STANDARD TREATMENT GUIDELINE FOR PSYCHIATRIC DISORDERS

Amanuel Mental Specialized Hospital

FIRST EDITION

2015/2022

Acknowledgment

We would like to forward our gratitude and acknowledgement toindividualsand Federal Ministry of Health (MoH) for their tirelessly participated in the development of this Standard Treatment Guideline

Generally; we would also like to extend our heartfeltappreciation to AMSH management staffs, who are participating and supporting throughout this STG development period without hesitate to provide necessary financial and material facilitation, without whom the STG development would not have been possible.

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Forward

Amanuel Mental specialized hospital was established in 1930 E.C during the invasion of Italy. It is the only tertiary specialized mental hospital in the country and since from its foundation it has been serving the community coming from all regions of the country.

The service given is mainly treating psychiatric problems and associated co-morbid illness. The Hospital is providing service on daily average for 1000 patients at OPD level. To provide quality of service standardization of the treatment is paramount. So for the first time our hospital has prepared this standard treatment guideline/STG/ to improve the quality of service provision as well as standardize the treatment for mental illness. Given the rapid advances in psychiatric treatment, and some important changes related to drug policy in the country as well as internal and external factors which hinders or limit the treatment option of psychiatric disease like shortage of medication,unaffordable price and gap on knowledge of concerned professionals, this quick desktop or pocket guide/pocketbook is obviously required.

This guideline will help to put direction for prescribing, dispensing, counseling of prescribed medication and to increase knowledge of psychiatric service practitioners. The guideline is also used as a reference in all others health institutions (both governmental and non-governmental) which are providing psychiatric service in the country since this hospital is the only specialty hospital for psychiatric services in the country,

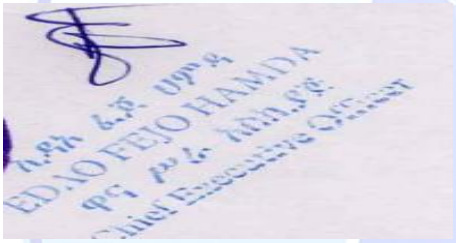
The STG is intended to be a quick reference. Thus it cannot contain all the information necessary to prescribing and dispensing. The selection of drugs relevant to the situation in Ethiopia without too much of a compromise on the benefits to be gained from the recent advances is thus the major challenge in this undertaking. Every effort has been made to include basic psychiatry drugs for a cost effective care of sick patients in our setup. However, it is recognized that what is feasible usually falls for short of what is desirable. Therefore this will rely heavily on the users to exercise judgment in striking a balance between what may be possible and what is desirable and feasible in specific circumstances.

I would like to seize this opportunity to thank all experts and participants for having and take the initiative of preparing this 1st edition of guideline. Your strong effort has been visible on the quality content of guideline prepared.

Finally I would like to appreciate and acknowledge our sponsors, partners and Ministry of Health for the publication of this guideline. I hope your strong participation on the progressive development of psychiatric service will proceed with us as before.

It is my sincerest hope that it will be a useful guideline to all health care workers providing care for psychiatric patients in Ethiopia and it is with great preference that I urge all health care workers to use this STG as a reference and guiding document on the treatment of mental illness in our country.

Thank You



Edao Fejo (BSC PH, MPH, MHA)

Message from DTC Secretary

Psychiatric problems are a critical concern from those epidemiologically high rates of occurring diseases in the world as well as our country. In Ethiopia mental health problem is being treated in Amanuel mental specialized Hospital exclusively for more than 84 years and it has been serving as a reference for other health facilities which work on mental health services.

Despite the Hospital is expanding its health care service to different sites, there is a practice discrepancies to implement treatment protocol because of unstandardized materials for practice at institutional level. To provide consistencequality of care and minimize/avoid treatment variation standard documents are essential.

The Standard Treatment Guidelines (STGs) is a good example of guideline documents to ensure safe and effective use of drugs and medical supplies rationally. The overall goal of the STGs is to help physicians, pharmacists, and all other healthcare professionals to responsibly use medications for the benefit and wellbeing ofthe patients. In order to fill the existing gap and improve the quality of service updated and evidence based standard treatment guideline preparation is a cornerstone for health care services. The psychiatric service for the community at Amanuel mental specialized Hospital hasattempted to implement different EHSTG strategic plans for service expansion and quality improvement.

Additionally, there is a strong need for control mechanisms for how psychiatric drugs are handled by pharmacy, prescribed by physicians, and used by patients. As a result, preparing treatment guideline can ensure responsibility and accountability towards use of medications in the health care services.

So, for the first time, our hospital has prepared this treatment guideline and tailored its content for tertiary psychiatric treatment level. This shows our commitment towards universal health care (UHCs) in general and to achieve the health sector transformation plan-II (HSTP-II) of Ministry of health in particular.

Finally, I would like to express my gratitude for all teams, individuals and organization that have been participated on the preparation and publication of this guideline.

Thank You!

ABERA GELAN ABEBE (B Pharm)

Pharmacy service Directorate Director.

Contents

Abbreviation and Acronyms

AMSH: Amanuel Mental Specialized Hospital

ASD: Acute Stress Disorders

AAU: Addis Ababa University

BRD: Bipolar Related Disorders

CBC: Complete Blood Count

CBT: Cognitive Behavioral Therapy

CGI-I: Clinical Global Impression Scale Severity Items

DBT: Dialectical Behavioral Therapy

DT: Delirium Tremens

DSM-V: Diagnostic and Statistical Manual of Mental Disorders-V

ECT: Electro Convulsive Therapy

EKGH: Eka Kotebe General Hospital

EMDR: Eye movement Desensitization and Reprocessing

FDA: Food and Drug Administration

FGAs: Fist Generation Antipsychotics

LFT: Liver Function Test

MAOIs: Monoamine Oxidase Inhibitors

MDD: Major Depressive Disorder

MDE: Major Depressive Episode

MI: Motivational Interviewing

MoH: Ministry of Health

NMS: Neuroleptic Malignant Syndrome

PTSD: Post-Traumatic Stress Disorders

SGAs: Second Generation Antipsychotics

STG: Standard Treatment Guideline

SPHMMC: St. Paulo's Millennium Hospital Medical College

SSRIs: Selective Serotonin Reuptake Inhibitors

SNRIs: Serotonin Norepinephrine Reuptake Inhibitors

TCA: Tricyclic Antidepressants

TWG: Technical Working Group

TFT: Thyroid Function Test

Standard Treatment GuidelineDevelopment Process

In health care system treatment protocols are a useful tool and improving the quality of health care by promoting rational medicine use. Because of the absence of standard treatment guideline,there is a serious and widespread problem of quality in medical practice, the use of multiple medical literatures has demonstrated unexplained variations in clinical practice and health outcomes, significant rates of inappropriate care, inconsistent involvement of patients in decision making, and high health care costs.As a result, developing and implementing standard treatment recommendations is an important method for prioritizing and customizing care to the local environment, guaranteeing effective and safe drug usage, controlling health-care expenditures, and reducing disease complications.

STGs encourage an effective and cost-effective use of medications at the specialized level of health institutions by offering specific and unambiguous recommendations for each clinical condition treatment. Therefore, a complete treatment guideline in the Amanuel Mental Specialized Hospital should provide up-to-date knowledge related to the prevention, diagnosis, and treatment of common mental health care problems in order to provide quality care to their patients.

The guideline has been developed based on this knowledge and will include the following critical elements:

1) The disease/conditions to be covered to the Hospital context.

2) **Guideline category and level of application:** Mental specialized level as per the Ethiopian healthcare system and pharmaceutical delivery context.

3) **Intended users of the guideline:** the psychiatrist, physicians, prescribers, nurses, clinical pharmacists, and other allied health professionals.

4) **Guideline objective(s):** focus on the inclusion of specific and treatment individualized recommendations to these particular hospital health care services.

5) **Interventions and practice considerations**: the following key practice areas were specifically considered as guiding scopes of the development process for Amanuel Mental Specialized Hospital healthcare problem to be addressed

Topic	
Subtopics	
Brief description	• Definition or simple description and/or classification and/or epidemiology and/or causes and/or risk factors • Present based on relevance • Incorporating local epidemiologic data studies, Ethiopian WHO reports etc…are preferred) • Fitting (for broader topics) to the points that will be addressed in the consecutive diagnosis and treatment is required.
Clinical features:	• Symptoms and/or • Signs
Investigations and diagnosis	• Most appropriate and practical investigations • Diagrammatic illustrations if likely (if possible extend to include treatments for each algorithm point) • Not to miss popular/confirmatory methods
Treatment	• Goals of treatment • Pharmacologic (most appropriate and practical once) ✓ Not to miss specific dose and administration points ✓ Not to miss discussing clinically significant side effects and there management ✓ Will be good if special population considerations forwarded • Non pharmacologic (most appropriate and practical once)
	• Additional considerations, ✓ Special population considerations
Prevention	• As necessary
References	• Relevant and/or most-up-to-date once • Focus on local studies and resource • Please do not hesitate to included important points if no reference

Treatment algorithm	• Figurative summary of the recommended algorithm of treatment
Annex	• Any screening, assessment, diagnostic or follow-up tools recommended in the STG • Any other relevant document supporting the STG

Adopted from National Standard Treatment Guideline: 2021

Based on the foregoing considerations, the STG development process began year ago, by establishing a guideline development committee containing multi-disciplinary professionals from different specialty to address the guideline's development, determine how the guideline development committee will operate on the selected disease topics that are common in the hospital, and determining the guideline's scope. Identifying diseases that the guideline will cover, as well as disease subjects that the STG will include, and then allocate the disease topics that are selected to be included into the STG to various specialists based on their field of expertise to create first draft document, exposing the drafted file to internal consultative workshop, external reviewers and several editing process has been done to create validated and print readydocument

Given that health care is a dynamic process and that change is constantly imminent, periodic monitoring and assessment of STG implementation are essential for future enrichment. The results of the monitoring and evaluation data should be used as for every five yearsfurther updating.

INTRODUCTION

Since 1930the establishment of Amanuel Mental Specialized Hospital in the country, it has no standard protocol for the appropriate management of mental illness encountering, so the reason that the need to develop STG for this specific hospital.

This standard treatment guideline comprises about sixteen chapters, which is organized by major disease topics and sub-topics, which can deals with common psychiatric disorders that are commonly and frequently practiced mental illnesses within the hospital.

The format of this guideline is such that it provides detailed description the disease, important features of the disease, important diagnostic criteria and investigations,and followed by non-pharmacological and pharmacological treatments. Non-pharmacological treatment as an important aspect was very clearly explained. Pharmacological treatment includes drug recommendation level with appropriate treatment regimen, special precautions, and treatment-related warnings. It also includes an assessment of response to treatment and key metrics (signs/symptoms, surveys, etc.) with monitoring intervals. The guidelines state treatment goals and, if there is no response to the preferred treatment, indicate a step-up therapy based on the patients clinical scenario.

Medications are selected based on a balance of efficacy, safety, compatibility, tolerability,cost, and national essential medicines list. Only the medicines for which the best available evidence is available are listed in the STG. The use of certain drugs that are not supported by reasonably acceptable evidence or are outdated but still prescribed is not included in the guideline.

Note: We believe that the recommendations of the guidelines will strengthen your best decisions when you are in a familiar area and provide new suggestions in the event of psychiatricproblems. The users should be aware of the level of scope of this standard treatment recommendation.Care has been taken to confirm the accuracy of the information presented and avoid symptomatic management of uncertain diagnoses. However, the authors, and editors are not responsible for errors or for any consequences from application of the information in this STG and application of the information in a particular situation remains the professional responsibility of the practitioner.

CHAPTER ONE

1. Schizophrenia and Related Psychotic Disorders

1.1.Schizophrenia

1.1.1. Introduction

1.1.1.1.Brief description

- Schizophrenia spectrum and other psychotic disorders include schizophrenia and other disorders with primary psychosis. In addition to schizophrenia the diagnostic category includes schizophreniform disorder, brief psychotic disorder, schizoaffective disorder and delusional disorder. In this document, however, clinical practice guideline for schizophrenia is mainly discussed.
- Schizophrenia is a mental disorder involving chronic or recurrent psychosis. It is commonly associated with impairments in social and occupational functioning. Signs and symptoms are variable and include changes in perception, emotion, cognition, thinking, and behavior. The expression of these manifestations varies across patients and over time, but the effect of the illness is always severe and is usually long lasting.

1.1.1.2.Epidemiology

- According to DSM-V, the lifetime prevalence of schizophrenia appears to be approximately 0.3%-0.7%, although there is reported variation by race/ethnicity, across countries, and by geographic origin. The average national prevalence of schizophrenia is 0.5% (ENMHS 2020-2025)**).**

1.1.1.3.Causes and risk factors

- Schizophrenia has complex etiology. There is interaction of genetic and environmental risk factors in the etiology of the disorder. The etiology of schizophrenia is associated with 80% genetic heritability. However, there is no Mendelian type single-gene inheritance pattern. Multiple susceptibility genes have been described and these genes act in concert with epigenetic and environmental factors.
- There has been clear role for environmental stress in the etiology of schizophrenia. In genetically vulnerable individuals, stressful social environmental factors account for increased risk of schizophrenia. Socio-demographic factors such as poverty and low socio-economic class have been identified to increase risk. There has been increased risk among individuals born in urban areas, as well as ethnic minority migrant populations.
- Perinatal and early childhood factors such as maternal infection, malnutrition, stress, diabetes mellitus and smoking have been implicated. Obstetric complications associated with hypoxia were associated with increased risk. Other social factors associated with increased risk of schizophrenia include mother-infant relationship, family dynamics, misuse of psychoactive substances, and presence of neurodevelopmental disorders.

1.1.2. Clinical features

- The clinical manifestation of schizophrenia characteristically includes a range of cognitive, behavioral and emotional dysfunctions. However, there is no pathognomonic clinical manifestation for the disorder.
- The clinical manifestation of schizophrenia involves the presence of at least two of the following five acute phase clinical features (delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms) each present for a significant portion of time during a one month period; at least one of the clinical features must be either delusions, hallucinations, or disorganized speech. The presence of schizophrenia characteristically involves declining of level of functioning including occupational, interpersonal, or physical in adults; in children or adolescents there is failure to achieve expected level of functioning.
- Schizophrenia is characterized by the presence of continuous signs of the disturbance for at least 6 months including prodromal phase manifestations, one month of acute phase symptoms and signs, as well as residual manifestations.

1.1.3. Physical examination

- Individuals with schizophrenia have increased standardized death rates compared with the general population.
- A 5 year cohort study done in Butajira, Ethiopia, on 307patients with schizophrenia showed thatmean age (SD) of mortality for both sexes was 35 year (7.35). The study didn't show significant difference between men and female sex.
- Approximately two-thirds of this premature death are due to cardiovascular disease, smoking-related lung disease and type II diabetes. Therefore, it is important to look for physical health problems in patients with schizophrenia. Pertinent physical examination (including vital signs and neurologic examination) are recommended.

1.1.4. Diagnosis and Investigations

1.1.4.1.Diagnosis and differential diagnosis

- Complete psychiatric and general medical histories should be taken to make accurate diagnosis of schizophrenia and comorbid mental and physical health problems. Physical and mental status examinations are crucial part of the assessment of patients with schizophrenia.
- Schizophrenia is diagnosed using DSM criteria (refer DSM-5 diagnostic criteria).
- Differential diagnostic considerations should be made to exclude schizophrenia from schizoaffective disorder. In case of schizoaffective disorder diagnosis requires the occurrence of a major depressive or manic episode concurrently with the active-phase symptoms.
- Besides, the mood symptoms should be present for a majority of the total duration of the active periods of the illness for the diagnosis of schizoaffective disorder.
- Schizophrenia should be differentiated from major depressive disorder and bipolar disorder with psychotic features. This differentiation can be made based on the temporal relationship between the mood disturbance and the psychosis, and on the severity of the depressive or manic symptoms.
- If delusions or hallucinations occur exclusively during a major depressive or manic episode, the diagnosis favors depressive or bipolar disorder with psychotic features.

- Schizophrenia should be differentiated from autism spectrum disorders. Autism spectrum disorders could also have symptoms similar to schizophrenia. However, the deficits in social interaction, having repetitive and restricted behaviors together with cognitive and communication problems serve as important differentiating features. Besides, an individual with autism spectrum disorder must have symptoms that meet full criteria for schizophrenia, with prominent hallucinations or delusions for at least one month, in order to be diagnosed with schizophrenia as a comorbid condition.

1.1.4.2.Laboratory and imaging

- Use of laboratory tests and imaging studies is not mandatory to make a diagnosis of schizophrenia. However, it is necessary to conduct laboratory and imaging studies based on the history and physical examination findings.
- The laboratory investigations essential for all patients with schizophrenia at least once include CBC, LFTs, RFTs. As indicated, TFTs, RBS/FBS, Lipid profile, serum electrolytes, and additional tests may be considered.
- ECG may be needed if there is a pre-existing cardiac disease and when planning to start an antipsychotic. Radiological assessment (as indicated) may include MRI, Chest X-ray, Ultrasonography, etc.

1.1.5. Treatment

- Schizophrenia treatment has three phases, i.e. acute phase treatment, continuation phase treatment, and maintenance phase treatment. The goals of treatment will vary according to the phase of treatment.

1.1.5.1.Goal of treatment

Goal of treatment during acute phase

- An acute phase occurs when patients with a prior history of schizophrenia have a psychotic relapse or during the first episode of psychosis.
- This phase usually lasts from 4 to 8 weeks.
- The aims of treatment during the acute phase of treatment are to prevent harm, to control disturbed behaviour, to reduce the severity of psychosis and associated symptoms (e.g., agitation), to determine and address the factors that led to the occurrence of the acute episode, to effect a rapid return to the best level of functioning, and to develop an alliance with the patient and family.
- Efforts to engage and collaborate with family members and other natural caregivers are often successful during the crisis of an acute psychotic episode and are strongly recommended.
- Treatment for patients with schizophrenia during the acute phase has the following goals:

  - Ensure safety of the patient
  - Reduce or eliminate target symptoms

- Developing a therapeutic alliance and promoting treatment adherence through providing psycho-education to patient and family

- During the acute phase, treatment should target the following conditions in patients with schizophrenia:

  - Positive and negative symptoms of schizophrenia
  - Mood (affective) symptoms
  - Suicidal/homicidal ideation and behaviors
  - Substance use disorders
  - Medical comorbidities
  - Psychological conditions such as loss (loved one, property, etc.)…
  - Potential community adjustment problems, including homelessness, social isolation, unemployment, victimization, and involvement in the criminal justice system etc…

Goal of the continuation phase of treatment

- During the continuation phase the goals of treatment are to:

  - Reduce stress on the patient and provide support to minimize the likelihood of relapse
  - Enhance the patient's adaptation to life in the community
  - Facilitate continued reduction in symptoms and consolidation of remission
  - Identify early relapse signs
  - Promote the process of recovery
  - Monitor side effects

Goal of the maintenance phase of treatment

- During the maintenance phase the goals of treatment are to:

  - Ensure that symptom remission or control is sustained
  - Ensure the patient is maintaining or improving his or her level of functioning and quality of life
  - Ensure increases in symptoms or relapses are effectively treated
  - Continue monitoring for adverse treatment effects
  - Monitor physical health and nutritional status (increased mortality in people with Schizophrenia)
  - Maximize quality of life and adaptive functioning
  - Promote and maintain recovery from the debilitating effects of illness to the maximum extent possible.

1.1.5.2.General principles of management

- Determining the treatment setting is important to achieve the goals set at the beginning of treatment. Decision to admit patients or to treat them as outpatient should be carefully made. Indications for hospitalization include the following:

    - Symptoms are severe or are rapidly progressing
    - Patient considered posing a serious threat of harm to self or others
    - Inability of the patient to care for self and needing constant supervision or support
    - If there is uncertainty about the diagnosis
    - Co-morbid physical health problems that make outpatient treatment unsafe or ineffective
    - Rupture of a patient's usual support systems
    - Severe medication adverse side-effects
    - When electroconvulsive therapy (ECT) is needed

- If the patient has achieved an adequate therapeutic response with minimal side effects or toxicity with a particular medication regimen, he or she should be monitored while taking the same medication and dose for the subsequent 12 months from the time of remission.
- During the continuation phase, continue acute-phase medication treatment which was effective. Consider maintenance ECT for patients who have responded to an acute course of ECT and whose symptoms cannot be con-trolled with medication maintenance therapy alone.
- In case of relapse or acute exacerbation of schizophrenia, consider doing the following:
- First assess the reason for the relapse or exacerbation of the illness despite being on treatment. The most common contributors to symptom relapse or exacerbation are:

    - Antipsychotic medication non-adherence
    - Substance use
    - Drug- drug interactions
    - Stressful life events
    - General medical health as well as medical conditions that could contribute to symptom exacerbation.

- Regarding the duration of maintenance phase of treatment after the first episode of illness there is no cut-off point for the duration of maintenance therapy but it's recommended to continue the medication for 1-2 yrs. Indefinite maintenance antipsychotic medication is recommended for patients who have had multiple prior episodes or two episodes within 5 years.

- A number of psychosocial treatments have demonstrated effectiveness during the maintenance phase. They include family intervention, supported employment, assertive community treatment, skills training, and cognitive behaviorally oriented psychotherapy.

1.1.5.3.Non-pharmacologic treatment

- A variety of psychosocial stressors can precipitate the initial development or recurrence of symptoms in a vulnerable person.
- Treatment strategies include preventing the development or accumulation of stressors and helping the patient develop coping strategies that keep tension levels within manageable bounds.
- Psychosocial interventions can provide additional benefits for patients such as relapse prevention, improved coping skills, better social and vocational functioning, and ability to function more independently.
- The choice of psychosocial approaches and particular interventions depends on the particular needs of the patient at various phases of his or her life and illness.

Psycho-education

- Psycho-education is an effective way of addressing important therapeutic goals including adherence to treatment. In psycho-education it is necessary to address the following points:

  - Provide information to the patient and family on the nature and management of the illness
  - Antipsychotics do not ‘cure’ schizophrenia. They treat symptoms in the same way that insulin treats diabetes
  - Long-term treatment is generally required to prevent relapses
  - Discuss the potential risks and benefits of the medication with the patient
  - Discuss side effects of medications

Family interventions

- The patient’s family members should be involved and engaged in a collaborative treatment process to the greatest extent possible.
- The goals of family interventions are to decrease the risk of the patient’s relapse, improving patient functioning, decreasing family burden, and improving family functioning.
- Effective family interventions include education about the illness and its course, training in coping and problem-solving skills within the family, improved communication, and stress reduction. These interventions use practical educative and behavioral methods.
- The acute phase or times of crisis may be the best time to engage the family in psycho educational family meetings, because it is during the time when patient is most ill that the family members tend to be most motivated to reach out and make contact, ask questions, and seek information to reassure and guide them.

Cognitive behavior therapy

- In cognitive behavior therapy specific problematic symptoms are identified together with the patient and targeted.
- The therapist does not challenge these symptoms as irrational but helps the patient through guided questions to focus on his or her own beliefs about the symptoms. The patient will then be enabled to employ appropriate coping mechanisms to deal with the symptoms.
- Cognitive behavior therapy techniques may have value in improving positive symptoms with low risk of side effects.

Social skills training

- Social skills training for schizophrenia should be targeted rather than broad. The approach should be highly structured.
- The aim is to systematically train patients about specific behaviors that are critical for success in social interactions. It can include teaching patients about how to manage antipsychotic medications, identify side-effects, identify warning signs of relapse, negotiate medical and psychiatric care, and express their needs to community agencies, and interview for a job. It can also target specific social behaviors such as gaze and voice volume.
- Skills are taught through a combination of strategies such as therapist's modeling (demonstration), patient's role playing usually to try out a particular skill in a simulated interaction with positive and corrective feedback to the patient, and homework assignments by which the patient can practice a skill outside the training session. The strategies can be done individually or in a group setting.

1.1.5.3.Pharmacotherapy

Selection of an antipsychotic drug

Consider the following points in choosing among medications:

- Try to identify, with the patient, the target symptoms (e.g., anxiety, delusions)
- The patient's past responses to treatment
- The medication's side effect profile
- The patient's preferences for a particular medication based on past experience
- The intended route of administration
- The presence of comorbid medical conditions
- Potential interactions with other prescribed medications
- Past history of drug adherence
- Affordability and availability

Prescribing strategy

- First episode patients usually require lower antipsychotic dosing and should be closely monitored due to greater sensitivity to medication side-effects.
- If a patient is inadequately adherent to treatment at any stage, the clinician should assess contributing factors and consider a long-acting antipsychotic preparation, such as fluphenazine decanoate.
- A recommended dose is one that is both effective and unlikely to generate subjectively difficult-to-tolerate adverse effects.
- Anti-cholinergic (e.g. Trihexyphenidyl) should not be routinely prescribed as prophylaxis against extra-pyramidal side-effects.
- A critical review done in Zambia (2019) consolidates the above statement suggesting even patients with who are already on Trihexyphenidyl for stable EPS should be discontinued (*Medical Journal of Zambia, Vol. 46 (2): 133 - 139 (2019).* However, they can be given to people who come from far away and cannot access appropriate emergency care in case they develop acute dystonia.
- The transition from oral to long acting injectable medication can begin during the acute phase; however, the long acting injectable agents are not usually prescribed for acute psychotic episodes because these medications can take months to reach a stable steady state and are eliminated very slowly.

Switching between antipsychotics

- When there is a need to substitute one antipsychotic with another, it's important to consider the class and potency of both drugs. If the antipsychotic in use is going to be substituted with another antipsychotic from the same class (e.g., typical antipsychotic) and the same potency, it can be substituted with an equivalent dosage of the new antipsychotic at once without any need of cross tapering.
- If the antipsychotic in use is going to be substituted with another antipsychotic from the same class but with different potency (e.g., from a high potency antipsychotic to a low potency antipsychotic) or with an antipsychotic from a different class (e.g., from typical antipsychotic to an atypical antipsychotic), it's important to switch by cross tapering over few days to weeks.

Depot antipsychotic medications indication

- Long-acting injectable antipsychotics (LAIs) for patients with schizophrenia with a history of good response to oral antipsychotics but noncompliance
- Patients seeking to relieve the burden of medication-taking (Patients who experience frustration or challenges with regimens associated with taking pills, sometimes 2 to 3 times a day as well as the associated frequency of visits to the physician and pharmacy)

- Patients who indicate using a LAM as their personal preference.
- Non-adherence leads to relapse and hospitalization

Note:LAI antipsychotics are not recommended for acute psychotic episodes b/c take months to reach a steady-state concentration and are eliminated very slowly

On prescribing fluphenazine decanoate the following should be considered:

- Begin with the lowest therapeutic dose: Dose range is from 12.5mg-50mg/week. (escalate the dose based on patient condition)
- Admonition of fluphenazine decanoate can be individualized. A starting dose of 12.5 mg every 2 weeks until achieving steady state, followed by a single injection, which could last 4-6 weeks. Use e caution titrating dosages
- Adjust doses only after an adequate period of assessment.
- Attainment of peak plasma level, therapeutic effect and steady-state plasma levels are all delayed.
- Doses may be reduced if adverse effects occur, but should only be increased after careful assessment over at least one month, and preferably longer.

