrated significantly greater and earlier reductions in manic and depressive symptoms in patients with mixed episodes inadequately controlled with Divalproex.

In rapid cycling, which is reported in about 13-20% of patients with Bipolar disorder, and more often in women predominance. The definition of four or more episodes per year is largely an arbitrary cut-off and it is hypothesized that rapid cycling exists on a continuum of cycle lengths.

Hypothyroidism, antidepressants and substance abuse may con- tribute to rapid cycling.

The combination of Lithium and Divalproex has been shown to improve response rates ECT may also prove efficacious in selected cases (CANMAT2005).

Not recommended:

Monotherapy: Gabapentin, Topiramate, Lamotrigine, Verapamil, Tiagabine Combination Therapy: Risperidone + Carbamazepine, Olanzapine+ Carbamazepine.

Clinical point could be a focus of interest.

How long a medication should be tried before adding or switching therapies?

Within the first 1-2 weeks, active treatment has superior effects compared with placebo. If the starting dose of the medication was lower and/or dose titration was slower, it would take a few days to achieve the target.

So, pharmaco-therapeutic regimen must be tried for at least 2 weeks at adequate doses before concluding that the patient is unlikely to respond (30% reduction in symptoms).

The role of psychosocial treatments in management of acute mania? Although pharmacotherapy is the foundation of treatment for an acute manic episode, all patients require some psycho education, which should be undertaken once the patient- physician therapeutic alliance is established.

Evidence suggests that a range of adjunctive psychological approaches offer some benefit during maintenance therapy.

In case of combination of mood-stabilizer and an atypical antipsychotic with successful result, should one be discontinued and if so when?

The prophylactic efficacy of lithium is well established and there are some research data and a wealth of clinical experience supporting the utility of Divalproex.

This is not the case with atypical anti psychotics other than Olanzapine.

In an effort to minimize the side effect burden, it is prudent to minimize the number of medications whenever possible.

It is also important to recognize that monotherapy may be insufficient to prevent relapses in many patients with bipolar I disorder. A patient's prior history of mood stability on Lithium or Divalproex monotherapy should serve as a clinical guide as to whether mono- therapy is adequate for that individual or combination therapy is required. (CANMAT 2005).

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Ministry of Health

C. ACUTE MANAGEMENT OF BIPOLAR DEPRESSION

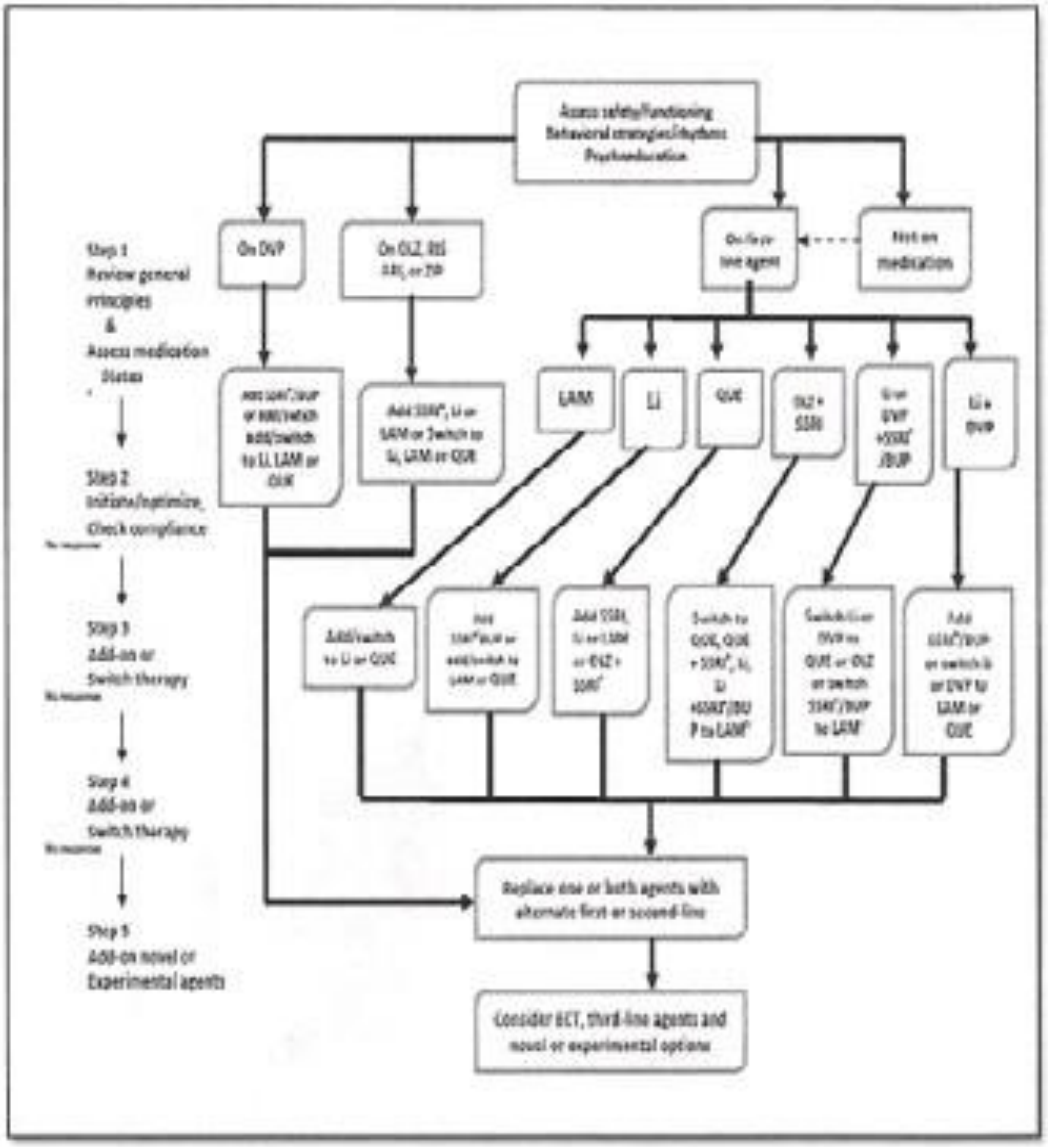


Fig. (1) **Treatment algorithm for the management of bipolar 1 depression Novel/experimental agents:**adjunctive pramipexole, eicosapentaenoicaiod (EPA), riluzole, topiramate, N-acetyl cysteine (NAC), ketamine, armodafinil, and chronotheraphy. DVP = divalproex; OLZ = olanzapines; RIS = risperidone; ARI = aripirazole; ZIP = ziprasodine; SSRI = selective serotonin reuptake inhibitor; BUP = bupropion; Li = Lithium; LAM = lamotrigine; QUE = quetiapine; ECT = electroconvulsive therapy. [a]Exceptparoxitine. [b]Or switch the SSRI to another SSRI. [c]Or switch the SSRI or BUP to another SSRI or BUP.

Tab of Recommendations for pharmacological treatment of acute- bipolar 1 depression

First line	Monotherapy Lithium, lamotrigine, quetiapine. Combination therapy: lithium or divalproex + SSRI, olanzapine SSRI, lithium+ divalproex, lithium or divalproex + bupropion
Second Line	Monotherapy divalproex Combination therapy quetiapine + SSRI - lithium or divalproex + lamotrigine, lithium or divalproex
Third Line	Monotherapy carbamazepine, olanzapine, Combination therapy lithium+ carbamazepine, lithium+ lithium or divalproex + venlafaxine lithium+ MAOI, lithium or divalproex or AAP + TCA, lithium or divalproex or carbamazepine + SSRI + lamotrigine, quetiapine + lamotrigine
Not recommended	Monotherapy Gabapentin, topiramate, lamotrigine, verapamil, tiagabine Combination therapy Risperidone + carbamazepine, olanzapine + carbamazepine

AAP = atypical antipsychotic agent, ECT = electroconvulsive therapy, MAOI = monoamine oxidase inhibitor, TCA = tricyclic antidepressant, SSRI = selective serotonin reuptake inhibitor xr = extended release.

The management of a bipolar depressive episode with antidepressants remains complex, the clinician must balance the desire effect of remission with the undesired effect of switching.

Except paroxetine, new or change to recommendation could be used as first-line treatment in certain situations (see text)

Epidemiology of Bipolar Depression

Depression is mostly a chronic illness especially depressive episode of bipolar disorder which is chronic in 20 % of patient and can cause more functional impairment, more disability and more decline in the quality of life than any other phase of the illness.

Depressive episode in rapid cycling bipolar patients, have been found to be more refractory to treatment than hypomanic or manic episodes. Suicidality is a major issue especially in patients with in- crease severity of depressive episode or with mixed phase of illness with high depression score and more frequent depressive episode beside other risk factor of suicidal acts.

Psychosocial Interventions

Psychosocial therapies could be applied early in the course of illness for the following reasons:

- Detect the prodromes of relapse.
- Improve adherence to medication.
- Motivate the patients toward a more comprehensive recovery.
- Ameliorate the residual depressive symptoms.
- Reduce suicidal behaviour: the use of psychotherapy that was tailored to bipolar disorder or intensive clinical management as adjuncts to lithium therapy were associated with significant reductions in suicidal behaviour in high-risk depressed patients with bipolar I disorder compared to prior treatment with lithium alone (CANMAT 2005).

In the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-SD) trial, 293 patients with BD I or BD II depression were randomized to receive intensive psychotherapy (n= 163) or collaborative care (n = 130), i.e., a brief psycho educational intervention as an adjunct to pharmacotherapy.

Intensive psychotherapy included family-focused therapy (FFT), IPSRT, and CBT weekly and biweekly for up to 30 sessions in nine months, and collaborative care consisted of three sessions in six weeks.

Discontinuation rates were similar with both treatments. Patients receiving intensive psychotherapy had significantly higher year-end recovery rates (64.4% versus 51.5%) and shorter times to recovery than patients in collaborative care.

There were no statistically significant differences between the three types of intensive psychotherapies.

In a subsequent report of 152 patients from this study, intensive psychotherapy was associated with better total functioning, relationship functioning and life satisfaction scores but not work/role functioning or recreation scores over nine months compared to collaborative care.

Pharmacological Treatment

In meta-analysis included 19 trials assessing mainly Quetiapine (five trials) and Lamotrigine (six trials), but also Paroxetine, Lithium, Olanzapine, Aripiprazole, Phenelzine, and Divalproex for the treatment of Bipolar depression found the highest reductions in Montgomery-Asberg Depression Rating Scale (MADRS) scores with the Olanzapine plus Fluoxetine combination and Quetiapine monotherapy compared to placebo.

In this analysis, Lamotrigine, Paroxetine, Aripiprazole and Lithium were not significantly different from placebo in improving depression scores. However, as cited in previous iterations, a meta-analysis of individual patient data supported the efficacy of Lamotrigine monotherapy.

Step 1. Review General Principles and Assess Medication Status:

When a patient present in a depressed state, certain general principles should be followed:

1) The patient should be assessed for a risk of suicide/self-harm behaviour, ability to adhere to treatment plan, psychosocial support network and the ability to function.
2) Based on these factors, a decision can be made as to whether the patient requires admission to hospital or can be safely managed in an outpatient setting.
3) Behavioural and educational strategies are important to improve symptoms and prevent relapse.
4) In order to direct subsequent therapeutic choices, current therapy should be assessed, including what medications the patient is taking and at what dose.

Step 2. Initiate or Optimize therapy and check adherence (first-Line therapies):

First line	Monotherapy: Lithium, Lamotrigine, quetiapine. Combination therapy: Lithium or divalproex + SSRI, Olanzapine + SSRI or lithium + divalproex, Lithium or divalproex + bupropion.

Data may suggest predictor of eventual non-response, suggesting that these patients may benefit from a change in therapy.

Lithium

Quetiapine monotherapy: Four large published RCTs demonstrating the efficacy of Quetiapine monotherapy in bipolar depression (CANTMAT 2013)

Olanzapine + Fluoxetine: level 1 data demonstrating the efficacy of Olanzapine-Fluoxetine combination (OFC) therapy for the treatment of BD I depression However, OFC treatment was associated with a significantly increased risk of treatment-emergent hypercholesterolemia and weight gain. (CANMAT 2013)

Lithium or Divalproex + Bupropion: ln a small RCT, Bupropion and Desipramine were equally effective when combined with Lithium or Divalproex in acute and maintenance treatment of bipolar disorder, but Bupropion had a much lower manic switch rate. (CANMAT 2005)

Step 3. Add-on or switch therapy (alternate first-or second-line therapies:

Second-line option

Second line	Monotherapy: Divalproex Combination therapy : quetiapine + SSRI, lithium or divalproex + Lamotrigine, lithium or divalproex

Divalproex Monotherapy: Two meta-analyses concluded that Divalproex was more effective than placebo for the treatment of Bi- polar depression, but the strength of the conclusions was limited by sample size (CANMAT 2013). Therefore, given the limited evidence, Divalproex continues to be recommended as a second-line option.

Lamotrigine + Lithium or Divalproex: Given the slow titration required for Lamotrigine, this treatment is recommended either in monotherapy or as an add-on therapy primarily for those with mild-to-moderate bipolar depression,

and in particular for those with depression recurrences, given its efficacy in preventing depressive relapses.

Step 4. Add-on or switch therapy (alternate first- or second-line therapies):

Where necessary, steps 2 and 3 should be repeated due to their efficacy with further therapeutic choices being based on current medication, third-line agents is not recommended until these classes of agents have been tried alone or in combination.

Step 5. Add-on or switch therapy (third-line agents and novel/ experimental therapies):

Third-line option

Third line	Monotherapy: carbamazepine, olanzapine, ECT Combination therapy: lithium + carbamazepine, lithium + lithium or divalproex +venlafaxine, lithium + MAOI, lithium or divalproex or AAP + TCA, lithium or divalproex or carbamazepine + SSRI + lamotrigine Quetiapine + Lamotrigine

Olanzapine Monotherapy: Demonstrated a statistically significant but clinically modest antidepressant effect in a large (n = 833), eight week RCT and was associated with significantly greater rates of metabolic changes recommended as a third-line option (CANMAT 2013)

Carbamazepine: ER Carbamazepine was as effective as the immediate-release form with fewer autonomic and gastrointestinal ad- verse events (CANMAT - 2013).

Quetiapine + Lamotrigine: beneficial in treatment-resistant bipolar depression (level 3) (CANMAT - 2013).

ECT: Should be considered earlier in psychotic bipolar depression when:

- Patients at high risk for suicide.
- Patient with significant medical complications due to not drinking and eating.

In an open trial, similar rates of response and remission were observed in patients with bipolar depression (70% and 26%, respectively) and those with mixed states (66% and 30%, respectively) (CANMAT - 2013).

New or Experimental Agents:

- Data described the benefits of adjunctive use of the following agents.
- Pramipexole (level 2).
- Eicosapentaenoic acid (EPA) (level 2).
- Riluzole (level 3)
- Topiramate (level 3)
- N-acetyl Cysteine (NAC) (level 2)
- Adjunctive Riluzole
- Adjunctive NAC
- Adjunctive Ketamine, Armodafinil
- Adjunctive combined chronotherapy (sleep deprivation, exposure to bright light, and sleep phase advance) demonstrated a more rap- id and sustained antidepressant response compared to medication alone (lithium + antidepressant) (level 3) (CANMAT 2013)

Not recommended for the treatment of acute bipolar depression:

Not recommended	Monotherapy : Aripiprazole

Not recommended for the treatment of acute bipolar depression Adjunctive therapies with negative data requiring further study: Adjunctive Aripiprazole.

<u>Clinical point could be a focus of interest</u>

What is the role of antidepressants in patients with bipolar depression?

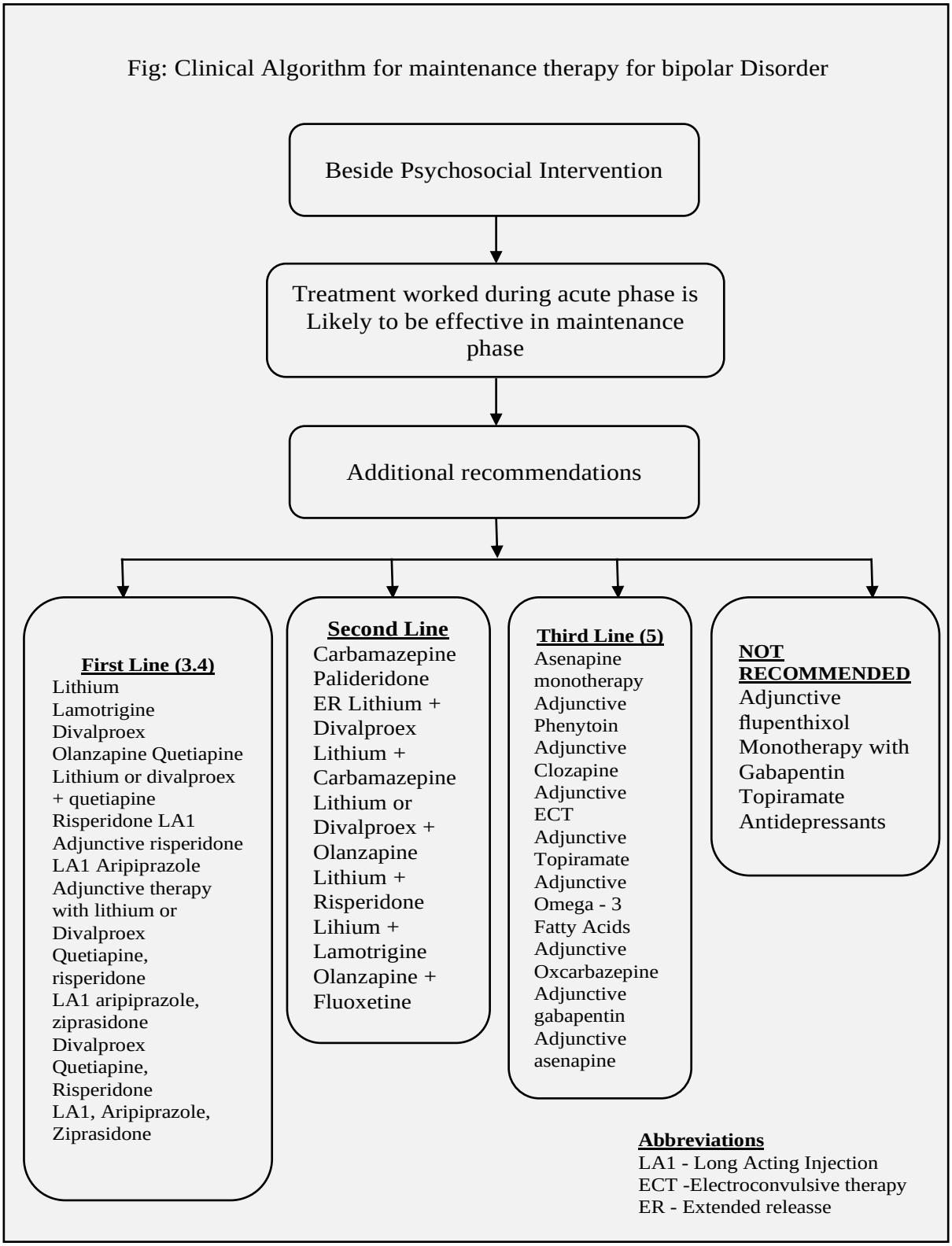
One of the most controversy large areas in psychiatry clinicians continue to believe that, based on their clinical experience, these are effective for bipolar depression but growing body of clinical trial data has not been consistent in supporting their role (CANMAT 2013).

The following conclusions and recommendations are warranted regarding the use of antidepressants for bipolar depression:

1) SSRIs (other than Paroxetine) and Bupropion could be used as first-line treatments in conjunction with a mood stabilizer for acute short term treatment, with the objective of tapering and discontinuing antidepressants 6-8 weeks after full remission of depression.
2) Avoid the use of Tricyclic antidepressants and Venlafaxine (131,132) as they are associated with an increased risk of manic switch.
3) Antidepressants should not be used to treat a current mixed episode or in patients with a history of rapid cycling.
4) Monotherapy with antidepressants is not recommended for bi- polar depression.

D. MAINTENANCE THERAPY FOR BIPOLAR DISORDER

Fig: Clinical Algorithm for maintenance therapy for bipolar Disorder



Adherence

It is one of the most important factors in preventing relapses in bi- polar disorder.

It is positively associated with higher satisfaction with medication, monotherapy, a college degree, and fear of relapse, and negatively associated with illness factors (substance use, previous hospitalization, psychotic symptoms, reduced insight into illness), medication factors (side effects, no perceived daily benefit, difficulties with medication routines), and patient attitudes (belief that medications are unnecessary, negative attitudes toward medications, perceived change in appearance, perceived interference with life goals). Un- der-dosing and high frequency of episodes (particularly depressive episodes), a higher risk of hospitalization and emergency room vis- its, as well as higher employee costs of absenteeism, short term dis- ability, and worker's compensation.

Some factors can predict recurrence

Predictors of symptomatic remission and recovery during 1-2 years of follow-up in patients with manic episodes included:

- Caucasian ethnicity;
- A previous manic episode;
- Good social functioning (no work or social impairment, living independently or with family);
- Outpatient treatment, and being neither satisfied nor dissatisfied with life;
- In patients with rapid cycling treated with lithium or Divalproex;
- Increased risk or non-stabilization was associated with a history of recent substance use disorder (SUD);
- Female gender, and late onset of first depressive episode;
- Early-life verbal abuse.

Among responders to long-term lithium therapy, the risk of recurrence was higher in those with atypical features (mainly mood-in- congruent psychotic symptoms), inter-episodic residual symptomatology, and rapid cycling.

Psychosocial interventions for Maintenance Therapy

As in case of acute management of BD the role of psychosocial intervention is supported by the data that have supported the benefits of adjunctive psycho-education, CBT, family therapy, and IPSRT in reducing recurrences and improving symptoms in patients with BD.

RCTs of adjunctive group psychoeducation programs demonstrated a longer time to recurrence, fewer recurrences of any type, less time acutely ill, and fewer days of hospitalization during 1-5 years of follow-up.

Pharmacological Treatments for Maintenance Therapy

See Table (4) Recommendations for maintenance pharmacotherapy of bipolar disorder I

Recommendations for maintenance pharmacotherapy of bipolar disorder I

First line	**Monotherapy**: lithium, lamotrigine, (Limited efficacy in preventing mania), divalproex, risperidone LA1b, Aripiprazole **Adjunctive therapy with lithium or divalproex**: quetiapine, risperidoneLA1b, aripiprazole
Second Line	**Monotherapy**: Carbamazepine, palideridone ER **Combination therapy**: Lithium or divalproex + lithium + Carbamazepine, lithium or divalproex + olanzapine, lithium + risperidone, lithium + lamotrigine, olanzapine + fluoxetine
Third Line	**Adjunctive therapy**: phenytoin, clozapine, ECT, omega-3- fatty acids,
Not recommended	**Adjunctive therapy**: flupenthixol

LAI - Long acting injection, ER - extended release, ECT - electroconvulsive therapy.

Given the metabolic side effects, use should be carefully monitored

Mainly for the prevention of mania

New or change to recommendation

First-line options

First line	**Monotherapy**: lithium, lamotrigine, (Limited efficacy in preventing mania), divalproex, olanzapine, quetiapine, risperidone LA1b, Aripiprazole **Adjunctive therapy with lithium or divalproex**: quetiapine, risperidoneLA1b, aripiprazole.

Continue to be first-line monotherapy options for maintenance treatment of BD

- Lithium / Divalproex: lithium monotherapy and combination with Divalproex were significantly more effective than Divalproex monotherapy in preventing relapse during up to two years of follow-up.
- Lamotrigine: as effective as Lithium
- Olanzapine: A large, observational study (EMBLEM) compared Olanzapine monotherapy or as an adjunct and found no significant difference in rates of improvement, remission, or recovery, but significantly lower relapse rates with Olanzapine alone compared to adjunctive Olanzapine
- Quetiapine.
- Risperidone LAI.
- Aripiprazole.

Second-line options

Second Line	**Monotherapy**: Carbamazepine, palideridone ER **Combination therapy**: Lithium or divalproex + lithium + Carbamazepine, lithium or divalproex + olanzapine, lithium + risperidone, lithium + lamotrigine, olanzapine + fluoxetine

Carbamazepine: maintenance treatment with Carbamazepine has a similar efficacy to Lithium for rates of relapses, significant tolerability issues with Carbamazepine and the difficulty in combining this agent with other psychotropic medications because of its hepatic microsomal enzyme induction properties, Carbamazepine continues to be recommended as a second-line option

Paliperidone ER

Third-line Options

Third Line	**Adjunctive therapy**: phenytoin, clozapine, ECT, omega-3- fatty acids,

Asenapine. Based on evidence of maintenance of benefits, but in the absence of relapse prevention data and clinical experience, Asenapine is recommended as a third-line option for maintenance therapy. (CAN MAT 2013).

Not recommended	**Adjunctive therapy**: flupenthixol

Rapid Cycling

There were no significant differences between combination of Lithium and divalproex and Lithium monotherapy in the rate of relapse or time to relapse. In the STEP-Bo study, among patients who were responders to adjunctive antidepressants and continued this treatment, those with a rapid cycling Course had three times more depressive episodes compared to those without rapid cycling (CAN- MAT 2013).

Mixed States

In a post-hoc analysis of patients with mixed episodes where responders to Olanzapine were randomized to continue Olanzapine or switch to placebo, there were significant reductions in relapse rates with Olanzapine compared to placebo open-label extension treatment, patients with manic or mixed episodes, with or without psychotic symptoms, showed' comparable improvements in mania and overall subtypes across subgroups (CANMAT 2013).

In an open-label trial of adjunctive Risperidone in 114 patients with mixed or manic episodes, significant reductions from baseline in manic, depressive, and overall symptom scores were observed with combination therapy in both the manic and mixed groups. (CAN- MAT 2013).

E. BIPOLAR DISORDER IN SPECIAL PATIENT POPULATION

In Females

Premenstrual syndrome (PMS)/ premenstrual dysphoric disorder (PMDD):

Women with premenstrual exacerbation are prone to have more episodes (mainly depressive) and also manic symptoms as well, more severe symptoms and a shorter time to relapse (CAN MAT - 2013)

Pre-conception: careful review of risks and benefits and a treatment plan and ongoing monitoring are critical for women in Child-bearing age with BD.

A study revealed that (12%) of women with BD or MOD were receiving category 0 and 1% category X during pregnancy (CANMAT 2013)

Pregnancy: The most recent recommendations on the use of psychiatric medications during pregnancy and lactation are available from the American Congress of Obstetricians and Gynecologists (ACOG), the reader is referred to this Practice Bulletin for more information. In addition, please visit the Canadian Hospital for Sick Children Mothers website (see table of psychiatric medication and lactation)

- The use of psychotropic medications should be carefully weighed against the risks to the mother and the fetus as well during the 1st trimester.
- In the second and third trimester, psychotropic medications can be used if necessary.
- It is critical to monitor the lithium levels because of blood volume changes during pregnancy. Different patient populations' studies have proved Divalproex and Carbamazepine teratogenicity risk.
- Topiramate was associated with reduced birth weight but no de- crease in gestational age and no increase in structural defects.
- No increased risk of major congenital anomalies compared to unexposed controls pregnancy with antidepressants use, however some studies showed complications, including induced delivery, preterm birth, caesarean section and increased risk of persistent pulmonary hypertension of the new born as well.

- Cardiac anomalies are concerns with the use of Fluoxetine, Paroxetine, and Citalopram although the absolute risk for these specific effects was not that much.
- New drug labels of atypical antipsychotic drugs contain information about the potential risk for abnormal muscle movements and withdrawal symptoms including agitation, abnormal muscle tone, and tremor, sleepiness, breathing, and feeding difficulties in new-borns (CANMAT 2013).

Psychiatric medications in pregnancy and lactation			
Agent	**Pregnancy risk category**	**American Academy of Pediatric rating**	**Lactation, risk category**
Anxiolytic Medications			
Benzodiazepines Alprazolam	D	Unknown, of Concern	L3
Chlordiazepoxide	D	N / A	L3
Clonazepam	D	N / A	L3
Clonazepam	D	N / A	L3, L4 is used
Diazepam	D	Unknown, of Concern	cautiously
Lorazepam	D	Unknown, of Concern	L3
Oxazepam	D	N / A	L3
Benzodiazepines for insomnia			
Estazolam	X	N / A	L3
Fluraz.epam	X	N / A	L3
Quarepam	X	Unknown, of Concern	L2
Tomazepam	X	Unknown, of Concern	L3
Triazolam	X	N / A	L3
Non-benzodiazepine anxiolytics and hypnotics			
Bupropion	B	N/A	L3
Chloral hydrate Eszopllcone	C	Compatible	L3
Zaleplon	C	N/A	N/A
Zolpidem	C	Unknown, of concern	L3
	B	N/A	L3
Antiepileptic and mood-stabilizing medications			
Lithium carbonate	D	Contra indicated	L4
Valprolic acid	D	Compatible	L2
Carbamazepine	D	Compatible	L2
Lamotrigine	C	Unknown	L3
Selective serotonin re-uptake Inhibitors			
Citalopram	C	N / A	L3
Escitalopram	C	N / A	L3 in older infants
Fluoxetine	C	Unknown, of Concern	l2 in oacter infants, L3 if used in Neonatal periods
Fluvoxamine	C	Unknown, of Concern	l2
Paroxetine	D	Unknown, of Concern	l2
Sertraline	C	Unknown, of Concern	l2
Other anti-depressants			
Bupropion	B	Unknown, of Concern	L3
Duloxetine	C	N / A	N/A
Mirtazapine	C	N / A	L3
N efazod one	C	N / A	L4
Trazodone	C	Unknown, of Concern	L2
Venlafaxine	C	N / A	L3

Antipsychotic Medications I Typical antipsychotic agents			
Chlorpromazine	C	Unknown, of Concern	L3
Fluphenazine	C	N / A	L3
Haloperidol	C	Unknown, of Concern	L2
Loxapine	C	N / A	L4
Perphenazine	C	Unknown, of Concern	N/A
Pimozide	C	N / A	L4

Postpartum period:

- Distinguishing bipolar depression from MDD can be hard to achieve due to lack of screening instruments designed specifically for use during this period
- Hypomanic symptoms have shown to increase in in the early postpartum period (11.7%) compared to during the first trimester (1.4%) and to eight weeks postpartum (4.9%)
- Previous diagnosis of BD was the strongest predictor of readmissions 10-19 days postpartum, psychotic illness has been shown to peak immediately following a first childbirth (CANMAT 2013).

Menopause:

- In a STEP-BD analysis of 164 patients with BD followed for an average of 30 months, menopausal transition was associated with significantly more visits due to depressive symptoms and fewer euthymic visits compared to a comparison group of non-menopausal women and men (CANMAT 2013).

<u>Issues in the Management of BD in Children and Adolescents</u>

- Recommendations for levels of treatment will not be offered, refer to American.
- Academy of Child and Adolescent Psychiatry (AACAP) guidelines for further information (CANMAT 2013).

Presentation and Diagnosis

The clinical presentation and diagnosis of BD in children and adolescents remains debatable, mainly because pediatric BD has focused on the group of

youth with severe, chronic, non-episode irritability which has led to the proposed DSM-5 diagnosis of Disruptive Mood Dysregulation Disorder (DMDD)

- Among adolescents (15-19 years), BD is leading cause of disability
- The overall prevalence of BD was 1.8% between the ages of 7 and 21 years,
- Among Canadian adolescents and young adults (15-24 years), lifetime prevalence of BD of 3.0% (2.1% in those aged 15-18 years; 3.8% in those aged 19-24 years)
- In patients 12 years old, first episodes were generally depressive, while those in patients less than 12 years old, first episodes were more likely to be sub syndromal manic/hypomanic symptoms.
- In the COBY study in youth (age 7-17 years) and over a five-year follow-up period, the rate of suicide attempts was found to be 18%.
- Self-injury (non-suicidal) has also been reported in more than 20% of BD children and adolescents.

Comorbidities and Mimics:

Anxiety disorder (44%), separation anxiety (24%) and generalized anxiety disorder (GAD) (16%) (CANMAT 2013).

A family history study for patients (age 6-17 years) with BD I revealed extremely high rates of co morbid attention-deficit hyper- activity disorder (ADHD) (85%), oppositional defiant disorder (90%), two or more anxiety disorders (64%), conduct disorder (51%), and SUD (12%) (CANMAT 2013).

Early BD onset (age <12 years) has been associated with ADHD, whereas later BD onset (age 12 years) was associated with panic, conduct, and SUD. Psychotic symptoms have been reported in about one-third of youth with BD, and confer a significantly greater likelihood of lifetime GAD, agoraphobia, social phobia, and obsessive compulsive disorder (OCD) (CANMAT 2013)

Some comorbidities such as obesity, type 2 diabetes mellitus, other endocrine disorders, central nervous system disorders/epilepsy, organic brain disorders/ mental retardation, migraine headaches, cardiovascular disorders, and asthma in a large cohort study were significantly more prevalent among BD children and adolescents patients.

Among 30 adolescents in the COBY study, 40% had levels of high-sensitivity C-reactive protein that are considered to confer a high risk for cardiovascular disease among adults (CANMAT 2013).

Acute and Maintenance Treatment of BD in pediatrics population

Some treatment plans of BD that are efficacious in adults might not be that efficacious in children and adolescents, so that the guide- lines developed for adults with BD should be cautiously applied to youth until further studies become available.

Psychosocial Interventions

No differences in time to recurrence of depression or mania was found when comparing adjunctive family-focused treatment (FFT) and enhanced care, but FFT group patients have spent fewer weeks in depressive episodes.

A modified FFT was associated with improved depression, hypo- mania, and psychosocial functioning scores in youth who were thought to be at high risk for developing BD (according to a one- year open trial)

Preliminary findings suggest that child and family-focused CBT, dialectical behavior therapy (DBT), and IPSRT may be promising in the management of BD in this patient population. (CANMAT 2013)

Pharmacological Management

Atypical Antipsychotic

For pediatric patients, US FDA has approved Quetiapine for the first-line treatment of acute manic/mixed episodes in light of tolerability/safety Other Antipsychotics such as Olanzapine (side effects: weight gain and metabolic disturbances) were approved as second-line treatments Effect sizes were greater for the atypical antipsychotic agent group compared to a mood stabilizer group Mood stabilizer group included studies on Topiramate revealed efficacy as mood stabilizers.

Weight gain (medication-associated) was much greater with atypical antipsychotic agents when compared to mood stabilizers (effect size 0.53 versus 0.10)

Adolescents also had significant changes in fasting Blood Glucose level, total Cholesterol, Triglycerides, Alanine Aminotransferase, and Prolactin as well

When Topiramate was added to Olanzapine therapy in pediatric patients with BD (n=40) resulted in much lesser weight gain than with Olanzapine alone, no differences in mania symptom scores have been noted.

When comparing Risperidone, Lithium and Divalproex, the response rate for Risperidone (68.5%) was much greater than for Lithium (35.6%) and Divalproex (24.0%). However, increased weight gain, Body mass index (BMI), and Serum Prolactin levels were also much greater with Risperidone than with the others.

Patients with BD manic/mixed episodes and comorbid ADHD experienced significant reductions in manic -but not depressive or ADHD- symptoms with Aripiprazole when compared to placebo group (level 1).

Analysts suggest a much lower response to atypical antipsychotic agent therapy in pediatric patients with BD and comorbid OCD, but not in those with autism comorbidity.

Anticonvulsants

Several small open-label trials revealed very good improvements with Lamotrigine monotherapy in both depressive and manic clinical end points as well as an adjunct to atypical antipsychotic agents.

A four-week RCT of Divalproex ER in 150 pediatric patients (age 10- 17 years) with BD mania/mixed episodes found the same results with of active treatment and the placebo However, a six-month open label study in 226 youth with BD I mania/mixed episodes found that Divalproex ER reduced mania scores and was more tolerability in general.

In an eight-week, open-label trial in 27 youth with Bipolar spectrum disorders, Carbamazepine ER was associated with improvements in mania, depression, psychosis, and ADHD symptoms, but drop-out rates were high (CANMAT 2013)

Issues in the Management of BD in Older Patients

Presentation and Course

The two-year EMBLEM study included 475 patients more than 60 years with acute BD mania/mixed found that:

Older patients had a history of more rapid cycling, less severe manic and psychotic symptoms and fewer suicide attempts.

No difference in depressive symptomatology (CANMAT 2013).

Older patients with late-onset BD (age>50 years) experienced a better 12-week outcome with a faster recovery and earlier discharge compared to older patients with early-onset BD (age <50 years). (CANMAT 2013)

The prevalence of mixed episodes was reported at 10% in patients' > 60 years in an RCT (CANMAT 2013).

Comorbidity

In a case-controlled study, there was a higher prevalence among older patients (n = 82, age> 60 years) when compared to age- matched controls with BD of diabetes mellitus (27%), atopic diseases (20%), Smoking (24%), and unfavorable social functioning (22%) (CANMAT 2013).

A large survey found the use of anticonvulsants to be associated with an over two fold increased risk of fracture in geriatric patients. Patients with BD had a 20% increased risk of fracture compared to those without BD, independent of the use of anticonvulsants.

Older adults with BD have been shown to have much higher levels of cognitive dysfunction than age-matched mentally healthy control group.

Among older patients with BD, a greater burden from vascular risk factors has been associated with poorer outcomes on some cognitive measures. (CANMAT 2013).

Several analyses have failed to detect a significant association between dementia or cognitive performance in older patients and the use of lithium (CANMAT 2013).

Treatment of BD in Older Patients

Data assessing pharmacotherapy specifically in older patients with BD remain insufficient.

In a post-hoc, pooled analysis of two Quetiapine monotherapy RCTs in patients with acute BD mania, subgroup analysis of 59 older adults (age>55 years) demonstrated significant improvement in manic symptoms as early as day four versus placebo (CANMAT 2013).

At 12 weeks, the results from an open-label study of adjunctive Lamotrigine in older patients (n=57, age>60 years) with BD I or BD II indicated an overall

significant decline in depressive symptoms, with a 65% response rate and a low rate of discontinuations because of adverse events (10%) (CANMAT 2013).

Issues in the Management of BD in Patients with Comorbid Conditions

For more information, refer to a task force report on the management of patients with mood disorders and co morbid psychiatric and medical conditions developed by the CAN MAT Co morbidity Task Force (CANMAT 2013).

Prevalence

Medical

It was found that the prevalence of one or more general medical conditions in patients with BD I was 32%. This is according to large US National Epidemiologic Survey on Alcohol and Related Conditions study.

Patients with BD I or BD II were found to have a mean of 2.5 co morbid medical conditions (in another study). Patients with BD have five times prevalence of cardiovascular disease and hypertension when compared to controls. Patients with BD I have more than two times risk of cardiovascular mortality when compared to those with BD II, in a long-term follow-up study

Patients with BD are at very high risk for hospital readmission due to cardiovascular troubles.

Patients with BD have increased rate of metabolic syndrome two times more than the general population.

In patients with BD, comorbid metabolic disturbances have been associated with more complicated illness presentation, lesser response to treatment, and worse illness course.

In patients with BD, a higher BMI has been associated with increased frequency of manic and depressive relapses, more suicidal attempts, and much less psychosocial functioning, sub threshold anxiety disorders, a greater frequency of type II diabetes and hypertension as well.