Conversion plan from fluphenazine decanoate to haloperidol decanoate and vice versa in case of shortages:

- Fluphenazine decanoate can be shifted to haloperidol decanoate and vice versa for patients on stable maintenance doses of fluphenazine decanoate or haloperidol decanoate.
- If conversion to Haloperidol Deaconate requires initial dose >100 mg, administer in 2 injections (e.g. 100 mg initially, then remainder in 3-7 days). Before starting the changeover, those who have never been treated with fluphenazine or haloperidol will require an oral test dosage.
- Oral potency of fluphenazine and haloperidol are similar 1:1 (i.e. 5 mg of oral haloperidol is equivalent to 5 mg of oral fluphenazine). Dose equivalents are given in the table below.

	Dose/ Frequency	**Dose/ Frequency**	**Dose/ Frequency**	**Dose/ Frequency**	**Dose/ Frequency**	**Dose/ Frequency**
Haloperidol decanoate	50 mg every 4 weeks	100 mg every 4 weeks	150 mg every 4 weeks	200 mg every 4 weeks	250 mg every 4 weeks	300 mg every 4 weeks
Fluphenazine decanoate	12.5 mg every 2 weeks	25 mg every 2 weeks	37.5 mg every 2 weeks	50 mg every 2 weeks	62.5 mg every 2 weeks	75 mg every 2 weeks

Atkins M, Burgess A, Bottomley C, Riccio M. Chlorpromazine equivalents: a consensus of opinion for both clinical and research applications. Psychiatric Bulletin 1997, 21: 224-226. Revised on October 2019.

- Patients may be switched from fluphenazine decanoate to haloperidol decanoate or from haloperidol decanoate to fluphenazine decanoate at the new dose and frequency at the next scheduled injection.
- Patients should be monitored closely for loss of therapeutic effect or an increase in adverse effects and adjust accordingly. Switching to a lower dose and supplementing orally with the new agent can also be considered, followed by tapering the oral medication. It is possible to request pharmacy consultation as needed.

Aggressive or agitated patients with schizophrenia

See details of the section for management of acutely disturbed patient. (see psychiatry Emergency chapter).

The use of electroconvulsive therapy (ECT)

- Certain group of patients with schizophrenia may benefit from ECT treatment. Patients with severe psychotic symptoms that have not responded to first antipsychotic treatment could benefit from adjunct administration of ECT.
- It is also administered for patients with prominent catatonic features that have not responded to an acute trial of diazepam or Lorazepam (see detail on treatment of catatonia chapter).
- ECT can be a useful additional treatment for patients with schizophrenia and comorbid depression, or schizoaffective disorder if depressive symptoms are resistant to treatment.
- ECT can be used in continuation/maintenance therapy for patients responding to an acute course of ECT in whom pharmacological prophylaxis alone has been ineffective or cannot be tolerated.

Managing treatment resistant schizophrenia

- Treatment resistance is defined as little or no symptomatic response to multiple (at least two) antipsychotic trials of an adequate duration (at least 6 weeks) and maximum effective dose.
- A treatment refractory evaluation should be performed to reexamine diagnosis, substance abuse, medication adherence, and psychosocial stressors.
- When there are ongoing psychosocial stressors, cognitive behavioral therapy and other psychosocial augmentations should be considered.
- In patients with treatment resistance, it is recommended to follow the following procedures:

  - Assess adherence of the patient to the prescribed medication
  - Check for doses of the prescribed antipsychotic and for how long it was taken
  - Check if patient has been taking any other medication having interaction with the prescribed antipsychotic
  - Check if there is substance use

- If you find anything from the above mentioned points, manage it accordingly.
- In truly treatment-resistant cases, trial of clozapine should be considered first. (See Ethiopian Psychiatric Association – Clozapine Treatment Guideline).
- If clozapine does not result in the desired effect, it could be augmented by another antipsychotic or by electroconvulsive therapy (ECT).
- Combination of first generation (FGA) and/ or second generation (SGA) antipsychotics, combination of FGA or SGA with ECT, or combination of an antipsychotic (FGA or SGA) with mood stabilizer can be considered as a final strategy.

Health monitoring in patients receiving antipsychotics

- Because of the effects of the second generation antipsychotics and clozapine on insulin metabolism, patients on these medications should be monitored for a number of health indicators, including BMI, fasting blood glucose, and lipid profiles at baseline and for every visit for 6 months after start of the medication.
- Patients who are taking first generation antipsychotics should be monitored for extrapyramidal side effects at every visit.

Treatment of comorbid depressive symptoms

- When there are significant depressive symptoms in patients with schizophrenia, rule out side effects of antipsychotic medications, demoralization, primary negative symptoms of schizophrenia, or schizoaffective disorder.
- Concurrent abuse or the sudden withdrawal of substances such as cannabis, cocaine, narcotics, alcohol, nicotine, and caffeine can also lead to symptoms of depression.
- Adding antidepressants as an adjunct to antipsychotics is recommended when the depressive symptoms meet the diagnostic criteria for a major depressive disorder.
- In treatment of comorbid depressive disorder, the same dose of antidepressants as that are used for treatment of major depressive disorder should be used. However, it is recommended for the clinician to be cautious about drug-drug interactions.

Managing suicidal behavior in schizophrenia patients

- It is important to consider suicide risk at all stages of the illness and to perform an initial suicide risk assessment and regular evaluation of suicide risk as part of each patient's psychiatric evaluation (see the details under suicide chapter).
- Treatment with clozapine is found to be effective for patients with recurrent suicidal behavior.

Discontinuation of antipsychotics

- The decision to stop antipsychotic drugs requires a thorough risk and benefit analysis for each patient. Withdrawal of antipsychotic drugs after long-term treatment should be gradual and closely monitored.
- Gradual withdrawal is defined as slowly tapering down over at least 3 weeks for oral antipsychotics; abrupt stopping of depot preparations can also be considered as gradual withdrawal due to their long half-life.
- The relapse rate in the first 6 months is doubled after abrupt withdrawal compared to gradual withdrawal.
- Abrupt withdrawal may also lead to discontinuation symptoms (e.g. headache, nausea, insomnia) in some patients.

1.1.5.4.Treatment in special population groups

1.1.5.5.Pregnancy and breast-feeding considerations

- In treating patients with schizophrenia using antipsychotic drugs one should consider the risks of inadequately treated schizophrenia (e.g. on antenatal care, on good pregnancy health, on self-neglect, and other vulnerability) when inadequate doses of antipsychotic medication are used for fear of adverse effects.
- On the other hand, the potential risks of various psychotropic medications to the fetus, new-born, and breast-fed infant should be considered. Generally, in patients with schizophrenia who are on treatment, there is an increased risk of obstetric complications and the pregnancy should be considered HIGH RISK.
- All women of reproductive age should be considered as being at risk of unplanned pregnancy. It must be noted that there is little evidence of risk of teratogenicity or breastfeeding problems with first generation antipsychotics.
- Regarding second-generation antipsychotics, Risperidone may reduce the chance of pregnancy and be unacceptable to some women who wish to have children. The problem with the use of olanzapine during pregnancy is that it may cause gestational diabetes.

Note: For mood stabilizers, see guideline for bipolar disorder.

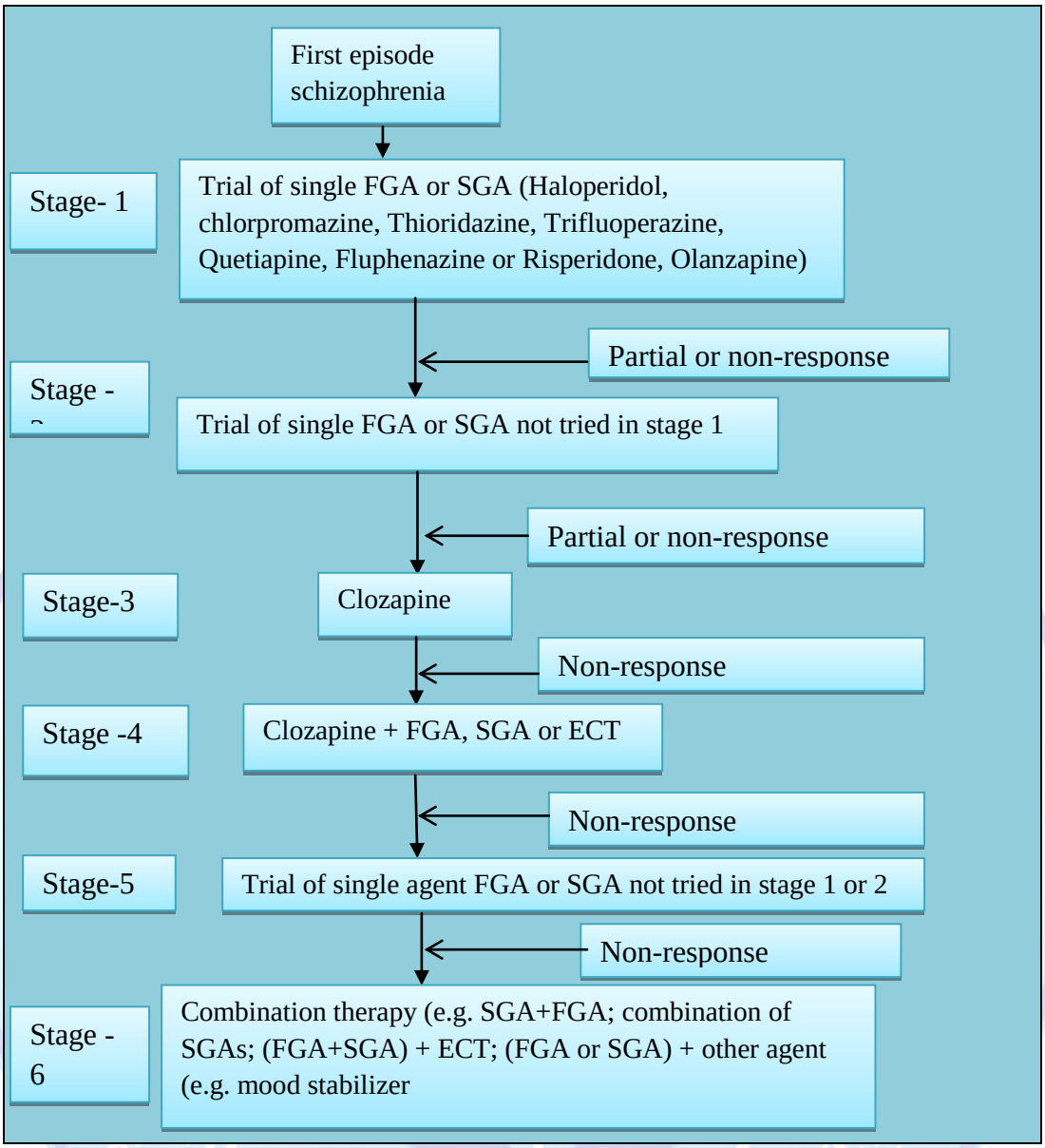
1.1.5.6.Pediatric considerations

- The U.S. Food and Drug Administration (FDA) approved the use of FGAs and SGAs for the treatment of schizophrenia and bipolar mania in children (≤ 18 years of age).
- The US-FDA also approved their use in the treatment of irritability associated with autism in children 5 years or older and of Tourette's syndrome in children aged 6-18.
- There do not appear to be advantages of SGAs (except for clozapine) over FGAs in treating psychosis in children and adolescents.
- Choice may therefore be guided by the side-effect profile. Indeed, the weight gain and metabolic problems associated with SGAs raise important public health concerns given the widespread use of these medications.

- Caution is further heightened by the finding that, generally, side-effects in children and adolescents appear more severe than in adults. Importantly, dosing should be more conservative for untreated new-onset patients than for those with multiple episodes.

1.1.5.7.Geriatric considerations

- Elderly people show variable responses and increased sensitivity to medications in general and to antipsychotics in particular.
- Age-related bodily changes affect the pharmacokinetics and pharmacodynamics of anti-psychotic drugs, which have numerous side-effects that can be more persistent and disabling in older people.
- Tardive dyskinesia, for example, can lead to a number of physical and psychological complications, including difficulty in eating and swallowing, weight loss, falls, difficulty in keeping balance and depression.
- The risk of developing tardive dyskinesia from typical (older) antipsychotics is 5–6 times higher in older people, although recent studies indicate that the newer atypical antipsychotics may pose a lower risk of this side-effect and may therefore be safer for older people.
- Antipsychotics can also increase the rate of cognitive decline; they have been associated with neuroleptic malignant syndrome, a potentially lethal adverse effect.
- For other antipsychotics, both typical and atypical, the choice of prescription should be based on the side-effect profile and risk factors such as cerebrovascular events, postural hypotension and tardive dyskinesia.



Adopted from Texas Antipsychotic Algorithm for Schizophrenia: 2007

Fig 1: Treatment Algorithm for Schizophrenia

1.2. Other Psychotic Disorders

1.2.1. Schizoaffective disorder

- The pharmacotherapy and psychotherapy for schizophrenia apply to patients with schizoaffective disorder. In addition, patients with schizoaffective disorder often need treatment with antidepressants or mood stabilizers for optimal treatment of affective symptoms. For the treatment of depressive and manic episodes in the schizoaffective disorder, refer the guidelines for the treatment of depressive disorders and bipolar disorders, respectively (see chapter two).

1.2.2. Schizophreniform disorder

- Schizophreniform disorder is an acute psychotic disorder that has a rapid onset and lacks a long prodromal phase.
- Although many patients with schizophreniform disorder may experience functional impairment at the time of an episode, they are unlikely to report a progressive decline in social and occupational functioning.
- The initial symptom profile is the same as that of schizophrenia in that two or more psychotic symptoms (hallucinations, delusions, disorganized speech and behavior, or negative symptoms) must be present.
- Also an increased likelihood is found for emotional turmoil and confusion, the presence of which may indicate a good prognosis.
- Although negative symptoms may be present, they are relatively uncommon in schizophreniform disorder and are considered poor prognostic features. The duration, however, for schizophreniform disorder should be between 1 and 6 months.
- Hospitalization, which is often necessary in treating patients with schizophreniform disorder, allows effective assessment, treatment, and supervision of a patient's behavior. The psychotic symptoms can usually be treated by a 3- to 6-month course of antipsychotic drugs (e.g. Risperidone).
- Psychotherapy is usually necessary to help patients integrate the psychotic experience into their understanding of their own minds and lives.
- ECT may be indicated for some patients, especially those with marked catatonic or depressed features.

1.2.3. Brief psychotic disorder

- Brief psychotic disorder is a disturbance that involves the sudden onset of at least one positive psychotic symptom (delusion, hallucination, disorganized speech, grossly abnormal psychomotor behaviours, including catatonia). An episode of the disturbance lasts at least 1 day but less than 1 month, and the individual eventually has a full return to the premorbid level of functioning.
- Sudden onset is defined as change from a non-psychotic state to a clearly psychotic state within 2 weeks, usually without a prodromal symptom. Although the disturbance is brief, the

level of impairment may be severe, and supervision may be required to ensure that nutritional and hygienic needs are met and that the individual is protected from the consequences of poor judgment, cognitive impairment, or acting on the basis of delusions.

- Individuals with brief psychotic disorder typically experience emotional turmoil or overwhelming confusion. They may have rapid shifts from one intense affect to another.
- Hospitalization may be needed if patient poses danger to self or others, and for diagnostic purposes.
- The two major classes of drugs to be considered in the treatment of brief psychotic disorder are the antipsychotic drugs and the benzodiazepines.
- Clinicians should avoid long-term use of any medication in the treatment of the disorder; treatment should be discontinued as soon as symptoms disappear.
- Benzodiazepine treatment should be for short term treatment of agitation and insomnia.
- Psychotherapy is of use in providing an opportunity to discuss the stressors and the psychotic episode.
- Exploration and development of coping strategies are the major topics in psychotherapy.
- Family involvement in the treatment process may be crucial to a successful outcome.

1.2.4. Delusional disorder

- The diagnosis of delusional disorder is made when a person exhibits psychosis experience characterized by delusions of at least 1 month duration.
- The delusion should not be attributed to other psychiatric disorders such as schizophrenia.
- Risk factors associated with delusional disorder are advanced age, social isolation, family history, recent migration, personality features and sensory impairment.
- The disorder has generally been regarded as resistant to treatment. Interventions have often focused on an attempt to establish therapeutic alliance, managing the morbidity of the disorder by reducing the impact of the delusion on the patient's life, and exploring over time how the delusion interferes with the patient's life.
- Individual psychotherapy more effective than group therapy. Insight-oriented, supportive, cognitive, and behavioral therapies are often effective.

References

1. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, text revision. Washington DC, American Psychiatric Association, 2022.
2. St Paul's Clinical Practice Guideline for Mental Disorders; 2019
3. Correll CU, Kim E, Sliwa JK, Hamm W, Gopal S, Mathews M, Venkatasubramanian R, Saklad SR. Pharmacokinetic Characteristics of Long-Acting Injectable Antipsychotics for Schizophrenia: An Overview. CNS Drugs. 2021 Jan;35(1):39-59.
4. Sadock, and Pedro Ruiz. Kaplan & Sadock's Synopsis of Psychiatry: Behavioral Sciences/clinical Psychiatry. Eleventh edition. Philadelphia: Wolters Kluwer, 2015.
5. American Psychiatric Association (1997): Practice Guideline for the Treatment of Patients with Schizophrenia. *American Journal of Psychiatry* 154:1-63.
6. Chue P, Eerdekens M, Augustyns I, et al (2005): Comparative efficacy and safety of long-acting risperidone and risperidone oral tablets. *European Neuropsychopharmacology* 15:111-7.
7. Nayak RK, Doose DR, Nair NP (1987): The bioavailability and pharmacokinetics of oral and depot intramuscular haloperidol in schizophrenic patients. *J Clin Pharmacol* 27:144-50.
8. Schooler NR, Levine J (1976): Initiation of long-term pharmacotherapy in schizophrenia - Dosage and side-effect comparisons between oral and depot fluphenazine.
9. Woods SW (2003): Chlorpromazine equivalent doses for the newer atypical antipsychotics. *Journal of Clinical Psychiatry* 64:663-667.
10. Taylor DM, Barnes TR, Young AH. The Maudsley prescribing guidelines in psychiatry. John Wiley & Sons; 2021 Jul 13
11. Ethiopian Essential Medicines List, Ministry of Heath/ EFDA, Sixth edition, 2020.
12. Keepers GA, Fochtmann LJ, Anzia JM, Benjamin S, Lyness JM, Mojtabai R, Servis M, Walaszek A, Buckley P, Lenzenweger MF, Young AS. The American Psychiatric Association practice guideline for the treatment of patients with schizophrenia. American Journal of Psychiatry. 2020 Sep 1;177(9):868-72.

13. D Kebede , A Alem, T Shibre, A Negash, A Fekadu, D Fekadu, et al. Onset and clinical course of schizophrenia in Butajira-Ethiopia--a community-based study. Soc Psychiatry Psychiatr Epidemiol 2003; 38(11):625-31.
14. Zafar U Khan, Elisa Martin-Montanez and E. Chris Muly. Schizophrenia: Causes and Treatments. Current Pharmaceutical Design, 2013; 19: 6451-6461
15. Smith DJ, Langan J, McLean G, et al. BMJ Open 2013;3:e002808.
16. M. Lynn Crismon, Tami R. Argo, Alexander L. Miller, Troy A. Moore, Sherrie D. Bendele, Brandon T. Suehs (2008). Schizophrenia Treatment Algorithms. Texas Medication Algorithm Project Procedural Manual
17. Atkins M, Burgess A, Bottomley C, Riccio M. Chlorpromazine equivalents: a consensus of opinion for both clinical and research applications. Psychiatric Bulletin 1997, 21: 224-226. Revised October 2019
18. Anthony C. James. Prescribing antipsychotics for children and adolescents. Advances in psychiatric treatment (2010), vol. 16, 63–75
19. Salman Karim and Eleanor J. Byrne. Treatment of psychosis in elderly people. Published online by Cambridge University Press: 02 January 2018
20. Teferra, S., Shibre, T., Fekadu, A., Medhin, G., Wakwoya, A., Alem, A. & Jacobsson, L. (2011)

CHAPTER TWO

2. Bipolar Disorders

2.1.Introduction

2.1.1. Brief description

- Bipolar disorder is a name given to a group of affective mental disorders characterized by episodes of either mania or hypomania, and with or without history of episode(s) of depression. Bipolar disorders are one group of the most disabling affective disorders.
- Bipolar disorders sometimes occur with overlapping symptoms with other disorders. The symptoms can also be secondary to substance use or other medical disorders which usually could be overlooked.
- The bipolar disorders occur in a spectrum and the main presentations include bipolar I disorder, bipolar II disorder, and cyclothymia.
- The presentation of bipolar disorder could be secondary to substances/ medications or another medical condition.
- The main feature of bipolar I disorder is the presence of a manic episode; there could be a hypomanic of a major depressive disorder.
- The main feature of bipolar II disorder is the occurrence of a hypomanic episode and a major depressive disorder in the clinical picture; a manic episode should never happen in the clinical picture for the diagnosis to be made.
- Cyclothymic disorder involves presentation characterized by several periods of hypomanic symptoms which fall short of fulfilling the full criteria for a hypomanic episode, as well as several periods of depressive symptoms which fall short of fulfilling full criteria for major depressive episode.

2.1.2. Epidemiology

- Studies show that the aggregate global lifetime prevalence figures were 0.6% for bipolar I disorder, 0.4% for bipolar II disorder. The figures also showed prevalence for sub-threshold bipolar disorder was 1.4%.

- The prevalence for the full bipolar spectrum disorder was 2.4%. The prevalence in Ethiopia is estimated to be 0.1 to 1.83%. In addition, Bipolar disorder has significant morbidity and mortality; a recent study showed more than 30% of those suffering commit suicide.

2.1.3. Causes and risk factors

- Genetics: Families, twins, and adoption studies showed that inherited variables are implicated in the pathophysiology of bipolar illness.
- Neurobiology: Multiple lines of evidence show that brain anatomy and function was altered in bipolar disorders. It's unclear if the observed changes were due to etiologic factors, sequelae, neither, or both.
- Inflammation: Bipolar disorder is related with immune system dysregulation, as seen by elevated inflammatory markers in the blood.
- Overlap with other disorders: Neurobiology of bipolar disorder overlaps with that of other mental illnesses, such as schizophrenia.
- Psychosocial factors: Advancing paternal age has been associated with higher prevalence of bipolar disorder.

2.2. Clinical features

- Bipolar disorder is characterized by mood fluctuations that alternate between mania (or hypomania) and depression.
- The entire criteria for mania are missing in bipolar II disorder, and the repeated depressions are interrupted by intervals of modest activation and enhanced energy (hypomania).
- In bipolar I disorder a manic episode is defined as a period of abnormally elevated or irritated mood and increased goal-directed activity/energy that lasts for at least one week or less if hospitalization is required. Reduced desire for sleep, distractibility, slurring of speech, psychomotor agitation, inflated self-esteem, and risky behaviors are some of the other indications and symptoms.
- In bipolar II disorder the presence of at least one major depressive episode and one or more hypomanic episode manifesting similar with manic episode but lasting at least 4 days (see MDD chapter-5).
- Hypomanic episodes differ from manic episodes in that they last less time and are less severe in terms of causing functional impairment, hospitalization, or psychosis. Psychosis, on the other hand, necessitates the diagnosis of mania.

- Cyclothymic disorder manifests with sub-threshold hypomania and depressive symptoms that don't meet the diagnostic criteria for major depressive episode or manic/hypomanic episode. It is a rather chronic condition lasting 2 years and above (1 year for children).
- Physical examination should include all pertinent examinations guided by findings from the history, but should include vital signs and neurological examination.

2.3.Diagnosis and investigations

2.3.1. Diagnosis and differential diagnosis

- Diagnosis of bipolar and related disorders is based on severity of mood symptoms that is experienced during acute phase of the illness**.**
- For a diagnosis of bipolar I disorder, it is necessary to meet the criteria for a manic episode. The manic episode may have been preceded by and may be followed by hypomanic or major depressive episodes.
- For a diagnosis of bipolar II disorder, it is necessary to meet the criteria for a current or past hypomanic episode and the criteria for a current or past major depressive episode. Diagnosis of a bipolar disorder should be made according to DSM 5. (for the details; refer DSM-V)
- Clinical assessment should include issues related to safety of the patient. In this regard immediate assessment of aggression, suicidality and violence should be made. Ability to adhere to treatment should be assessed. The presence of comorbid medical conditions such as thyrotoxicosis, HIV, seizure disorders, other neurologic disorders, etc. should be checked. Substance misuse history and history of use of antidepressants should be part of the history.
- The assessment should include detailed information (collateral history) from family members, friends, colleagues, health care providers, etc.
- Differential diagnosis should consider a number of disorders which look like bipolar disorders. In a patient who presents with major depressive episode, it is advisable to look for past episodes of mania or hypomania. The diagnosis of bipolar II disorder must be differentiated from the diagnosis of bipolar I disorder by the absence of a history of manic episode.
- The diagnosis of bipolar I disorder must be differentiated from a substance/medication-induced manic symptoms. Since there is a tendency for individuals with bipolar I disorder to misuse substances during an episode, a primary diagnosis of bipolar disorder must be established based on symptoms that remain once substances are no longer being used.

- Attention-deficit/hyperactivity disorder (ADHD) may be misdiagnosed as bipolar disorder, especially in adolescents and children. Many symptoms overlap with the symptoms of mania, such as rapid speech, racing thoughts, distractibility, and less need for sleep. In bipolar I disorder, however, the symptoms occur as distinct episodes rather than continuously.
- Borderline personality disorder may have substantial symptomatic overlap with bipolar disorders, since mood lability and impulsivity are common in both conditions. Symptoms must represent a distinct episode, and the noticeable increase over baseline for the diagnosis of bipolar I disorder. In individuals with severe irritability, particularly children and adolescents, care must be taken to apply the diagnosis of bipolar disorder only to those who have had a clear episode of mania or hypomania, which is distinct from baseline.
- Bipolar II disorder should be distinguished from cyclothymic disorder. In cyclothymic disorder, there are numerous periods of hypomanic symptoms and numerous periods of depressive symptoms that do not meet symptom or duration criteria for a major depressive episode. Likewise, a cyclothymic disorder can be differentiated from bipolar I disorder because it lacks the manic episode which is characteristic of bipolar I disorder.
- Schizophrenia, schizoaffective disorder, and delusional disorder can be differentiated from bipolar disorders because they are all characterized by periods of psychotic symptoms that occur in the absence of prominent mood symptoms.