Obesity or even overweight have also been shown to have a negative impact on long-term treatment response and on cognitive function in euthymic patients with BD

Comorbid migraine affects nearly one in every four patients with BD, and confers a very high risk for suicidal behavior, comorbid psychiatric diseases, rapid cycling, a greater number of mood episodes as well as increase in life time hospitalizations compared to patients without migraine. The prevalence of migraine is reportedly higher in patients with BD II than in those with BD I (35% versus 19%)

Up to 12% of patients with epilepsy may have a diagnosis of BD; however, only 1.4% had pure BD, as all other cases were associated with differing states relating to the primary diagnoses of epilepsy. (CANMAT 2013)

Psychiatric

A retrospective analysis of four trials including 566 patients with rapid-cycling BD I or BD II found lifetime rates of anxiety disorders and SUD of 46% and 67%, respectively.

Comorbid SUD has been linked to an increased risk of suicide and suicide attempts, other unnatural deaths, nicotine dependence, and other SUDs in patients with BD Patients with BD have a five times higher risk of current cigarette smoking compared to the general population.

In addition, suicidal behavior has been associated with others such as border line personality disorder (BPD), panic disorder, alcoholism, other drug addictions, and GAD. Only BPD and alcoholism were independently associated.

In patients with BD, Comorbid SUD confers significant impairment in social functioning compared to patients without SUD.

In patients with rapid cycling BD, comorbid SUD was associated with a two times increased risk of being not properly medicated (not receiving a mood stabilizer after the onset of first mania/hypomania).

An uncontrolled study suggested that comorbid SUD may be associated with a very high risk of antidepressant-induced switch to mania (76%).

A functional assessment of patients (n = 206) with BD I or BD II noted that more than one-third had missed more than 2 years of work time over a 5-year period. Also, it was found that extended un- employment was associated with increased rates of panic disorder and alcohol abuse as well.

The presence of comorbid panic disorder in patients with BD I (compared to those with no panic disorder) was associated with much more depressive, manic, any mood episodes, and increased risk of lifetime SUD and eating disorders as well.

The prevalence of lifetime eating disorders, particularly binge eating disorder, is high (14%) in patients with BD.

Patients with BPD are noted to be at high risk of being misdiagnosed as having BD, and vice versa.

The prevalence of lifetime ADHD in adults with BD was 18%, which was substantially higher than that found in patients with MDD (5%). (Reported by the International Mood Disorders Collaborative Project)

Comorbid ADHD has been associated with a much higher number of comorbid psychiatric conditions.

Negative impact on the course of BD in adulthood impaired psychosocial functioning, and poorer overall quality of life. (CANMAT 2013)

Treatment of BD in Patients with Co-morbidities

Bipolar collaborative chronic care model was as effective in patients with BD and comorbid conditions (SUD, psychiatric, and / or medical) as in those without. It is necessary to pay specific attention to physical quality of life in patients with cardiovascular disease.

BD medical care model six-month pilot study revealed a decline in physical health-related quality of life compared with usual care in patients with BD and cardiovascular disease-related risk factors. Improvements in mental health-related quality of life were also seen, but were not that significant. (CANMAT 2013)

Medical

14-week, small (n = 10) pilot study of an integrated psychosocial treatment model including 3 treatment modules (nutrition/weight loss, exercise, and wellness treatment) administered in group sessions as well as weekly exercise, demonstrated improvements in quality of life, weight and depressive symptoms.

Open-label adjunctive Ziprasidone was effective in significantly improving weight-related parameters while maintaining or even improving mood symptoms in obese/overweight patients (n=25) with BD taking atypical antipsychotic agents, Lithium, or Divalproex. In a recent report, Bariatric surgery for weight reduction was as effective in patients with BD as in those without. (CANMAT 2013)

Psychiatric

Integrated group therapy, which employed a cognitive-behavioral model integrating treatment of both conditions, resulted in an increased likelihood of achieving total abstinence and a better overall composite outcome compared to regular group counseling.

Psychosocial interventions review for the treatment of comorbid anxiety in patients with BD showed that CBT, mindfulness-based CBT, and relaxation training may be effective. On the other hand, interpersonal and family therapy and psychoeducation alone did not seem to be beneficial in treating comorbidity.

In patients with BD and comorbid alcohol abuse or dependence, adjunctive Quetiapine did not show significant improvements in measures of alcohol use and dependence compared to placebo. Although depressive symptoms improved in one trial as well.

Adjunctive Naltrexone in 50 patients with BD I or BD II and co- morbid alcohol dependence demonstrated a trend toward greater decrease in alcohol-related outcomes compared to placebo (in a 12-week RCT). Response to Naltrexone was significantly related to medication adherence.

Both Quetiapine and Risperidone improved manic and depressive symptoms, as well as drug craving, with no significant differences between treatments as shown in a 20-week RCT involving 80 patients with BD and comorbid SUD, however, this study lacked a placebo group.

Patients with rapid cycling BD and comorbid SUD, were stabilized on the combination of lithium plus Divalproex. There is no significant difference in mood relapse rates between patients randomized to continue combination

therapy and those who received Lithium alone. (As shown in a small RCT involving 31 patients).

An analysis of 98 patients from the acute open-label phase of this study found that these patients have a very low response to treatment and a high burden of serious medical comorbidity.

A six-week RCT in 43 pediatric patients with BD manic/mixed episodes and comorbid ADHD demonstrated significant improvements in manic, but not depressive or ADHD symptoms with Aripiprazole versus placebo (level 1).

In a small randomized crossover trial in youth with BD (n=16 & age 8-17 years) who had responded to Aripiprazole, the addition of methylphenidate did not result in significant reductions in ADHD or mania symptoms compared to placebo, however no effect was seen on depressive symptoms.

In 111 patients with BD and comorbid panic disorder or GAD, Risperidone was no more effective than placebo on any of the anxiety measures (as shown in an eight-week RCT).

A post-hoc analysis of the BOLDER I and BOLDER II trials reported significant improvements in anxiety symptom scores as early as week one and these were sustained through week eight with Quetiapine compared to placebo (as done in 1051 patients with BD I or BD II depression).

This suggests that Quetiapine should be investigated in patients with BD and comorbid Anxiety disorders (CAN MAT 2013).

F. ACUTE AND MAINTENANCE MANAGEMENT OF BIPOLAR II DISORDER

Acute Management of Hypomania

Two small, eight-week RCTs indicated that Quetiapine (n = 39) and Divalproex ER (n = 60) were superior to placebo in treating patients with hypomania or mild mania. In addition, a previously described six-month, open-label trial suggested efficacy for Risperidone. Clinical practice suggests that medications that are effective in mania are efficacious in treating hypomanic symptoms. (CAN- MAT 2013)

Acute Management of Bipolar ll Depression

Recommendations for pharmacological treatment of acute bipolar II depression

First line	Quetiapine.
Second Line	Lithium, lamotrigine, divalproex, lithium or divalproex. Antidepressants, lithium + divalproex. Atypical antipsychotic agents + antidepressants.
Third Line	Antidepressant monotherapy (primary for those with infrequent hypomania's), switch to alternative antidepressant, quetiapine + lamotrigine, adjunctive ECT adjunctive NAC, adjunctive T3
Not recommended	See text on antidepressants for recommendations regarding antidepressant monotherapy

ECT = electroconvulsive therapy; NAC = N-acetyl cysteine; T3 = triiodothyronine; XR = extended release.

New or change to recommendation.

Psychotherapy

The role of psychotherapy in the treatment of BD II depression has also been understudied.

12-week feasibility study demonstrating that 41 % of patients with BD II depression achieved a response with IPSRT monotherapy without an increase in mania scores.

Pharmacotherapy

First-line Options:

Quetiapine

The four large RCTs demonstrating the efficacy of Quetiapine monotherapy in combined groups of patients with BD I or BD II depression, 335). Quetiapine doses of 300 mg/day and 600 mg/ day were both associated with significantly greater improvements com- pared to placebo.

Significant improvements in core depressive symptoms, including reported sadness, anhedonia, negative thoughts, and suicidality, as well as anxiety symptoms.

Second-line Options:

Lithium

The EMBOLDEN I trial included a lithium comparator arm, and provides the only placebo controlled, parallel-group RCT data for Lithium in acute BD II depression (CANMAT 2013).

In this trial, neither lithium nor Quetiapine were superior to placebo in improving depression scores in patients with BD II, raising the possibility that this was a failed, rather than negative, trial. In addition, the mean Lithium levels were <0.8 mEq/L.

Divalproex

A meta-analysis of four small studies (total n = 142) in patients with BD I or BD II depression found that the RR of response was double, and of remission almost two-thirds greater, with Divalproex mono- therapy compared to placebo. Other study showed no separation from placebo, Thus, the data in aggregate are mixed.

Lamotrigine

In one study, 221 patients with BD II received Lamotrigine 200 mg/day or placebo for eight weeks, while in the second 206 patients with BD I or BD II depression were randomized to Lamotrigine 100-400 mg/day or placebo. In neither trial was Lamotrigine superior to placebo.

Third-line Options:

Antidepressant monotherapy

Paroxetine was not superior to placebo, in BD ll DEPRESSIVE EPISODE, interestingly; switch rates into hypo / mania were similar with Paroxetine and placebo. In a one study of Fluoxetine mono- therapy, 60% of patients responded and 58% remitted (. Although about 24% experienced hypomania / subsyndromal hypomania, this did not result in treatment discontinuation.

Quetiapine + lamotrigine

Combination was associated with improvements in BD patients (an open lable trial) but Data were not reported separately for patients with BD II.

Adjunctive ECT

An open-label study of twice weekly bilateral ECT included patients with BD II who were medication refractory (n = 67). They achieved a response rate of 79% and a remission rate of 57% (343). This response rate was intermediate between patients with MDD (94%) and those with BD l

Novel Treatments

In a sub-analysis of a small number of patients with BD II (n = 14) participating in a 24-week RCT, significantly more patients achieved full remission of both depressive and manic symptoms with adjunctive NAC compared to placebo (344). In a retrospective chart review of patients with treatment-resistant BD II or BD NOS depression (n = 159), treatment with supra physiologic doses of T3 was associated with response in a majority of patients.

<u>Maintenance therapy for Bipolar II Disorder</u>

First line	Lithium, lamotrigine, quetiapine
Second Line	Divalproex; lithium or divalproex or atypical antipsychotic+ antidepressant; adjunctive quetiapine adjunctive lamotrigine; combination of two of; lithium, divalproex, or atypical antipsychotic
Third Line	Carbamazepine, atypical antipsychotic agent ECT, fluoxetine

ECT = electroconvulsive therapy

New or change to recommendation.

Psychotherapy

A post-hoc analysis of 20 patients with BD II who participated in a single-blind RCT demonstrated the benefits of adjunctive psycho education compared to unstructured support groups, with lasting benefits for up to five years.

Pharmacotherapy

The major focus of maintenance therapy for patients with BD II is prevention of depressive episodes. New data support the addition of Quetiapine monotherapy as first-line, and adjunctive Quetiapine as second-line options for maintenance treatment for BD II.

Lithium and Lamotrigine continue to be recommended as first-line agents and Fluoxetine has been added as a third-line treatment option.

First-line Options:

Quetiapine

From EMBOLDEN 1 and 2 trails, among patients with BD II who achieved remission during acute-phase treatment with Quetiapine, those who continued Quetiapine monotherapy for up to 52 weeks were significantly less likely to experience relapse into any mood episode or depressive mood episode compared to those who switched to placebo.

Second-line Options:

Adjunctive Lamotrigine

A retrospective chart review reported that the majority of patients with treatment-resistant BD II depression who received adjunctive Lamotrigine for + 6 months were much or very much improved (348). The mean dose of Lamotrigine was 199 mg I day and the maximum 400 mg I day.

Adjunctive Quetiapine

Naturalistic studies in combined populations of patients with BD I and BD II demonstrated high rates of sustained euthymia with adjunctive Quetiapine, neither of these studies reported separate results for patients with BD II.

Third-line Option

- Carbamazepine
- Fluoxetine monotherapy.
- ECT

Clinical point could be a focus of interest

Is cognitive dysfunction an issue in patients with BD II? Persisting cognitive dysfunction is common and debilitating in patients with BD II.

- In a meta-analysis, patients with BD II had lower performance scores than healthy controls in all cognitive domains (357). Cognitive impairment in 80 II was as severe as in BD I, with the exception of memory and semantic fluency.
- In a case series of 58 BD I, BD II, or BD NOS patients who received Donepezil for memory problems 84% with BD II (36/43) showed improvement, No improvement with BD I (017) and 50% improvement of patients with BD NOS (4/8)
- More than half of the patients with BD I had worsening of affective symptoms compared to only 2% of those with D II and 25% of those with BD NOS. (CANMAT 2013 Ref. 358).
- Do the clinical features of depressive episodes inform treatment decisions in BD II?

Data from STEP-BD show that:

Mixed hypomanic symptoms are common during depressive episodes, occurring in 70% of patients with BD II, compared to 66% of patients with BD I (CANMAT 2013)

Adjunctive antidepressants did not lead to greater recovery rates among patients with mixed symptoms, and were in fact associated with greater manic symptom severity at the three-month follow-up (CANMAT 2013).

Recovery rates were not reported separately for patients with BD II in this sample, this suggests that antidepressants should be avoided in BD II depressive episodes with concomitant hypomanic symptoms.

Psychotic symptoms are also relatively common in BD II depression, and were present in 20% of patients with BD II in a Spanish study (CANMAT 2013).

There is little information to guide the treatment of psychotic depression in patients with BD II, but clinical experience and studies in MOD suggest that antipsychotic medications either as monotherapy (e.g., Quetiapine) or in combination with mood stabilizers may be required.

G. BIPOLAR SPECTRUM DISORDERS

Diagnosis

Formulating treatment recommendations for patients with bipolar spectrum disorders (BSDs, also referred to as BD NOS in the DSM- IV) remains hampered due to:

- lack of consensus regarding which disorders should be included in this category,
- Almost complete absence of well -designed clinical trials in this patient group.
- Uncertainty regarding the diagnostic stability of BSDs. In fact, BSDs may be prodromal to BD I and BD II in a substantial number of patients.

According to one longitudinal study of 57 people with cyclothymia or BD NOS, where 42% progressed to BD II and 10% to BD lover a 4.5-year follow-up period (CANMAT 2010).

Epidemiology

- The prevalence of BSDs was greater than those of BD I and BD II combined 1.4% of the population met life time criteria for sub threshold BD (CANMAT 2013)
- Lifetime prevalence of 2.4% reported in the National Comorbidity Survey Replication (NCS- R) (CAN MAT 2013)
- Over 35% of people with major depressive episodes also met the life time criteria for sub threshold hypomania (CAN MAT 2013)
- The NCS-R reported that, compared to people with major depressive episodes alone, those who had sub threshold hypo mania shared a number of clinical features with those suffering from BD I or BD II, including an earlier age of onset, more frequent depressive episodes, a greater number of suicide attempts, and higher rates of comorbidity

Management

Very few studies have investigated treatment options for BSD

The only RCT that has been reported to date was conducted in 56 youth with BSD or cyclothymia who were randomized to Divalproex or placebo for up to five years No differences between treatment groups in time to study discontinuation due to a mood episode or for any reason, severity of mood symptoms, or psychosocial functioning (CANMAT 2013).

A small case series reported rapid and sustained symptom remission in four patients with BD NOS and depressive or mixed symptoms with low dose Quetiapine (50-75 mg) (CAN MAT 2013).

In addition, a retrospective chart review of 34 patients with treatment-refractory BD NOS found that adjunctive treatment with supra physiologic doses of T3 was associated with an improvement in depressive symptoms in 85% of patients, and remission in 38% (CANMA T 2013).

In a case series of 58 patients with BD prescribed Donepezil for memory problems, 50% of those with BD NOS (4 /8) had improvements in memory; however, 25% had a worsening of affective symptoms.

In the absence of well-designed clinical trials, specific treatment suggestions for patients with BD NOS cannot be made. Clinicians should formulate treatment plans based on patients presenting symptoms, course of illness, previous treatment responses, and family history.

Monitoring and Safety

All available guidelines provided recommendations for initial and follow-up laboratory investigations and monitoring strategies for patients with BD.

BD and some of its treatments can increase the risk of comorbid medical conditions, as well as risk factors for cardiovascular disease such as overweight ⁄ obesity, diabetes, metabolic syndrome, and dyslipidemia.

Complete medical and laboratory investigations should be per- formed at baseline, with ongoing monitoring for weight changes and adverse effects of

medication, with attention to specific monitoring recommendations for individual agents.

The UNITE global survey of 1300 patients with BD found that monitoring of safety parameters does not occur in the majority of patients, with less than 30% undergoing weight and blood pressure measurements, and less than 5% undergoing a physical examination or blood tests during interactions with their principal health care provider.

Safety and tolerability of pharmacotherapy for BD

The previous iterations of the guidelines have extensively reviewed the safety and tolerability of pharmaco-therapeutic options; only new data are included here. (CANMAT 2013)

Weight gain

Many trials concluded that, in 47 patients with BD receiving maintenance therapy following their first manic episode, the mean 12-month weight gain was significantly greater compared to healthy control subjects (4.76 kg versus 1.50 kg; $p = 0.047$).

In addition, 12-month rates of overweight ⁄ obesity were > 50% in patients with BD, almost double those in healthy subjects. (CAN- MAT 2013)

Metabolic syndrome and type 2 diabetes

Some data continue to demonstrate high rates of diabetes and metabolic syndrome associated with atypical antipsychotic agent use in patients with BD. However, in a post-hoc analysis of a six month RCT, the incidence of metabolic syndrome with Aripiprazole maintenance therapy was similar to that of placebo. (CANMAT 2013) Many other data confirm the potential for metabolic disturbances with Divalproex treatment. In a cohort study, Divalproex was associated with significantly higher plasma insulin, triglyceride levels, and BMI, as well as lower fasting glucose and high-density lipoprotein cholesterol (HDL-C) levels.

Dyslipidemia

It is an important cardiovascular risk factor. As discussed in previous iterations of the guidelines, atypical antipsychotic agents as well as Lithium ⁄ Divalproex can cause dyslipidemia.

Other data from a cohort study found that Divalproex was associated with low HDL-C levels and high Adiponectin levels in patients with BD compared to non-psychiatric matched control subjects. (CANMAT 2013)

Lipid profiles should be monitored and appropriate lipid-lowering medications prescribed as needed, according to published recommendations for the management of dyslipidemia.

Endocrine side effects

Some study indicated higher risks of hypothyroidism in patients with BD who had used Carbamazepine alone [odds ratio (OR) = 1.68], combination Lithium and Valproate (OR = 2.40), combination Lithium and Carbamazepine (OR = 1.52), or all three agents (OR = 2.34) compared to patients who had never used any of these agents. A meta-analysis of 390 RCTs and observational studies found that Lithium was associated with an increased risk of clinical hypothyroidism (OR = 5.78), as well as increases in thyroid-stimulating hormone and parathyroid hormone. (CANMAT 2013)

Suicide

Many attempts found no significant differences between Lithium and Divalproex in time to suicide attempt or suicide event, al- though the trial was statistically underpowered to detect differences. (CANMAT 2013)

Cognitive impairment

Three meta-analyses have demonstrated persistent cognitive impairments in euthymic patients with BD, including deficits in executive functions, verbal memory, learning, processing speed, and attention. (CANMAT 2013)

In addition, patients tested during a manic ⁄ mixed or depressed state showed exaggerated impairment on measures of verbal learning.

There is greater cognitive dysfunction in euthymic BD patients who are taking antipsychotic medications compared to healthy control subjects or to those not taking antipsychotic agents. (CANMAT 2013)

Hypersensitivity and dermatological reactions

Additional data demonstrate the risk of serious rash, erythema multiform, Stevens–Johnson syndrome, or toxic epidermal necrolysis with Lamotrigine, Carbamazepine, and Divalproex. (CANMAT 2013)

A 12-week trial demonstrated a statistically significant reduction in the development of rashes with a slow titration of Lamotrigine compared to a standard titration schedule. (CANMAT 2013)

Sedation

In a pooled analysis of data from three short-term trials in patients with BD, Asenapine monotherapy and as an adjunct was associated with higher rates of somnolence than placebo, which occurred after 1–9 days of treatment and persisted for 1–4 weeks. (CANMAT 2013)

Gastrointestinal symptoms

ER Carbamazepine showed significantly fewer autonomic and gastrointestinal adverse events compared to the immediate-release formulation, in a three-month RCT.

Neurological side effects including EPS

An increased risk of Neuroleptic malignant syndrome associated with the use of antipsychotic medications (OR = 2.36) has been re- ported in patients with BD. (CANMAT 2013)

A studied analysis in patients with a mood disorder reported an increased rate of akathisia in patients receiving Aripiprazole (18%) compared to placebo (5%). (CANMAT 2013)

Fracture risk

In a Veterans Administration prospective cohort study, the use of anticonvulsants was associated with a twofold greater risk of fracture among patients (age ‡ 50 years) with BD.

A diagnosis of BD was associated with a 20% increased risk of fracture, independent of anticonvulsant use. Antidepressants and antipsychotic agents can similarly decrease bone mineral density. Screening for bone mineral density may be indicated in high risk populations. (CANMAT 2013)

Baseline laboratory investigations in patients with bipolar disorder

- Complete blood count (CBC)
- Fasting glucose
- Fasting lipid profile (TC, VLDL, LDL. HDL, TG)
- Electrolytes
- Liver enzymes
- Serum bilirubin
- Prothrombin Time and Partial Thromboplastin time
- (PT/PTI)
- Urinalysis
- Urine toxicology for substance use
- Serum Creatinine
- 24-hour Creatinine clearance (if history of renal disease)
- Thyroid stimulating hormone
- Electrocardiogram {>40 years or if indicated)
- Prolactin
- Pregnancy test (if relevant}

Baseline and Follow-up Investigations for antipsychotics						
Monitoring of antipsychotics	**Baseline**	**4 weeks**	**8 weeks**	**3 months**	**6 Months**	**Annually**
Weight Body mass index	All	All	All	All	All	Twice / year
waist circumference	All					All
Blood Pressure	All			All		All
Fasting plasma glucose HgbA1C	All			All		All
Fasting lipid profile	All			All	CLZ, QUE CLZ	All
Urea, Creatinine and Electrolytes	All			CLZ		All
Full Blood Count	All					All
Electrocardiogram (ECG)	All if above 40 ys or if Indicated			CLZ		CLZ
Prolactin	All				All	If symptoms suggest hyperprolactinemia
Liver Function Tests	All			CLZ		All CLZ
Serum C reactive protein	CLZ					
Troponin Level	CLZ					
Thyroid Function Tests	QUE					QUE
Ophthalmic exams	QUE				Que (Twice / T)	
Serum Ammonia	With symptoms of lethargy, mental status change					
Creatinine Phosphokinase	Baseline Temp. if NMS is suspected					
Pregnancy Test	All					
WBC Absolute neutrophil Count (ANC)	Basic, weekly for 1st 6 months, fortnightly for the 2nd 6 months, then monthly. If D/C weekly for additional 4 weeks If D/C due to leucopenia weekly for 12 months If D/C due to leucopenia / granulocytopnia, biweekly WBCs May need to be rest for 6 months period If D/C 3 days weekly hematologic testing for additional 6 weeks					
Adopted from	1. Canadian network for mood and anxiety treatments CANMAT 2009 2. Up-to-date 2013 3. The Maudsley Prescribing Guidelines in Psychiatry 10 Edition 4. National peer critics (NPS) Australia 2011					
Abbreviation	OLZ : Olanzapine, QUE : quetiapine, CLZ : Clozapine					

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Baseline and Follow-up Investigations for mood sterilizers					
Monitoring of Stabilizers	Baseline	8 weeks	12 months	Every 6 months	Annually
Weight (Body Mass Index)	Li, DVP, COZ			DVP, Li, CBZ	
Waist Circumference					
Vital Signs					
Fasting Plasma glucose Hgb A1c					
Fasting Lipid Profile					
Urea, Creatinine and Electrolytes	Li, CBZ	Li	Li	Li	
Full Blood Count	DVP, LI CAZ			DVP, CBZ	DVP, CBZ
Electrocardiogram (ECG)	Only if above 40 ys or if indicated				
Prolactin					
Liver Function Tests	DVP, LI CAZ			DVP, CBZ	DVP, CBZ
Serum C-reactive protein					
Troponin level					
Thyroid Function Tests	Li			Li	
Serum Calcium and magnesium	Li				Li
Parathyroid Hormone (PTH)	Li if serum calcium is elevated				
Fluid Status	Li, CBZ				
Serum iron	CBZ				DVP, CBZ (twice/year)
Ophthalmic exams	CBZ				
Serum ammonia	DVP : with symptoms of lethargy, mental status change				
Pregnancy test	All				
Serum level	- DVP: 5-7 days after dose adjustment then annually thereafter - Li: 5-7 5-7 days after dose adjustment then quarterly thereafter - CBZ : 5-7 days after dose adjustment then annually thereafter				
adopted from	1. Up-to-date 2013 2. The Maudsley Prescribing Guidelines in Psychiatry 10 Edition				
Abbreviation	DVP : divalproex, Li : lithium, CBZ : carbamazepine				

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Review sheet for inpatient manic and mixed episode whose admission exceeds 8 weeks

Patient name:		*File No:*
Ward		*Date of admission*
Treating doctor		*Duration of admission in weeks*
Current episode		*Medical comorbidity (if present)*
Severity of the episode		
-at admission	-week3	-week8

1- **Which step used at initiation**
   a- Monotherapy
      i- mood stabilizer or antipsychotic
      ii- with or without psychosocial intervention
   b- Combination therapy
   c- Psychotropic + ECT
   d- Psychotropic + ECT + psychosocial intervention

2- **Titration to therapeutic dose and serum level achievement after initial clinical and objective assessment**
   a- within a week
   b- more than one week ⟶ justify

3- **Objective and clinical assessment of level of response achieved**

4- **Time taken to change to the next trial**
   a- 2 weeks
   b- If more ⟶ justify .

5- **For non responder, which of the following measures were taken**
   a- Combination or switch with different psychotropics from 4 to 6
   b- Considered ECT
   c- If other ⟶ specify

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Review sheet for inpatient bipolar disorder whose admission exceeds 6 weeks

Patient name:	*File No:*
Ward	*Date of admission*
Treating doctor	*Duration of admission in weeks*
Psychiatric diagnosis	*Medical comorbidity (if present)*

1- **Titration to therapeutic dose achievement after initial clinical and objective assessment**
   a- within a week
   b- more than one week ⟶ justify

2- **Objective and clinical assessment of level of response achieved**
   a- ≥25 % response after one week if less ⟶ justify
   b- ≥ 50 % response after 2 weeks (remission) if less ⟶ justify
   c- Considering discharge at the end of 6 weeks if more ⟶ justify

3- **What the step used at initiation**

a- Monotherapy

i- mood stabilizer or antipsychotic

ii- with or without psychosocial intervention

b- Combination therapy

c- Psychotropic + ECT.

d- Psychotropic + ECT + psychosocial intervention

4- Time taken to change from one step to another until step 3 in the algorithm

a- 2 weeks

b- if more ⟶ justify

5- For non responder after step 3 of the algorithm, which of the following measures taken

a- Review of diagnosis and/or comorbidity

b- Considered ECT

c- Combination or switch with different psycotropics.

d- If other ⟶ specify.

References:

(CANMAT 2013).

• Chapter 3 (GUIDELINES FOR THE USE AND MANAGEMENT OF LONG ACTING INJECTABLE ANTIPSYCHOTICS IN SERIOUS MENTAL ILLNESS)

A. Indications

Indications for the use of LAI FGA and LAI SGA are summarized in the following Table.

LAI SGA are recommended (in mono or combination):

- As 1st line treatment in schizophrenia, delusional disorder and schizoaffective disorder.
- As 2nd line treatment in bipolar disorder and personality disorders.
- LAI FGA and LAI SGA indications according to the DSM-IV-TR criteria.

LAI FGA		LAI SGA
-	1st line treatment	-
-	-	Schizophrenia Delusional disorder, Schizoaffective disorder
-	2nd line treatment	-
Schizophrenia Delusional disorder Schizoaffective disorder	-	Bipolar disorder Personality disorder

They are contraindicated in organic mental disorders with behavioral disorders (Alzheimer's disease, vascular dementia).

LAI FGA are recommended (in monotherapy or combination):

As 2nd line treatment in schizophrenia, delusional disorder, schizoaffective disorder and personality disorders.

They are contraindicated in recurrent depressive disorder.

B. Most appropriate introduction period during the illness

The most appropriate period for the introduction of LAI FGA and SGA are summarized in the following Only LAI SGA are considered as a therapeutic option during the initial phase of schizophrenic illness:

- They are recommended from the first psychotic episode.

- Their introduction from the first recurrent psychotic episode is also recommended (if the patient was not treated with a LAI antipsychotic).

LAI FGA are not recommended during the early course of schizophrenia (i.e. in a patient who has been newly diagnosed with schizophrenia and who has had no previous antipsychotic treatment). They must be used as maintenance treatment during the long-term evolution of the illness in the case of efficacy of the corresponding oral formulation and when the benefit/risk ratio is considered as satisfactory.

Use of LAI FGA and LAI SGA according to the period of the illness.

LAI FGA	LAI SGA
Schizophrenia	
LAI FGA are not recommended in the initial phase of the disorder. LAI FGA can be used during the maintenance treatment in the case of the efficacy of the oral form and when the benefit/risk ratio is considered as satisfactory.	Very early introduction of LAI SGA is recommended (eventually from the 1st psychotic episode) It is recommended that an LAI SGA be introduced from the 1st recurrent psychotic episode (if the patient was not treated with an LAI antipsychotic).
Bipolar disorder	
LAI FGA are not recommended.	LAI SGA are not recommended in the initial phase of bipolar disorder.

Choice criteria for a LAI FGA or LAI SGA according to the clinical characteristics of patient.

The different clinical criteria for the use of LAI FGA and SGA are presented in the following table. Indications of LAI FGA and LAI SGA according to clinical characteristics of the illness.

Schizophrenia			Bipolar disorder	
1st line	LAI FGA or LAI SGA	Frequent relapses Non-adherence (partial/full) Hazard risk for others Low insight Patient preference Positive depot experienced	1st line	Non adherence Patient preferences Positive depot experience BDI LAISGA
2nd line	LAI SGA LAI FGA or SGA	Cognitive deficits Social isolation Positive symptoms	2nd line	SDI Manic polarity Rapid cycler Hazard risk for others Low insight
	LAI SGA	Negative symptoms Suicidal risk		

C. Schizophrenia

The preferential choice criteria for an LAI formulation (as 1st line treatment) in patients with schizophrenia are:

- Patients presenting frequent relapses, poor adherence or non-acceptance of a long-term treatment.

LAl FGA or LAI SGA are recommended as 1st line treatment. In the case of poor observance, LAl SGA are Considered as the treatment of choice.

- Patients presenting dangerous behaviour.

LAI FGA and LAl SGA are recommended as 1st line treatment.

- Patients presenting a low level of insight about illness and need for treatment.

LAI FGA and LAI SGA are recommended as 1st line treatment.

- Patients wishing treatment by LAI antipsychotic and/or having a history of effective treatment by LAl FGA or LAl SGA.

LAl FGA or LAl SGA are recommended as 1st line treatment.

- Patients presenting cognitive impairment with an impact on their functioning.

LAI SGA are recommended as 1st line treatment. LAl FGA are not recommended.

- Socially and family isolated patients.

LAl SGA as 1st line treatment (LAI FGA as a 2nd line treatment) are recommended for patients with poor social and family support.

- Patients receiving outpatient care without consent. When a compulsory outpatient care program is planned.

LAl SGA as 1st line treatment (LAl FGA as 2nd line treatment) are recommended. The experts failed to reach a favorable consensus for the preferential use of an LAl formulation (as 1st line treatment) for the following groups. They just specified the preferential category of LAl (FGA or SGA) for these groups.

- Patients presenting a predominant clinical dimension. The prevalence of positive or negative symptoms is not a specific factor in choosing to use a depot treatment. If a depot treatment is chosen:
- LAl SGA and LAl FGA are recommended (as 2nd line treatment) for clinical forms where positive symptoms prevail.

Only LAI SGA are recommended (as 2nd line treatment) in cases of predominant negative symptoms.

- Patients presenting a high level of suicide intention. Only LAl SGA are considered (as 2nd line treatment) for patients presenting suicidal behaviour during acute episodes.
- Patients presenting a high level of insight about their illness.

A high level of insight about the illness can be an indication for proposing an LAI SGA as a 2nd line treatment.

LAl FGA are not recommended in cases of high levels of insight about the illness.

D. Bipolar disorder

The preferential choice criteria for a LAl formulation (as 1st line treatment) in bipolar patients are:

- Patients presenting poor adherence with no acceptance of a long-term oral treatment.

LAl SGA are recommended as a 1st line treatment (in monotherapy or in combination).

Patients wishing for a LAl SGA treatment and/or having a history of effective treatment with LAl SGA for bipolar disorder symptoms. Irrespective of the clinical situation, LAl FGA are never recommended as maintenance treatment for bipolar disorder.

The experts failed to reach a favorable consensus for the preferential use of a LAl formulation (as 1st line treatment) for the following groups. They just specified the preferential category of LAl (FGA or SGA) for these groups.

- Patient presenting particular clinical characteristics.

Owing to the medications currently available, LAl SGA are recommended (as 2nd line treatment) in patients presenting a type I bi- polar disorder and/or a predominant manic polarity and/or rapid cycles.

- Patients presenting a dangerous behaviour or a history of impulsive behaviour.

LAl SGA are recommended as 2nd line treatment.

- Patients presenting a low level of insight about the need for treatment.

LAl SGA are recommended as 2nd line treatment.

Benefit/risk ratio for LAI FGA and LAI SGA in schizophrenia

	Prevention of psychotic recurrence
1st line treatment 2nd line treatment	Risperidone LAI Olanzapine pamoate Haloperidol deaconate Zuclopenthixol deaconate Flupentixo! deaconate Fluphenazine deaconate

Benefit/risk balance for LAI FGA and LAI SGA depending on the psychiatric disorder

In patients with schizophrenia the assessment of the benefit/risk ratio for each LAl formulation in the preventive treatment of psychotic recurrence is presented in the previous table.

The molecule ranking appears to be directly linked to the tolerance level for each LAl antipsychotic as shown in previous table.

In patients with bipolar disorder only two LAl SGA are recommended as 2nd line treatment: risperidone microsphere and olanzapine palmitate. LAl FGA are contraindicated as maintenance treatment of bipolar disorder.

Procedures for prescribing and use Patients stabilized by an antipsychotic treatment.

Switching from an oral form antipsychotic (FGA or SGA) to a LAI form First-line strategy is to start with the antipsychotic oral form for the length of time

required to obtain an effective dose and good tolerance before switching to the LAl form.

Note. Only risperidone microspheres have the pharmacokinetic characteristics that imperatively require an initial oral supplement.

The prescription of LAl SGA must be made while taking into ac- count the pharmacokinetic characteristics of each product. The dose of the introduced LAl form will correspond to the equivalent of the used oral dose (strategy of choice).

Switching from a LAI antipsychotic (FGA or SGA) to another LAI antipsychotic First-line strategy is to introduce the new LAl anti- psychotic after the discontinuation of the current LAl FGA or LAl SGA (when the time since the last injection corresponds to the interval between 2 injections). In 2nd line strategy, the switch from the current LAl FGA or LAl SGA to the new LAl SGA is recommended directly after having given an oral test dose of the newly introduced SGA LAl in order to eliminate any hypersensitivity. The initial dose for the oral form or for the new LAl SGA will correspond (if possible) to an equivalent dose of the previous LAl FGA or LAl SGA (1st line strategy).

Practical procedures for the introduction and for the injection re- minders

In order to help with the acceptance and understanding of the benefits of a LAl treatment, it is unanimously recommended by the experts (strategy of choice) to convey to the patient specific information concerning both the advantages and inconveniences of the FGA and SGA LAI, which are being considered, in the framework of shared decision making.

During the introduction of the treatment, initiation of the LAI form is recommended before the end of a full-time hospitalization for an acute episode (strategy of choice). Introduction of LAI antipsychotics can also be considered during outpatient care (as 2nd line strategy).

The 1st line strategy of performing the injections during the maintenance treatment in outpatients is to coordinate the follow-up psychiatric consultations with the dates of the injections. The injections can also be performed by a nurse in a hospital day care unit or at home (as 1st line strategy).

Benefit/risk ratio for LAI FGA and LAI SGA in bipolar disorder

	Prevention of manic recurrence	Prevention of depressive recurrence
1st _line treatment	-	-
2nd-line treatment	In monotherapy or in combination with a mood stabilizer Risperidone LAI Olanzapine palmitate	Always in combination with a mood stabilizer Risperidone LAI Olanzapine palmitate

Note: these injection procedures are not applicable to olanzapine palmitate as this treatment requires specific post-injection monitoring in a hospital. In order to improve patient compliance, it is recommended that the following reminder techniques are put in place:

- 1st line strategies, using telephone reminders and agenda given to the patient (follow-up diary).
- 2nd line strategies, by letter or eventually by text messages.

The prevention of local complications requires the injections to be performed:

- Deep intramuscularly (gluteal or deltoid muscle) (strategy of choice).

By changing the injection site each time (as 1st line strategy).

- By proposing a local transdermal anaesthetic (cream or patch) before the injection in order to reduce the pain at the injection site (as 2nd line strategy).

Specific therapeutic strategies according to the psychiatric disorder or its comorbidities.

Schizophrenia and delusional chronic disorder.

Acute psychotic episode with LA / FGA or LA / SGA treatment.

E. In the acute phase

Several therapeutic adaptations are recommended as 1st line strategies:

- Optimization of the current LAI antipsychotic.
- Either dose optimization of the current LAI FGA or LAI SGA by increasing the dose while monitoring tolerance.
- Or for LAI FGA: reduction of the time between 2 injections.
- Combination of an oral antipsychotic with the current LAI antipsychotic.

The discontinuation of the current LAI antipsychotic and the switch to an oral antipsychotic in the acute phase is only recommended as 2nd line strategy.

After stabilization of the psychotic episode:

It is recommended to continue as maintenance treatment the therapeutic strategy that allowed the reduction of symptoms and the stabilization of the episode (strategy of choice).

In the case of a switch to an oral antipsychotic treatment during the acute phase, switching to a LAI formulation as maintenance treatment is recommended as the 1st line strategy.

In the case of the combination of an oral antipsychotic and a LAI antipsychotic in the acute phase, optimizing the dose of the LAI antipsychotic and progressively discontinuing the oral antipsychotic while monitoring the clinical state is recommended as the 1st line strategy.

Residual symptoms with LAI antipsychotics justifying a reassessment.

It is successively recommended:

- In 1st line strategies:
  - To optimize the treatment by LAI FGA or LAI SGA.
  - By dose optimization of the current LAI antipsychotic by increasing the dose while monitoring tolerance.
  - Or for LAI FGA: by reducing the time between 2 injections.
- In 2nd line strategies:
  - Either through a combination of an oral antipsychotic with the current LAI antipsychotic.
  - Or by changing the current LAI FGA or LAI SGA for another LAI antipsychotic (preferably LAI SGA).

F. Bipolar disorder

<u>Manic episode with LAI SGA</u>

In the acute phase if monotherapy is ongoing, it is successively recommended:

- In 1st line strategy:

- To combine the current LAI SGA with an oral anti-manic mood stabilizer (without recommendation of a specific medication).