2.3.2. Laboratory and imaging

- The routine baseline investigations should include complete blood count (CBC), the liver transaminases (ALT, AST), renal function tests (BUN, Cr), thyroid function tests (T3, T4, and TSH), fasting blood sugar (FBS), and, for all women within the reproductive age group, urine HCG.. If there are clear indications, the following could be done: lipid profile (TG, HDL and LDL), electroencephalogram (EEG), electrocardiogram (ECG), brain magnetic resonance imaging (MRI), and urine drug screen.

2.4.Treatment

2.4.1. Goals of treatment

- Managing core symptoms of mania, depression and psychosis
- Minimizing drug side effects in order to improve adherence
- Early detection and treatment of symptoms
- Treat comorbid substance use and abuse

- Recovery of functional status

2.4.2. General principles of treatment

The treatment is expected to follow the following general principles:

- Making adequate initial assessment of patients, including for comorbid conditions, as well as regular review of progress during follow-up
- Making clear and documented assessment and adequate management of risk issues, including for suicidal behavior, aggressive and homicidal behavior, risk to property, etc.
- Choosing an appropriate setting for treatment; whether the patient should be admitted or treated at the outpatient department
- Involving the patient and caregivers in the management plan
- Stabilizing symptoms and avoiding relapses and recurrences in the mid- and long-term
- Minimizing drug adverse effects

2.4.3. Non-pharmacologic treatment

- Psychosocial intervention is primarily used to treat depressive episodes and to prevent relapse and improve quality of life. Since there is no evidence for its use in acute mania, there is no recommendation for its use in acute mania.
- Interventions with positive evidence include psychoeducation, cognitive behavioral therapy (CBT), family-focused therapy (FFT), interpersonal and social-rhythm therapy (IPSRT) and peer support.
- Electroconvulsive therapy (ECT) is used when pharmacologic treatment fails, or when rapid response is required in patients with catatonic presentations.

2.4.4. Pharmacologic treatment

2.4.4.1.Bipolar Mania: Acute Treatment

- The treatment modality should be based on efficacy, availability and cost, as well as tolerability of drugs.
- It is recommended that all patients should be initiated, or optimized to first line treatment. (See table below on level of recommendation).
- Level of recommendation can be monotherapy or combination treatment. (i.e. depends on the clinician decision on factors such as rapid response rate, prior response to treatment,

tolerability) About half of the patents on monotherapy treatment will respond within 3-4 weeks.

- First line combination therapy has greater efficacy than monotherapy especially for severe cases. If there is no response within 2 weeks of treatment with first-line therapy, considering optimum dose is used, then add on or switch therapy to alternate first line agents is recommended.
- There are multiple first-line agents with safety, tolerability andefficacy profiles, thus the use of second-line agents is only recommended after unsuccessful trials of these multiple first-line agents.
- Although drugs such as olanzapine, haloperidol and carbamazepine have level 1 efficacy they are considered a second line because of safety and tolerability.
- Olanzapine has the highest efficacy of all second-line agents, thus it should be the first choice of the entire list.
- Electroconvulsive therapy (ECT) is considered as second-line treatment. Studies show up to 80% clinical response rate.
- Adjunct use of benzodiazepines such as diazepam, Lorazepam, or clonazepam along with first line treatment can be used based on severity of manic episode.
- Lorazepam is the preferred benzodiazepine for acute manic agitation at 1 to 3 mg orally or 0.5 mg to 3 mg IM, with repeat doses at least 60 minutes apart (Maximum dose range 10-12mg) in the first 24 hours.

First Line therapy

- Lithium carbonate 300mg PO BID to TID and increased by 300mg 1-5 days interval (Treatment with lithium should be monitored by the serum levels of lithium. Therapeutic serum levels for acute mania are 0.8-1.2 mmol/L). The benzodiazepines Lorazepam or clonazepam can be given concomitantly to calm patients.

OR

- Sodium valproate 200 mg three times per day, increased by 200 to 500 mg every 2 to 3 days to obtain steady-state. Theoptimaldose of sodium valproate is 1500-2500mg/d (max 60mg/kg per day). Once stabilized, sodium valproate can be given divided twice daily.

The benzodiazepines Lorazepam or clonazepam can be given concomitantly to calm patients.

OR

- Risperidone. Dose of 1-6mg/day can be used.

Second line therapy

- Carbamazepine should be started at 100 to 200 mg twice daily. The dose should be increased by 200 mg every 3 to 4 days until adequate serum levels have been reached.

OR

- Olanzapine. For adults give 10 to 15 milligrams (mg) once a day or divided twice. Maximum dose is 20 mg/day

OR

- Haloperidol. Initial dose of 1.5 -5 mg. It can be titrated based on severity of symptoms, or adverse effects to 5-15 mg/d; maximum dose is 30mg/d.

Third-line therapy

- Olanzapine plus Lithium

OR

- Olanzapine plus Sodium Valproate

OR

- Lithium plus Sodium Valproate

OR

- ECT

2.4.4.2.Bipolar Depression: Acute Treatment

- Full assessment of nature and severity of depression including risk for suicide, adherence to treatment and psychosocial support should be conducted.
- Assessment for substance use and other medical condition is needed. Modality of treatment includes pharmacotherapy and psychosocial therapy. Often times both modalities are given together.

First-line therapy

- Lithium carbonate 300mg PO BID to TID increased by 300mg every 1 to 5 days based on upon patient response and tolerability (maximum dose range 900-1200mg). (Treatment with lithium should be monitored by the serum levels of lithium. Therapeutic serum levels for acute mania are 0.8-1.2 mmol/L).
- Lamotrigine 25mg once daily for the 1st and 2nd week of initial treatment and titrate up by 25mg for the 3rd and 4th weeks to reach 50 mg/day, then 100mg once daily in 5th weeks and maintain at 200mg in 6th weeks (daily dose range 50 to 200mg).

Second-line therapy

- Sodium valproate: initiate at 750 mg/day in divided doses; dose should be adjusted as rapidly as possible to desired clinical effect;
  OR
- Fluoxetine 20mg PO/day; adjust as tolerated to usual range of 20 to 50 mg/day
  OR
- Fluoxetine plus olanzapine. Initial 25 mg/6 mg PO qDay in evening, If needed, may titrate with 25-50 mg fluoxetine/6-12 mg olanzapine; do not exceed 75 mg/18 mg per day
  OR
- ECT

Table 1: Level of recommendation for bipolar depression

Level of Recommendation	**Drug**	**Formulation**	**Dose range per day**
First line	Lithium Carbonate	Tablet	900 to 1200mg
	Lamotrigine	Tablet	50-200mg
Second line	Sodium Valproate	Tablet	750- 2500 mg
	SSRI's(Fluoxetine)	Capsule	20-50mg
	Olanzapine plus Fluoxetine	Capsule	25/6mg- 75/18mg

2.4.4.3.*Maintenance treatment of bipolar disorders*

- Agents used for acute manic episodes have also prophylactic activities.
- All agents used for acute phase should be continued for maintenance treatment except the use of adjunct antidepressants.
- The use of adjunct antidepressant increases the potential risk of manic/hypomanic episode. However strong clinical justification is needed to withdraw antidepressants as patients who responded to combination treatment may destabilize upon withdrawal.
- The use of atypical antipsychotics can be effective in preventing relapse of mania/hypomania but not depression.
- Detailed evaluation of patients for medication adherence, monitoring of serum drug levels, and detection of early symptoms is needed on follow up visits. Optimization of treatment should follow the hierarchical flow seen on the table below.

Table 2: Maintenance therapy is advised in bipolar disorder based on a hierarchical ranking of first and second line treatments.

Level	Recommended drugs	Prevention of mania	Prevention of Depression	Remark
First line treatment	Lithium Carbonate	√√√√	√√√√	
	Sodium Valproate	√√	√√√	
	Lamotrigine	√√√	√√√√	
Second line treatment	Olanzapine	√√√√	√√√√	
	Risperidone	√√√√		No data available
	Carbamazepine	√√√	√√√√	

Adopted from Canadian guideline

2.4.4.4.Special considerations

- For pregnant bipolar patients treated with pharmacotherapy, clinicians should attempt to use drugs with fewer known teratogenic effects, use of monotherapy, and adjust doses at the low end of the therapeutic range.

Lithium in pregnancy

- Lithium has been associated with a variety of congenital malformations and category D (especially first trimester) with estimated overall risk for congenital malformations is approximately 4% to 12%.

Sodium valproate in pregnancy

- It has pregnancy category of X. It may cause major congenital malformations. Valproate is not recommended in women of childbearing potential for any other condition unless valproate is essential to manage her condition and alternative therapies are not appropriate **(**Effective contraception should be used during therapy**).**

Lamotrigine and carbamazepine

- Both drugs can cause serious fatal dermatologic reaction requiring hospitalization and discontinuation of treatment.

2.4.4.5.Safety and monitoring of pharmacologic agents

- Patients taking lithium should have their serum medication levels monitored regularly for safety reasons. If possible, serum level of sodium valproate may be measured as therapeutic drug monitoring measure. One importance is to check for adherence of medications. Patients on atypical antipsychotics should have their weight monitored monthly in the first 3 months then every 3 months thereafter. Blood pressure, fasting blood sugar (FBS), and lipid profiles should be assessed at 3 and 6 months. If there is sign of neurological, hepatic, renal, or hematological conditions, then additional treatment option is needed. (See table below).

Table 3: Monitoring for patients on drug treatment for bipolar disorders

Drug	**Monitoring parameters**	**Time interval**	**follow up**
Lithium Carbonate	Serum Lithium, Electrolytes, BUN, and Creatinine	Every 3-6 months	At least every 6 months in 80% patients for serum lithium and 70% for others
	Calcium and TSH	At baseline, after six months then annually	Annually for majority of patients
Sodium Valproate	CBC and Liver function tests	Annually	Annually for majority of patients
	Therapeutic Drug Monitoring (TDM) of	When clinically indicated	When clinically indicated

	sodium valproate, fasting blood glucose and lipid profile		
Carbamazepine	CBC, LFT, Electrolytes, BUN, and Creatinine	Annually	Annually for majority of patients
	TDM of carbamazepine	When clinically indicated	When clinically indicated
Olanzapine, Risperidone, and Quetiapine	Fasting Blood Glucose and Fasting Lipid Profile	Annually	Annually formajority

ISBD recommendation

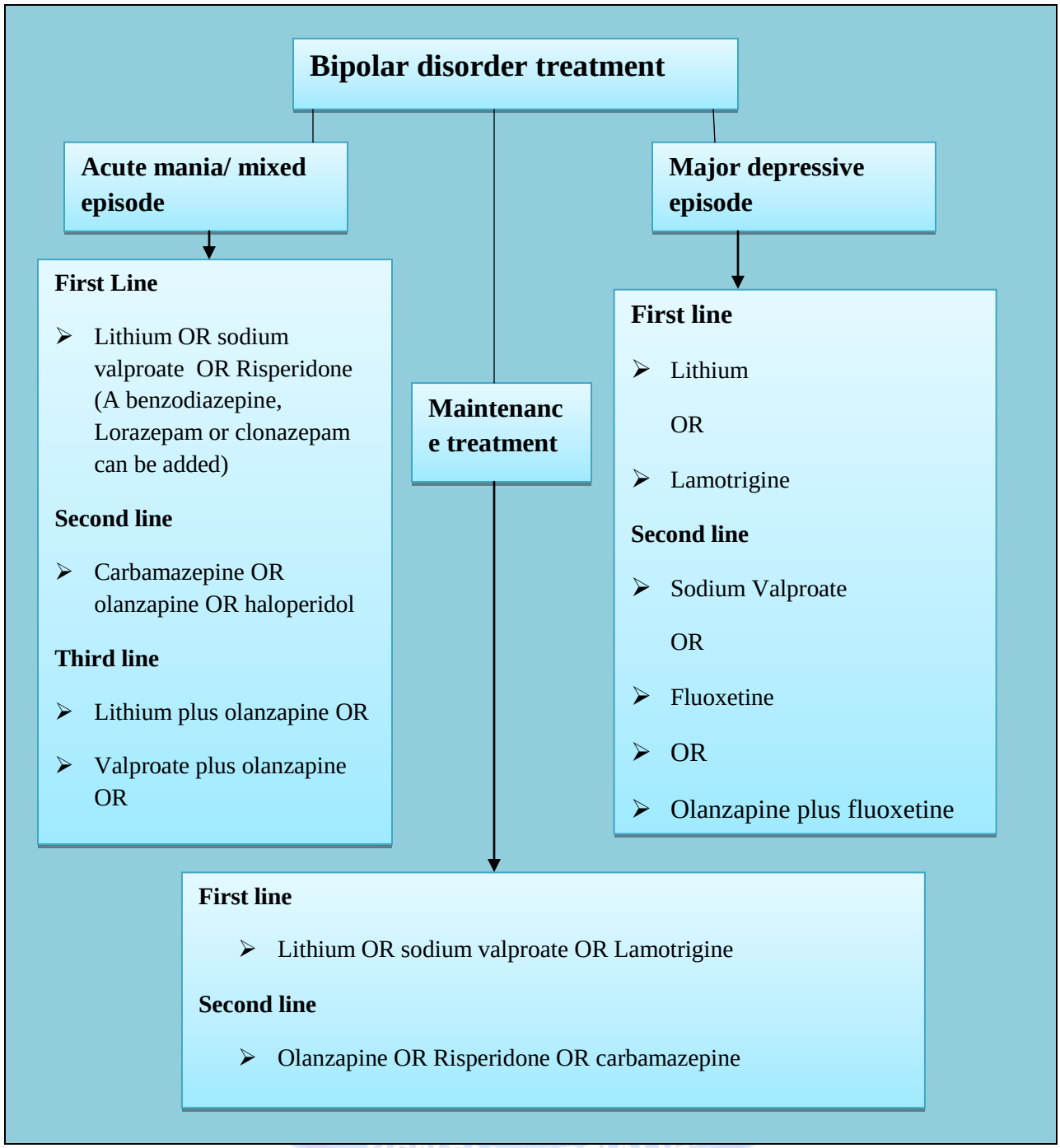


Figure 2: Algorithm for treatment of bipolar disorder

Reference

1. Esan O, Esan A. Epidemiology and burden of bipolar disorder in Africa: a systematic review of data from Africa. Soc Psychiatry PsychiatrEpidemiol. 2016;51(1):93–100.
2. Hirschfeld RMA. Guideline Watch for the Practice Guideline for the Treatment of Patients With Bipolar Disorder. 2005;(November):1–9.
3. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, text revision. Washington DC, American Psychiatric Association, 2022.
4. Merikangas KR, Jin R, He J-P, et al. Prevalence and correlates of bipolar spectrum disorder in the World Mental Health Survey Initiative. Arch Gen Psychiatry 2011; 68(3): 241-251.
5. Stephen Soreff, Francisco Talavera. Bipolar Disorder. Medscape: Updated Feb 11, 2022
6. Kennedy SH, Lam RW, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. Introduction. J Affect Disord. 2009; 11 (Suppl 1):S1–S2.
7. Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. Bipolar Disord. 2013; 15: 1–44.

CHAPTER THREE

3. Attention Deficit/ Hyperactivity Disorder (ADHD)

3.1.Introduction

3.1.1. Brief Description

- Psychiatric disorders that are present among children and adolescent tend to be genetic /Familial/ and often chronic. It is also associated with significant morbidity and mortality. Although it's difficult to identify the true magnitude of mental disorders among children, literatures suggest that about 12-22% of children and adolescents suffer from a psychiatric disorder. In this chapter, the treatment guideline for attention deficit/ hyperactivity disorder (ADHD) is written.
- Attention deficit hyperactivity disorder (ADHD) is a heterogeneous psychiatric disorder that consists of multiple subtypes; including inattention, hyperactivity/ impulsivity, and a combination of these two types.
- Untreated or ineffectively treated ADHD in children can result in low academic performance, poor sociability, and a higher risk of traffic accidents, psychiatric comorbidities, unemployment, and incarceration during adolescence and adulthood.

3.1.2. Epidemiology

- ADHD is a chronic neurobehavioral disorder, with the prevalence in school-age children estimated to be between 8 and 11 percent, making it one of the most common disorders of childhood. National studies in Ethiopia show that the prevalence of ADHD is estimated to be 7.3%.

3.1.3. Causes and risk factors

ADHD probably results from a combination of factors. The causes and contributors for ADHD include:

- Genetic factors,
- Environmental causes,
- Psychosocial factors (e.g. socioeconomic status and family relationships).
- The suggested contributory factors for ADHD include prenatal toxic exposures, prematurity, and prenatal mechanical insult to the fetal nervous system. Studies

suggest a potential link between cigarette smoking and alcohol use during pregnancy and ADHD in children.

- Preschoolers who are exposed to high levels of lead may have a higher risk of developing ADHD.

3.2.Clinical Characteristics

- The inability to sit still or inhibit activities is a hallmark of the hyperactive-impulsive subtype of ADHD.
  - This presentation includes excessive fidgetiness (eg, tapping the hands or feet, squirming in seat),
  - Difficulty remaining seated when sitting
  - Feelings of restlessness (in adolescents) or inappropriate running around or climbing in younger children,
  - Difficulty playing quietly,
  - Excessive talking,
  - Difficulty waiting turns,
  - Blurting out answers too quickly, and
  - Interruption or intrusion of others.
- The inattentive subtype of ADHD is characterized by a delayed rate of cognitive processing and response, as well as a reduced ability to focus attention. It includes features such as ;
  - Failure to provide close attention to detail,
  - Making careless mistakes,
  - Difficulty maintaining attention (in play, school, or home activities),
  - Seems not to listen even when directly addressed,
  - Fails to follow through (eg, homework, chores, etc),
  - Difficulty organizing (tasks, activities, and belongings),
  - Avoids tasks that require consistent mental effort,
  - Loses objects required for tasks or activities (eg, school books, sports equipment, etc),
  - Easily distracted by irrelevant stimuli, and forgetfulness in routine activities (eg, homework, chores, etc).

3.3.Diagnosis and investigation

3.3.1. **Diagnosis and differential diagnosis**

- Physical examination should be based on the findings of the history, but should include vital signs, body mass index (BMI) and neurologic examination.
- The diagnosis of ADHD is made when the diagnostic criteria are met according to the DSM criteria. (See DSM-V).

ADHD should be differentiated from important disorders which look like ADHD.

- The school aversion in ADHD must be differentiated from that of oppositional defiant disorder in that the aversion in ADHD is due to the challenges related to difficulty in sustaining mental efforts.
- The behaviour in oppositional defiant disorder is characterized by negativity, hostility, and defiance; and the resistance is due to resistance conforming to others' demands.
- ADHD shares high levels of impulsive behaviour with intermittent explosive disorder. In intermittent explosive disorder, however, patients show serious aggression toward others which is not characteristic of ADHD.
- In addition, patients have no problems with sustaining attention as seen in ADHD.
- Stereotypic movement disorder is another important syndrome that needs to be excluded. In this disorder the motor behavior is generally fixed and repetitive (e.g., body rocking, self-biting).
- The fidgetiness and restlessness in ADHD are typically generalized and not characterized by repetitive stereotypic movements.
- It is worth noting that the frequent multiple tics in Tourette's disorder can be mistaken for the generalized fidgetiness of ADHD.
- Children with specific learning disorder may appear inattentive because of frustration, lack of interest, or limited ability. This, however, is not impairing outside of academic work and should be differentiated from ADHD.

ADHD shares symptoms of inattention with anxiety disorders.

- Individuals with ADHD are inattentive because of their attraction to external stimuli, new activities, or preoccupation with enjoyable activities. This is distinguished from the inattention due to worry and rumination seen in anxiety disorders.

- Restlessness in ADHD is not associated with worry and rumination. ADHD could be mistaken for bipolar disorder. Individuals with bipolar disorder may have increased activity, poor concentration, and increased impulsivity. These features, however, are episodic; in addition, in bipolar disorder, increased impulsivity or inattention is accompanied by elevated mood, grandiosity, and other specific bipolar features.
- Disruptive mood dysregulation disorder is characterized by pervasive irritability, and intolerance of frustration.
- Unlike ADHD, however, impulsiveness and disorganized attention are not its essential features. Finally,
- ADHD is not diagnosed if the symptoms of inattention and hyperactivity occur exclusively during the course of a psychotic disorder.

3.4.Laboratory and imaging

- The laboratory tests required are decided by the findings of the history and physical examination. It is advisable to conduct CBC, ALT, AST, BUN, creatinine at the baseline. If there are indications the following can be conducted: Urine HCG (Caution when use of stimulants during pregnancy because of low birth weight, preterm), HDL, LDL, TG, Cholesterol, TSH, VDRL, RPR, EEG with concerns of comorbid seizure disorders and or other neurological soft signs, as well as ECG with concerns of cardiac problems or family history.

3.5.Treatment of Attention Deficit/Hyperactivity Disorder (ADHD)

3.5.1. Goals of treatment

The goal of treatment of patients with ADHD is to

- Improve psychological, social, educational and occupational functioning.
- ✓ It is meant to improve relationships, academic performance, self-esteem, increase independence, and reduce disruptive behavior. It must include setting target outcomes. It is necessary to agree on desired improvement with child, parents and teachers.
- ✓ The main goal of the psychosocial intervention is help parents of children with ADHD recognize and promote the notion that although the child may not “voluntarily” exhibit symptoms of ADHD but is still capable of being responsible for meeting reasonable expectations.

3.5.2. General management principles

- Medications prescribed for ADHD can be diverted, misused or even abused. One needs to assess substance use before prescribing stimulants.
- Titration of these drugs should be taken slowly in order to avoid adverse effects.
- A comprehensive, cardiovascular-focused patient history, family history, and physical examination should be completed.
- The child's baseline height, weight, blood pressure, and heart rate should be measured. A pretreatment baseline should be established (eg, appetite, sleep pattern, headaches, abdominal pain).
- Adolescent patients should be assessed for substance use or abuse. Combination of stimulants and non-stimulants can be effective in those patients non-responding to stimulants alone. However, caution should be takento address any side effects of ADHD.

3.5.3. Non-pharmacological treatment

- Some of the psychosocial interventions used in ADHD include psychoeducation, academic organization skills remediation, parent training, behavior modification in the classroom and at home, cognitive behavioral therapy (CBT), social skills training, and dietary interventions.

3.5.4. Pharmacologic treatment

- Pharmacologic treatment is considered to be the first line of treatment for ADHD.
- Central nervous system (CNS) stimulants are the primary choice of medicines since they have the highest efficacy and the fewest negative effects.
- International evidence suggests that the use of stimulants and non-stimulants are effective in treatment of ADHD.
- The Ethiopian Essential Medicines List includes bupropion, methylphenidate and Dextroamphitamine for the treatment of ADHD.

Table 4: Pharmacologic agents for treatment of ADHD

Agent	Preparation	Starting Dose
Stimulants		
Methylphenidate	Tablet ER, 5mg, 10mg, 20mg	5 mg two or three times daily; increase by 5-10 or 20 mg/day at weekly intervals
Dextroamphitamine	Tablet, 2.5mg,5mg,10mg Oral liquid, 5mg/5ml ER tablet, 10mg,15 mg	Initial dose of 5 mg BID; titrated by 5 mg weekly to max of 20 mg twice daily.
Non-Stimulant		
Bupropion	Tablet, 75 mg, 100mg	Initial dose of 150 mg daily, with slow titration up to a maximum of 450 mg per day.
Imipramine	Tablet, 10mg, 25mg	Start at a divided dose of 1mg/kg/day, with titration to doses of 2.0 to 2.5mg/kg/day over a 1 to 2 week period.

- Despite the above-mentioned agents being used as first line of choice for the treatment of ADHD;
- There are also other effective treatment options. Alpha-2 agonists such as Guanfacine (Children ≥6 years and Adolescents ≤17 years) Oral: Start with 1 mg once daily and gradually increase by no more than 1 mg/week. 0.05 to 0.12 mg/kg/dose (1 to 7mg) once daily is the recommended target dose, depending on clinical response and tolerability.
- Clonidine has been found to be effective in children and adolescents. Initial dose: 0.05 mg at bedtime; gradually increase by 0.05 mg increments every 3 to 7 days as twice daily, then 3 times daily, then 4 times daily; maximum daily dose: 0.2 mg for patients weighing 27 to 40.5 kg; 0.3 mg for patients weighing 40.5 to 45 kg.
- When stopping therapy, taper off gradually over a period of 1 to 2 weeks. However, their use in adults has not been studied extensively in terms of efficacy, safety, and tolerability.