- In 2nd line strategies:
  - To optimize the dose of the current LAI SGA by increasing the dose while monitoring tolerance.
  - Or to discontinue the current LAI SGA and switch to an oral anti-manic mood stabilizer (without recommendation of a specific medication).

If biotherapy is ongoing (LAI SGA + lithium or anticonvulsant), It is successively recommended:

- In 1st line strategy:
  - To optimize the dose of the oral anti-manic mood stabilizer.

- In 2nd line strategies.
  - Either to combine the current LAI SGA with another oral anti-manic mood stabilizer (without recommendation of a specific medication).
  - Or to optimize the dose of the current LAI SGA by increasing the dose while monitoring tolerance.
  - Or to discontinue the current LAI SGA and switch to a biotherapy of oral anti-manic mood stabilizers (without recommendation of a specific medication).
  - Or to continue the current treatment and combination with a 2nd oral anti-manic mood stabilizer (without recommendation of a specific medication).
  - Or to continue the current treatment and electroconvulsive therapy (ECT) administration.

After stabilization of the manic episode It is recommended to continue as maintenance treatment the therapeutic strategy that al- lowed the reduction of the symptoms and the stabilization of the episode (no precision on the duration) (strategy of choice).

Depressive bipolar episode with LAI SGA

In the acute phase if monotherapy is ongoing, it is successively recommended:

- In 1st line strategy:
  - To combine the current LAI SGA with an oral mood stabilizer with antidepressant effect (Le. lamotrigine, quetiapine, lithium).
- In 2nd line strategies:
  - Either to optimize the dose of the current LAI SGA by increasing the dose while monitoring tolerance.
  - Or to combine the current LAI SGA with an oral antidepressant or with a series of ECT.
  - Or to discontinue the current LAI SGA and switch to an oral mood stabilizer with antidepressant effect.

If biotherapy is ongoing (LAI SGA + antidepressant), it is successively recommended:

- In 1st line strategies.
  - Either to optimize the dose of the current oral antidepressant by increasing the dose while monitoring tolerance.
  - Or to continue the combination of a LAI SGA with an antidepressant and combination with an oral mood stabilizer with antidepressant effect.
- In 2nd line strategies.
  - Either to combine another oral antipsychotic with the current LAI SGA.
  - Or to optimize the dose of the current LAI SGA by increasing the dose while monitoring tolerance.
  - Or to discontinue the current LAI SGA and switch to a biotherapy of oral mood stabilizers and oral antidepressant.
  - Or to continue the current treatment and ECT administration. After stabilization of the depressive episode in the 1st line strategy, it is recommended to continue as maintenance treatment the therapeutic strategy that allowed the reduction of symptoms and the stabilization of the clinical state (no precision of the duration).

In the 2nd line strategy, in the case of the combination of an oral antidepressant with a LAI SGA in the acute phase, it is recommended to optimize the dose of the LAI SGA and to progressively discontinue the oral antidepressant, depending on the clinical state.

Psychiatric comorbidities associated with a schizophrenic or bi- polar disorder with an LAI antipsychotic Manifestations of anxiety (structured or non-structured)

It is recommended in 1st line treatment to associate an oral benzodiazepine, and in 2nd-line treatment to combine an antidepressant (as first-line treatment, an SSRI or SNRI).

Addiction to a psychoactive substance (alcohol, opiates...) Treatment by LAI SGA or LAI FGA can be continued. The prescription of opiate substitutes (buprenorphine or methadone) (1st line strategies) or disulfiram, acamprosate or naltrexone (2nd line strategies) depending on the addiction, is possible with LAI antipsychotics.

G. Procedures for follow-up and monitoring

Pre-therapeutic LAI antipsychotic summary as 1st line strategies, it is recommended to systematically search for the following clinical elements:

- Personal and family medical history (diabetes, dyslipidaemia).
- Healthy lifestyle (eating habits, physical activity, substance use, smoking).
- Weight, Body Mass Index calculation, waist circumference at umbilical and waist levels.
- Blood pressure.

It is recommended to perform the following para clinical checkups:

1st line para clinical exams:

- Complete blood count, blood electrolyte (+ urea, creatinine, fasting glucose).
- Liver function tests.
- Lipid profile.
- Beta HCG.
- Electrocardiogram.

Para clinical exams depending on the clinical state of patient (as 2nd line):

- Thyroid function test.
- Prolactinemia.
- Electroencephalogram.

All the experts recommend informing the patient and the family of the risks of adverse event occurrence (metabolic, neurological) as well as providing hygiene and diet advice (balanced diet, regular physical activity, reduction or help in stopping substance use) (Strategy of choice).

Monitoring procedures

Clinical and para clinical monitoring of LAI antipsychotics is the same as for oral antipsychotics The specific monitoring frequency will depend on the risk factors found in the patient and on the clinical signs that appear during the treatment as well (1st-line strategies)

H. Specific populations

Women during pregnancy:

<u>In the case of planned pregnancy in a woman treated with LAI antipsychotic:</u>

The experts failed to reach a favorable consensus for 1st-line strategies in this clinical situation. As a 2nd line strategy, it is recommended to discontinue the current LAI antipsychotic and switch to the oral form (at the minimum effective dose).

<u>In the case of discovering a pregnancy In the 1st, 2nd & 3rd trimester:</u>

The experts failed to reach a consensus for 1st line strategies. As 2nd line strategies continuation of the LAI antipsychotic or switching to an oral form (FGA or SGA at the minimum effective dose) is recommended.

Elderly patients

In elderly patients over 65 years, the use of a LAI antipsychotic is possible. Certain precautions are recommended as 1st line strategies when prescribing a LAI treatment:

- Dosage adjustment according to weight, liver or renal function tests.
- A longer titration than in adults with a lower target dose.
- Close medical follow-up (strategy of choice).
- Closer tolerance monitoring than in adults (strategy of choice).
- Prescription only by a psychiatrist.

Subjects in precarious situations

In subjects in a precarious situation, the use of a LAI SGA is recommended as 1st line treatment (LAl FGA as 2nd line treatment).

Subjects incarcerated in prison

With incarcerated patients, the use of a LAI antipsychotic can be considered. This prescription does not differ according to the length or the place of incarceration.

The psychiatric indications are the same as for the non-incarcerated population, with the difference being that LAI SGA appears as the treatment of choice for schizophrenic and delusional disorders.

The presence of the following clinical characteristics (aggressive- ness, previous history of risk for others) guides the therapeutic choice in favor of a LAI FGA or an LAI SGA in schizophrenic disorders or towards a LAI SGA in bipolar disorders (1st line strategies).

Discussion

The main interest of our work is to help clinicians make the choice of using a LAI antipsychotic in specific clinical circumstances, using the methodology of consensus based guidelines (CBG).

Evidence-based guidelines vs. consensus-based guidelines

Most guidelines for the treatment of psychiatric disorders are evidence-based guidelines (EBG) However, recommendations cannot be established if there is no evidence available, and in which case, CBG methodology can be used. The

French National Health agency recommends the Formal Consensus method when two of the following conditions are met:

- No or insufficient level of evidence addressing the question.
- Possibility to decline the topic in easily identifiable clinical situations.
- Need to identify and select the strategies deemed appropriate by an independent panel from amongst several alternative options.

This method is very close to the Expert Consensus Guidelines methodology and has been applied to 'a variety of psychiatric dis- orders. Combining EBG and CBG methodologies may help clinicians to have a real evidence-based clinical practice, including both clinical expertise and scientific evidence. In the field of LAI anti- psychotic use and management, CBG methodology appears to be particularly appropriate. Evidence concerning LAI antipsychotic efficacy and tolerability exists but it is lacking in many areas (i.e. indications or preferential patient profiles, a ranking system between LAI antipsychotics, the introduction stage, process for switching, medication management, specific populations...). CBGs allow the clinician to be led by recommendations that bear a closer relation to the characteristics of the patients followed in clinical practice than to the restrictive inclusion criteria of randomized-controlled trials.

Indications of LAI anti psychotics

According to our experts' panel, LAI antipsychotics are recommended as first-line treatment in various psychiatric disorders:

- Schizophrenia.
- Schizoaffective disorder.
- Delusional disorder.

But also as second-line treatment in:

- Bipolar disorder.
- Personality disorder.

If their use in schizophrenia is common and supported by evidence, their use in bipolar disorder is less obvious. Nevertheless, several placebo-controlled relapse prevention studies have shown the efficacy of risperidone microsphere as a monotherapy or as an adjunctive therapy to lithium or valproate in bipolar I patients. In September 2011, and based on this data, the Food and Drug

Administration Agency approved risperidone microsphere as a long- term treatment for bipolar I disorder. Scientific literature is currently limited to risperidone microsphere but the development of new drugs should allow further studies with LAI SGA as maintenance treatment for bipolar disorder.

The use of LAI antipsychotics in other indications (schizoaffective disorder, delusional disorder, personality disorder) is not based on evidence for these populations but is instead based on the clinical experience of our experts' panel. If scientific evidence is required, then the sharing of this experience can be considered as a real sup- port for the clinical use of these compounds.

Use of LAI antipsychotics during the different phases of the illness in recent years the interest of using LAI SGA in the early phase of schizophrenia has increased because the duration of untreated psychosis is associated with the prognosis of the illness. Recent studies have underlined the fact that their use, as early as the first psychotic episode, offers many advantages in terms of efficacy, tolerance and improved adherence. The available literature presents a weak level of evidence (open label, post-hoc analysis, and small sample) and placebo controlled studies are needed. The formalized consensus of our experts' panel is consistent with these preliminary results and recommends LAI SGA after the first schizophrenic episode.

The extension of this data to the first manic episode in bipolar disorder could be assumed but, to date, no data has emerged that com- pares the effect of the early introduction of oral or LAI antipsychotics on the course of the illness. This is probably the reason why the experts' panel did not recommend LAI SGA in the early course of bipolar disorder as a maintenance treatment.

What is the specific clinical profile of patients using LAI anti psychotics in clinical practice?

Our experts' panel considers that LAI antipsychotics should be used with any patients with schizophrenia for whom maintenance antipsychotic treatment is indicated. This is consistent with the results of a survey conducted among psychiatrists from Europe, Middle-East and Africa, in which clinicians considered switching to or adding a LAI antipsychotic as the preferential pharmacological approach for addressing adherence problems.

LAI antipsychotics have long been viewed as a treatment that could only be used for a small subgroup of patients with non-compliance, frequent relapses or who

pose a risk to others. A cluster analysis of French and German studies, surveying psychiatrists about patient attributes that potentially influence their qualification for de- pot treatment, identified two clusters of patients. Cluster I corresponded to the classical patient profile in whom depot forms are used (past history of relapse and poor compliance with oral forms). Cluster II was more unexpected and included patients with high levels of insight and of therapeutic alliance. The usefulness of depot formulations compared with oral treatment in terms of relapse prevention is not demonstrated in this population. However, even limited gaps of treatment with oral formulation (11-30 days a year) is enough to increase the risk of relapse by 2.81 in patients with schizophrenia. The identification of the two clusters, replicated in numerous countries, is consistent with the recommendation of our experts' panel. Considering the risks associated with non-compliance in bipolar patients, the experts' panel recommends LAI antipsychotics as a second-line treatment in bipolar disorder.

LAI FGA vs LAI SGA

If the superiority of LAI antipsychotics versus placebo, in terms of relapse prevention, has been demonstrated for schizophrenia, no study compares the LAI SGA versus LAI FGA.

We can only extrapolate the results from studies on oral antipsychotics. Some individual oral SGA (amisulpride, clozapine, olanzapine, risperidone) were better in overall efficacy in patients with schizophrenia than oral FGA. Other oral SGA were no more effective, even for negative symptoms. However, a meta-analysis which considered all oral SGA as a single group demonstrated that they were associated with fewer relapses, less treatment failures and fewer hospitalizations in the long-term treatment of schizophrenia. Oral SGA induced fewer extrapyramidal side effects than oral FGA but some SGA induced more weight gain or metabolic side effects than oral FGA. Tolerance profiles of oral SGA are more mixed and require the characteristics of each molecule to be taken into account on an individual basis.

In a one-year observational study including 1859 patients diagnosed with schizophrenia, an adjusted Poisson regression analysis showed that the use of risperidone microsphere was associated with a lower rate of hospitalization compared to the use of other LAI FGA.

So, with no evidence available, the experts' panel recommended that the clinician's decision-making process takes into account the benefit/risk balance and prioritizes LAI SGA (except for olanzapine palmitate, due probably to the risk of post-injection syndrome over LA! FGA, according to patient tolerance.

Use of LAI anti psychotics in clinical practice guidelines

The management of LAI antipsychotics in clinical practice can sometimes be complex for clinicians and there are limited data or recommendations in the literature. Our guidelines try to propose practical recommendations to facilitate the introduction, Switching and management of LAI antipsychotics in the different phases of schizophrenia or bipolar disorder. Indeed, the current EBG for biological treatment of schizophrenia and bipolar disorder propose few recommendations concerning LAI antipsychotics.

Most of them recommend the use of LAI antipsychotics only for patients with non-adherence, frequent recurrence or who prefer this formulation. The conditions of use and management are not, or are only briefly, described. LAI antipsychotics are presented separately from the oral medication strategies (except for the CANMAT guidelines in bipolar disorder).

The main reasons given in explanation for the limited number of recommendations regarding LAI antipsychotics are related to the lack of long-term studies and the lack of high-quality evidence comparing LAI SGA to oral SGA. Perhaps the follow-up period, lasting a year or less, may have been too short to reveal the longer-term benefits of depot treatment versus oral form.

However, in our opinion, the current criteria for level of evidence are probably not adapted to the studies dealing with LAI antipsychotics. Indeed, randomized controlled trials have a major selection bias and cannot assess the potential adherence benefits of LAI formulations (non-compliant patients do not participate in a trial and those who accept to be included are the most compliant). Therefore, it can be difficult to demonstrate the benefit of LAI antipsychotics compared with oral antipsychotics. Future studies with LAI antipsychotics should combine the strengths of the different study designs (randomized-controlled studies, mirror-image studies or cohort studies).

In addition to these EBG, there are some CBG focusing on the use and management of LAI formulations for the treatment of schizophrenia.

The first guidelines, published in 1998, already recommended that LAI FGA should be considered for “any patients with schizophrenia for whom long-term treatment is indicated. However, with the emergence in the years that followed of oral SGA, which are better tolerated compared to FGA, most of the guidelines have been in favor of the use of the oral formulation. Since the market authorization (2002) of the first LA! SGA (risperidone microsphere), two other specific guidelines concerning LA! Antipsychotics have been proposed. These guidelines recommended LA! SGA as first-line treatment for patients who request the long-acting formulations.

Their use after the first schizophrenic episode or for patients who are stable with oral antipsychotics has been discussed. In 2009, Velligan et al. published expert consensus guidelines about adherence problems in patients with serious mental illness. Use of LAI anti- psychotics was a personal choice for patients with frequent relapses associated with non-adherence, relapses because they stopped taking the medication, or because they expressed a preference for the LA! Formulation.

The Association des medecins psychiatres du Quebec (AMPQ) has also recently developed guidelines concerning LAI antipsychotics with a decisional algorithm, which places the depot formulation in every step of treatment as soon as possible.

References:

1. https://bmcpsychiatry.biomedcentral.com/articles/10.1186/1471-244X-13-340
2. https://pubmed.ncbi.nlm.nih.gov/24359031/ (French guidelines)
3. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3898013/
4. https://psychopharmacologyinstitute.com/section/management-of-mania-with-mixed-features-nodes-2a-2b-and-2c-2490-4691
5. https://www.psychiatrist.com/jcp/schizophrenia/psychotic-disorders/use-of-long-acting-injectable-antipsychotics-in-schizophrenia

The Association des médecins psychiatres du Québec(Canadian Guidelines)

https://pubmed.ncbi.nlm.nih.gov/21756451/

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• Chapter 4 (Appendix)

POSITIVE AND NEGATIVE SYNDROME SCALE (PANSS)

Publisher: Multi-Health Systems, Inc.
908 Niagara Falls Blvd.
North Tonawanda, NY 14120-2060
800-456-3003

Copyright: Multi-Health Systems, Inc.

Bibliography: Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull.* 1987;13:261-276.

Kay SR, Opler LA. The positive-negative dimension in schizophrenia: its validity and significance. *Psychiatr Dev.* 1987;5:79-103.

Kay SR, Opler LA, Lindenmayer JP. Reliability and validity of the Positive and Negative Syndrome Scale for schizophrenics. *Psychiatry Res.* 1988;23:99-110.

Population: Patients with schizophrenia

Rater: Personnel trained in psychiatric interviewing techniques, with experience working with populations with schizophrenia

Time to Administer: 30-40 minutes

Description: The Positive and Negative Syndrome Scale (PANSS) is a 30-item rating instrument that evaluates positive, negative, and other symptoms in patients with schizophrenia.

The PANSS was adapted by Kay et al (1987) from two earlier rating instruments, the Brief Psychiatric Rating Scale (BPRS) and the Psychopathology Rating Scale.[1] Although the items of the BPRS are embedded in the PANSS, they do not fully correspond to the original BPRS definitions. High interrater reliability and test-retest reliability have been demonstrated for the scale (Kay and Opler, 1987). In addition, the PANSS shows a close correspondence with the SANS and SAPS.

Ratings are derived from a formal, semi-structured, 30- to 40-minute clinical interview and additional sources of information. The 30 items in the PANSS are rated on a seven-point scale (1 = absent, 7 = extreme). Seven items are grouped to form a *Positive Scale*, which assesses features exhibited in schizophrenia that are not present in those with a normal mental state. Another seven items constitute the *Negative Scale*, assessing features that are absent in schizophrenia but that would be present in those with a normal mental state. Based on the differential between these scales, a bipolar *Composite Scale* specifies the degree of preponderance of one syndrome over the other. Finally, a fourth index, the *General Psychopathology Scale*, gauges the overall severity of the schizophrenic disorder by summation of the remaining 16 items. Three supplementary items assess the risk of aggression. Additional scores are available for clusters of symptoms, including anergia, thought disturbance, activation, paranoia/belligerence, and depression.

Interviews need to be performed by personnel trained in psychiatric interviewing techniques, with experience in working with populations with schizophrenia. Ratings are based on information relating to the previous week, derived from both the clinical interview and reports from hospital staff or family members. The reports on daily functioning are essential for assessing social and behavioral deviations—particularly the items on emotional withdrawal, poor impulse control, passive or active social avoidance, hostility, uncooperativeness, excitement, and motor retardation. These reports also help in assessing the severity of other dimensions of psychopathology, insofar as these appear in social interactions, general behavior, and adaptive functioning.

Reference

1. Singh MM, Kay SR. A longitudinal therapeutic comparison between two prototypic neuroleptics (haloperidol and chlorpromazine) in matched groups of schizophrenics. *Psychopharmacologia.* 1975;43:115-123.

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SCALE FOR THE ASSESSMENT OF NEGATIVE SYMPTOMS (SANS)

Publisher: N/A

Copyright: N. Andreasen

Bibliography: Andreasen N.C. Negative symptoms in schizophrenia. *Arch Gen Psychiatry*. 1982;39:784-788.

Andreasen N. Modified scale for the assessment of negative symptoms. In: *NIMH Treatment Strategies in Schizophrenia Study*. US Department of Health and Human Services, Public Health Administration; 1984. ADM 6 102. 6/86.

Andreasen N.C. Scale for the assessment of negative symptoms (SANS). *Br J Psychiatry*. 1989;155(suppl 7):53-58.

Population: Patients with schizophrenia

Rater: Clinician or trained rater

Time to Administer: 15-20 minutes

Description: The Scale for the Assessment of Negative Symptoms (SANS) assesses five symptom complexes to obtain clinical ratings of negative symptoms in patients without psychosis. Ratings of positive symptoms in this condition are commonly undertaken using the Scale for the Assessment of Positive Symptoms (SAPS). Both scales were developed and subsequently modified by Andreasen (1982, 1984) to provide a current and valid assessment of the symptoms of schizophrenia and to measure their change over time.