Table 5: Safety and monitoring of Pharmacologic agents

Parameter	Visit	Remark

Weight	• Every visit during titration • Every 3months after optimal dose titration	• Use anthropometric measurements for indicated age (wt/age, ht/age, ht/wt)
Height	• Every 3-6months	
Heart rate, Blood pressure	• Every visit	
ALT,AST	• Every 3-6 months	

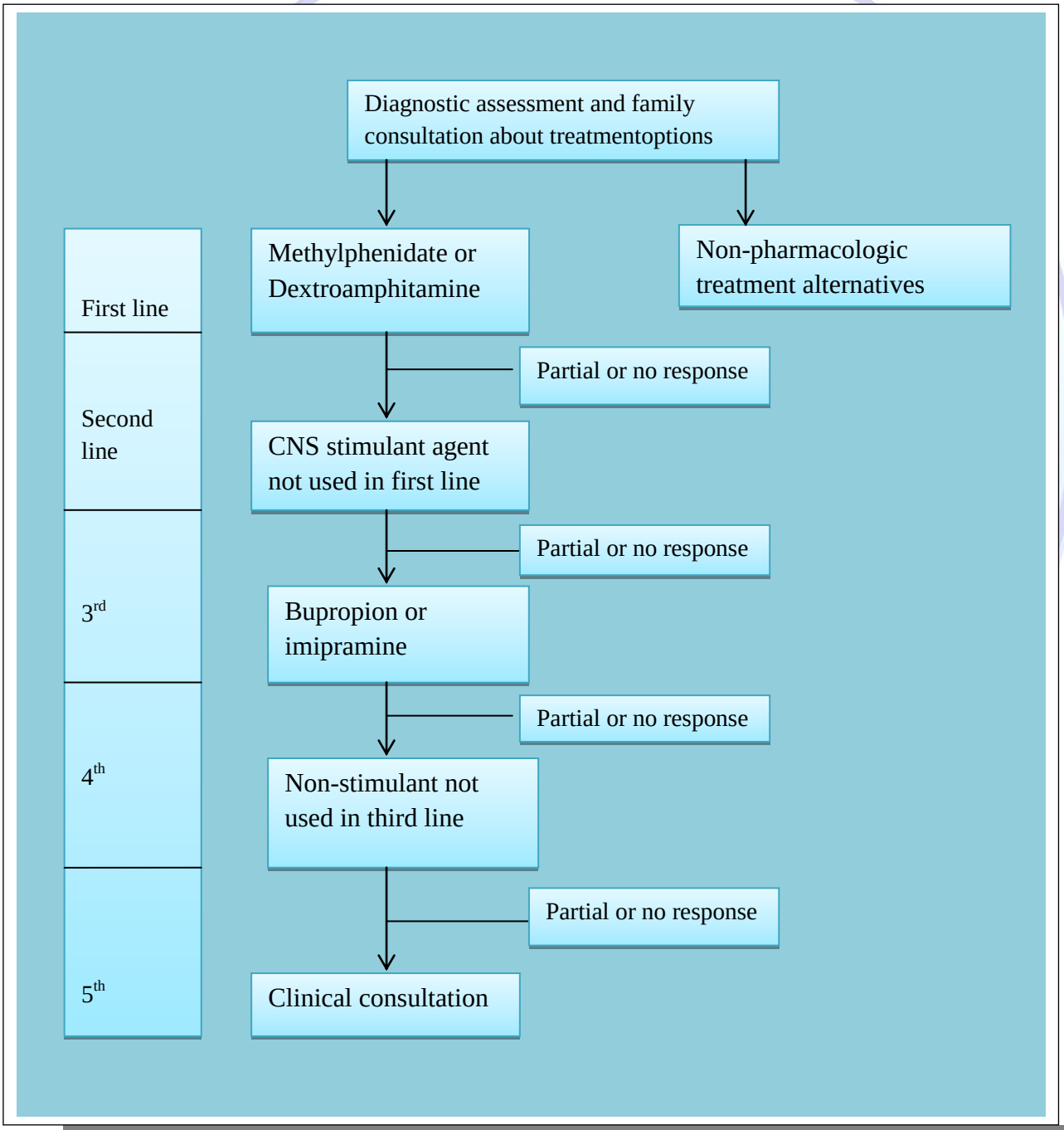


Figure 3: Algorithm for the management of ADHD

Reference

1. Lola HM, Belete H, Gebeyehu A, Zerihun A, Yimer S, Leta K. Attention Deficit Hyperactivity Disorder (ADHD) among Children Aged 6 to 17 Years Old Living in Girja District , Rural Ethiopia. 2019;2019.
2. Mulat H, Yegezaw N, Eyasu T. Co - morbidity of attention deficit hyperactivity disorder among children with seizure disorders at University of Gondar referral hospital Ethiopia (2016). Sci Rep [Internet]. 2021;(0123456789):1–7. Available from: https://doi.org/10.1038/s41598-021-95751-8
3. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, text revision. Washington DC, American Psychiatric Association, 2022.
4. Subcommittee on Attention-Deficit/Hyperactivity Disorder, Steering Committee on Quality Improvement and Management, Wolraich M, et al. ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Pediatrics 2011; 128:1007
5. Larson K, Russ SA, Kahn RS, Halfon N. Patterns of comorbidity, functioning, and service use for US children with ADHD, 2007. Pediatrics 2011; 127:462.
6. Perou R, Bitsko RH, Blumberg SJ, et al. Mental health surveillance among children--United States, 2005-2011. MMWR Suppl 2013; 62:1.
7. Visser SN, Danielson ML, Bitsko RH, et al. Trends in the parent-report of health care provider-diagnosed and medicated attention-deficit/hyperactivity disorder: United States, 2003-2011. J Am Acad Child Adolesc Psychiatry 2014; 53:34.
8. AyresJL.Intellectualdisability(Intellectualdevelopmentaldisorder).The5-MinuteClinical ConsultStandard2016:TwentyFourthEdition.2015
9. BOLAND R. DSM-5® Guidebook: The Essential Companion to the Diagnostic and Statistical ManualofMentalDisorders,FifthEdition.Vol.21,JournalofPsychiatricPractice.2015.171–173 p.

10. RobertsL,HalesR.AdvancePraiseforTextbookofPsychiatry,7thEdition
11. APA (2013). Diagnostic and Statistical Manual of Mental Disorders
12. Bibi Leila Hoseini, Maryam Ajilian, Habibolah Taghizade Moghaddam1, Gholamreza Khademi, Masumeh Saeidi. Attention Deficit Hyperactivity Disorder (ADHD) in Children: A Short Review and Literature. International Journal of Pediatrics, 2014; 2 (4-3)
13. National Institute of Mental Health: U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES. Attention-Deficit Hyperactivity disorder (ADHD)

CHAPTER FOUR

4. Anxiety Disorders

4.1.Introduction

- Anxiety is an emotion that can be experienced by almost everyone at some point in their life. It can only be a problem if symptoms are distressing or interfere with quality of life. According to the DSM-5 anxiety disorders include excessive fear and anxiety that accompany behavioral disturbances.
- In Ethiopia, anxiety is one of the most commonly identified priority mental illness with an estimated prevalence of 3.3% and accounting for 8.5% of all years lived with disability in the general population.
- According to the DSM-5 there are anxiety disorders that can occur specifically during childhood and adolescence such as separation anxiety disorder and selective mutism. Other disorders that may occur in different age groups include: panic disorder, agoraphobia, social anxiety disorder, generalized anxiety disorder, and specific phobia.

This chapter of the treatment guideline will discuss the following anxiety disorders:

4.1.1. Panic disorder
4.1.2. Agoraphobia
4.1.3. Specific phobia
4.1.4. Social anxiety disorderGeneralized anxiety disorder

4.1.1. Panic Disorder (PD)

4.1.1.1.Brief description

- Panic disorder (PD) is one of the anxiety disorders in which two or more sudden/spontaneous panic attacks have occurred. Panic attacks can range from multiple episodes in a single day to only a few attacks in a year.
- The key features of panic disorder are “recurrent unexpected panic attacks, and persistent concern about additional panic attacks and/or maladaptive change in behavior related to the attacks”.
- A panic attack is a sudden episode of intense fear that triggers severe physical reactions. Panic attacks can occur in many other psychiatric disorders for example in obsessive compulsive disorder, in post-traumatic disorder or in social anxiety disorder.

- Panic attacks may be either expected, occurring in a situation to a feared situation or object, or it can occur in unexpected situation, occurring for no apparent condition. In panic disorder, the panic attacks are recurrent and occur suddenly with no apparent triggering situation or object. In other disorders, if panic attacks occur, they are related to some triggering situation or object.

4.1.1.2.Epidemiology

- The global lifetime prevalence of panic disorder (PD) is estimated at 1.7%, with a 2.7%. The female to male ratio of prevalence is 2:1. The incidence of panic attacks in children is rare; the overall prevalence of PD is low before age 14 years (<0.4%).

4.1.1.3.Causes and risk factors

- Genetic risk factors are known to exist. Risk was higher for children of parents with anxiety, depressive, and bipolar disorders. Environmental risk factors include:
  - History of trauma, stressful life experiences and childhood adversities
  - Parental overprotection and low emotional warmth
  - Few economic resources
  - Smoking

4.1.1.2.Clinical features

- The clinical feature of panic disorder is a recurrent panic attack that occurs unexpectedly.
- Panic attacks comprise of abrupt surge of intense fear that reaches a peak within minutes.
- The attacks consist of physiological symptoms and signs (palpitations or pounding heart, sweating, sensation of shortness of breath, trembling or shaking, feeling of choking, nausea or abdominal distress, etc),
- Cognitive symptoms (feeling dizzy or light-headedness, fear of losing control or going crazy, fear of dying, etc), and
- Dissociative symptoms (depersonalization, depersonalization, etc).

4.1.1.3.Diagnosis and investigations

4.1.1.3.1. Diagnosis and differential diagnosis

- The diagnosis of PD is made based on the fulfillment of the diagnostic criteria for the disorder according to the DSM-5.
- Panic disorder should not be diagnosed if full criteria have not been met.

- Full medical history and physical examination (including neurological examination) should be conducted to identify medical conditions which have clinical features similar to PD.
- Important differential diagnostic work should be done and documented to differentiate PD from other medical and psychiatric conditions.
- Medical conditions and substance-related conditions that can cause panic attacks include:
  - Hyperthyroidism
  - Hyperparathyroidism
  - Pheochromocytoma
  - Vestibular dysfunctions
  - Seizure disorders
  - Cardiopulmonary conditions (e.g., arrhythmias, supraventricular tachycardia, asthma, chronic obstructive pulmonary disease [COPD])
  - Intoxication with central nervous system (CNS) stimulants (such as caffeine, cocaine or amphetamines) or cannabis
  - Withdrawal from CNS depressant substances and medications (such as alcohol or barbiturates)
- There are differential diagnostic considerations and co-morbid conditions which often present with PD and the most common is agoraphobia.
- Agoraphobia is the fear of being in situations where escape might be difficult. Specific phobia is associated with specific object or situation as its trigger.
- In social anxiety disorder the anxiety is associated with social encounters and fear of negative social evaluation. In PD, the anxiety has no known cause or trigger.
- Careful history taking will reveal the differential diagnosis from other anxiety disorders and comorbidities.

4.1.1.3.2. Laboratory and imaging

- Baseline laboratory tests include complete blood count (CBC), sedimentation rate (ESR), liver transaminases, renal function tests (urea and creatinine), fasting blood sugar (FBS), serum electrolytes, and thyroid function tests (TSH, T3, and T4).
- Other tests can be done when indicated. Electrocardiography (ECG) can be used to assess for pericardial problems and ventricular dysrhythmias in patients with chest pain, or syncope. Cardiac enzymes such as troponin could be indicated if myocardial injury is suspected.

- Chest x-ray can be used when pulmonary problems are suspected. Electroencephalogram (EEG) can be conducted if seizure disorder is considered.
- Urine drug screen should be considered if substances are suspected.
- D-dimer assay could be necessary when pulmonary embolism is suspected. Use of brain scanning such as brain MRI is optional and could be indicated if there is strong suspicion of partial seizure or other brain pathologies.

4.1.1.4.Treatment of panic disorder (PD)

4.1.1.4.1. Goals of treatment

- Treatment of PD has the following goals:
    - Reducing the number and severity of panic episodes
    - Provide effective coping
    - Treating co-morbid psychiatric disorders
    - Obtaining complete symptomatic remission
    - Preventing relapse
    - Adapting the treatment strategy to the needs of each individual
    - Achieving pre-morbid level of functioning

4.1.1.4.2. General principles of treatment

- The treatment of panic disorder should be based on realistic collaboration with the patient.
- Treatment should start with providing psychoeducation, teaching relaxation techniques and lifestyle modification. Lifestyle modification may include doing regular physical exercise, maintaining sleep hygiene, reducing consumption of psychoactive substances (caffeine, alcohol, tobacco and others).
- Symptoms of panic disorder that do not interfere with daily functioning do not require pharmacotherapy at first
- Patients with mild panic disorder may respond to psychoeducation and reassurance. However watchful monitoring of such patient every 3 month (or more frequently when indicated) is important to determine if symptoms were worsening and/or patient has declining functionality.

4.1.1.4.3. Non-pharmacologic treatment for PD

- Psychotherapy, especially cognitive and behavioral therapy (CBT) is the preferred modality for PD.

- Cognitive behavioral therapy should be conducted by a professional well trained in CBT for PD. Cognitive behavioral therapy for PD should be done on a weekly basis with an 8-12 sessions either given individually or as a group. Cognitive-behavioral therapy for PD generally includes psychoeducation, self-monitoring, countering anxious beliefs, exposure to fear cues, modification of anxiety-maintaining behaviors, and relapse prevention. Cognitive behavioral therapy for PD generally includes 3 stages:
    - Stage 1: Psychoeducation, setting treatment goal
    - Stage 2: Identifying cognitive distortion, exposure therapy, reducing avoidance
    - Stage 3: Relapse prevention

4.1.1.4.4. Pharmacological treatment for Panic disorder

- Consider the following variables while selecting pharmaceutical treatments for panic disorder.
    - Efficacy
    - Adverse effects
    - Drug-drug interaction
    - Presence of comorbidities (either medical or psychiatric)
    - Cost, availability, patient choice
- Most studies show SSRIs, tricyclic antidepressants (TCAs) and benzodiazepines to be efficacious in the treatment of panic disorder.
- The preferred initial choice of pharmacotherapy is SSRIs which include sertraline and fluoxetine. The SSRIs are first-line pharmacologic agents due to their safety profile.
- The TCAs (such as amitriptyline, imipramine and clomipramine) are second-line pharmacologic agents.
- The use of benzodiazepines should be judicious considering side effects and potential for dependence. Generally, benzodiazepines should be used temporarily to manage severe distress in which rapid symptomatic control is desired, or together with drugs such as fluoxetine to alleviate the restlessness and aggravation of anxiety at onset of treatment.
- The SSRIs and TCAs should be initiated at lower doses (such as half the initial dose for depression) and dose escalation should be slow and based on tolerability.
- The timeframe for response to pharmacotherapy could extend from 2 weeks up to 12 weeks. If response is not adequate despite adequate dose administration, then shift to other SSRIs or TCAs.

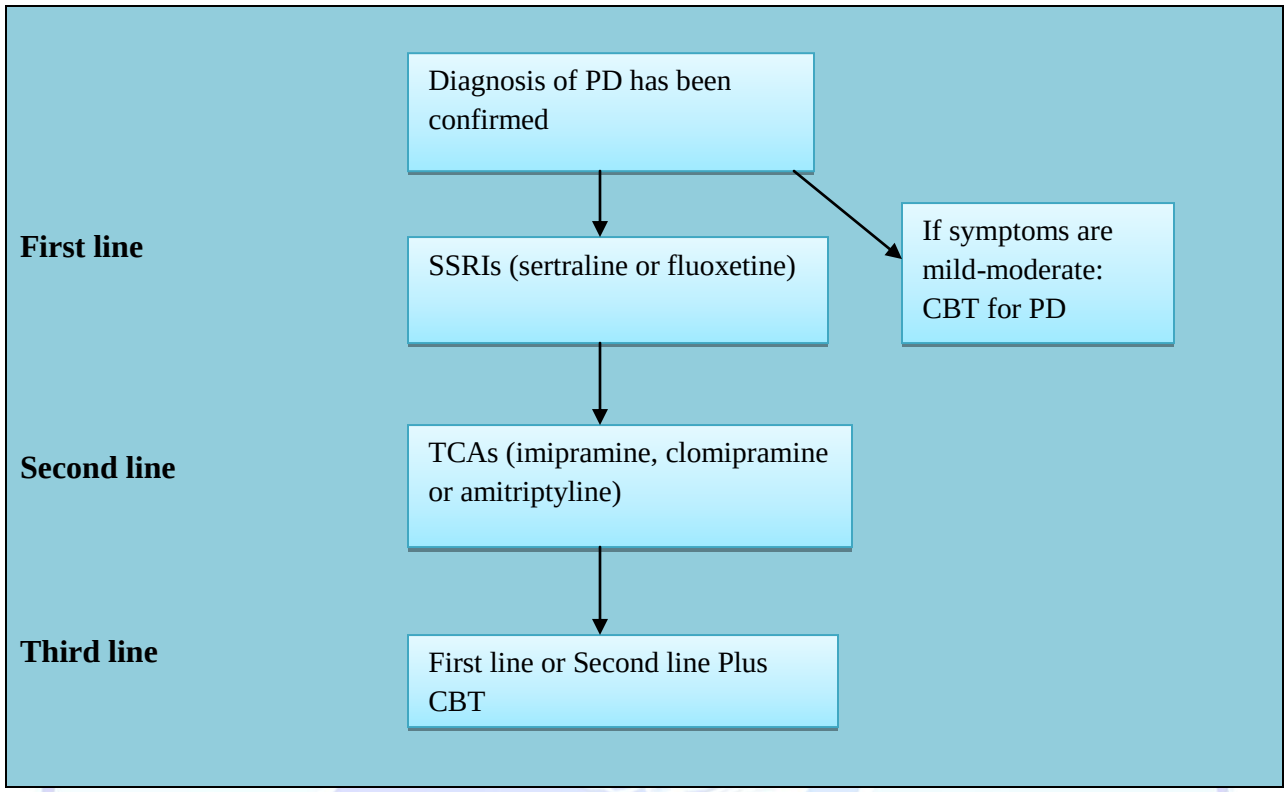


Figure 4: Algorithm for the treatment of panic disorder (PD)

4.1.2. Agoraphobia

4.1.2.1. Brief description

- Agoraphobia refers to a fear of or anxiety regarding situations from which escape might be difficult. It can be the most disabling of the phobias because it interferes with activities of daily life affecting functionality both at work and social circumstances. Most of the time agoraphobia often exists with panic disorder.

4.1.2.2.Epidemiology

- The 12-month prevalence rate for agoraphobia is about 1%–1.7%. The female to male ration of prevalence is 2:1. Agoraphobia may occur in childhood, but incidence peaks in late adolescence and early adulthood.

4.1.2.3.Causes and risk factors

- The contribution of genes is 61%. On top of genetic vulnerability, the following environmental factors increase the risk of agoraphobia:
  - Negative events in childhood (e.g., separation, death of parent)

- Family climate and child-rearing behavior characterized by reduced warmth and increased overprotection
- Being attacked or mugged

4.1.2.4.Clinical features

- The essential feature of agoraphobia is "avoidance and fear of situation where escape may be difficult and where help may not be available". The fear or anxiety is almost inevitable when the individual is exposed to agoraphobic situation. The agoraphobic situation could be one of the following:
  - Using public transportation (buses, trains, planes, etc)
  - Being in open spaces (parking lots, marketplaces, bridges, etc)
  - Being in enclosed spaces (shops, theatres, cinemas, etc)
  - Standing in line or being in a crowd
  - Being outside of the home alone
- Fear may manifest with a full panic attack or limited panic like attacks. Active avoidance is a behavior that the individual deliberately tries to minimize or prevent agoraphobic situations.

4.1.2.5.Diagnosis and investigations

4.1.2.5.1. Diagnosis and differential diagnosis

- Diagnosis of agoraphobia should be based on the DSM-5 diagnostic criteria.
- The diagnosis of agoraphobia could be confused with other anxiety disorders.
- Agoraphobia should be differentiated from specific phobia, situational type.
- The diagnosis of specific phobia, situational type should be favored if the fear, anxiety, or avoidance is limited to a single agoraphobic situation; the presentation of agoraphobia is associated with fears from two or more of the agoraphobic situations.
- The other differential diagnosis consideration is separation anxiety disorder. The fear or anxiety in separation anxiety disorder is associated with the cognition about detachment from a significant attachment figure; the fear or anxiety in agoraphobia is focused the occurrence of panic-like symptoms in situations where help is not available.
- Social anxiety disorder could be confused with agoraphobia; however, the fear in social anxiety disorder is focused on being negatively evaluated. If the diagnostic criteria for panic disorder are met, the diagnosis of agoraphobia should not be made unless the avoidance involves at least two agoraphobic situations.

4.1.2.5.2. Laboratory and imaging

- Baseline laboratory tests include complete blood count (CBC), sedimentation rate (ESR), liver transaminases, renal function tests (urea and creatinine), fasting blood sugar (FBS), serum electrolytes, and thyroid function tests (TSH, T3, and T4).
- Other laboratory or imaging studies could be considered if history and physical examination suggests any other medical conditions.

4.1.2.6.Treatment of agoraphobia

4.1.2.6.1. Goals of treatment

- Controlling agoraphobia and avoidance behavior
- Treating co-morbid psychiatric disorders
- Obtaining complete symptomatic remission
- Adapting the treatment strategy to the needs of each individual
- Returning to pre-morbid function

4.1.2.6.2. General principles of treatment

- Treatment should start with providing psychoeducation, teaching relaxation techniques and lifestyle modification.
- Lifestyle modification may include doing regular physical exercise, maintaining sleep hygiene, reducing consumption of psychoactive substances (caffeine, alcohol, tobacco and others).
- In mild to moderate cases, psychotherapy could be attempted as first line of treatment for agoraphobia. However, if symptoms are severe and functional impairment is remarkable, treatment could be initiated with pharmacotherapy. Combination treatment should also be considered.

4.1.2.6.3. Non-pharmacologic treatment agoraphobia

- Psychotherapy may involve behavioral techniques such as exposure therapy, as well as cognitive behavior therapy (CBT).

Behavior therapy

- Behavior therapy for agoraphobia involves exposure therapy. Evidence supports the benefit for the in-vivo exposure treatment in agoraphobia.

- Graduated levels of exposure to the feared situation based on a hierarchy of the least fear-provoking situation to the greatest fear-provoking situation.
- The patient should come up with hierarchy of anxiety-provoking agoraphobic situations; if the patient could not, by themselves, come up with the list, the therapist can assist them. Once the hierarchy has been determined, the patient can be exposed in vivo, starting from the least anxiety-provoking situation to the greatest fear-provoking situation. Each situation in the hierarchy must be mastered before continuing to the next level.
- Studies also suggest similar efficacy for imaginal exposure to hierarchical situations. Clinical gains are maintained at 2-year follow up.

Cognitive behavioral therapy (CBT)

- Cognitive behavioral therapy (CBT) addresses irrational or distorted thoughts associated with the agoraphobic stimuli. These maladaptive automatic thoughts are modified to more reasonable and realistic thoughts during therapy. Studies suggest CBT for agoraphobia has similar efficacy to in vivo exposure therapy.

4.1.2.6.4. Pharmacotherapy for agoraphobia

- Consider the following variables while selecting pharmaceutical treatments for panic disorder.
  - Efficacy
  - Adverse effects
  - Drug-drug interaction
  - Presence of comorbidities (either medical or psychiatric)
  - Cost, availability, patient choice
- There are no studies which show the benefit of pharmacologic agents for agoraphobia in the absence of panic attacks. However, limited evidence suggests the benefit of sertraline and clomipramine. The evidence for fluoxetine and imipramine has been minimal.
- The first line pharmacologic treatment for agoraphobia, therefore, is sertraline or clomipramine; second line pharmacologic agents are fluoxetine and imipramine.
- The medications should be initiated at lower doses (such as half the initial dose for depression) and dose escalation should be slow and based on tolerability.

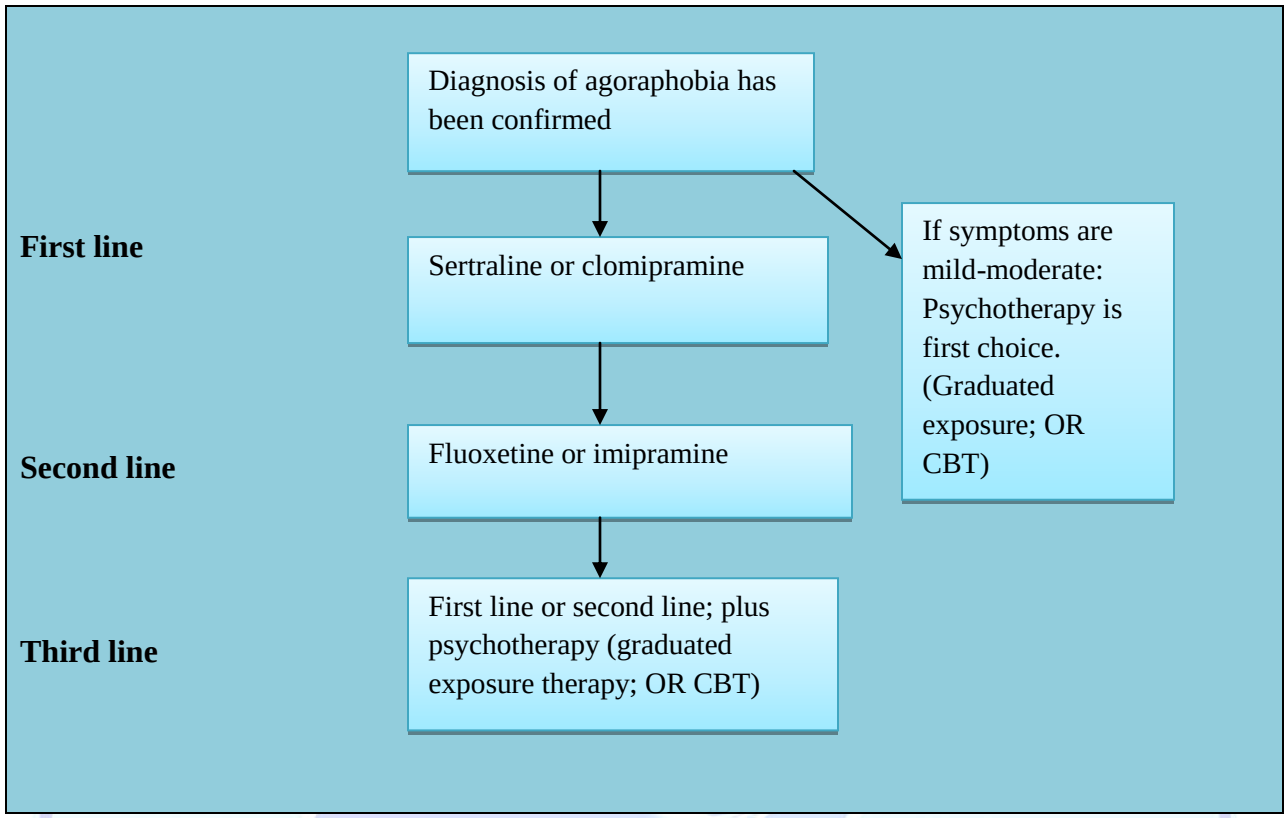


Figure 5: Algorithm for the treatment of agoraphobia

4.1.3. **Specific Phobia**

4.1.3.1.Brief description

- A specific phobia is an intense fear of a specific object or situation and is usually associated with avoidance of the feared object.
- The most common types of phobia include animal (e.g., insects, rodents' snakes), natural environment (e.g., heights, storms, water), situational (e.g., flying, enclosed spaces), and blood-injection injury (B-I-I) (e.g., blood, injection needles, hospitals). Specific phobias are one of the commonest mental disorders could be highly disabling to patients.

4.1.3.2.Epidemiology

- The 12-month prevalence estimates for low and middle income countries of Africa, Asia and Latin America range 2-4%. The female to male ratio of prevalence across subtypes is 2:1.

4.1.3.3.Causes and risk factors

- There is genetic susceptibility to specific phobia. The heritability of the disorder across subtypes ranges from 25-33%. The environmental risk factors include:

- Parental over-protectiveness
- Parental loss and separation
- Physical and sexual abuse

4.1.3.3.Clinical features

- A specific phobia involves persistent and intense fear on a particular object or state of affairs. The fear or anxiety is out of proportion to the particular risk. Here are some of the categories of specific phobias;
  - Situations: such as airplanes, enclosed areas or going to school
  - Nature: such as thunderstorms or heights
  - Animals or insects: such as puppies or spiders
  - Blood, injection or injury: such as needles, injuries or clinical procedures
  - Others: such as choking, vomiting, loud noises or clowns
- The diagnosis of specific phobia should be made based on fulfillment of the DSM-5 diagnostic criteria for the disorder.
- It is important to make a differential diagnosis from other anxiety disorders or other psychiatric or medical conditions that may have similar presentations.
- Specific phobias may also occur alongside other forms of anxiety disorders and should be considered during making the differential diagnosis.
- Specific phobias may be tough to differentiate from panic disorder if the patient presents with recurrent panic attacks. Main difference is that the panic attacks in panic disorder are sudden with no triggering situation or object whereas in specific phobia, panic attacks (if present), are associated with a situation or object that the individual has the phobia for.