The SANS measures five features of the negative syndrome of schizophrenia: affective blunting, alogia (impoverished thinking), avolition/apathy, anhedonia/asociality, and inattention of attention. Each of these features is rated using a six-point scale (0 = not at all, 5 = severe). An initial interview and observation of the patient's behavior provide the essential data for determining ratings, but these should also be based on other sources of information, including observations by hospital personnel and the family. The rating of each of the battery and components is followed by the patient's subjective evaluation of the symptoms.

Although the scale was designed to assess negative symptoms in schizophrenia, it should not be assumed that these are specific to schizophrenia. Many of the individual items, such as poverty of speech or psychomotor slowing, will be present in patients with other psychiatric disorders, particularly depression. Secondary negative symptoms can also be caused by psychosis and drug induced extrapyramidal symptoms. Careful assessing these symptoms retrospectively can help to identify their causes. Patients with affective disorders might also score very high on individual subscales of the SANS, such as the one pertaining to anhedonia-asociality. For the purpose of the symptom, consultation for course and family history, and other factors the patients with schizophrenia from those with affective disorders.

The reliability of the SANS has been tested repeatedly in a number of cultural settings, and raters from studies conducted in the United States, Japan, Italy, and Spain have achieved a consistently high level of reliability for the global ratings (Andreasen, 1990). The SANS has been found to correlate well with the UPRS negative items and with the negative scale of the PANSS, suggesting that it has good concurrent validity.

YOUNG MANIA RATING SCALE (YMRS)

Publisher: N/A

Bibliography: Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity, and sensitivity. *Br J Psychiatry*. 1978;133:429-435.

Population: Patients with symptoms of mania

Rater: Trained clinician

Time to Administer: 15-30 minutes

Description: The Young Mania Rating Scale (YMRS) is an 11-item instrument used to assess the severity of mania (Young et al, 1978).

The YMRS was developed in 1978, and inter-rater reliability for the scale is high (Young et al, 1978). The choice of items was made on the basis of published descriptions of the core symptoms of the manic phase of bipolar disorder and includes abnormalities that exist over the entire range of illness, from mild to severe. Depressive symptoms are not assessed. The YMRS follows the style of the Hamilton Rating Scale for Depression, and is designed to be administered by a trained clinician in a 15- to 30-minute interview. The severity rating for each of the 11 items is based on the patient's subjective report of his or her condition over the previous 48 hours and on the clinician's behavioral observations during the interview, with emphasis on the clinician's observations. Scoring for the items is made on a five-point scale, with varying descriptions for each. Four items are given twice the weight of the remaining seven to compensate for poor cooperation from severely ill patients. Clearly described anchor points are included for all items.

Other scales for the assessment of mania include the Manic State Rating Scale (MSRS),[1] which is a 26-item nurse-rated scale for manic behaviors that might typically be seen in an inpatient unit. Although the MSRS has been demonstrated to be reliable and valid, its length is a disadvantage. The Petterson scale is a seven-item mania rating scale with excellent reliability but a relatively narrow focus.[2]

References

1. Beigel A, Murphy DL, Bunney WE Jr. The Manic-State Rating Scale: scale construction, reliability, and validity. *Arch Gen Psychiatry*. 1971;25:256-262.
2. Petterson U, Fyro B, Sedvall G. A new scale for the longitudinal rating of manic states. *Acta Psychiatr Scand*. 1973;49:248-256.

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HAMILTON RATING SCALE FOR DEPRESSION (HRSD, HAM-D)

Publisher:	N/A
Copyright:	Public domain
Bibliography:	Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960;23:56-62. Guy W, ed. ECDEU Assessment Manual for Psychopharmacology. Rev ed. Washington DC: US Department of Health, Education, and Welfare; 1976.
Population:	Patients diagnosed with depression
Rater:	Physicians or trained raters
Time to Administer:	30 minutes

Description:

The Hamilton Rating Scale for Depression (HRSD or HAM-D; Hamilton, 1960) is a 17- to 21-item clinician-rated scale that assesses depressive symptoms. It is one of the most widely used instruments for the clinical assessment of depressive states. Hamilton originally stated that the HRSD was a scale for the assessment of severity of depression in patients with a diagnosis of primary depressive disorders. Some consider the HRSD to be inappropriate for individuals with primary psychiatric diagnoses other than major depression, although it is still often used in studies involving patients with bipolar disorder or other disorders. The HRSD emphasizes somatic symptoms of depression and works best for those with more severe depressive illness. The HRSD relies very heavily on the clinical interviewing skills of the rater (i.e. the rater is responsible for observing behaviors associated with depressive symptoms).

The scale was developed in 1960 and has been well validated. Although the HRSD has 17 to 21 items, depending on the version used (Guy, 1976), most studies rely on the 17-item version.

The rater evaluates the severity of 17 symptoms on the basis of information gained during an interview. Additional information obtained from relatives, friends, nurses, and others who can interact with the patient may also be taken into consideration. The interview requires a minimum of 30 minutes. As the scale is intended to measure the severity of the symptoms considered characteristic of the patient's condition during the past few weeks or days. Symptoms are rated either on a five-point scale or coarsely on a three-point scale. Scores on the five-point scale are explained for absent, doubtful or minor, mild, moderate, and severe. Those on the three-point scale are explained for absent, no delay or mild, and obvious, distinct, or severe. If the HRSD is utilized in the assessment of individuals with schizophrenia, it should always be paired with a scale that is more specific to schizophrenic symptoms (for example, the BPRS or PANSS).

PANSS QUIKSCORE™

Write the appropriate number in the box adjacent to each symptom using the following scale.

1 = Absent
2 = Minimal
3 = Mild
4 = Moderate
5 = Moderately severe
6 = Severe
7 = Extreme

P1. DELUSIONS	G1. SOMATIC CONCERN
P2. CONCEPTUAL DISORGANIZATION	G2. ANXIETY
P3. HALLUCINATORY BEHAVIOR	G3. GUILT FEELINGS
P4. EXCITEMENT	G4. TENSION
P5. GRANDIOSITY	G5. MANNERISMS and POSTURING
P6. SUSPICIOUSNESS / PERSECUTION	G6. DEPRESSION
P7. HOSTILITY	G7. MOTOR RETARDATION
N1. BLUNTED AFFECT	G8. UNCOOPERATIVENESS
N2. EMOTIONAL WITHDRAWAL	G9. UNUSUAL THOUGHT CONTENT
N3. POOR RAPPORT	G10. DISORIENTATION
N4. PASSIVE / APATHETIC SOCIAL WITHDRAWAL	G11. POOR ATTENTION
N5. DIFFICULTY IN ABSTRACT THINKING	G12. LACK OF JUDGMENT and INSIGHT
N6. LACK OF SPONTANEITY and FLOW OF CONVERSATION	G13. DISTURBANCE OF VOLITION
N7. STEREOTYPED THINKING	G14. POOR IMPULSE CONTROL
	G15. PREOCCUPATION
	G16. ACTIVE SOCIAL AVOIDANCE
	G17. ANOSIA
	G18. DIFFICULTY IN DELAYING GRATIFICATION
	G19. AFFECTIVE LABILITY
	TOTAL SCORE

MODIFIED SANS

Instructions: Questions not based on direct patient observation. Refer to patient functioning during the past week.
(Put appropriate code in boxes below)

AFFECTIVE FLATTENING OR BLUNTING

1. UNCHANGING FACIAL EXPRESSIONS

☐

1 = Not at all; patient is normal or [illegible]
2 = Mild; some decrease in facial expressiveness
3 = Moderate; facial expressiveness is significantly decreased
4 = Marked; facial expressiveness is markedly decreased
5 = Severe; facial expression is essentially unchanging

2. DECREASED SPONTANEOUS MOVEMENT

☐

1 = Not at all; patient moves normally or [illegible]
2 = Mild; some decrease in spontaneous movements
3 = Moderate; significant decrease in spontaneous movements
4 = Marked; movements are markedly decreased
5 = Severe; patient sits motionless throughout the interview

3. PAUCITY OF EXPRESSIVE GESTURE

☐

1 = Not at all; patient uses expressive gestures normally or excessively
2 = Mild; some decrease in expressive gestures
3 = Moderate; significant decrease in expressive gestures
4 = Marked; marked decrease in gestures
5 = Severe; patient never uses body or hands in expression

4. POOR EYE CONTACT

☐

1 = Not at all; good eye contact and expression
2 = Mild; some decrease in eye contact and eye expression
3 = Moderate; significant decrease in eye contact
4 = Marked; very infrequent eye contact
5 = Severe; patient almost never looks at interviewer

5. AFFECTIVE NONRESPONSIVITY

☐

1 = Not at all
2 = Mild; slight but definite lack in responsivity
3 = Moderate; moderate decrease in responsivity
4 = Marked; marked decrease in responsivity
5 = Severe; patient essentially unresponsive, even on prompting

6. LACK OF VOCAL INFLECTIONS

☐

1 = Not at all; normal vocal inflections
2 = Mild; slight decrease in inflections
3 = Moderate; definite decrease in vocal inflections
4 = Marked; marked decrease in vocal inflections
5 = Severe; nearly all speech in a monotone

7. GLOBAL RATING OF AFFECTIVE FLATTENING

☐

1 = No flattening; normal affect
2 = Mild affective flattening
3 = Moderate affective flattening
4 = Marked affective flattening
5 = Severe affective flattening

MODIFIED SANS (CONT'D)

ALOGIA

9. POVERTY OF SPEECH

1 = No poverty of speech: a suitable (at least approximate number of replies to questions and adequate length of responses)
2 = Mild: occasional replies do not include elaborated information even though this is appropriate
3 = Moderate: some replies do not include appropriately elaborated information and many replies are mono-syllabic or very brief ("yes, no, maybe, I don't know, last week")
4 = Marked: answers are usually more than a few words in length
5 = Severe: patient says little and occasionally fails to answer questions

9. POVERTY OF CONTENT OF SPEECH

1 = No poverty of content
2 = Mild: occasional replies are too vague to be comprehensible or can be markedly condensed
3 = Moderate: frequent replies which are vague or can be markedly condensed to make up at least a quarter of the interview
4 = Marked: at least half of the patient's speech is composed of vague or incomprehensible replies
5 = Severe: nearly all speech is vague, incomprehensible or can be markedly condensed

10. BLOCKING*

1 = No blocking
2 = Mild: a single instance noted during a 15-minute period
3 = Moderate: occurs twice during 15 minutes
4 = Marked: occurs 3 times during 15 minutes
5 = Severe: occurs more than 3 times

11. INCREASED LATENCY OF RESPONSE

1 = No, e. g.
2 = Mild: occasional brief pauses before replying
3 = Moderate: significant increase in latency of response
4 = Marked: marked increase in latency of response
5 = Severe: long pauses (often > 10 seconds) before nearly all replies

12. GLOBAL RATING OF ALOGIA

1 = No alogia
2 = Mild: mild but definite impoverishment in thinking
3 = Moderate: significant evidence for impoverished thinking
4 = Marked: pathetic thinking: seems impoverished much of the time
5 = Severe: pathetic thinking: seems impoverished nearly all of the time

AVOLITION - APATHY

13. GROOMING AND HYGIENE

1 = No evidence of poor grooming and hygiene
2 = Mild: some slight but definite neglect of attention to appearance
3 = Moderate: appearance is somewhat disheveled
4 = Marked: appearance is significantly disheveled
5 = Severe: appearance is grossly disheveled

MODIFIED SANS (CONT'D)

14. IMPERSISTENCE AT WORK OR SCHOOL*

☐

1 = No evidence of impersistence at work or school
2 = Mild; slight indication of impersistence
3 = Moderate; definite indication of impersistence
4 = Marked; significant indications of impersistence
5 = Severe; patient consistently fails to maintain a record at work or in school
6 = Cannot be assessed adequately because of severe formal thought disorder, uncooperativeness, or marked overawareness / guardedness or not assessed

15. PHYSICAL ANERGIA*

☐

1 = No evidence of physical anergia
2 = Mild anergia
3 = Moderate anergia
4 = Marked anergia
5 = Severe anergia
6 = Cannot be assessed adequately because of severe formal thought disorder, uncooperativeness, or marked overawareness / guardedness or not assessed

16. GLOBAL RATING OF AVOLITION

☐

1 = No avolition
2 = Mild, but definitely present
3 = Moderate avolition
4 = Marked avolition
5 = Severe avolition
6 = Cannot be assessed

ANHEDONIA- ASOCIALITY

17. RECREATIONAL INTERESTS AND ACTIVITIES*

☐

1 = No inability to enjoy recreational interests or activities
2 = Mild inability to enjoy recreational activities
3 = Moderate inability to enjoy recreational activities
4 = Marked inability to enjoy recreational activities
5 = Severe inability to enjoy recreational activities
6 = Cannot be assessed adequately because of severe formal thought disorder, uncooperativeness, or marked overawareness / guardedness or not assessed

18. SEXUAL INTEREST AND ACTIVITIES*

☐

1 = No inability to enjoy sexual activities
2 = Mild but definite loss of ability to enjoy sex
3 = Moderate loss of ability to enjoy sex
4 = Marked loss of ability to enjoy sex
5 = Severe loss of ability to enjoy sex
6 = Cannot be assessed adequately because of severe formal thought disorder, uncooperativeness, or marked overawareness / guardedness or not assessed

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YOUNG MANIA RATING SCALE (YMRS)

GUIDE FOR SCORING ITEMS

The purpose of each item is to rate the severity of that abnormality in the patient. When several boxes are given for a particular grade of severity, the presence of only one is required to qualify for that rating.

The keys provided are guides. One can ignore the keys if that is necessary to indicate severity, although this should be the exception rather than the rule.

Scoring between the points given (whole or half points) is possible and encouraged after experience with the scale is acquired. This is particularly useful when severity of a particular item in a patient does not follow the progression indicated by the keys.

Specify one of the responses listed below by putting the appropriate number in adjacent box.

1. ELEVATED MOOD

☐

0 - Absent
1 - Mildly or possibly increased or questioning
2 - Definite subjective elevation, optimistic, self-confident, cheerful, appropriate to content
3 - Elevated, inappropriate in content; humorous
4 - Euphoric, inappropriate laughter, singing

2. INCREASED MOTOR ACTIVITY ENERGY

☐

0 - Absent
1 - Subjectively increased
2 - Animated; gestures increased
3 - Excessive energy; hyperactive at times; restless (can be calmed)
4 - Motor excitement; continuous hyperactivity (cannot be calmed)

3. SEXUAL INTEREST

☐

0 - Normal; not increased
1 - Mildly or possibly increased
2 - Definite subjective increase on questioning
3 - Spontaneous sexual content; elaborates on sexual matters; hypersexual by self-report
4 - Overt sexual acts toward persons, staff, or interviewer

4. SLEEP

☐

0 - Reports no decrease in sleep
1 - Sleeping less than normal amount by up to one hour
2 - Sleeping less than normal by more than one hour
3 - Reports decreased need for sleep
4 - Denies need for sleep

5. IRRITABILITY

☐

0 - Absent
2 - Subjectively increased
4 - Irritable at times during interview; recent episodes of anger or annoyance on ward
6 - Frequently irritable during interview; short, curt throughout
8 - Hostile, uncooperative; interview impossible

YOUNG MANIA RATING SCALE (YMRS) (CONT'D)

6. SPEECH (Rate and Amount)

☐

0 - No increase
2 - Feels talkative
4 - Increased rate or amount at times, verbose at times
6 - Push; consistently increased rate and amount; difficult to interrupt
8 - Pressured; uninterruptible, continuous speech

7. LANGUAGE – THOUGHT DISORDER

☐

0 - Absent
1 - Circumstantial; mild distractibility; quick to digress
2 - Distractible; loses goal of thought; change topics frequently; racing thoughts
3 - Flight of ideas; tangentiality; difficult to follow; rhyming, punning
4 - Incoherent; communication impossible

8. CONTENT

☐

0 – Normal
2 - Questionable plans, new projects
4 - Special projects; hyperreligious
6 - Grandiose or paranoid ideas; ideas of reference
8 - Delusional; hallucinations

9. DISRUPTIVE - AGGRESSIVE BEHAVIOR

☐

0 - Absent, cooperative
2 - Variable; loud at times, guarded
4 - Demanding; threats on ward
6 - Threatens interviewer; shouting, interview difficult
8 - Assaultive, destructive; interview impossible

10. APPEARANCE

☐

0 - Appropriate dress and grooming
1 - Minimally unkempt
2 - Poorly groomed; moderately disheveled; overdressed
3 - Disheveled; partly clothed; garish make up
4 - Completely unkempt; decorated; bizarre garb

11. INSIGHT

☐

0 - Present; admits illness; agrees with need for treatment
1 - Possibly ill
2 - Admits behavior change, but denies illness
3 - Admits possible change in behavior, but denies illness
4 - Denies any behavior change

HAMILTON RATING SCALE FOR DEPRESSION (HAM-D)

SCORES
INSTRUCTIONS: Using the ***HAMILTON Rating Scales for Depression***, record the score for each item.
DO NOT LEAVE ANY BLANK.