4.1.3.4.Diagnosis and investigations

4.1.3.4.1. Diagnosis and differential diagnosis

- The diagnosis of specific phobias should be made based on the fulfillment of the DSM-5 diagnostic criteria for the disorder.
- The key feature of the disorder is that the fear or anxiety is circumscribed to the presence of a particular situation or object, which is known as the phobic stimulus.
- The patient with specific phobia experiences fear and an increase in physiological arousal in anticipation and/or upon exposure to the phobic stimulus. A behavior of avoidance toward the phobic stimulus is another characteristic of patients with the disorder.

- The differential diagnosis of specific phobias involves other types of anxiety disorder. The core cognition of the anxiety makes the differential among the different anxiety disorders. Situational specific phobia has resemblance with agoraphobia. If the agoraphobia involves a single agoraphobic stimulus, the diagnosis of specific phobia, situational type may be the preferred diagnosis; in agoraphobia, there are two or more agoraphobic situations. Social anxiety disorder is differentiated from specific phobia because the anxiety in social anxiety disorder is associated with negative evaluation in social situations. Likewise, separation anxiety disorder is differentiated from specific phobia because the anxiety in separation anxiety disorder is associated with separation from attachment figures.

4.1.3.4.2. Laboratory and imaging

- Baseline laboratory tests include complete blood count (CBC), sedimentation rate (ESR), liver transaminases, renal function tests (urea and creatinine), fasting blood sugar (FBS), serum electrolytes, and thyroid function tests (TSH, T3, and T4).
- Other laboratory or imaging studies could be considered if history and physical examination suggests any other medical conditions.

4.1.3.5.Treatment of specific phobia

4.1.3.5.1. Goals of treatment

- Control or eliminate symptoms of specific phobia
- Treat co-morbid psychiatric disorders
- Restore premorbid level of functioning
- Prevent relapses

4.1.3.5.2. General principles of treatment

- It is a priority to decide the level of distress, interference of symptoms with functioning, and the impact of the disorder on the quality of life of the patient
- If there is another mental disorder comorbid with specific phobia, it is advisable to treat the comorbid condition first
- If symptoms of specific phobia are severe and life threatening, such as choking and fear of medical procedures, they warrant priority for treatment

4.1.3.5.3. Non-pharmacologic treatment

- The two commonly used and effective treatment psychotherapeutic modalities are exposure therapy (ET) and cognitive behavioral therapy (CBT).
- Psychotherapy should be conducted by a clinician who is well trained in the procedure that is used for treatment.
- Exposure therapy (ET): Both imaginal and in vivo exposure approaches can be used. Imaginal ET involves exposure to the phobic stimulus through imagination. In the in vivo exposure approach the patient confronts the actual phobic stimulus. Exposure should be done in the graduated ET approach, in which exposure starts from the least anxiety-provoking stimulus to the most. The hierarchy should be decided together with the patient and each level should be mastered before going to the next level.
- Cognitive behavioral therapy (CBT): This approach involves identifying maladaptive thoughts associated with the anxiety and replacing them with more adaptive thoughts.

4.1.3.5.4. Pharmacological treatment

- No controlled studies have demonstrated the efficacy of pharmacotherapy for specific phobia.

4.1.4. Social Anxiety Disorder (SAD)

4.1.4.3.Brief description

- Social anxiety disorder (also referred to as social phobia) involves the fear of social situations, including situations that involve scrutiny or contact with strangers.
- The individual feels intense fear and anxiety when they feel that they are the subject of attention.
- People with social anxiety disorder (SAD) have trouble talking to people, meeting new people, and attending social gatherings. The disorder can be persistent, debilitating and functionally disabling.

4.1.4.4.Epidemiology

- The 12-month prevalence rates for most of the world are around 0.5-2.0%. Women are more affected than men.

4.1.4.5.Causes and risk factors

- Social anxiety disorder (SAD) has genetic predisposition; there is a two to six times increased risk for people who have first-degree relatives with SAD. Environmental risk factors include:
  - Negative social experiences, such as peer victimization
  - Child maltreatment and adversity

4.1.4.6.Clinical features

- People who suffer from SAD are afraid of humiliating themselves in public. (i.e.,social gatherings, oral presentations, meeting new people). They may have particular phobias about certain actions, such as eating or speaking in front of others, or they may have a generic, nonspecific dread of "embarrassing oneself."

4.1.4.7.Diagnosis and investigations

4.1.4.7.1. Diagnosis and differential diagnosis

- The essential feature of SAD is the fear of negative evaluation leading to anxiety in social situations; the other characteristic feature is avoidance of social situations or use of safety-seeking behaviors. The diagnosis of social anxiety disorder should be based on the DSM-5 diagnostic criteria for the disorder.
- In the differential diagnosis of SAD, the disorder should be differentiated from shyness. Shyness is a common personality trait and it even is positively evaluated in some Ethiopian

cultures. While shyness is not pathological, in SAD there is significant adverse impact on social, occupational, and other important areas of functioning. The distinction of SAD from agoraphobia lies on the cognitive aspect of the anxiety; in SAD the fear's cognition focuses on negative evaluation, while in agoraphobia it focuses on the difficulty of escape from the situation.

4.1.4.7.2. Laboratory and imaging

- Baseline laboratory tests include complete blood count (CBC), sedimentation rate (ESR), liver transaminases, renal function tests (urea and creatinine), fasting blood sugar (FBS), serum electrolytes, and thyroid function tests (TSH, T3, and T4).
- Other laboratory or imaging studies could be considered if history and physical examination suggests any other medical conditions.

4.1.4.8.Treatment of social anxiety disorder

4.1.4.8.1. Goals of treatment

- Controlling or eliminating symptoms
- Changing negative thoughts related to social conditions
- Improving coping skills
- Treating co-morbid psychiatric disorders.
- Returning to pre-morbid function
- Preventing relapse

4.1.4.8.2. General principles of treatment

- The level of functional impairment should be determined and treatment approach decided based on that
- Treatment should be individualized; similar approach does not work for every person with SAD
- Mild symptoms may be at first managed by psychoeducation, lifestyle modification and teaching relaxation techniques
- Participating patient in management decisions is important
- Both psychotherapy and pharmacotherapy are effective for SAD

4.1.4.8.3. Non-pharmacologic treatment for SAD

- Psychotherapy for SAD involves exposure therapy (ET) and cognitive behavioral therapy (CBT). Both approaches are effective and the choice should be based on availability of expertise.
- Psychotherapy should be administered by a clinician well trained in the procedures used. Exposure therapy can be delivered using different approaches. Self-exposure therapy may be used for appropriate patients. If self-exposure therapy is not feasible, the next measure should be clinician-led exposure. In some cases, combination of the self-exposure and clinician-led exposure can be utilized.
- Cognitive behavior therapy for SAD should be done on a weekly basis with an 8-12 sessions either given individually or as a group. The traditional CBT for SAD generally includes 4 stages:
    - Stage 1: Psycho-education, setting treatment goal
    - Stage 2: Cognitive restructuring
    - Stage 3: In vivo exposure therapy
    - Stage 4: Social skill training

4.1.4.8.4. Pharmacotherapy for SAD

- When choosing pharmacological modalities for social anxiety disorder, considering the following factors in important.
    - Adverse effects
    - Drug-drug interaction
    - Presence of comorbidities (either medical or psychiatric)
    - Cost, availability, patient choice.
- The selective serotonin reuptake inhibitors (SSRIs) are the first-line pharmacologic agents for SAD.
- Sertraline has better evidence for this indication, but fluoxetine can also be used. Dose of the medication should be started at half the dose for depression, such as sertraline 25 mg/day. The dose should be titrated gradually to the minimum effective dose. Dose increase should be made every two weeks until maximum dose is reached or side-effects appear. Trial of a medication should be for at least 6 weeks at optimal dose.

- The benzodiazepine clonazepam can be used as second-line treatment. The beta-blockers, such as atenolol and propranolol, can be used on as needed basis for the situational (performance) anxiety.
- Atenolol 50-100 mg, or propranolol 20-40 mg can be given one hour before performance. However, beta-blockers are blood pressure lowering medications and should be avoided in patients with hypotension as it may worsen their condition and become life threatening.
- Consider tapering medications slowly after 6-12 months of full response. If symptoms reoccur following taper, restart therapy and continue indefinitely.

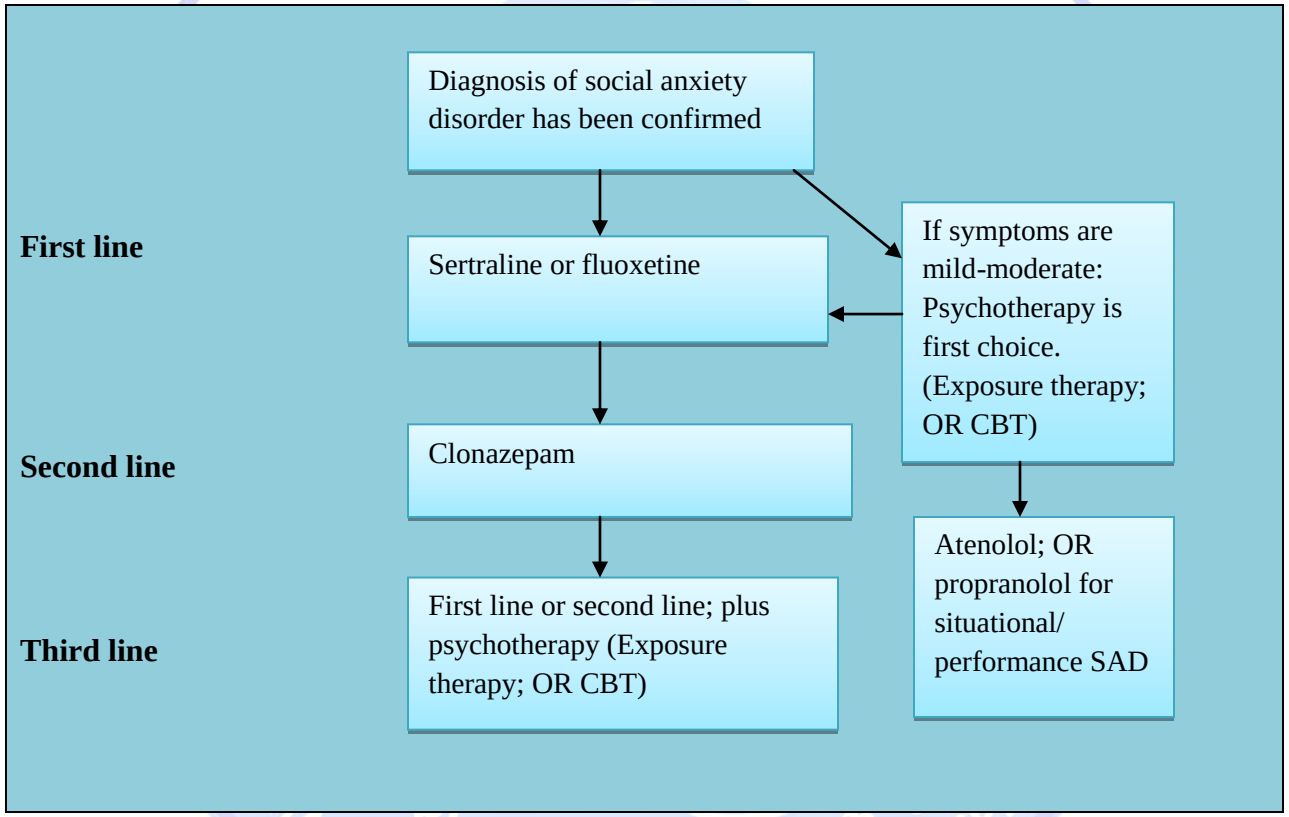


Figure 6: Algorithm for the treatment of social anxiety disorder (SAD)

4.1.5. Generalized Anxiety Disorder (GAD)

4.1.5.1.Brief description

- Generalized anxiety disorder (GAD) is defined as excessive anxiety and worry about several events or activities for most days during at least a 6-month period. The worry is difficult to control and is not restricted to a particular circumstance. It is often associated with symptoms such as muscle tension, apprehension, irritability, difficulty sleeping, and restlessness.

4.1.5.2.Epidemiology

- The 12-month mean prevalence globally is estimated at 1.3%, with the range of 0.2%-4.3%. There is a female to male ratio of 2:1.

4.1.5.3.Cause and risk factors

- Genes explain for one-third of the risk for GAD. Environmental factors include:
  - Childhood adversities
  - Poor parenting practices (overprotection, over-control, reinforcement of avoidance)

4.1.5.2.Clinical features

- The key features of generalized anxiety disorder are continuing excessive worry over everyday matters, and feeling keyed up or being on the edge.
- Individuals find it difficult to control the worry, despite the fact that they think it is excessive and unreasonable.
- There could be a variable combination of three or more features together with the worry, including:
  - Restlessness or feeling keyed up or on edge
  - Being easily fatigued
  - Difficulty concentrating or mind going blank
  - Irritability
  - Muscle tension
  - Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep)

4.1.5.3.Diagnosis and investigations

4.1.5.3.1. Diagnosis and differential diagnosis

- Diagnosis should be made upon the fulfillment of the DSM-5 diagnostic criteria for the disorder.

- The essential feature of generalized anxiety disorder is excessive anxiety and worry (apprehensive expectation) about a number of events or activities that has been there for at least 6 months.
- The worries are excessive and interfere with functioning and they are difficult to control. There are additional features such as fatigue, restlessness, muscle tensions, sleep problems, difficulty concentrating, irritability, etc.
- The differential diagnosis for GAD should consider other medical conditions which may cause similar symptoms and signs including hyperthyroidism and pheochromocytoma.
- The possibility of substance-induced anxiety disorders should also be considered. There could be anticipatory anxiety in social anxiety disorder (SAD); however, the anticipatory anxiety in SAD is related to social situations.
- The worry in separation anxiety disorder is related to separation from attachment figures. People with GAD could also have worries about separation; however, the worry in patients with GAD is not confined to separation.
- Illness anxiety disorder also resembles GAD in that patients worry about their health; however, patients with GAD worry about multiple events, situations, or activities, only one of which may involve their health.

4.1.5.3.2. Laboratory and imaging

- Baseline laboratory tests include complete blood count (CBC), sedimentation rate (ESR), liver transaminases, renal function tests (urea and creatinine), fasting blood sugar (FBS), serum electrolytes, and thyroid function tests (TSH, T3, and T4).
- Other laboratory or imaging studies could be considered if history and physical examination suggests any other medical conditions.

4.1.5.4.Treatment of GAD

4.1.5.4.1. Goals of treatment

- Controlling the core symptoms of GAD (both the psychological and somatic), including restoration of sleep
- Improve patient function and quality of life
- Obtaining complete symptomatic remission
- Treating co-morbid psychiatric disorders

- Preventing relapse

4.1.5.4.2. General principles of treatment

- Treatment should be individualized and should consider level of functional impairment
- Mild symptoms may be at first managed by psychoeducation, lifestyle modification and teaching relaxation techniques
- Participating patient in management decisions is important
- Both psychotherapy and pharmacotherapy are effective for GAD

4.1.5.4.3. Non-pharmacologic treatment of GAD

- Psychotherapy is effective for treating GAD. Cognitive behavioral therapy (CBT) is the psychotherapy of choice. However, other forms of psychotherapy could also be effective for some patients; for example, acceptance and commitment therapy (ACT) can also be of help.
- *Cognitive behavioral therapy (CBT)*focuses on the interplay between the conscious thoughts, feelings, and behaviors that perpetuate anxiety. Treatment with CBT involves identifying and correcting maladaptive thoughts.
- *Acceptance commitment therapy (ACT)* focuses on reducing the struggle of the patient to control anxious thoughts or uncomfortable sensations. It helps patients divert themselves towards increasing their involvement in meaningful activities.

4.1.5.4.4. Pharmacologic treatment of GAD

- Selective serotonin reuptake inhibitors (SSRIs) are the first line pharmacologic treatment. Sertraline is preferred, but fluoxetine can also be used. Other agents, such as serotonin norepinephrine reuptake inhibitors (SNRIs) and buspirone can also be effective, but availability and cost make their use impractical.
- Tricyclic antidepressants (TCAs) are the second line pharmacotherapeutic agents. The side effects profile of the TCAs makes their use limited.
- Benzodiazepines should not be used except for relieving acute anxiety on short-term basis.

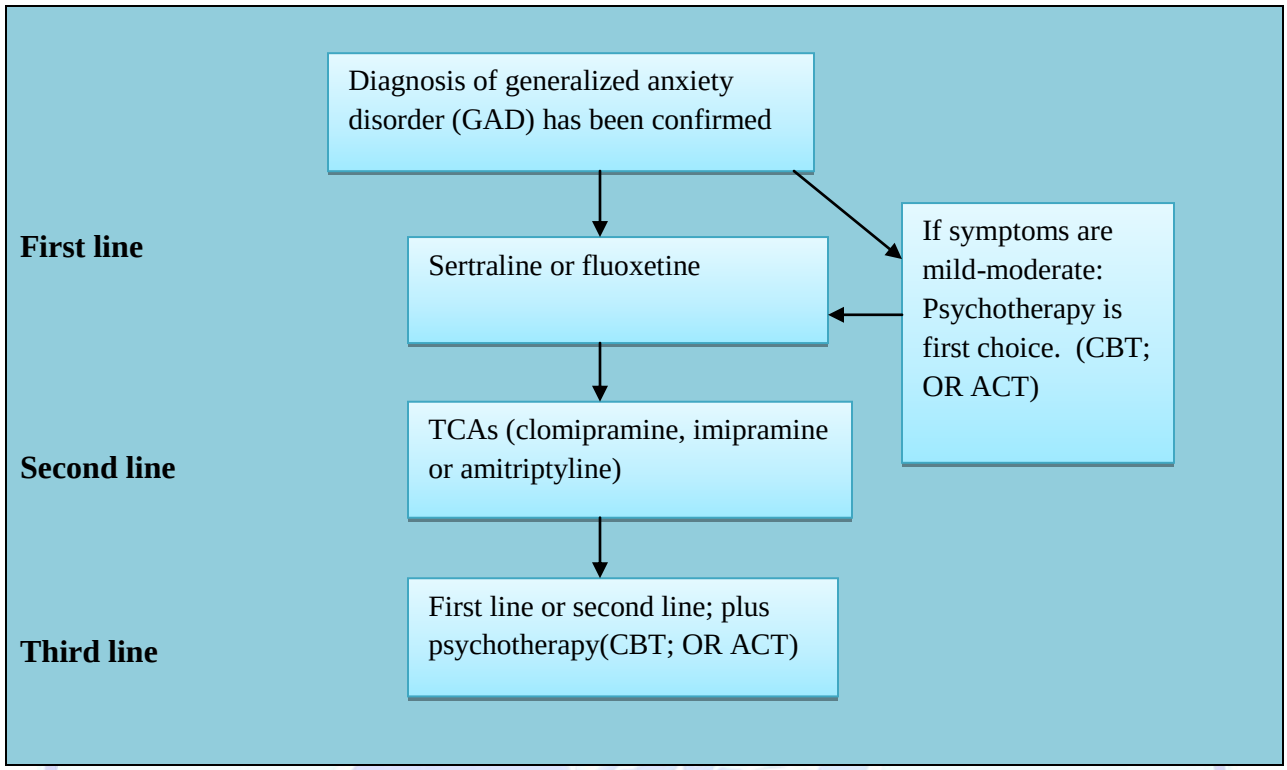


Figure 7: Algorithm for the treatment of generalized anxiety disorder (GAD)

Reference

1. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, text revision. Washington DC, American Psychiatric Association, 2022.
2. Andrews G, Bell C, Boyce P, Gale C, Lampe L, Marwat O, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of panic disorder, social anxiety disorder and generalised anxiety disorder. Aust N Z J Psychiatry [Internet]. 2018;52(12):1109–72. Available from: https://doi.org/10.1177/0004867418799453
3. BOLAND R. DSM-5® Guidebook: The Essential Companion to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Vol. 21, Journal of Psychiatric Practice. 2015. 171–173 p.
4. Michael Gelder, Nancy Andreasen, Juan Lopez-Ibor and John Geddes. New Oxford Textbook of Psychiatry. Oxford University Press; 2nd edition (April 7, 2012)
5. Katzman MA, Bleau P, Blier P, Chokka P, Kjernisted K, Van Ameringen M, et al. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. BMC Psychiatry. 2014; 14(SUPPL.1):1–83.
6. Berhanu Boru B, Yonas Deressa G. A Systematic Review and Meta-Analysis of Anxiety among Children and Youth in Ethiopia. J Depress Anxiety Disord. 2021; 3(2):89–100.
7. Roberts L, Hales R. Advance Praise for Textbook of Psychiatry. American Psychiatric Association Publishing; 7th edition(2019)
8. Weinstein RS. Treating panic disorder. Am J Manag Care. 1997; 3(8):1232.
9. Practice guidelines for the treatment of patients with panic disorder. American Psychiatric Association (APA) 2010.
10. Elizabeth Winter. Agoraphobia. Johns Hopkins Psychiatry Guide 2017.
11. Nita V Bhatt and David Bienenfeld. Anxiety Disorders Treatment & Management. Medscape, updated Mar 2019
12. Global Health Estimates. World Health Organization, Geneva 2017.

CHAPTER FIVE

5. Major Depressive Disorders(MDD)

5.1. Introduction

5.1.5. Brief description

- Depressive disorders are disorders which are manifested by persistent feelings of sadness as well as a lack of desire to participate in formerly enjoyable activities. A depressive episode can be categorized as mild, moderate, or severe depending on the number and severity of symptoms, as well as the impact on the individual's functioning.
- Major depressive disorder (MDD) is a mood condition that develops in the absence of a previous manic, mixed, or hypomanic episode. It might be seen in all age groups but the symptoms might be different in children. The majority of patients in Ethiopia present with physical symptoms, sleep difficulties, morbid nightmares, and extreme concern. They rarely disclose depression until directly questioned, and even then, many deny or minimize it as a result of recognized symptoms such as headache or insomnia.
- Most cases of suicide or attempted suicide are from depression. Statements made by patients like "I want to die", "life is not worth living", and "I am fed up with life" should be taken seriously.

5.1.6. Epidemiology

- Post world war-II the lifetime incidence of depression has been rising steadily in studied populations.
- According to a recent study, the annual incidence of mood disorders in the adult population is around 10%, and one in every 15 persons (6.7%) would experience a major depressive episode within any 12-month period.
- Eighteen-country adult based study reported that the life time prevalence of MDD was 14.6% in 10 high income countries and 11.1% in 8 low and middle income countries.
- There is twofold greater prevalence of major depressive disorder in women than in men. In Ethiopia, prevalence estimates of depression range from 5% in large sample population studies, to 9.1% in a nationally representative sample.

5.1.7. Causes and risk factors

- Both genetic and environmental factors play a role in the causation of MDD.
    - Genetic factors appear to play a major role in the cause of depression.

- Genetic factors may also predispose individuals to an earlier onset of depression (younger than 30 years of age). Genetic factors, however, are not enough to cause MDD. Environmental factors should occur on top of genetic vulnerability. Environmental factors causing stress can result in depression in vulnerable individuals. Among the risk factors with evidence, being female, lower socioeconomic status, and experiencing divorce are associated with the onset of MDD.

5.2. Clinical features

- Major depressive disorder (MDD) is clinically characterized by the presence of at least one major depressive episode in the absence of history of manic or hypomanic episode.
- Major depressive episode is characterized by at least two week duration of depression or loss of interest in activities which were previously enjoyable to the individual.
- Additional symptoms include changes in appetite or weight, sleep, and psychomotor activity; decreased energy; feelings of worthlessness or guilt; difficulty thinking, concentrating, or making decisions; or thoughts of death, suicidal ideation, a suicide attempt, or a specific plan for suicidal behavior.
- Symptoms cause significant functional impairment in the individual. Severe cases may be associated with secondary psychosis, including catatonic presentation.

5.3. Diagnosis and investigations

5.3.5. Diagnosis and differential diagnosis

- The diagnosis of MDD can be made using the diagnostic criteria given by the Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition (DSM-5).
- According to this criteria the diagnosis of MDD requires the presence of five (or more) of the symptoms of depression during the same 2- week period and represent a change from previous functioning; at least one of the symptoms is either depressed mood or loss of interest or pleasure.
- Additionally, the presence nearly every day of symptoms is required including significant weight loss when not dieting or weight gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive or inappropriate guilt, diminished ability to think or concentrate (or indecisiveness), and recurrent thoughts of death.

- The symptoms should cause significant distress or functional impairment. The symptoms should not be a result of physiological effects of substances or another medical condition.
- Differential diagnosis should exclude some medical conditions that could be mistaken for depression. Some of the important differential diagnosis considerations are provided below.

Central nervous system: Alzheimer disease, epilepsy, multiple sclerosis, Parkinson's disease, bipolar disorder depressive episode, schizoaffective disorder depressive type, and borderline personality disorder.

Cardiovascular: Cerebral arteriosclerosis, congestive heart failure, and myocardial infarction.

Endocrine: Addison disease,diabetes mellitus (types 1 and 2), hypothyroidism.

Women's health: Premenstrual dysphoric disorder and perimenopause.

Nutritional deficiency: folic acid and vitamin B12.

*Psychoactive substance-related:*Intoxication, withdrawal and persistence.

Medications: Medications such as triptans, ß blockers, methyldopa, steroids, oral contraceptives, and tamoxifen.

5.3.6. Laboratory and imaging

- Although an extensive literature describes neuroanatomical, neuro-endocrinological, and neurophysiological correlates of major depressive disorder, no laboratory test has yielded results of sufficient sensitivity and specificity to be used as a diagnostic tool for this disorder.
- Hypothalamic-pituitary-adrenal axis hyperactivity appears to be associated with melancholia (a particularly severe type of depression), psychotic features, and risks for eventual suicide.
- Molecular studies implicated peripheral factors, including genetic variants in neurotrophic factors and pro-inflammatory cytokines.
- Volumetric and functional magnetic resonance imaging studies provided evidence for abnormalities in specific neural systems supporting emotion processing, reward seeking, and emotion regulation in adults with major depression.
- However, the diagnosis of MDD is purely clinical and uses the DSM-5 criteria. The use of laboratory and imaging is to diagnose comorbid other medical conditions and general physical health.

- Baseline laboratory tests include complete blood count (CBC), sedimentation rate (ESR), liver transaminases, renal function tests (urea, creatinine), fasting blood sugar (FBS), thyroid function tests (TSH, T3, T4), serum electrolytes (especially Na^+) and, in female patients of reproductive age, urine HCG. Other investigations should be directed by clinical condition and differential diagnoses of major depressive disorder.

5.4. Treatment

5.4.5. Goals of treatment

- ✓ Eliminate symptoms of acute depression
- ✓ Identify suicidal risk and manage it
- ✓ Facilitate the patient's return to a full level of functioning
- ✓ Prevent further episodes of depression

5.4.6. General principles of treatment

There are three phases of treatment for patients with MDD:

- *The acute phase:*The acute phase of treatment lasts approximately 6 to 12 weeks in which the goal is remission (i.e., absence of symptoms).
- *The continuation phase:*The continuation phase of treatment lasts 4 to 9 months after remission is achieved. The goal of treatment in this phase is to eliminate residual symptoms or prevent relapse (i.e., return of symptoms within 6 months of remission).
- *The maintenance phase:*The maintenance phase of treatment lasts at least 12 to 36 months in which the goal is to prevent recurrence (i.e., a separate episode of depression).

Decision to prescribe maintenance treatment is based on the following:

- Number of previous episodes
- Severity of previous episodes
- Family history of depression
- Patient age (worse prognosis if elderly)
- Response to antidepressant
- Persistence of environmental stressors

Indefinite maintenance treatment is recommended if any one of the following criteria is met:

- Three or more previous episodes (regardless of age)

- Two or more previous episodes and age older than 50 years
- One or more and age older than 60 years

5.4.7. Non-pharmacologic treatment

- Psychotherapy is indicated for mild and moderate MDD and as an adjunct together with pharmacotherapy.
- Cognitive behavioral therapy (CBT) and interpersonal therapy (IPT) are two evidence-based psychotherapies.
- In addition to psychotherapy life style modification is helpful in the long-term management of MDD. In this regard, regular physical exercise and healthy and balanced diet are important considerations.
- More severe cases of MDD can be managed by electroconvulsive therapy (ECT). Electroconvulsive therapy is indicated for:
  - Severe MDD
  - Highly suicidal patients
  - When a rapid response is needed (malnutrition)
  - Risks of other treatments outweigh potential benefits(during pregnancy)
  - A history of poor response to antidepressants or a history of good response to ECT.

5.4.8. Pharmacologic treatment

- Studies have found that antidepressants are of equivalent efficacy in groups of patients when administered in comparable doses. Selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), and newer agents were first-line medications because they have better safety and tolerability profiles than older medications like tricyclic antidepressants (TCAs) and monoamine oxidase (MAO) inhibit.

Factors to be considered in selecting an antidepressant

- Prior response to the medication
- Safety, tolerability, and anticipated side effects
- Co-occurring psychiatric or general medical conditions
- Pharmacological properties of the medication (e.g., half-life, actions on CYP450 enzymes, and other drug interactions)

- Affordability and continuous availability of the drug
- Patient preference

Important considerations:

- Patients showing more than minimal improvement (e.g., ≥20% improvement in scores on a depression rating scale) after 4–6 weeks should continue on the antidepressant for another 2–4 weeks before considering additional strategies.
- Achieving and sustaining symptomatic remission is an essential first step toward functional recovery, but naturalistic treatment studies show that up to 2/3 of patients will not experience full remission with the first antidepressant.
- When there has been no improvement following an optimized (i.e., increased) dose of an antidepressant, the first step should be to re-evaluate diagnostic issues (e.g., bipolarity, depressive subtype, comorbidity including substance abuse) and treatment issues (e.g., adherence, side effects, suicidality).
- Using validated rating scales to measure response can help in the clinical decision-making process. Hamilton Depression Rating Scale (HDRS), the 17 item scale can be used to evaluate the response to treatment.

Treatment-resistant depression (TRD):

- The most commonly used definition of treatment-resistant depression (TRD) is failure (i.e., lack of improvement, or <20% reduction in depression scores) following adequate trials of two or more antidepressants.
- Treatment options for TRD include adding an evidence-based psychotherapy, switching to a neuro-stimulation treatment such as electroconvulsive therapy, and continuing with pharmacological strategies.
- Pharmacological strategies include switching to a different antidepressant monotherapy, or adding another antidepressant agent to the first antidepressant (combination).
- The term “augmentation” has been used to describe adding a medication that is not considered an antidepressant (e.g., lithium or thyroid hormone). If there is no response after 3 to 4 weeks of augmentation therapy, then alternate strategies should be considered.
- Augmentation strategies with good evidence include lithium in therapeutic serum levels, atypical antipsychotics (e.g.Olanzapine, and Risperidone), Lamotrigineand Tri-iodothyronine (T3, liothyronine).

Shifting to another antidepressant

- Shifting strategy is considered when a patient has either poorly tolerated the medication or has poor response. This strategy could apply to both antidepressants in the same group or different ones.
- The main point that should be considered when shifting from one antidepressant to the other is the pharmacokinetic profile of the drugs. For example, when shifting from a TCA to fluoxetine, reduce the TCA dose and stop, then start fluoxetine the next day. When shifting from fluoxetine to a TCA, need to wait for 5 days with no fluoxetine before starting a low dose TCA.

Augmentation strategies for poor response while on antidepressants

- Lithium (Aim for plasma level of 0.4–0.8mmol/L initially, increasing to up to 1.0mmol/L if suboptimal response).
- Atypical antipsychotics (e.g. olanzapine with fluoxetine).
- Lamotrigine (100-400mg).
- Thyroid supplements (T3, 20–50µg/day)

Discontinuation of antidepressants

- Abrupt discontinuation of antidepressants could cause relapse and withdrawal symptoms like dizziness, nausea, anxiety, insomnia, flulike symptoms. So tapering schedule should be set when it's decided to discontinue the antidepressant especially for patients receiving long-term treatment.

Tapering schedule

Antidepressant class	**Antipsychotic medication**	**Tapering schedule**
SSRIs	Fluoxetine	Generally unnecessary (since it has longer half-life and active metabolite).
	Sertraline	decrease by 25–50 mg every 1–2 weeks
TCA		decrease by 10%–25% every 1–2 weeks

Note:

- ✓ Antidepressants raised the risk of suicide thoughts and behavior in pediatric and young adult patients, especially when they were first begun or withdrawn, therefore the same level of caution should be used in risk assessment.
- ✓ To avoid dependence, Diazepam 5-10 mg or Lorazepam 1-2 mg orally could be given for not more than 2 weeks at a time when night sedation is required.
- ✓ Stop antidepressants immediately if manic swing occurs.
- ✓ Admit patients with suicidal tendencies and keep under close observation.
- ✓ To improve adherence on antidepressants patients should be told that adverse effects might occur immediately, while resolution of symptoms may take 2 to 4 weeks or longer.

Precautions

Lower starting doses and strict monitoring is recommended for

- ✓ Elderly patients (65yrs and above) (monitor sodium concentration closely when initiating or adjusting the dose in older adults.)
- ✓ Panic disorder,

- ✓ Significant anxiety symptoms
- ✓ Hepaticdisease and comorbid medical conditions.

Side effects of antidepressants

The side effects of the commonly used antidepressants and the management of the side effects are discussed in the table below.

Table 6: Side effects of antidepressants and their management

Responsible drug	Side effect	Management
TCA	**Orthostatic hypotension**	Lower the dose/wait for the person to accommodate to the medication/swap to another.
	Arrhythmia	Best avoided in patients with at risk of serious arrhythmia. If use of a TCA cannot be avoided, an ECG should be performed at baseline, 1 week after each increase in dose and periodically throughout treatment
	Constipation	Encourage adequate hydration. Consider laxative with caution
	Dry mouth	Suggest use of sugarless gum if possible or candy, drinking water
	Delirium	Evaluate for other possible contributors to delirium
	Visual changes	Add pilocarpine eye drops and consider ophthalmology consultation
	Myoclonus	Add clonazepam for few days or change in to SSRI
	Seizure	Assess for other etiologies, and add anticonvulsant medication, if clinically indicated or change to SSRIs
	Sedation	Use bedtime dosing
SSRIs	**Nausea, vomiting**	Administer after food or in divided doses(morning & noon)

	Insomnia	Use morning dosing. Consider adding short-term prescription of a benzodiazepine in severe sleep disturbance & educate on sleep hygiene.
	Gastrointestinal bleeding	Identify whether concomitant medications may affect clotting
	Akathisia	Add a beta-blocker or benzodiazepine
	Headaches	Assess for other etiologies (e.g., caffeinism, bruxism, migraine, tension headache)
Both TCA & SSRIs	**Sexual dysfunction**	Patience (may improve 2-4 weeks later). Decrease dose. Treat with sildenafil citrate 50-100mg PRN
	Fall risk	Monitor blood pressure for evidence of hypotension or orthostasis; assess for sedation, blurred vision, or confusion; modify environment to reduce risk
	Hyponatraemia Risk is high in SSRIs and moderate in TCAs.	Assess for dizziness, nausea, lethargy, confusion, cramps and seizures. Demands careful monitoring (at baseline and 2 and 4 weeks, and then 3-monthly for those who are at risk.) If serum sodium is >125mmol/L consider withdrawing the offending agent. If serum sodium is < 125mmol/L, discontinue medication immediately.
	Weight gain	Exercise and diet

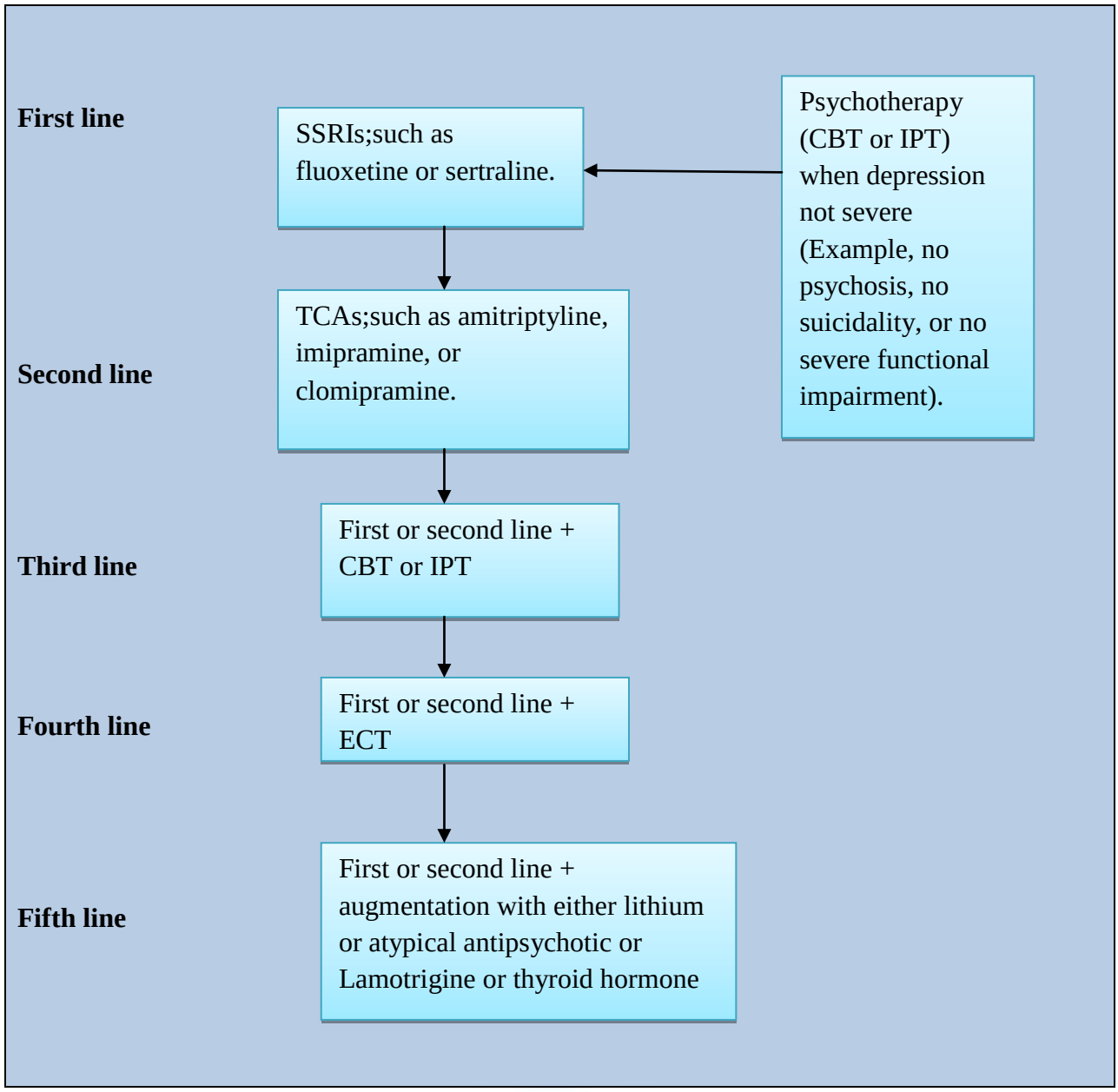


Figure 8: Algorithm for the treatment of MDD

References

1. Quick Guide to Psychiatric Emergencies: Tools for Behavioral and Toxicological Situations. Ed. Nordstrom KD. And Wilson MP; 2018

2. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, text revision. Washington DC, American Psychiatric Association, 2022.
3. Clinical Practice Guideline: Psychiatric Treatment Guideline. St. Paul's Hospital Medical College. Volume 1, 2019.
4. Clinical Guidelines for the Management of Adults with Major Depressive Disorder. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016.
5. Practice Guideline for the Treatment of Patients with Major Depressive Disorder. AmericanPsychiatric Association, 2010.http://www.psychiatryonline.com/pracGuide/pracGuideTopic_7.aspx
6. Gin S Malhi, Erica Bell, Darryl Bassett, Philip Boyce, Richard Bryant, Philip Hazell, Malcolm Hopwood, Bill Lyndon, Roger Mulder, Richard Porter, Ajeet B Singh and Greg Murray. The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. Australian & New Zealand Journal of Psychiatry 2021, Vol. 55(1) 7–117 DOI: 10.1177/0004867420979353
7. Ethiopia's National Mental Health Strategy. Federal Ministry of Health-Ethiopia, 2012/13-2015/16
8. Ambaw F, Mayston R, Hanlon C, et al. Burden and presentation of depression among newly diagnosed individuals with TB in primary care settings in Ethiopia. BMC Psychiatry 2017; 17: 57.
9. Hailemariam S, Tessema F, Asefa M, et al. The prevalence of depression and associated factors in Ethiopia: findings from the National Health Survey. Int J Ment Health Syst 2012; 6: 23.

CHAPTER SIX

6. Delirium

6.1. Introduction

6.1.5. Brief description

- Delirium can be described as a rapid change in cognition particularly impairment in attention, in the context of an underlying medical disease, or substance intoxication or withdrawal.
- It is also associated with additional disturbance in memory, orientation, language, perception, etc.
- There are three types in which delirium can present. In the hyperactive type the patient has hyperactive psychomotor level, with associated labile mood or agitation. In the hypoactive type the patient has hypoactive psychomotor level, with sluggishness and lethargy.
- There is also a mixed type of presentation in which the patient has a normal level of psychomotor activity.

6.1.6. Epidemiology

The prevalence of delirium varies significantly depending on the patient population under consideration.

- Patients with advanced age, cognitive decline, and with more severe medical illness are at higher risk to develop delirium.
- Most studies have explored delirium in the hospital setting and almost always in older individuals (e.g., > 65 years). Delirium affects up to 30% of hospitalized adults.
- Delirium affects nearly 20% of patients over age 75 on medical inpatient units. In intensive care unit (ICU) settings the prevalence is significantly higher, where rates of over 80% have been reported in mechanically ventilated patients.
- Finally, among patients who have undergone surgery, the incidence of post-operative delirium ranges from 13% to over 50%
- The proportion of the subtypes is hypoactive (56%- 68%), hyperactive (1%-10%), and mixed (21%-31%).
- In a general population study, the prevalence of delirium was 1%–2% in subjects >65 years old and 10% in subjects >85 years old

6.1.7. Causes and risk Factors

It would have been appropriate to divide the causes and risk factors for delirium; however, there is a lot of overlap between causes and risk factors, as well as predisposing and precipitating factors. Therefore, it has become more logical to collectively describe them. The causes and risk factors of delirium are

- Old age,
- male sex,

- Underlying cognitive impairment,
- infection, fever, hypoxia, hypoglycemia, electrolyte imbalance,
- Medical conditions (such as cardiovascular, renal, and hepatic diseases),
- Use of drugs such as benzodiazepine and narcotic analgesics,
- Metabolic disorders such as encephalopathy, and
- Central nervous system diseases (such as stroke, traumatic brain injury, and epilepsy).

There is a particular type of delirium which occurs in some cases of alcohol withdrawal. This type of delirium is known as delirium tremens (DTs). Delirium tremens manifests with features of delirium together with signs and symptoms of autonomic hyper-arousal (**see Delirium tremens in the substance-related disorders chapter**).

6.2. Clinical characteristics

The characteristic feature of delirium:

- Disturbance of attention or awareness that is accompanied by a change in baseline cognition that cannot be better explained by a pre-existing or evolving neurocognitive disorder (NCD).
- The disturbance in attention manifests as reduced ability to direct, focus, sustain, and/or shift attention.
- The disturbance in attention can be identified during mental status examination as easy distractibility.
- The manifestation of disturbance in awareness is by reduced orientation to the environment.

Delirium has an acute presentation and develops over few hours or few days. The presentation is also characterized by

- Fluctuations of severity over the day;
- Symptoms often worsen in the evening and night when external orienting stimuli decrease.
- It cannot be overemphasized that delirium occurs as a result of an underlying medical condition or substance (or medication) intoxication or withdrawal, or a combination of these factors.
- Due to the fact that delirium occurs as a result of underlying medical condition or substances (medications) the manifestation includes the presentation of the underlying condition which precipitated it; another neurocognitive disorder such as major neurocognitive disorder (dementia) may have predisposed the patient to delirium and the presentation could become more complicated.
- Delirium is often associated with a disturbance in the sleep-wake cycle, resulting in sleep abnormalities. In addition, the individual with delirium may exhibit emotional disturbances, such as anxiety, fear, depression, irritability, anger, euphoria, and apathy.

- The clinician should always be aware that delirium has hypoactive, hyperactive and mixed type presentations. Therefore, the clinical presentation of delirium could vary widely. Only thorough evaluation of the patient could reveal the diagnosis.

6.3. Diagnosis and investigations

6.3.1. Diagnosis and differential diagnosis

- Diagnosis of delirium should be made with fulfillment of the DSM-5TR criteria for the disorder. The clinician is expected to do intensive evaluation and workup to include the specific etiology which caused the delirium and document the evaluations and investigations conducted and their outcome. It must be emphasized that, the search for the underlying medical or substance (or medication)-related disorder is of paramount importance, since the management of delirium mainly depends on diagnosing and treating the underlying cause(s).
- Searching for potential treatable or reversible causes for the delirium is a critical part of the diagnostic process and its consideration must be clearly documented.
- The criteria met during the initial diagnosis must be clearly documented and updated as frequently as possible to show progress. Documentation must clearly show the essential workup for any specific causative condition.
- Careful differential diagnosis consideration should be made during assessment of a patient with possible delirium. Delirium that manifests by vivid hallucinations, delusions, language disturbances, and agitation must be distinguished from brief psychotic disorder, schizophrenia, or other psychotic disorders; it must also be distinguished from other disorders in which psychosis could occur as key presenting feature, such as severe bipolar disorder or depressive disorder. In delirium, unlike in such disorders, there is severe disturbance of attention and awareness, and the hallucinations are predominantly visual. The fluctuation of symptoms of delirium throughout the day is another differentiating feature. The etiological evidence of underlying medical (substance/ medication) condition also favors the diagnosis of delirium.
- Delirium associated with fear, anxiety, and dissociative symptoms, such as depersonalization, must be distinguished from acute stress disorder. The evidence of symptoms being precipitated by exposure to a severely traumatic event in acute stress disorder distinguishes it from delirium. Delirium can be distinguished from malingering and factitious disorder on the basis of the often atypical presentation of manifestations in malingerers and individuals with

factitious disorder. The latter also have underlying motives which could help making a correct differential diagnosis.

- Patients with hypoactive withdrawn delirium may be misdiagnosed as having depression. Patients with depression may also have cognitive symptoms, but the patient's level of consciousness is normal. The most common differential diagnosis dilemma, however, arises when making distinction between delirium and major neurocognitive disorder (dementia). The patient could have pure delirium, a delirium superimposed on dementia (such as Alzheimer's disease), or dementia without delirium. The presence of impaired sensorium and fluctuation of symptoms during the day favor the diagnosis of delirium, with or without underlying NCD; careful history taking must detect the presence of prior NCD.

6.3.2. ***Laboratory and imaging***:

- A complete medical history and physical examination, as well as relevant laboratory and other investigations are mandatory in patients with delirium. At onset of treatment, the minimal baseline workup should be done and documented. Based on the index of suspicion created after the history and physical examination, and as resource allows it, the following workup can be conducted for a patient with delirium:

6.3.2.1.Laboratory studies

- Complete blood cell count with differential
- Serum electrolytes
- Serum glucose level
- Renal and liver function tests
- Thyroid function studies
- Urine analysis
- Urine and blood drug screen
- Thiamine and vitamin B-12 levels
- Tests for bacteriological and viral etiologies including syphilis
- Sedimentation rate (ESR)
- HIV tests
- Tests for other infectious causes if indicated
- Lumbar puncture is indicated when CNS infection is suspected

6.3.2.2.Imaging studies

- CT scan or MRI of the brain
- Electroencephalography (EEG)
- Chest radiograph if pneumonia or congestive heart failure is suspected

- Pulseoximetry to diagnose hypoxia
- Electrocardiograph (EKG) to diagnose ischemic or arrhythmic causes

6.4. Treatment

6.4.1. Goals of treatment

- ✓ The main goal is to treat the underlying cause.
- ✓ To provide physical, sensory, and environmental support.
- ✓ To alleviate distress and achieve behavioral control.

6.4.2. General principles of treatment

- Assessment for delirium should involve a multidisciplinary team approach
- In people diagnosed with delirium, identify and manage the possible underlyingcause or combination of causes
- Provide supportive medical care as appropriate
- Ensure effective communication and reorientation
- Consider involving family, friends and carers to help with management when necessary
- Provide a suitable care environment
    - ✓ Avoid moving people within and between wards or rooms unless absolutely necessary
    - ✓ Provide appropriate lighting and clear signage; a clock and a calendar should be placed and become easily visible to the patient
    - ✓ Facilitate regular visits from family and friends when possible

Supportive medical care

- Ensure adequate hydration (consider intravenous fluids if necessary and involve specialists when managing fluid balance in special population groups such as those with heart failure or chronic kidney disease).
- Optimise oxygen saturation as clinically appropriate
- Look for and treat infections and avoid unnecessary catheterization
- Address immobility, including to patients who are bedridden
- Manage pain by looking for non-verbal signs of pain
- Carry out a medication review for people taking multiple drugs

- Address poor nutrition
- Address sensory impairment
  - ✓ Resolve any reversible cause of the impairment, such as impacted ear wax
  - ✓ Ensure hearing and visual aids are used when applicable
- Promote good sleep patterns and sleep hygiene
  - ✓ Avoid nursing or medical procedures during sleeping hours, if possible
  - ✓ Schedule medication rounds to avoid disturbing sleep
  - ✓ Reduce noise to a minimum during sleep periods

Treating distress

6.4.3. Non-pharmacologic

- A patient with delirium could be psychologically distressed, and sometimes could be considered a risk to themselves. It is important to recognize the early signs of agitation, irritation, anger and aggression. Clinician also needs to understand the likely causes of the aggression. It is recommended to first use verbal and non-verbal techniques to de-escalate the situation. Techniques for distraction and calming, and ways to encourage relaxation should be tried. It is necessary to avoid provocation, and allow the patient personal space. Clinicians should respond to the patient's anger in an appropriate, measured and reasonable way.

6.4.4. Pharmacologic treatment

- Pharmacologic treatment is warranted if the patient with delirium is severely distressed or considered a risk to themselves or others. In such cases, giving short-term (usually for 1 week or less) of haloperidol should be considered.
- Start haloperidol at the lowest clinically appropriate dose and titrate cautiously according to symptoms. Haloperidol could be given orally or parenterally, as appropriate.
- The use of antipsychotic drugs for patients with conditions such as Parkinson's disease or dementia with lewy bodies should be either avoided or made with extreme caution and consultation with an expert specialist.
- The use of low potent antipsychotics such as chlorpromazine (tablet or injection), which can have anticholinergic adverse effects could aggravate the delirium.
- The use of diazepam (tablet or injection) can also aggravate the delirium by excessively sedating the patient. If the use of a benzodiazepine is considered mandatory, it is advisable to

use a short acting drug like Lorazepam. Treating the underlying cause(s) of the delirium at the same time should be given due emphasis while treating the distress caused by it.