☐ 1. DEPRESSED MOOD

☐ 2. GUILT

☐ 3. SUICIDE

☐ 4. EARLY INSOMNIA

☐ 5. MIDDLE INSOMNIA

☐ 6. LATE INSOMNIA

☐ 7. WORK AND ACTIVITIES

☐ 8. RETARDATION

☐ 9. AGITATION

☐ 10. ANXIETY (Psychic)

☐ 11. ANXIETY (Somatic)

☐ 12. SOMATIC SYMPTOMS (Gastrointestinal)

☐ 13. SOMATIC SYMPTOMS (General)

☐ 14. GENITAL SYMPTOMS

☐ 15. HYPOCHONDRIASIS

☐ 16A. LOSS OF WEIGHT (History)

☐ 16B. LOSS OF WEIGHT (Actual)

☐ 17. INSIGHT

☐ 18A. DIURNAL VARIATION (Presence)

☐ 18B. DIURNAL VARIATION (Severity)

☐ 19. DEPERSONALIZATION AND DEREALIZATION

☐ 20. PARANOID SYMPTOMS

☐ 21. OBSESSIONAL AND COMPULSIVE SYMPTOMS

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A. MANAGEMENT OF THE SUICIDAL PATIENT

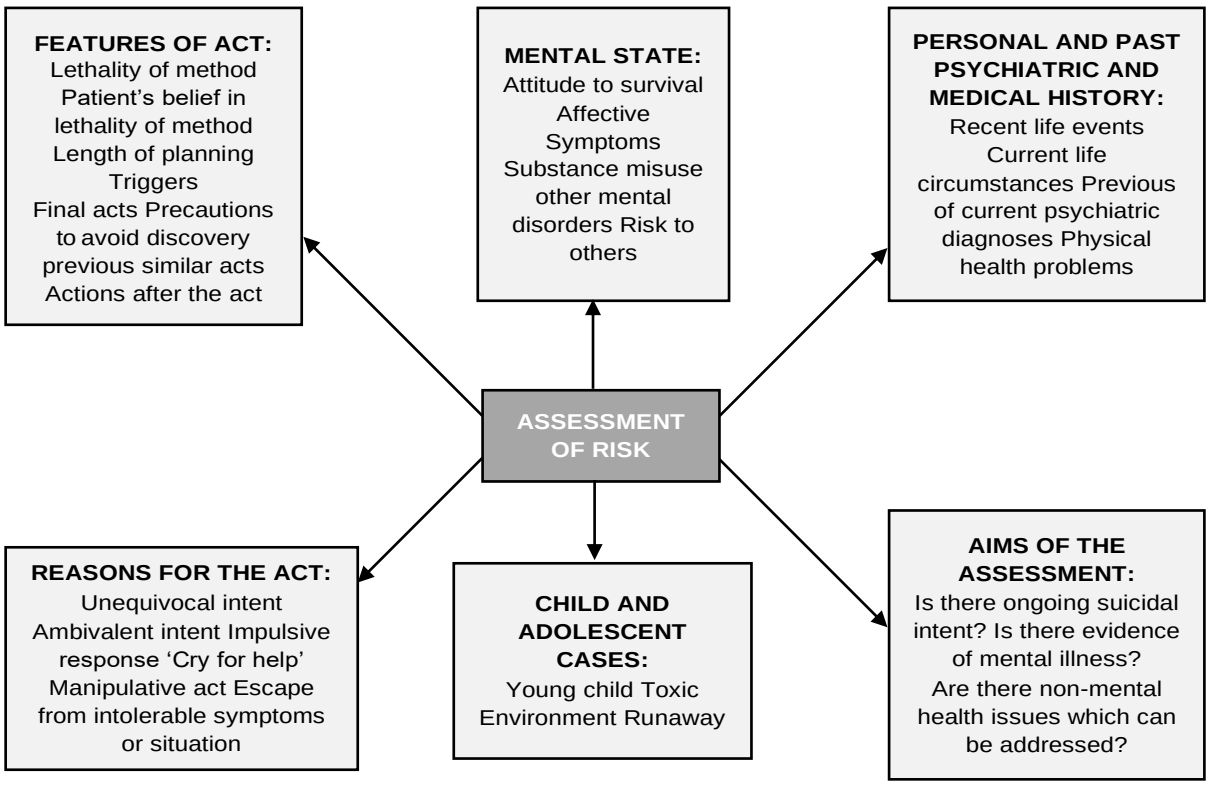
EPIDEMIOLOGY

- Increased during the 20th Century
- Rates: 25/100000 (N. Europe) – 10/100000 (S. Europe)
- Two peaks: 15-24 years and over 45years
- 3rd cause of death in adolescents (12%) - steadily increasing
- Completed suicide: male: female 3:1
- Attempted suicide: male: female 1:4

RISK FACTORS FOR SUICIDE

- Male
- Elderly
- Single, divorced, widowed
- Living alone, poor social support
- Unemployed
- Low socioeconomic status
- Previous suicide attempt or self-Harm
- Any mental disorder
- Alcohol/ drug abuse/dependence
- Recent in-patient Psychiatric treatment
- Concurrent physical disorder

ASSESSMENT



MANAGEMENT

- Assess suicide risk
- Liaise with relevant parties
- Consider the need to hospitalize
- Form a contract with the patient
- Treat mental disorder
- Provide emergency contacts
- Refer to relevant professionals
- Regular follow-up

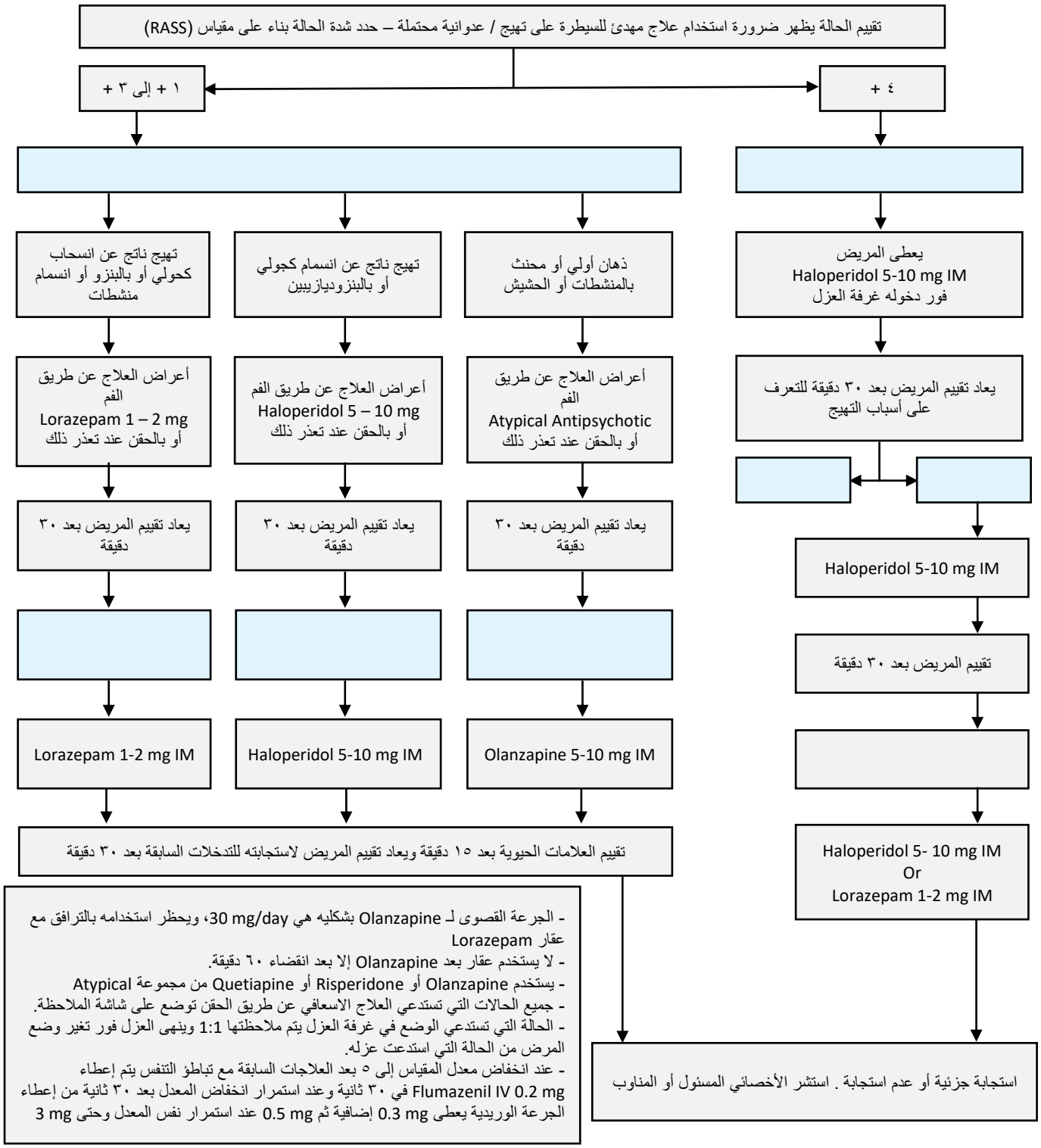
IMMEDIATE PSYCHOPHARMACOLOGICAL INTERVENTIONS:

The most common psychiatric symptoms associated with acute risk for suicidal behaviors include: agitation, anxiety, insomnia, acute substance abuse, affective dysregulation, profound depression, and psychosis. The only two evidence-

based medications that have been shown to lower suicidal behaviors are lithium (usually prescribed for bipolar disorder and recurrent unipolar depression) and clozapine (usually prescribed for schizophrenic disorders). However, these medications do not reach therapeutic levels immediately. In addition, sedatives/hypnotics are recommended for symptoms of insomnia, and anxiolytics for the treatment of anxiety and agitation.

It is indicated to prescribe anxiolytics, sedative/hypnotics, and short-acting antipsychotic medications up to or at the maximum indicated dosages to directly address agitation, irritability, psychic anxiety, insomnia, and acute psychosis, until such time as a behavioral health assessment can be made. The amount and type of medications to address these clinical presentations needs to be carefully chosen and titrated when the individual is deemed to be under the influence of alcohol, illicit substances, or other medication in prescribed or overdose amounts.

Although depressive symptoms are often associated with risk for suicide, no antidepressant medication has yet to be shown to lower suicide risk in depressed patients. However, because of the relation- ship between low CSF serotonin levels and the emergence of aggression and impulsivity, the selective serotonin reuptake inhibitors (SSRIs) have been recommended for the treatment of depressive disorders when suicidal risk is present. However, treatment with SSRIs must be carefully monitored and managed during the initial treatment phase because of the potential for the possible emergence of suicidal ideation and behaviors during this time. The FDA has recently created a black box warning when prescribing SSRIs for persons under the age of 25.


تقييم الحالة يظهر ضرورة استخدام علاج مهدئ للسيطرة على تهيج / عدوانية محتملة – حدد شدة الحالة بناء على مقياس (RASS)
١ + إلى ٣ +
٤ +
تهيج ناتج عن انسحاب كحولي أو بالبنزو أو انسمام منشطات
تهيج ناتج عن انسمام كحولي أو بالبنزوديازيبين
ذهان أولي أو محنث بالمنشطات أو الحشيش
يعطى المريض Haloperidol 5-10 mg IM فور دخوله غرفة العزل
أعراض العلاج عن طريق الفم Lorazepam 1 – 2 mg أو بالحقن عند تعذر ذلك
أعراض العلاج عن طريق الفم Haloperidol 5 – 10 mg أو بالحقن عند تعذر ذلك
أعراض العلاج عن طريق الفم Atypical Antipsychotic أو بالحقن عند تعذر ذلك
يعاد تقييم المريض بعد ٣٠ دقيقة للتعرف على أسباب التهيج
يعاد تقييم المريض بعد ٣٠ دقيقة
يعاد تقييم المريض بعد ٣٠ دقيقة
يعاد تقييم المريض بعد ٣٠ دقيقة
Haloperidol 5-10 mg IM
تقييم المريض بعد ٣٠ دقيقة
Lorazepam 1-2 mg IM
Haloperidol 5-10 mg IM
Olanzapine 5-10 mg IM
Haloperidol 5- 10 mg IM
Or
Lorazepam 1-2 mg IM
تقييم العلامات الحيوية بعد ١٥ دقيقة ويعاد تقييم المريض لاستجابته للتدخلات السابقة بعد ٣٠ دقيقة
- الجرعة القصوى لـ Olanzapine بشكليه هي 30 mg/day، ويحظر استخدامه بالترافق مع عقار Lorazepam
- لا يستخدم عقار بعد Olanzapine إلا بعد انقضاء ٦٠ دقيقة.
- يستخدم Olanzapine أو Risperidone أو Quetiapine من مجموعة Atypical
- جميع الحالات التي تستدعي العلاج الاسعافي عن طريق الحقن توضع على شاشة الملاحظة.
- الحالة التي تستدعي الوضع في غرفة العزل يتم ملاحظتها 1:1 وينهى العزل فور تغير وضع المرض من الحالة التي استدعت عزله.
- عند انخفاض معدل المقياس إلى ٥ بعد العلاجات السابقة مع تباطؤ التنفس يتم إعطاء Flumazenil IV 0.2 mg في ٣٠ ثانية وعند استمرار انخفاض المعدل بعد ٣٠ ثانية من إعطاء الجرعة الوريدية يعطى 0.3 mg إضافية ثم 0.5 mg عند استمرار نفس المعدل وحتى 3 mg
استجابة جزئية أو عدم استجابة . استشر الأخصائي المسئول أو المناوب

B. BLACK-BOX WARNING AND PSYCHIATRIC DRUGS

The FDA requires a black-box warning for one of the following three situations:

The medication can cause serious undesirable effects (such as a fatal, life-threatening, or permanently disabling adverse reaction) compared with the potential benefits of the drug.

A serious adverse reaction can be prevented, reduced in frequency, or reduced in severity by proper use of the drug; for example, a medication may be safe for use in adults, but not in children. The drug may be safe for use in adult women who are not pregnant.

Antidepressant drugs

In 2004, the FDA communicated about suicidality among children and adolescents using all classes of antidepressant drugs and placed the following warning 'antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder and other psychiatric disorders.

Antipsychotic drugs in elderly

In 2005, the FDA issued a black-box warning of an increased risk of mortality with the use of atypical antipsychotics compared with a placebo (relative risk 1.6–1.7). The mortality rate in antipsychotic-treated patients was about 4.5% compared with about 2.6% in the placebo group. Although the causes of death varied, most were due to cardiovascular reasons (heart failure, sudden death) or infections (pneumonia). A black-box warning was placed on atypical antipsychotics as a class.

Antiepileptic drugs

In 2008, the FDA placed a black-box warning on all antiepileptic drugs because of fears about the risk of suicidal thoughts and behavior associated with the use of epilepsy drugs. The FDA wanted to place the warning even for those drugs that did not have documented risk factors.

Topiramate:

A black-box warning was also placed on Topiramate as it was found to cause 'A syndrome consisting of acute myopia associated with secondary angle closure glaucoma.

Atomoxetine

In 2005, the FDA issued a public health advisory about rare reports of suicidal thinking in children and adolescents taking atomoxetine, a drug approved for the treatment of ADHD in adults and children.

C. LABORATORY AND OTHER TESTING FOR PATIENTS TAKING PSYCHOTROPIC MEDICATIONS

Psychopharmacology has become more complex over the past de- cade or so, with many more medications available from different pharmacologic classes. Boundaries between medication classes and linkages between drug categories and psychiatric diagnoses have become more ambiguous. The selection of drugs for treating general medical illnesses has similarly expanded, increasing the number of potential drug interactions, particularly in an aging population.

It has been a long time since BTP reviewed the issue of laboratory (and related) testing for patients taking psychiatric medications. We attempt to do that here, but first offer several qualifications. The text and tables are neither exhaustive nor definitive, but rather an informed compilation of research-based knowledge and clinical consensus. They represent guidelines to be weighed by individual clinicians tailoring decisions to specific cases. Moreover, the comments that follow pertain to usual therapeutic dosing and drug plasma levels. Situations of overdose and toxicity require different thinking and concerns and, therefore, different laboratory tests.

The standard medical approach begins with diagnosis. Diagnosis, in turn, starts with a history (ideally through multiple sources), proceeds through examination, and then moves to indicated laboratory and other testing. An initial psychiatric examination (including a medical history and review of systems), leading to a psychiatric diagnosis, requires a differential diagnosis.

Potential medical, neurological, toxic, and other causes of psychiatric symptoms must be considered and eliminated or dealt with. When coexisting medical conditions are identified, the needs of these conditions may necessitate more frequent monitoring of pertinent laboratory tests. All that follows in this article

presupposes the application of these principles in the ordering and interpretation of appropriate diagnostic tests. Even if a patient has had a thorough medical evaluation by a primary care physician in the recent past, a psychiatrist must bring a knowledgeable and skeptical eye to consider occult conditions that sometimes masquerade as psychiatric disorders and may have been overlooked previously.

As part of a comprehensive psychiatric evaluation and periodic re-evaluation, the possibility of drug or alcohol abuse should be assessed. Laboratory screening can form part of this consideration. Some psychiatric disorders may result from toxic agents, which might also be considered based on a history or physical signs. Women of childbearing potential require specific consideration of pregnancy. Based on menstrual status, a pregnancy test may be required before starting psychiatric medicines.

The electrocardiogram (ECG) is often informative and is noninvasive and relatively inexpensive. Many psychiatric drugs—such as ziprasidone (Geodon), tricyclic antidepressants, and lithium—affect cardiac electrical conduction and repolarization, sometimes as a result of an interaction with other medications. In addition, many individuals have asymptomatic pre-existing cardiac problems, such as prolonged cardiac conduction. Therefore, a pretreatment ECG and, if indicated, periodic monitoring, might be necessary.

The accompanying tables group psychotropic medications in standard categories. Under “mood stabilizers,” for example, we have listed three, although the number of proposed mood stabilizers and those approved by the US Food and Drug Administration (FDA) is growing. (Some of the medications we discuss are used “off-label” for treating psychiatric disorders. For example, carbamazepine is listed as a mood stabilizer but is not FDA-approved for the treatment of bipolar disorder.) Some mood stabilizers, such as lamotrigine, do not require routine laboratory testing. However, plasma levels of lamotrigine and other mood stabilizers may need to be monitored during concomitant use with other antiepileptic medications in case of pharmacokinetic interactions.

Oxcarbazepine is a chemical congener of carbamazepine but requires fewer routine laboratory tests. Monitoring of serum sodium levels should be considered during oxcarbazepine maintenance treatment, especially if the patient is taking other drugs known to decrease serum sodium levels, because of an elevated risk of the syndrome of inappropriate secretion of antidiuretic

hormone (SIADH). Although less likely to increase metabolism and decrease levels of other drugs than carbamazepine, oxcarbazepine can have this effect in some patients, so plasma levels may need to be monitored.

With valproic acid, there might be an in- creased risk of polycystic ovary syndrome in women of childbearing potential. If the clinical history and physical examination find obesity, hirsutism, or loss of menses, a serum assay for androgens may be in order. In addition to the tests listed in the table for valproic acid, the Physicians' Desk Reference recommends periodic monitoring of liver function tests since this agent carries a low risk of inducing potentially severe hepatic cellular damage, particularly when multiple anticonvulsants are combined in children. Other experts believe that periodic monitoring is not necessary, but that liver function tests should be performed when indicated by symptoms. For that matter, there has emerged a clear divergence in the field between common practice among neurologists and psychiatrists, who tend not to obtain routine blood tests in patients treated with valproic acid and carbamazepine, and more cautious guidelines, such as the PDR. For purposes of completeness, we have included the more cautious recommendations in our tables. How- ever, many knowledgeable, experienced, and thoughtful clinicians employ laboratory tests less frequently.

Second-generation antipsychotics increasingly are being used, singly or in combinations, for a growing list of psychiatric indications, including mood stabilization. Currently, olanzapine, quetiapine, risperidone, and ziprasidone have been approved by the FDA for mania, and olanzapine has been approved also for long-term mood stabilization in bipolar disorder.

There is mounting concern over the potential of second-generation antipsychotics to induce weight gain and associated metabolic side effects, including diabetes mellitus, hyperlipidemia, and hyperglycemia. The table from the American Diabetes Association consensus conference, adapted below, is minimalist. Plasma lipids and glucose should probably be monitored more frequently, particularly for older patients, or those with high (or rising) body mass indices (BMIs) or other risk factors. Because of special concerns about toxicity, clozapine is presented in its own table. In addition to the tests listed for clozapine, a patient's white blood cell count and plasma level of troponin should be measured if myocarditis is suspected. Clinicians should be aware of and monitor regularly for symptoms of increased prolactin in patients taking

antipsychotics. If clinically indicated, * prolactin should be measured, and if elevated, a work- up for the cause of the elevation initiated.

Ziprasidone may prolong the QTC interval. A baseline ECG is in order for patients taking ziprasidone or another antipsychotic who have known heart disease, a history of syncope, a family history of sudden death at an early age, congenital long QT syndrome, or who are receiving other cardiac depressants.

** Subsequent ECGs are worthwhile if symptoms associated with a prolonged QT interval (e.g., syncope) occur. Patients taking ziprasidone who are at risk for significant electrolyte disturbances should have baseline serum potassium and magnesium assayed, because hypokalemia or hypomagnesemia can increase the risk of QT prolongation and arrhythmias, including torsade's de pointes. (Thankfully, there have been no reports of serious arrhythmias in humans as a result of this.) Monitor serum electrolytes periodically in patients for whom diuretic therapy is introduced during ziprasidone treatment.

Animal studies have suggested that quetiapine may be associated with the development of cataracts. Although there is insufficient evidence that this association occurs in humans, the product labeling recommends that patients treated with this antipsychotic have a slit-lamp eye examination or a similarly sensitive eye examination shortly after initiation of treatment and at 6-month intervals. Clinicians should inquire about vision changes in patients taking other antipsychotics and request ocular evaluations once a year in patients over 40 years and once every 2 years in those under 40 years. The PDR recommends baseline and periodic eye examinations, including slit-lamp, funduscopy, and tonometry, in patients taking carbamazepine, because related drugs have been shown to cause eye changes.