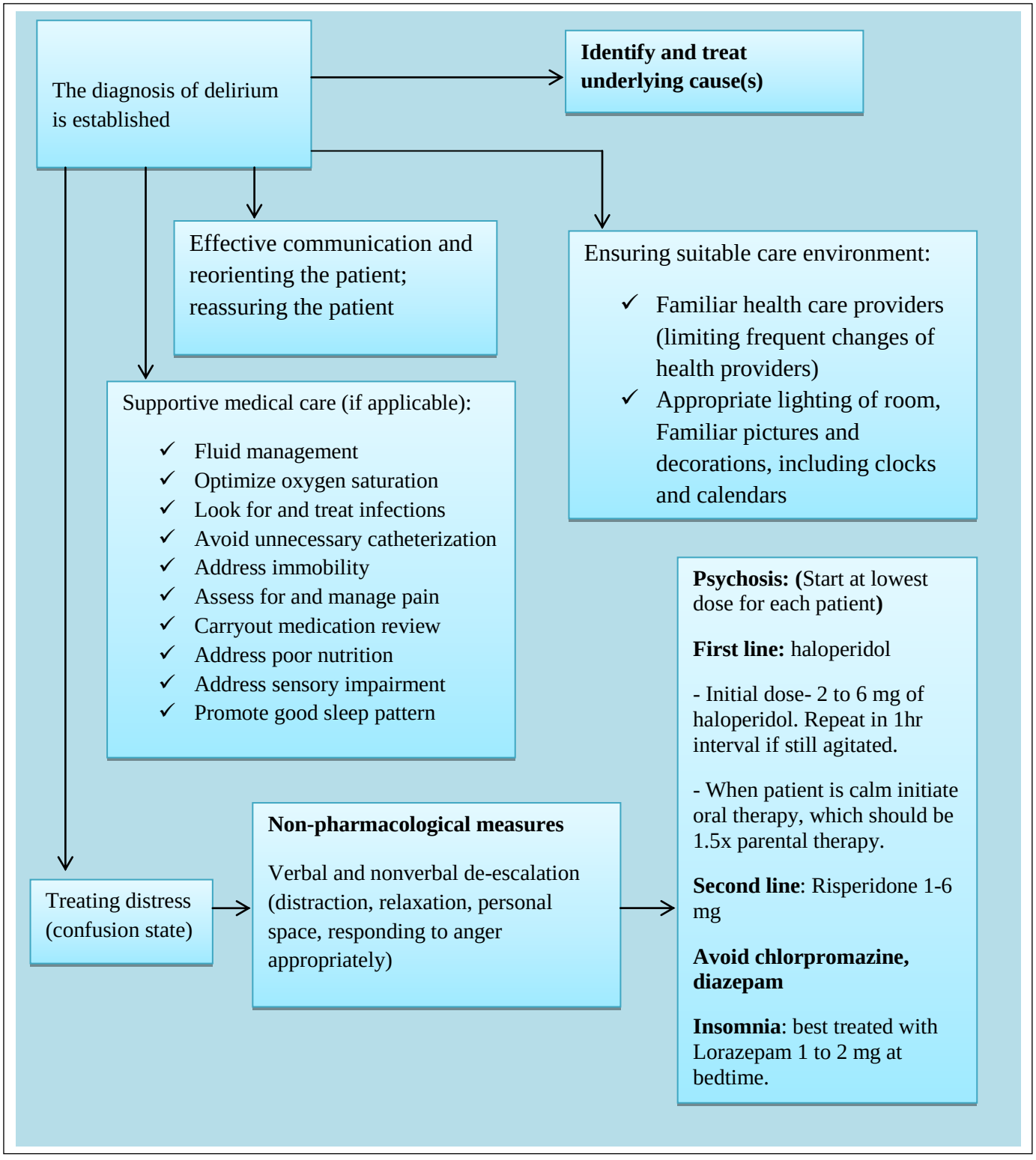


Figure 9: Algorithm for the treatment of delirium

References

1. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, text revision. Washington DC, American Psychiatric Association, 2022.
2. Delirium: Prevention, diagnosis and management. National Institute for Health and Care Excellence (NICE, 2013)www.nice.org.uk/guidance/cg103
3. Carrie M. Goodson, YuiChang andRakesh C. Arora. What type of delirium would you like: Hyperactive, hypoactive, or mixed? None, thanks. The Journal of Thoracic and Cardiovascular Surgery c January 2018.
4. Juan PabloOspina, Franklin King IV, Elizabeth Madva, Christopher M Celano. Epidemiology, Mechanisms, Diagnosis, and Treatment of Delirium: A Narrative Review. Clinical Medicine and Therapeutics 2018;1(1):3. DOI: 10.24983/scitemed.cmt.2018.00085
5. Harin Kim,Seockhoon Chung, Yeon Ho Joo, Jung Sun Lee. The major risk factors for delirium in a clinical setting. Neuropsychiatric Disease and Treatment 2016:12 1787–1793
6. Jo Ellen Wilson, Matthew F. Mart, Colm Cunningham, YahyaShehabi, Timothy D. Girard, Alasdair M. J. MacLullich, Arjen J. C. Slooter and E. Wesley Ely. Delirium. NATURE REVIEWS | DISEASE PRIMERS | Article citation ID: (2020) 6:90
7. Sadock, B. J., Sadock, V. A., & Ruiz, P. Kaplan & Sadock's synopsis of psychiatry: Behavioral sciences/clinical psychiatry (Eleventh edition). Philadelphia: Wolters Kluwer; 2015.

CHAPTER SEVEN

7. CATATONIA

7.1.Introduction

7.1.1. Brief Description

- Catatonia is a neuropsychiatric syndrome characterized by change in motor symptoms and signs (mutism, immobility, abnormal posturing, stereotypy, negativism and waxy flexibility, purposeless agitation), withdrawal symptoms (refusal to eat and/or drink, avoid eye contact, staring) and echophenomena (echolalia and echophraxia).
- Lack of movement is often quickly recognized as catatonia but purposeless movements and other agitated behaviors are commonly missed.
- Many variants of catatonia exist in the clinical settings. However; most common types are retarded type of catatonia, excited type of catatonia and malignant type of catatonia.
- Malignant type of catatonia is the most severe type and needs emergency interventions. Life-Threatening signs and symptoms associated with malignant catatonia are fever (exclude infection first), autonomic instability (unstable blood pressure, tachycardia, tachypnea), diaphoresis, rigidity, and delirium. The syndrome progresses rapidly within a few days.

7.1.2. Epidemiology

- International review of prevalence study reported that 10% of acutely admitted psychiatric patients had received a diagnosis of catatonia.
- Studies showed that among the patients diagnosed with catatonia, 20-25% is related to mood disorders and 10% are related to schizophrenia.
- About 20% of catatonia inpatients have schizophrenia diagnosis, while 45% have mood disorder diagnoses. Retarded catatonia is the most common catatonia form.
- Results from a study in Ethiopia showed similar findings. A facility based survey conducted in Amanuel Mental Specialized Hospital involving 346 patients showed that 10% of acutely admitted psychiatric patients had catatonia. Catatonia is more common among males than females and younger age group (25-34 years). In Ethiopia, catatonia is common among patients with major depressive disorder followed by schizophrenia and bipolar disorder.

7.1.3. Causes and risk factors

- Catatonia is likely to be the consequence a heterogeneous group of etiologies. Several conditions may cause catatonia including;

- Neurodevelopmental disorders,
- Psychotic disorders,
- Bipolar disorders,
- Depressive disorders,
- Other medical conditions (such as cerebral folate deficiency,
- Rare autoimmune disorders, and paraneoplastic disorders which are related to cancerous tumors),
- Neurological disorders (such as epilepsy, head trauma, cerebrovascular disease, and encephalitis),
- Metabolic disorders (such as hypercalcemia, hepatic encephalopathy, homocystinuria, and diabetic ketoacidosis),
- Infections,
- Neuroleptic medications and withdrawal from benzodiazepines or clozapine.

Case report presents LSD and possible cannabis induced etiologies of catatonia.

- Clinical risk factors for malignant catatonia include dehydration, exposure to high temperatures, substantial agitation or excitement, thyrotoxicosis, past or present catatonic features, high potency antipsychotics, neuroleptic-induced movement disorders, recent alcohol abuse with liver dysfunction.

7.2.Clinical Characteristics

- The clinical presentations of catatonia are numerous. Catatonia has been described as having three subtypes and patients may move between types. The clinical features will accordingly be variable for each subtype of catatonia.

I. The stuporous (retarded) form manifests with signs and symptoms of mutism, rigidity, immobility, negativism, posturing, and catalepsy.

II. The excited form manifests with excitement, aggression, and impulsivity.

III. The most severe and life-threatening form is malignant catatonia. Malignant (lethal) catatonia also closely resembles NMS, and some consider NMS a variant of malignant catatonia or drug-induced catatonia. Malignant features include fever, tachycardia, elevated blood pressure, and autonomic instability, which can be life-threatening.

- Physical examination is an important aspect of evaluation of patients with catatonia. Vital signs and neurological examination are crucial. Other pertinent physical examination should be performed based on the history of presenting illness. Because patients with catatonia may

not be cooperative, specific neurologic signs characteristic of catatonia must be quickly elicited, especially in emergency settings. In particular, rigidity, *gegenhalten* (passive resistance of the patient to the active movement of the patient's extremities by the examiner), and a grasp reflex are readily apparent signs of catatonia in such settings.

- Grasp reflex is a secondary feature of catatonia. Commonly observed signs of catatonia include immobility (hypokinesis or akinesis), mutism (absence of speech), stupor (decreased alertness and response to stimuli), negativism (resistance to all instructions or all attempts to be moved), waxy flexibility (slight, even resistance to positioning by examiner), posturing, excitement (excessive, purposeless motor activity), staring, echophenomena including echolalia (senseless repetition of another person's utterances) and echopraxia (senseless repetition of another person's movements).
- If the patient is cooperative the neurological examination should include the following: the pupillary reaction, ocular movements, corneal reflex, reaction to pain, the presence of drooling, blink response to threat, reaction to light or sound, frontal release signs, assessment of motor system (such as tone, deep tendon reflexes) and the plantar response.

7.3.Diagnosis and Investigation

7.3.1. Diagnosis and differential diagnosis

- Diagnosis of catatonia is based on the criteria of the Diagnostic and Statistical Manual (DSM). The current edition is DSM-5 and the criteria are included under the annex section.
- Complete clinical history, physical examination, or laboratory investigations are essential to rule out disturbance is either due to the direct pathophysiological consequence of another medical condition, neurologic conditions or psychiatric illness.
- A number of neurological conditions may appear similar to catatonia, and may even have substantial overlap with respect to pathophysiological mechanisms.
- Catatonia should be differentiated from extrapyramidal side effects of antipsychotic medications. Like patients with catatonia, patients with drug-induced parkinsonism may present with immobility, staring, and rigidity. This distinction is an important one to make, since the benzodiazepine medication used to treat catatonia may exacerbate the postural instability that is often associated with parkinsonism. The posturing and immobility of catatonic patients can be mistaken for dystonia and the psychomotor agitation of excited catatonia can appear similar to akathisia. In patients being treated with antipsychotic

medication, care must be taken in assessing these clinical features to ensure diagnostic accuracy.

- Neuroleptic malignant syndrome is a life-threatening reaction to antipsychotic treatment (including treatment with atypical antipsychotics). Patients develop rigidity, mutism, and delirium accompanied by diaphoresis, hypertension, tachycardia, and fever. It may sometimes be indistinguishable from malignant catatonia except for the precipitating factor of antipsychotic treatment.
- Non-convulsive status epilepticus can be clinically indistinguishable from catatonia. In both cases, patients can be immobile, mute, rigid, and unable to eat, drink, or cooperate with an examination.
- Electroencephalogram (EEG) is crucial to making the correct diagnosis.
- Disorders of diminished motivation exist on a spectrum including abulia (moderate) and akinetic mutism (severe).
- In the extreme case, there could be a complete lack of spontaneous speech or movement due to a lack of motivation or drive. Patients are fully aware and visual tracking is preserved.
- Overt signs of catatonia such as negativism and echophenomena may differentiate the two disorders sometimes.
- A trial of Lorazepam may be helpful in identifying catatonia.
- Locked-in syndrome is usually associated with ventral pontine lesions, and results in near complete paralysis, while blinking and vertical eye movements are spared.
- Patients are aware and, unlike catatonic patients, generally eager to communicate through blinking. However, some patients with locked-in syndrome are unable to blink or move their eyes. Magnetic resonance imaging (MRI) or brainstem evoked potentials help to identify patients with the locked-in syndrome.
- Vegetative state is characterized by a complete lack of awareness of the self or surroundings, often secondary to a severe cerebral injury. The patient makes no voluntary responses to stimuli, and does not visually track objects, but sleep-wake cycles are preserved. Confidently assessing a lack of awareness can be problematic. EEG and MRI techniques can be used. Unlike the normal EEG of catatonia, the EEG in vegetative states is almost always abnormal. Stiff person syndrome is an autoimmune disorder frequently presenting with low back and lower extremity stiffness and spasms, as well as exaggerated lumbar lordosis, which can be

mistaken for posturing. Like catatonia, the condition can render patients immobile. Episodes are typically triggered when patients are startled or experience emotional stress. Unlike in catatonia, patients with stiff person syndrome are not mute and will often indicate that they are in great pain as a result of the muscle spasms.

7.3.2. Laboratory and imaging

- Laboratory investigations should include a complete blood count, blood urea nitrogen, creatinine, muscle and hepatic enzymes, thyroid function tests, electrolytes, blood glucose, and urinalysis to assess for comorbid conditions, causes, or complications of catatonia. Elevated creatine phosphokinase, decreased serum iron, and leukocytosis may herald the onset of malignant catatonia or neuroleptic malignant syndrome if the patient has received antipsychotic agents.
- All patients suspected of having catatonia should have EEG testing as a screen for other neurological conditions. This will typically show epileptiform activity in non-convulsive status epilepticus and slowing in cases of encephalopathy. The EEG in catatonia is typically normal unless there is a concurrent condition that may be causing the abnormality. Given that catatonia can develop in the context of a wide array of neurological conditions, brain imaging, preferably by MRI, is recommended.

7.4.Treatment of Catatonia

7.4.1. Goals of treatment

- The failure to recognize catatonia in a timely fashion allows depressed, manic, and psychotic patients to remain ill for lack of proper diagnosis and treatment. It is important to consider that catatonia is associated with a number of medical complications if not treated and managed adequately and that some of these complications are serious and life threatening. Pulmonary thromboembolism is a frequent cause of death in this patient group. Early recognition is important in catatonia, as are close observation and frequent measurement of vital signs. Therefore, the goal of treatment of catatonia is
  - Early recognition and management, and
  - Prevention of medical complications and death.

7.4.2. General principles of management

- Supportive care for patients with catatonia consists of hydration, nutrition, mobilization, anticoagulation (to prevent thrombophlebitis), and aspiration precautions.

- Neuroleptics and other dopamine depletes should be discontinued, and recently withdrawn dopamine agonists may need to be restarted.
- Marked dehydration is not uncommon in catatonic patients, and must be attended to.
- Vital signs should be assessed frequently, as hypertension and fever (often accompanied by elevated creatine phosphokinase, decreased serum iron, and leukocytosis) may herald the onset of malignant catatonia or neuroleptic malignant syndrome.
- If hyperthermia or autonomic instability emerge or if malignant catatonia is suspected, intensive care unit supportive measures should be initiated.
- Clinicians should maintain a high index of suspicion for development of medical complications and new medical problems.
- As soon as catatonia is diagnosed, obtaining consent for electroconvulsive therapy (ECT) is a prudent measure given the possibility of progression to malignant catatonia, which is associated with significant morbidity and mortality if ECT is not administered expeditiously.
- In summary, identifying and treating the underlying disorder is essential in the treatment of catatonia.

7.4.3. Non-pharmacologic treatment

- Catatonic patients, especially those with syndromes of acute onset, need protection and care.
- Checking vital signs and monitoring input- output is essential in the emergency settings.
- Secure IV line for resuscitation and medication administration for malignant catatonia.
- Advise the family to encourage feeding.

7.4.4. Pharmacologic treatment

Benzodiazepines

- Treatment with benzodiazepines is the most extensively studied treatment method. Lorazepam is the most widely studied medication, which is administered in doses varying from 2 to 16 mg/day. If PO administration is not possible because of the patient's mental health state, parenteral methods (IM or IV) are used. Some studies chose diazepam, or clonazepam as IM or IV therapy.
- Duration of therapy varies from the administration of just one dose to continued administration for as long as catatonic symptoms persist. The effect of Lorazepam wears off after 3–5 hours and that the symptoms subsequently return. The average percentage,

represented in terms of response and remission, reported in Western studies varies between 66% and 100%.

- Asian studies report percentages between 0% and 100%. The percentages in India lie between 17% and 100% (full remission plus partial remission).
- If patients respond to benzodiazepines, the effect is usually visible within a few days. Studies in which the patients displayed long-term symptomatology prior to treatment reported lower response and/or remission percentages. Overall, benzodiazepines seem to be well tolerated. It was observed that a high dose of Lorazepam (16 mg/day) was tolerated without sedation.

Electroconvulsive therapy (ECT)

- In trials, ECT was not only initiated after ineffective pharmacotherapy, but also as primary therapy, for example, in life-threatening situations. The reported frequency of bilateral ECT was 3 times per week on average. The total number of ECT sessions in the included studies varied from two to 13. The percentages, represented in terms of response and remission, ranged from 59% to 100%. It was described in some studies that all patients tolerated ECT well without major adverse effects or cognitive impairment.
- However, in other studies, patients treated with ECT were observed to have cognitive/memory impairment or complained of headache during treatment. The risk of cognitive adverse effects may be related to higher ECT frequency and must be balanced against the risk of morbidity and mortality due to catatonia.

Antipsychotics

- Clozapine has a beneficial effect on catatonic symptoms. On the other hand, classic antipsychotics may result in clinical deterioration and appear to be associated with the development of lethal catatonia or malignant neuroleptic syndrome.
- Patients responded better to an antipsychotic drug with low affinity for dopamine receptors.
- Studies showed mixed results for the benefits of olanzapine and Quetiapine.
- Patients on first-generation antipsychotics and Risperidone developed a neuroleptic malignant syndrome.

Other treatment methods

- The use of carbamazepine in the acute phase of catatonia was examined. Carbamazepine was administered when patients did not sufficiently respond to Lorazepam. This study revealed that Lorazepam initially produces good results, but its effect wears off after a few hours. Carbamazepine showed good results. In one trial, catatonic symptoms in four cases unresponsive to benzodiazepines and antipsychotics responded to carbamazepine. Therapeutic efficacy of the N-methyl-D-aspartate (NMDA) antagonist amantadine has also been reported.

Recommendations: Benzodiazepines and ECT are the only treatments for which there is clinical evidence.

- Benzodiazepines are the first-line treatment for catatonia regardless of the underlying cause.
- ECT has also been established as being highly effective for catatonia and is suggested in benzodiazepine-resistant cases, and in cases with life-threatening features.
- The benzodiazepine is usually continued at the effective dose until the treatment of the underlying condition is well underway and is then slowly tapered and discontinued.

- *Lorazepam*: Lorazepam is the most studied and first line of all benzodiazepines, but still successful use of diazepam or clonazepam has also been reported. Start with 1-2 mg every 4-12 hr. (average-TID) to be escalated by 3mg/day every 1-2 days. The commonly prescribed dose is 8-16mg/day. If intravenous administration is used, it can be given at a rate of 0.5 mg/kg infused over 2-5 minutes or 2 mg/min and 8-24 mg/day. At this rate it can be tolerable without respiratory depression and extensive sedation for normal adult. However, it needs frequent check-up because of precipitation and absorption to IV bags.
- *Diazepam*: Dose equivalent to Lorazepam is 5:1 in mg and the Maximum dose to use is (30-40) mg/day. Continuous infusion is not recommended because of precipitation in I.V. fluids and absorption of drug into infusion bags and tubing.

- *Clonazepam*: Dose equivalent to Lorazepam is 1:0.25.

Adverse effects of benzodiazepines:Benzodiazepines may be associated with the following adverse effects: sedation, dizziness, drowsiness, unsteadiness, paradoxical aggression, hypotension, local pain and/or erythema at the injection site, muscular weakness, respiratory

failure and memory impairment. The prolonged use of benzodiazepines may also carry a risk of tolerance and withdrawal reactions.

Electroconvulsive therapy (ECT): ECT should be administered according to the protocol.

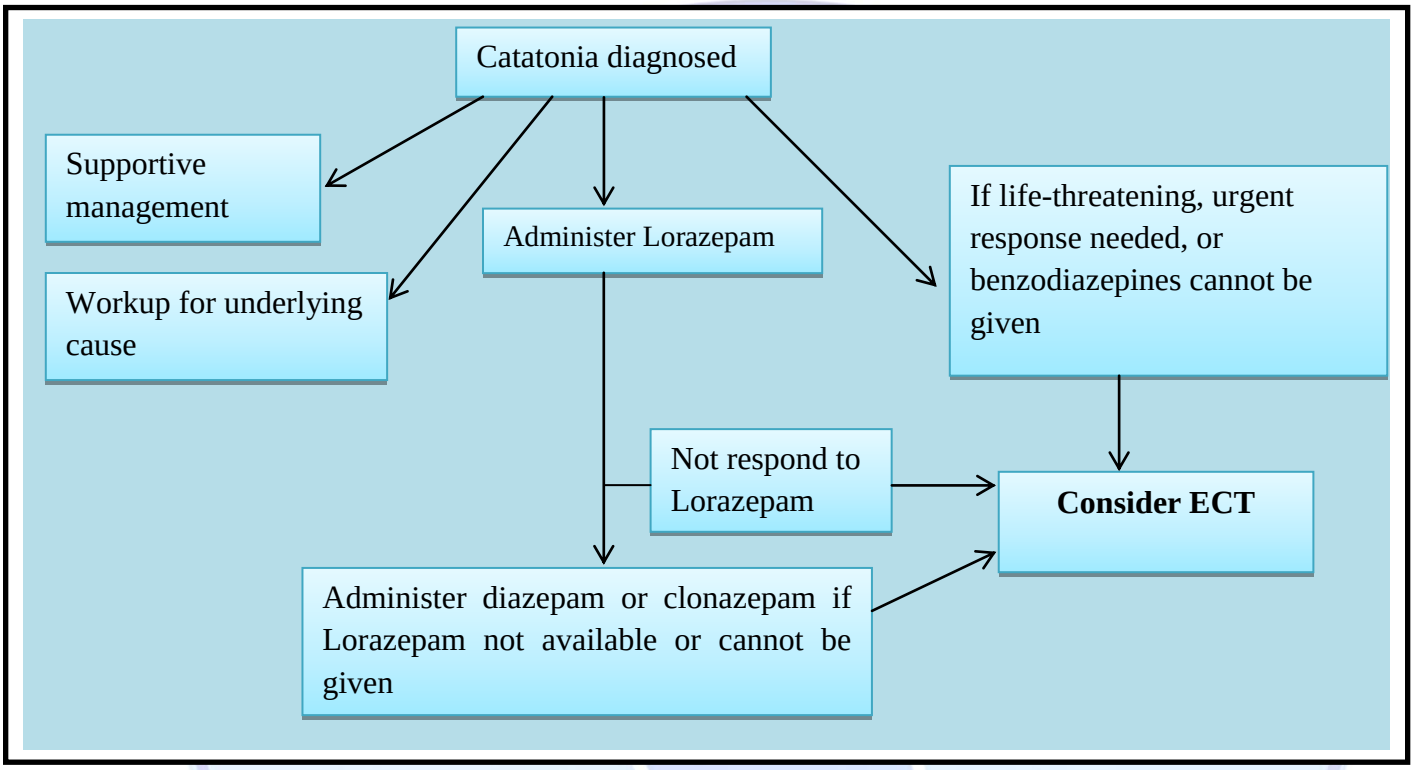


Figure 10: Algorithm for the management of catatonia

References

1. Quick Guide to Psychiatric Emergencies: Tools for Behavioural and Toxicological Situations. Ed. Nordstrom KD. and Wilson MP;2018
2. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, text revision. Washington DC, American Psychiatric Association, 2022.
3. Seethalakshmi R, Dhavale S, Suggu K, et al. Catatonic syndrome: importance of detection and treatment with lorazepam. Ann ClinPsychiatry. 2008;20(1):5–8.

4. Kroll KE, Kroll DS, Pope JV, Tibbles CD.Catatonia in the emergency department. J Emerg Med. 2012;43(5):843–6.
5. James Robert Brasic. Catatonia clinical presentation. Medscape, updated 2018
6. Sean A Rasmussen et al. Catatonia: Our current understanding of its diagnosis, treatment and pathophysiology. World J Psychiatr 2016 December 22; 6(4): 391-398
7. Anne CM Pelzer et al. Systematic review of catatonia treatment. Neuropsychiatric Disease and Treatment 2018:14 317–326
8. Tiao-Lai Huang. Catatonic features: Differential diagnosis and treatments at an emergency unit. Psychiatry and Clinical Neurosciences (1999), 53, 63–66
9. Ericka L. Crouse and Joel B. Moran. Catatonia: Recognition, management, and prevention of complications. Current Psychiatry 2018; 17 (12): 45-49
10. Parna Ramprasad et al (2016) Clinical Course and Management of Drug-Induced Catatonia and Paranoid Behavior in an Adolescent,Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology, 26:3, 310-315
11. Rustad JK, Landsman HS, Ivkovic A, et al. Catatonia: an approach to diagnosis and treatment. *Prim Care Companion CNS Disord.* 2018;20(1):17f02202.

CHAPTER EIGHT

8. Somatic Symptom and Related Disorders

8.1.INTRODUCTION

8.1.1. Brief Descriptions

- Somatic symptom and related disorders are characterized by the repeated subjective experience of physical symptoms which are not explained by any physical illness. It is the manifestation of one or more physical symptoms accompanied by excessive thoughts, emotion, and/or behavior related to the symptom, which causes significant distress and/or dysfunction.
- Somatic symptom disorder is diagnosed when a person's attention is drawn to bodily sensations like pain, weakness, or dizziness to the point where it causes considerable distress and/or interferes with daily tasks.
- Individuals have excessive worries, feelings and behaviors relating to the physical (somatic) symptoms.
- All the disorder subtypes share one common feature, that is, predominance and persistence of somatic symptoms associated with significant distress and impairment.

8.1.2. Epidemiology

- Somatic symptom and related disorders are among the most common psychiatric disorders in general practice, with a prevalence of 16%.
- The lifetime risk, prevalence, and incidence of somatic symptom disorders are unclear pending further research. The prevalence of somatic symptom disorder is estimated to be 5% to 7% of the general population, with higher female representation (female-to-male ratio 10:1), and can occur in childhood, adolescence, or adulthood.
- Transient conversion symptoms are common, but the precise prevalence of the disorder is unknown. This is partly because the diagnosis usually requires assessment in secondary care, where it is found in approximately 5% of referrals to neurology clinics. The incidence of individual persistent conversion symptoms is estimated to be 2-5/100,000 per year.

8.1.3. Cause and Risk Factors

- Somatic symptoms may result from a heightened awareness of certain bodily sensations, combined with a tendency to interpret these sensations as indicative of a medical illness.The etiology of somatic symptom disorder is unclear.

- However, studies have determined that risk factors for chronic and severe somatic symptoms include
  - ✓ Childhood neglect,
  - ✓ Sexual abuse,
  - ✓ Chaotic lifestyle, and
  - ✓ History of alcohol and substance abuse.
  - ✓ In addition, somatic symptom disorder has been associated with personality disorders.

8.2.Clinical Features

- There are two core features that both occur in somatic symptom disorder
  - One or more current somatic symptoms that are long-standing and cause distress or psychosocial impairment. Multiple symptoms are typically present, but one severe symptom (e.g. pain) is sufficient to make the diagnosis.
  - Excessive thoughts, feelings, or behaviors related to the somatic symptoms or associated health concerns as manifested by at least one of the following:

    1. Disproportionate and persistent thoughts about the seriousness of one's symptoms.
    2. Persistently high level of anxiety about health or symptoms.
    3. Excessive time and energy devoted to these symptoms or health concerns (See DSM-V).

  - Age of onset
    - ✓ Manifests in adolescence and early adulthood
    - ✓ Older adults presenting for the first time with somatic symptoms are much more likely to have an occult organic condition than somatic symptom disorder.

- Symptoms may include (but are not limited to) nonspecific pain, fatigue GI distress, palpitations, weakness, and numbness.
  - ❖ Note: Descriptions of somatic symptoms may vary depending on cultural factors.
- Emotional complaints
  - ✓ Patients are significantly distressed about their symptoms and have a high level of worry about their health.

- ✓ Patients concerns are time consuming and limit activities of daily living.