Two antidepressants for which laboratory testing is required are phenelzine and nefazodone, both of which call for repeated monitoring of liver function to minimize the risk of hepatotoxicity. Tricyclic antidepressants can slow cardiac conduction, which means a pretreatment ECG should be considered (looking for pre-existing prolongation of conduction) with follow-up as treatment is established. Even selective serotonin reuptake inhibitors (SSRIs), generally relatively safe medicines, can induce SIADH, especially in the elderly. Once again, clinical observation and considerations should lead to indicated laboratory tests; in this case, confusion or other central nervous system side effects should prompt consideration of determining serum sodium and urine

osmolality. Routine monitoring of serum sodium might be considered in the elderly. Some patients gain weight with SSRIs and, even more so, with mirtazapine.

When weight gain occurs, weight should be monitored along with plasma lipids and glucose. Agranulocytosis may occur with mirtazapine. A complete blood count should be done if symptoms arise. Venlafaxine (Effexor) can raise blood pressure in a dose-dependent fashion. It is safest, therefore, to obtain baseline and periodic blood pressure measurements when venlafaxine is prescribed. Postural blood pressures should be considered if orthostatic symptoms arise (e.g., with monoamine oxidase inhibitors).

Among drugs used to treat dementia, only tacrine requires laboratory testing: serum levels of hepatic enzymes should be measured every 2 weeks for 16 weeks, then every 3 months thereafter.

MOOD STABILIZERS

Carbamazepine

In addition to the tests listed in the following chart, elderly patients should be monitored for signs of liver or bone marrow failure.

Laboratory Test	Baseline	2 Wks	Monthly	Quarterly	Annually	When symptoms arise
Pregnancy test*	X					X
Complete blood count	X	X	X**	X		X
Liver function tests	X	X	X**	X		X
Blood chemistries***	X				X	X
Urinalysis	X					X
Thyroid function tests	X				X	
Serum plasma concentrations		X		X		X

* In women of childbearing potential based on menstrual status.

** For 3 months.

*** Rule out hyponatremia.

Lithium						
	Baseline	Weekly for 4 Wks	Monthly for 3 Months	Quarterly	Annually	When symptoms arise
Pregnancy test* Complete blood count Blood chemistries (including renal tests)**	X X X				X	X X X
ECG*** Urinalysis Thyroid function tests Serum plasma concentrations Weight/ BMI/Waist circumference	X X X X	X	X	X	X X X	X X X

* In women of childbearing potential based on menstrual status.

** Check creatinine levels and if creatinine and symptoms warrant, creatinine clearances.

*** In patients 45 years or older or with preexisting cardiac disease.

	Baseline	2 Wks	Monthly for 6 Months	Quarterly	Every 6 Months	Annually	When symptoms arise
Pregnancy test*	X						X
Complete blood count**	X		X		X		X
Blood chemistries	X		X		X		X
Serum plasma concentrations		X		X			X
Prothrombin time	X				X		X
Weight/BMI/Waist circumference	X					X	
Amylase							X

* In women of childbearing potential based on menstrual status.

** Include differential and platelets.

SECOND-GENERATION ANTIPSYCHOTICS*

	Baseline	4 Wks	8 Wks	12 Wks	Quarterly	Annually
Pregnancy test** Personal/family history	X X					X
Weight/BMI	X	X	X	X	X	
Waist circumference	X					X
Blood pressure***	X			X		X
Fasting plasma glucose	X			X		X
Fasting lipid profile	X			X		X

* More frequent assessments may be warranted based on clinical status (e.g., more frequent lipid and glucose assessment in the event of marked weight gain).

** In women of childbearing potential based on menstrual status.

*** Orthostatic in elderly.

Note: Second-generation antipsychotics include aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone. The consensus statement notes that there is less experience with aripiprazole and ziprasidone and that these medications appear to induce less weight gain.

Clozapine

In addition to the tests listed in the table below, orthostatic blood pressure should be measured weekly until the dose is stable and then monthly in the elderly.

	Baseline	Weekly for 6 Months	Every Other Week from 6 Months on	1X or 2X per year	Inadequate response or adverse effects
Weight/BMI Waist circumference White blood cell count	X X X	X X	X X	X	

Neutrophil count Fasting glucose	X X	X	X	X	
Fasting lipid panels Serum plasma concentrations	X			X	X

CLOZAPINE MONITORING

Recommended Monitoring Frequency and Clinical Decisions by ANC Level

* If clinically appropriate

** Confirm all initial reports of ANC less than 1500/µL (ANC < 1000/µL for BEN patients) with a repeated ANC measurement within 24 hours

Normal Range for a New Patient General Population (ANC ≥ 1500/µL)	Initiate treatment If treatment interrupted: < 30 days, continue monitoring as before ≥ 30 days, monitor as if new patient Discontinuation for reasons other than neutropenia	Weekly from initiation to 6 months Every 2 weeks from 6 to 12 months Monthly after 12 months See Section 2.4 of the full Prescribing Information
BEN POPULATION BEN Population (ANC ≥ 1,000/µL) Obtain at least two baseline ANC levels before initiating treatment		
Mild Neutropenia (1000 to 1499/µL)*	GENERAL POPULATION Continue treatment	GENERAL POPULATION Three times weekly until ANC ≥ 1500/µL Once ANC ≥ 1500/µL, return to patient's last "Normal Range" ANC monitoring interval**
	BEN POPULATION Mild Neutropenia is normal range for BEN population, continue treatment Obtain at least two baseline ANC levels before initiating treatment If treatment interrupted < 30 days, continue monitoring as before ≥ 30 days, monitor as if new patient Discontinuation for reasons other than neutropenia	BEN POPULATION Weekly from initiation to 6 months Every 2 weeks from 6 to 12 months Monthly after 12 months See Section 2.4 of the full Prescribing Information

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Moderate Neutropenia (500 to 999/µL)*	GENERAL POPULATION Recommend hematology consultation Interrupt treatment for suspected clozapine induced neutropenia Resume treatment once ANC normalizes to ≥ 1000/µL	GENERAL POPULATION Daily until ANC ≥ 1000/µL, then Three times weekly until ANC ≥ 1500/µL Once ANC ≥ 1500/µL, check ANC weekly for 4 weeks, then return to patient's last "Normal Range" ANC monitoring interval**
	BEN POPULATION Recommend hematology consultation Continue treatment	BEN POPULATION Three times weekly until ANC ≥ 1000/µL or ≥ patient's known baseline. Once ANC ≥ 1000/µL or patient's known baseline, then check ANC weekly for 4 weeks, then return to patient's last "Normal BEN Range" ANC monitoring interval**
Severe Neutropenia (less than 500/ mL)*	GENERAL POPULATION Recommend hematology consultation Interrupt treatment for suspected clozapine induced neutropenia Do not rechallenge unless prescriber determines benefits outweigh risks	GENERAL POPULATION Daily until ANC ≥ 1000/µL Three times weekly until ANC ≥ 1500/µL If patient rechallenged, resume treatment as a new patient under "Normal Range" monitoring once ANC ≥ 1500/µL
	BEN POPULATION Recommend hematology consultation Interrupt treatment for suspected clozapine induced neutropenia Do not rechallenge unless prescriber determines benefits outweigh risks	BEN POPULATION Daily until ANC ≥ 500/µL Three times weekly until ANC ≥ patients established baseline If patient rechallenged, resume treatment as a new patient under "Normal Range" monitoring once ANC ≥1000/µL or at patient's baseline

D. LITHIUM MONITORING

Lithium (lithium carbonate, lithium extended-release, lithium citrate)					
	Baseline	**6 months**	**At Dosage Change**	**Annually**	**As Clinically Indicated**
Serum Level (taken 12 hours post dose, immediately prior to morning dose; therapeutic conc.: 0.6-1.2 mEq/L, toxic level: > 1.5mEq/L Levels should be closely monitored if start or discontinue NSAIDs, ACEIs, diuretics, medications that interact)	√ (5-7 days after starting; then establish 2 consecutive serum levels within therapeutic range)	√	√ (5-7 days post dosage change)		√
Complete Blood Count (CBC)	√			√	√
Thyroid Function (assess thyroid function once or twice in the first 6 months then every 6-12 months thereafter. Refer to endocrinologist if TSH is repeatedly abnormal and/ or goiter or nodules are detected.)	√	√ (every 6-12 months)			√
BUN/Creatinine Clearance (risk factors for lithium induced renal disease include longer duration and higher dose of lithium, hypertension, diabetes, use with other nephrotoxic drugs, prior history of lithium toxicity, nephrogenic diabetes insipidus)	√ (test every 2-3 months during first 6 months of treatment)	√ (every 6-12 months in stable patients)			√
Electrolytes (at baseline, calcium also after 6 months, then annually. Discontinue if serum calcium is > 11.5 mg/ dL10 and refer to internist or endocrinologist upon confirmation of high value)	√	√*		√	√
Fasting Blood Glucose	√				√

Assess side effects, symptom severity, and adherence to treatment plan – [including signs of toxicity such as diarrhea, vomiting, tremor, ataxia, drowsiness or muscle weakness; polyuria, polydipsia (advise BHR to avoid high calorie beverages), drowsiness]			√	√	√
Electrocardiogram (ECG) (if over 40 or presence of cardiovascular risk factors)	√				√

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Liver function monitoring scheme with Valdoxan

Valdoxan 25 mg
Initiation of 25mg ALT.....U/L
AST U/L
Week 3 ALT .....U/L AST ..... U/L
Week 6 ALT .....U/L AST .... U/L
Week 12 ALT .....U/L AST .....U/L
Week 24 ALT .....U/L AST .....U/L

In case of dose increase at 50mg, restart the monitoring scheme.

Initiation of 50mg	ALT	U/L
	ALT	U/L
Week 3	ALT	U/L
	ALT	U/L
Week 6	ALT	U/L
	ALT	U/L
Week 12	ALT	U/L
	ALT	U/L
Week 24	ALT	U/L
	ALT	U/L

Patient name: .....

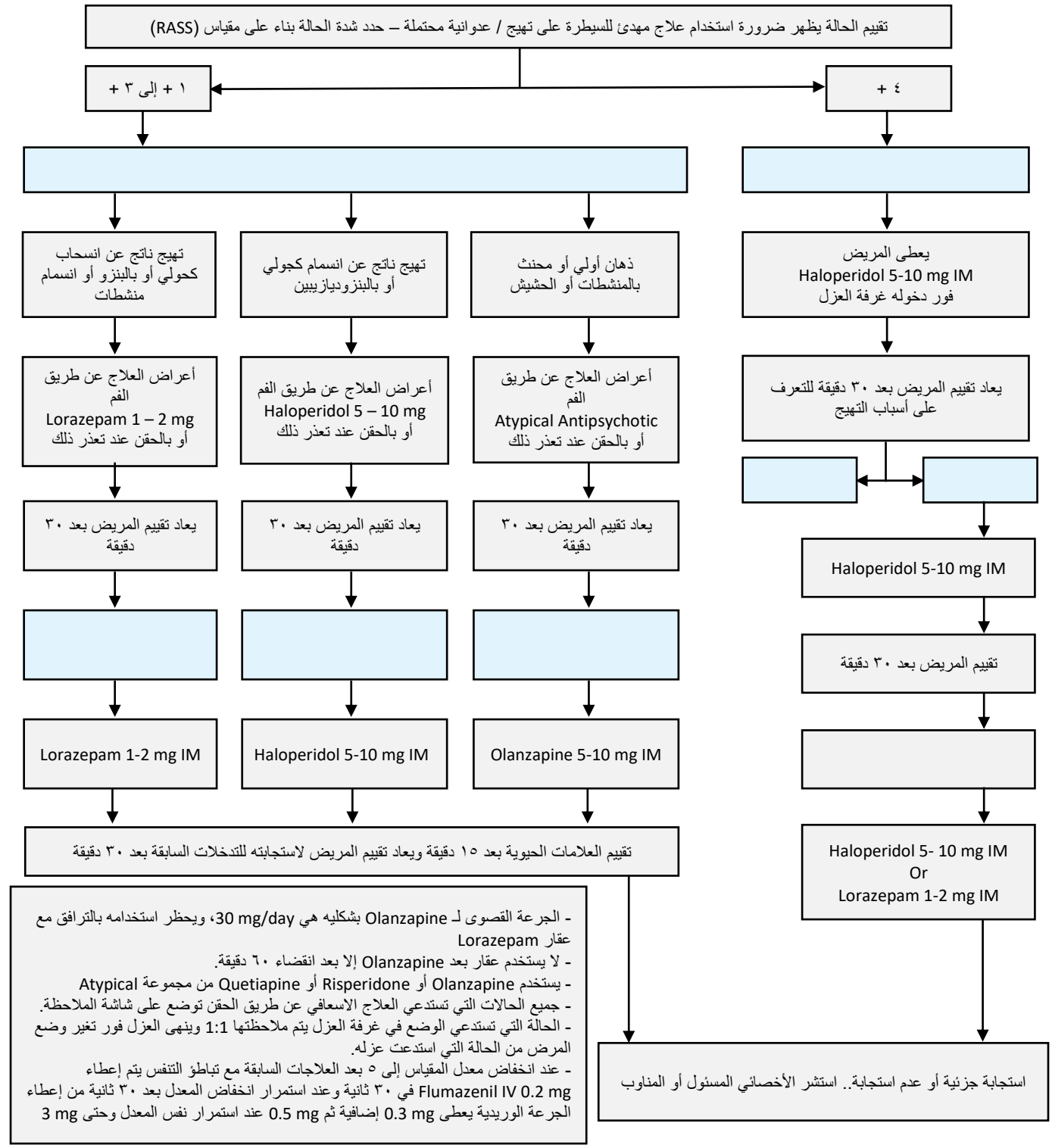
Date of initiation: .....

Serum transaminases (ALT, AST)

- Symptoms or any sign of potential liver injury* → ✘ Discontinue the Treatment Liver function Tests (including transaminases should be performed
- ALT and/or AST > 3 times the upper limit of normal → ✘ Discontinue the treatment Repeat liver function tests regularly until serum transaminases return to normal
- ALT and/or AST ≤ 3 times the upper limit of normal → Symptoms or any sign of potential liver injury* → ✘ Discontinue the treatment Repeat liver function tests regularly until serum transaminases return to normal
- ALT and/or AST ≤ 3 times the upper limit of normal → No symptom or sign of liver injury Repeat liver function tests within 48 hours
  - ALT and/or AST > 3 times the upper limit of normal → ✘ Discontinue the treatment Repeat liver function tests regularly until serum transaminases return to normal
  - ALT and/or AST ≤ 3 times the upper limit of normal → ✓ Continue the treatment Follow the time schedule for liver monitoring tests
- Normal → ✓ Continue the treatment Follow the time schedule for liver monitoring tests

Liver function monitoring scheme with Valdoxan

* Such as dark urine, light colored stools, yellow skin/eyes, pain in the upper right belly, sustained new-onset and unexplained fatigue


تقييم الحالة يظهر ضرورة استخدام علاج مهدئ للسيطرة على تهيج / عدوانية محتملة – حدد شدة الحالة بناء على مقياس (RASS)
١ + إلى ٣ +
٤ +
تهيج ناتج عن انسحاب كحولي أو بالبنزو أو انسمام منشطات
تهيج ناتج عن انسمام كحولي أو بالبنزوديازيبين
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أعراض العلاج عن طريق الفم Atypical Antipsychotic أو بالحقن عند تعذر ذلك
يعاد تقييم المريض بعد ٣٠ دقيقة للتعرف على أسباب التهيج
يعاد تقييم المريض بعد ٣٠ دقيقة
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يعاد تقييم المريض بعد ٣٠ دقيقة
Haloperidol 5-10 mg IM
تقييم المريض بعد ٣٠ دقيقة
Lorazepam 1-2 mg IM
Haloperidol 5-10 mg IM
Olanzapine 5-10 mg IM
Haloperidol 5- 10 mg IM
Or
Lorazepam 1-2 mg IM
تقييم العلامات الحيوية بعد ١٥ دقيقة ويعاد تقييم المريض لاستجابته للتدخلات السابقة بعد ٣٠ دقيقة
- الجرعة القصوى لـ Olanzapine بشكليه هي 30 mg/day، ويحظر استخدامه بالترافق مع عقار Lorazepam
- لا يستخدم عقار بعد Olanzapine إلا بعد انقضاء ٦٠ دقيقة.
- يستخدم Olanzapine أو Risperidone أو Quetiapine من مجموعة Atypical
- جميع الحالات التي تستدعي العلاج الاسعافي عن طريق الحقن توضع على شاشة الملاحظة.
- الحالة التي تستدعي الوضع في غرفة العزل يتم ملاحظتها 1:1 وينهى العزل فور تغير وضع المرض من الحالة التي استدعت عزله.
- عند انخفاض معدل المقياس إلى ٥ بعد العلاجات السابقة مع تباطؤ التنفس يتم إعطاء Flumazenil IV 0.2 mg في ٣٠ ثانية وعند استمرار انخفاض المعدل بعد ٣٠ ثانية من إعطاء الجرعة الوريدية يعطى 0.3 mg إضافية ثم 0.5 mg عند استمرار نفس المعدل وحتى 3 mg
استجابة جزئية أو عدم استجابة.. استشر الأخصائي المسئول أو المناوب

E. MAX. DOSES OF PSYCHOTROPIC DRUG

Drug Name	Max Dose	Dosage Form	Route of Administration
Alprazolam	10mg	Tablet	Oral
Paliperidone tab	12 mg	Tablet	Oral
Paliperidone PALIMATE	150 mg / month	Ampule	Injection
Paroxetine	75 MG	Tablet	Oral
Amisulpride	1200mg	Tablet	Oral
Amitriptyline	300mg	Tablet	Oral
Aripiprazole	30mg	Tablet	Oral
Benzhexol	15mg	Tablet	Oral
Benztropine	6mg	Tablet	Oral
Bupropion	300mg	Tablet	Oral
Carbamazepine	1600mg	Tablet	Oral
Chlorpromazine	1000mg	Tablet	Oral
Citalopram	60mg	Tablet	Oral
Clomipramine	250mg	Tablet	Oral
Clonazepam	20mg	Tablet	Oral
Clozapine	900mg	Tablet	Oral
Diazepam (anxiety)	30mg	Tablet	Oral
Escitalopram	20mg	Tablet	Oral
Fluoxetine	60 mg	Capsule	Oral
Flupenthixol depot	100mg/week	Ampule	Injection
Fluphenazine decanoate	100 mg	Ampule	Injection
Fluvoxamine	300mg (social phobia) 450 mg (OCD)	Tablet	Oral
Haloperidol Tab	40mg	Tablet	Oral
Haloperidol decanoate	300 mg/ 4week	Ampule	Injection
Imipramine	300mg	Tablet	Oral
Lamotrigine	500mg	Tablet	Oral
Lithium carbonate	1800 mg	Tablet	Oral
Lorazepam	10mg	Tablet	Oral
Maprotiline	225 mg	Tablet	Oral
Memantine	20mg	Tablet	Oral
Mirtazapine	45 mg	Tablet	Oral
Moclobemide	600mg	Tablet	Oral

Olanzapine	20mg	Tablet	Oral
Phenobarbitone	400mg	Tablet	Oral
Phenytoin	1200mg	Capsule	Oral
Quetiapine	800mg	Tablet	Oral
Risperidone Consta	50mg/2week	Ampule	Injection
Risperidone	8mg (bipolar) 16 mg (schizophrenia)	Tablet	Oral
Sodium valproate	2500mg	Tablet	Oral
Sulpiride	2400mg	Tablet	Oral
Topiramate	800mg	Tablet	Oral
Trazodone	400mg	Tablet	Oral
Trifluoperazine	30mg	Tablet	Oral
Venlafaxine XR	225mg	Tablet	Oral
Zuclopenthixol Tab	150mg	Tablet	Oral
Zuclopenthixol INJECTION	600 mg / 1-4 week	Ampule	Injection

References:

- The Maudsley Prescribing Guidelines 12th Edition
- American Psychiatric Association Practice Guideline (Copyright 2010)
- Nice Guideline February 2014