8.3.Diagnosis and Investigation

8.3.1. Investigations and Differential diagnosis

- The following diagnostic tests may be used to explain or rule out physical causes of the symptoms based on the history and physical examination of the patient by a trained clinician.
  - ✓ CBC
  - ✓ Basic metabolic panel
  - ✓ Thyroid panel
  - ✓ Liver function tests
  - ✓ Urinalysis
  - ✓ Toxicology screen
  - ✓ Imaging
- The diffuse, non-specific symptoms in somatic syndrome disorder may confound and mimic presentations of other medical illnesses, making diagnosis and treatment difficult. Excessive and disproportionate emotional and behavioral responses may be present in
  - ✓ Adjustment disorder,
  - ✓ body dysmorphic disorder,
  - ✓ obsessive-compulsive disorder, and
  - ✓ anxiety disorders
- Other medical disorders of unclear etiology, including fibromyalgia and irritable bowel syndrome, o not typically manifest with excessive thoughts, emotions, or maladaptive behavior

The three component of Psycho-social assessment

1. Individual factor
   - ✓ Temperament(anxious, behavioral inhibition, harm avoidance)
   - ✓ Poor coping skills
   - ✓ Borderline intellectual functioning
   - ✓ Underlining psychiatric illness (anxiety, depression)
2. Family related factors

- ✓ Coping skills of family members
- ✓ Response of family members towards the child's problem
- ✓ Poor communication with the child
- ✓ Parenting style
- ✓ Intra-familial relationships
- ✓ Physical and psychiatry problems in the family members

3. Environmental factors

- ✓ Few years of education,
- ✓ Low socioeconomic status, and
- ✓ Those who have recently experienced stressful life events

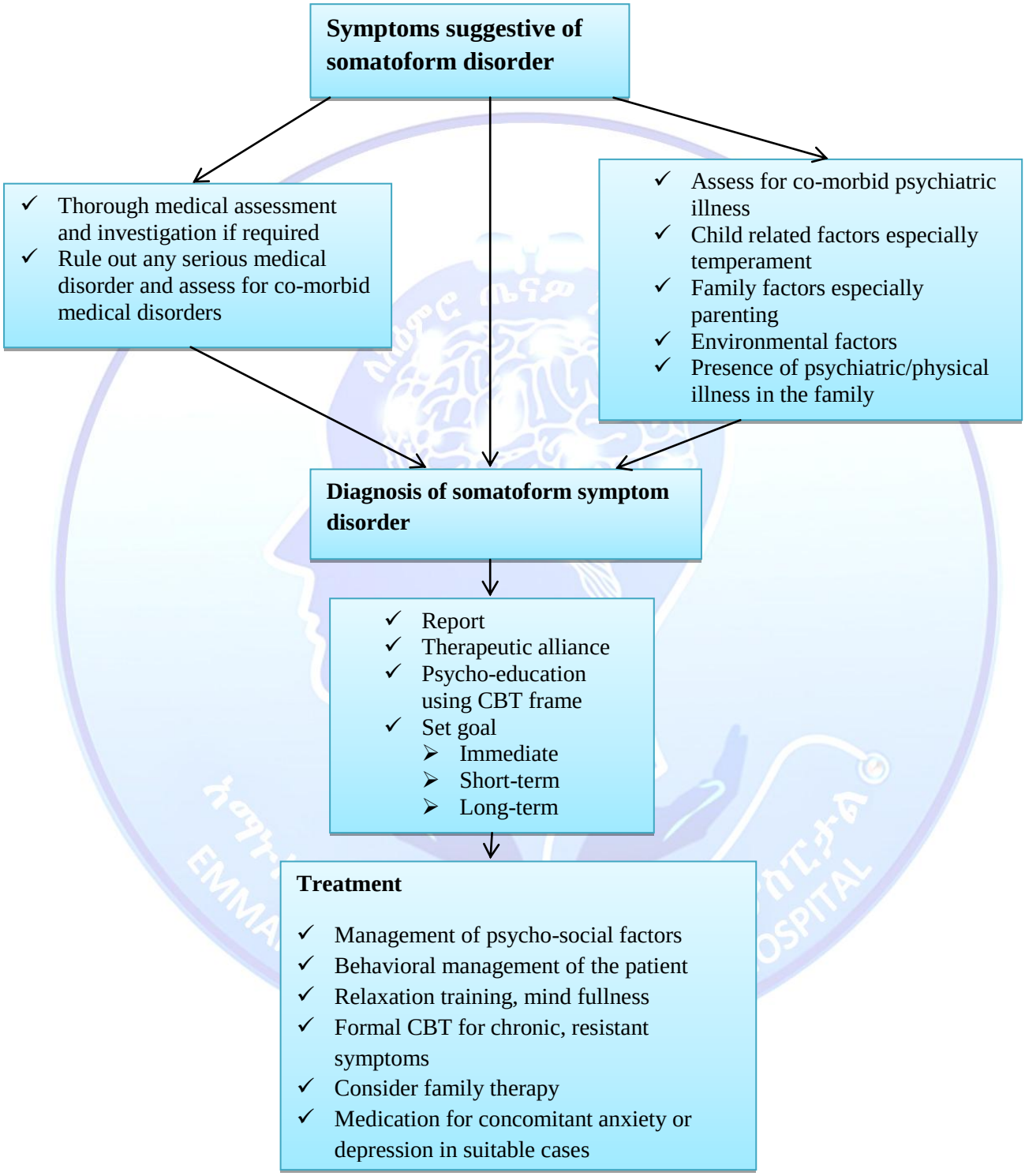


Figure 11: Schematic presentation of treatment algorithm for the management of Somatic Symptom and related disorders

8.4.Treatment

8.4.1. Treatment approach

- The crucial objective is to assist the patient manage with physical symptoms, including health anxiety and maladaptive behaviors, as opposed to eliminating the symptoms.
- Care must be exercised when conveying to patients that their physical symptoms are exacerbated by anxiety or excessive emotional problems as patients may be resistant to this suggestion.
- The clinician should schedule regular visits to reinforce that symptoms are not suggestive of a life threatening or disabling medical condition.

8.4.2. Treatment goal

1. Immediate
   - ✓ Cessation of inappropriate medical intervention
2. Short term goals
   - ✓ Preventing further unnecessary medical intervention
   - ✓ Symptom reduction
   - ✓ Initiation of age appropriate activities
3. Long term goal
   - ✓ Appropriate use (not over use) of medical care
   - ✓ Resolution /minimization of symptoms and psychosocial stressor
   - ✓ Development of appropriate copying skills to deal with psychological and environmental stressor
   - ✓ Resumption of age appropriate activities
   - ✓ Aim for goal in severe, long standing case.

8.4.3. *Non Pharmacological treatment*

1. Accept that patients can have distressing, real physical symptoms and medical conditions with coexisting psychiatric disturbance without malingering or feigning symptoms
2. Once the diagnosis is confirmed, provide patient education on the individual disorder using empathy and avoiding confrontation.
3. Avoid unnecessary medical tests and specialty referrals, and be cautious when pursuing new symptoms with new tests and referrals.
4. Focus treatment on function, not symptom, and on management of the disorder, not cure.
5. Address lifestyle modifications and stress reduction, and include the patient's family if appropriate and possible.
6. Treat comorbid psychiatric disorders with appropriate interventions.

7. CBT-typeinterventions appear to help patients by modifying thoughts and behaviors associated with somatization.

- Other interventions, including the use of brief psychodynamic psychotherapy, and exercise, have also shown beneficial effects on some of these symptoms.

I. ***Non Pharmacological treatment of*** **Illness Anxiety Disorder:**

1. CBT interventions, making CBT the prototype, first-line treatment for illness anxiety disorder.
2. Other types of therapy, including mindfulness training, exposure therapy, and acceptance and commitment therapy, have also demonstrated some efficacy.

II. ***Non Pharmacological treatment of*** **Conversion Disorder**

1. Many conversion syndromes have an acute, benign course and may remit spontaneously with understanding and support.
2. Early intervention can forestall potential chronicity and the progression into a well-entrenched somatization disorder.
3. Intensive treatment may use all treatment modalities, including hospitalization when there are comorbidities or severe medical compromise as a result; individual or group therapy, insight-oriented therapies, and behavioral techniques,
4. Behavioral interventions should focus on improving self-esteem, the capacity for emotional expression and assertiveness, and the ability to communicate comfortably with others.

III. ***Non Pharmacological treatment of Factitious Disorder***

1. Keep in mind that active pursuit of a prompt diagnosis can minimize the risk of morbidity and mortality.
2. Minimize harm. Avoid unnecessary tests and procedures, especially if they are invasive. Treat according to clinical judgment, keeping in mind that subjective complaints may be deceptive.
3. Arrange regular interdisciplinary meetings to reduce conflict and splitting among staff. Manage staff counter transference.
4. Steer the patient toward psychiatric treatment in an empathic, non-confrontational, face-saving manner. Avoid aggressive direct confrontation.
5. Treat underlying psychiatric disturbances. In psychotherapy, address coping strategies and emotional conflicts.

6. As a behavioral disincentive, consider prosecution for fraud

7.4.3. Non Pharmacological treatment of Factors Affecting Other Medical Conditions

- Treatment frequently involves communication with the patient's primary medical team as well as family.

1. The psycho-educational intervention clarifies the role that emotional and behavioral factors play in aggravating the underlying medical condition.

   Medication to treat another underlying psychiatric disorder may be necessary

8.4.4. Pharmacological treatment

- **All classes of antidepressants** have some effectiveness against somatic symptom and related disorders with the most researched being TCAs. SSRIs are more effective against illness anxiety disorder, and SNRIs appear to be more effective than other antidepressants when pain is the predominant symptom
- From Tricyclic antidepressant - Amitriptyline is first choice of drug for many symptoms

1. **From SSRIS Drugs –** Fluoxetine has a remarkable effect for general wellbeing, functionality and reducing pain
2. MAOIs - Lessor effect

   For Augmentation treatment
3. **Antipsychotics** - Typical antipsychotics
   - **Atypical antipsychotics**

Typical antipsychotics are more effective than atypical ones

4. **Anxiolytics / Sedatives**

Table 6: Treatment recommendation for somatic symptom and related disorders

s. no	Drugs	Dose range mg/d	Pregnancy category	Titration dose
1	Amitriptyline 25 mg	50- 150mg	c	Initially start with 25 mg/d at bed time and gradual increase after a weeks
2	Fluoxetine 20 mg	20 - 80mg	C	Initially start with 20 mg/d in morning after breakfast and gradual

				increase after a weeks
3	**Imipramine 25 mg**	**75 –200mg**	**C**	**Initially start with 25 mg/d and gradual increase after a weeks in divided dose**
4	**Sertraline 50, 100mg**	**50- 200mg**	**c**	**Start with 50mg /d and gradual increase of 25 mg in weekly intervals**

Reference

1. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, text revision. Washington DC, American Psychiatric Association, 2022.
2. Scher LM, Knudsen P, Leamon M. Somatic symptom and related disorders. In: The American Psychiatric Publishing Textbook of Psychiatry, Sixth Edition, Hales RE, Yudofsky SC, Roberts LW (Eds), American Psychiatric Publishing, Washington, DC 2014. p.531.
3. Benjamin James Sadock,M.D;Virginia Alcott Sadock,M.D;PedroRuiz,M.D; Kaplan and Sadock, Synopsis OfPsychiatry, eleventh edition. Chapter 13, psychosomaticmedicine.page no.465-4966.
4. Dr. Kunjan Gupta1, Dr. Vipul Singh2, Dr. Saurabh Agarwal et al, Somatoform Disorders To Somatic Symptom And Related Disorders, An Overview.
5. Sadock, and Pedro Ruiz. Kaplan & Sadock's Synopsis of Psychiatry: Behavioral Sciences/clinical Psychiatry. Eleventh edition. Philadelphia: Wolters Kluwer, 2015.

CHAPTER NINE

9. Obsessive-Compulsive Disorder (OCD)

9.1.Introduction

9.1.1. Brief Description

- Obsessive-compulsive disorder (OCD) is characterized by the presence of obsessions and/or compulsions.
- Obsessions are recurrent and persistent unwanted intrusive thoughts, urges, or images.
- Compulsions are repetitive behaviors or mental acts that an individual feels driven to perform in response to an obsession or according to rules that must be applied rigidly.
- Obsessive-compulsive disorder is associated with significant impairment in functioning, quality of life and disability. If untreated, OCD is a chronic illness with a waxing and waning of symptoms.
- Early diagnosis and appropriate treatment may improve outcomes. Despite OCD being a common mental illness, most seek treatment after several years of suffering.

9.1.2. Epidemiology

- The lifetime prevalence rates for OCD globally have been estimated at 1.5 percent for women and 1.0 percent for men.Prevalence rates for adults show slightly higher figures for females, although males are more commonly affected in childhood.

9.1.3. Causes and risk factors

- Genes have been found to contribute to the risk of OCD. The rate of OCD is twice when the individual has first-degree relatives with the disorder than otherwise. Environmental risk factors include:
  - Adverse perinatal events
  - Premature birth
  - Maternal tobacco use during pregnancy
  - Physical and sexual abuse in childhood and other stressful or traumatic events
  - Infectious agents and a post-infectious autoimmune syndrome

9.2.Clinical features

- Obsessive-compulsive disorder is characterized by the presence of obsessions or compulsions, or both. Obsessions are recurrent intrusive thoughts, images, or urges that typically cause anxiety or distress.

- Compulsions are repetitive mental or behavioral acts that the individual feels driven to perform, either in relation to an obsession or according to rules that he or she believes must be applied rigidly or to achieve a sense of "completeness."
- Obsessive-compulsive disorder has four commonly seen symptoms and signs:
  - Contamination-cleansing: obsessions about being contaminated followed by compulsions of washing or avoidance of contaminating objects.
  - Pathological doubt-checking: obsessions about doubt (e.g., forgetting to turn off the stove or not locking a door) followed by compulsions of checking.
  - Forbidden thoughts: obsessions about forbidden thoughts or acts (e.g., thoughts of sexual or aggressive act) without compulsions.
  - Symmetry-ordering: obsessions about the need for symmetry or precision followed by compulsion of slowness.

9.3.Diagnosis and investigations

9.3.1. Diagnosis and differential diagnosis

- The diagnosis of OCD should be made upon fulfillment of the DSM-5 diagnostic criteria for the disorder. The defining characteristic of OCD is the presence of obsession, compulsions, or both. The obsessions or compulsions are time consuming (at least one hour per day), and the symptoms and signs are not secondary to another medical or psychiatric condition.
- The disorder should be differentiated from anxiety disorders. There are worries about real life concerns in generalized anxiety disorder (GAD) which are not associated with rituals; in OCD obsessions usually do not involve real life concerns. In specific phobia, there is fear reaction towards objects and situations which are more circumscribed, and there are no rituals. In social anxiety disorder (SAD) the fear is limited to social situations, and there are no rituals.
- The rumination in major depressive disorder (MDD) may resemble obsessions; however, the thoughts in MDD are mood congruent and not considered as intrusive. Obsessive-compulsive disorder should also be differentiated from hoarding disorder, tic disorder, psychotic disorder and obsessive-compulsive personality disorder.

9.3.2. Laboratory and imaging

- Baseline laboratory tests include complete blood count (CBC), sedimentation rate (ESR), liver transaminases, renal function tests (urea and creatinine), fasting blood sugar (FBS), serum electrolytes, and thyroid function tests (TSH, T3, and T4).
- Other laboratory or imaging studies could be considered if history and physical examination suggests any other medical conditions.

9.4.Treatment of OCD

9.4.1. Goals of treatment

- Control or eliminate symptoms and signs
- Alleviate distress and restore full functioning
- Treat comorbid conditions
- Prevent relapse

9.4.2. General principles of treatment

- Choosing treatment setting: Outpatient treatment is usually sufficient for most OCD patients who are mild to moderately ill and for those who are likely to be adherent to treatment. Hospital treatment may be considered for those who are at high suicide risk, dangerous to self or others, and intolerant to side-effects.

9.4.3. Non-pharmacologic treatment

- Cognitive behavioral therapy (CBT) with exposure and response prevention (ERP) approach has been found to be effective psychotherapeutic treatment for OCD. Obsessive-compulsive disorder has a cycle which involves obsessions- anxiety- compulsion- temporary relief.
- Exposure and response prevention cuts this cycle by exposing the patient to things that trigger the anxiety in a graduated manner and in a controlled environment and preventing response. The patient is then helped to replace negative thoughts with more adaptive and productive ones, as well as learn new ways to respond.
- Psychotherapy should be administered by a clinician who is well trained in its application.

9.4.4. Pharmacologic treatment

- Selective serotonin reuptake inhibitors (SSRIs) are the first line pharmacologic treatment agents due to their efficacy and their safety profile.

- Sertraline and fluoxetine are available and there is good clinical experience in their use. The tricyclic antidepressant clomipramine is equally effective to the SSRIs, but the latter have better safety record; therefore, clomipramine is second line treatment for OCD.
- The SSRIs and clomipramine should be used in higher doses than for depression.
- Sertraline 200 mg/day, fluoxetine 80 mg/day and clomipramine up to 250 mg/day may be needed.
- Clomipramine has significant anticholinergic adverse effects (dry mouth, constipation, etc), antihistaminic adverse effects (sedation and weight gain), alpha adrenergic antagonism (orthostatic hypotension).
- Clomipramine also has significant arrhythmogenic adverse effects and doses above 250 mg may necessitate electrocardiograph (ECG) monitoring. Clomipramine also may cause seizures when used above 250 mg/day.

Table 7: Medications recommended as first and second line for OCD

Medication	**Recommended dose (mg/day)**
Sertraline	150-200
Fluoxetine	60-80
Clomipramine	150-225

- In OCD treatment, the medications should be taken for longer periods than for depression to show results. Because response to pharmacotherapy in OCD is gradual, treatment should be taken for 12 weeks before considered ineffective.
- Treatment-resistant OCD is defined as failure of response to two trials of SSRIs and/or clomipramine of adequate dose and duration.

9.4.4.1.Augmentation strategies

- There are two types of augmentation strategies in the treatment of OCD.
- Augmentation with CBT/ERP is relatively safe but there could be lack of the expertise. In treatment-resistant OCD, augmentation with CBT with ERP should be the third line of treatment.

- Augmentation with antipsychotics has potential for adverse effects from antipsychotic use, therefore, should not be considered in the absence of treatment-resistant OCD, and it is the fourth line of treatment.

9.4.4.2.Considerations in pediatric age groups

- In children, there are concerns regarding side effects of medications. Higher doses of SSRIs or clomipramine have benefits in adults; however, the benefit from higher doses of the medications has not been demonstrated in the pediatric population.
- The SSRIs are approved for use in children include fluoxetine (age 7 and above) and sertraline (age 6 and above).
- Clomipramine is also approved for children 10 and above.

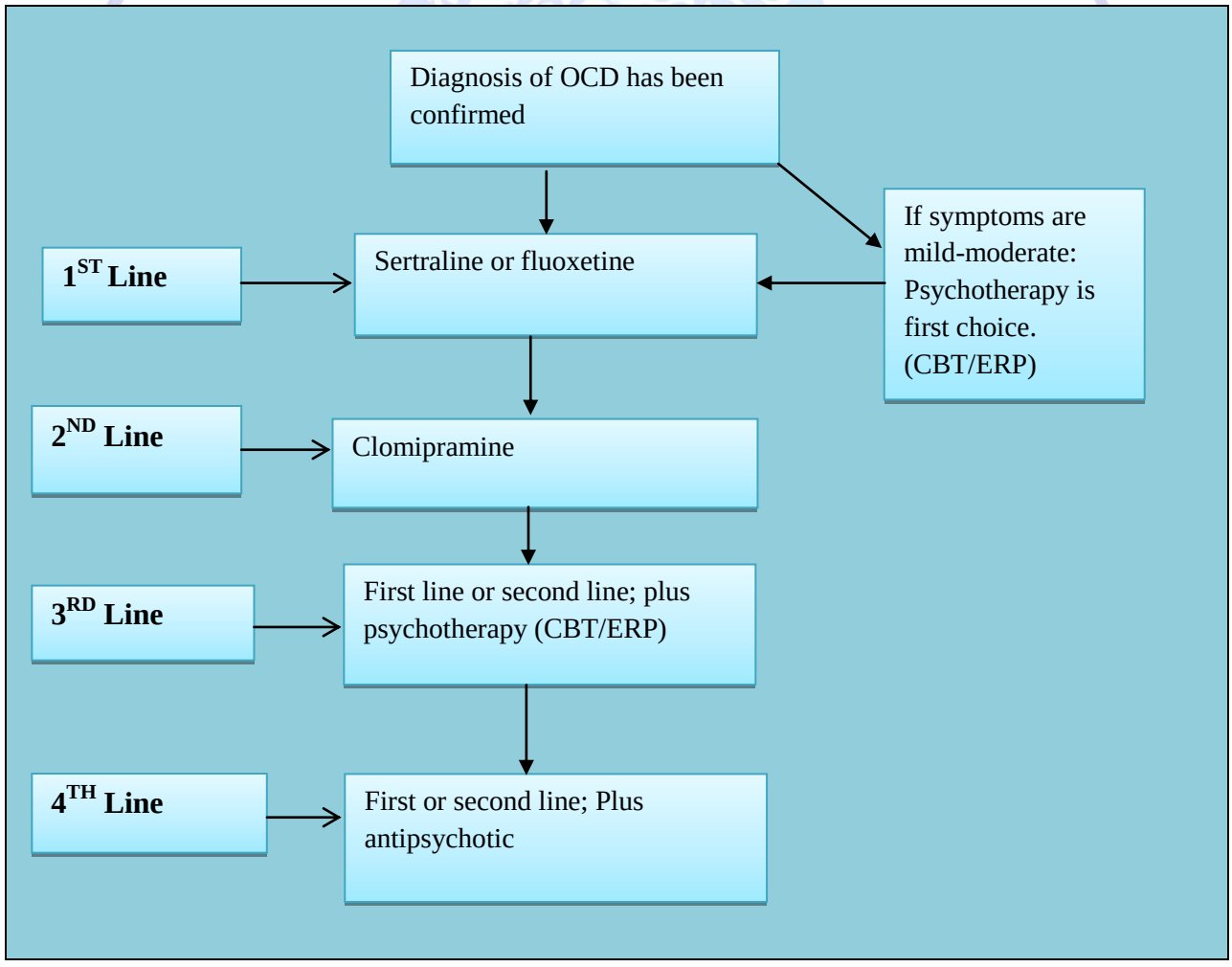


Figure 12: Algorithm for the treatment of obsessive-compulsive disorder (OCD)

Reference

1. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, text revision. Washington DC, American Psychiatric Association, 2022.
2. Ruscio AM, Stein DJ, Chiu WT, Kessler RC. The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. *Molecular Psychiatry.* 2010; 15:53–63.
3. Skapinakis P, Caldwell DM, Hollingworth W, Bryden P, Fineberg NA, Salkovskis P, et al. Pharmacological and psychotherapeutic interventions for management of obsessive-compulsive disorder in adults: a systematic review and network meta-analysis. *The Lancet Psychiatry.* 2016;3:730–739.
4. Fineberg NA, Reghunandanan S, Brown A, Pampaloni I. Pharmacotherapy of obsessive-compulsive disorder: evidence-based treatment and beyond. *The Australian and New Zealand Journal of Psychiatry.* 2013;47:121–141.
5. National Collaborating Centre for Mental Health(UK) *Obsessive-Compulsive Disorder: Core Interventions in the Treatment of Obsessive-Compulsive Disorder and Body Dysmorphic Disorder, National Institute for Health and Clinical Excellence: Guidance.* Leicester (UK): British Psychological Society; 2006.
6. Albert U, Aguglia A, Bogetto F, Cieri L, Daniele M, Maina G, et al. Effectiveness of cognitive-behavioral therapy addition to pharmacotherapy in resistant obsessive-compulsive disorder: a multicenter study. *Psychotherapy and Psychosomatics.* 2012;81:383–385.
7. Arumugham SS, Reddy YC. Commonly asked questions in the treatment of obsessive-compulsive disorder. *Expert Review of Neurotherapeutics.* 2014;14:151–163.
8. Arumugham SS, Reddy JY. Augmentation strategies in obsessive-compulsive disorder. *Expert Review of Neurotherapeutics.* 2013;13:187–202. quiz 203.

9. Sadock, B. J., Sadock, V. A., & Ruiz, P**.** Kaplan & Sadock's synopsis of psychiatry: Behavioral sciences/clinical psychiatry (Eleventh edition.). Philadelphia: Wolters Kluwer; 2015.

10. *Treatment of obsessive-compulsive disorder. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on June 19, 2022).*

11. Christopher Pittenger, Ben Kelmendi and Vladimir Coric. Clinical Treatment of Obsessive Compulsive Disorder. Psychiatry (Edgmont), 2005; 2 (11): 34-43.

12. Christopher Pittenger, and Michael H. Bloch. Pharmacological treatment of obsessive-compulsive disorder. Psychiatr Clin North Am, 2014; 37 (3): 375- 391.

CHAPTER TEN

10.Psychiatry Emergencies

10.1. THE ACUTELY DISTURBED PATIENT

10.1.1. Introduction

10.1.1.1. Brief description

- The acutely disturbed patient presents in an excited, agitated or aggressive state.
- There may be perceptual changes like hallucinations and disturbance in thinking such as delusions that overwhelm the patient.
- Disorientation and alteration in consciousness are often prominent in organic causes. When a patient first arrives to the emergency department with current history of agitation or violence, it is helpful to think of the condition as falling into one of four main groups of causes to guide immediate management. These include agitation or violence associated with delirium; agitation and violence due to current intoxication; agitation and violence associated with psychosis; and undifferentiated agitation and violence.

10.1.1.2. Causes and risk factors

- The causes for acute psychiatric disturbance of patients can be categorized into groups.
  - The first group is acute functional psychiatric disorders including mania, acute schizophrenia, schizophrenia relapse, agitated depression, catatonic excitement and acute psychosis.
  - The other group is acute organic psychiatric disorders such as toxic psychosis secondary to drug intoxication (with cocaine, marijuana, heroin etc), delirium tremens or alcohol intoxication syndrome, infectious diseases (e.g. typhoid, malaria, meningitis, encephalitis, acute hepatitis, etc) and seizures.

10.1.2. Clinical Features

- Acutely disturbed patients manifest with a constellation of symptoms and signs.
- Patients typically are restless, agitated or combative.
- They are often brought in forcibly restrained by more than two people or the police.
- They could be talking excessively and loudly, or mute in some cases.
- Disinhibited behavior or speech could be there, as well as verbal aggression.
- Patients could have auditory or visual hallucination, or delusion of the paranoid, grandiose or bizarre type.
- Euphoria, lack of insight, pressure of speech, hyperactivity, increased sexual desire, and over assertiveness could be found among the acutely disturbed patient.
- Physical aggression and destructive behavior are common manifestations of such patients.
- In organic disorders there could be fever and/or headache.
- There could be life-threatening manifestations related to medical causes.
- They include loss of memory, disorientation, extreme muscle stiffness or weakness, unintentional weight loss, new onset psychosis, and difficulty breathing.

- On physical examination there could be abnormal vital signs (pulse, blood pressure, or temperature), overt trauma, anisocoria (unequal pupil size), slurred speech, incoordination, acute seizure attack, and hemiparesis.

10.1.3. Diagnosis and investigation

10.1.3.1. Diagnosis and differential diagnosis

- Differential diagnosis considerations in cases of the acutely disturbed patient include acute pain, head trauma, infection, encephalitis, encephalopathy, toxins, metabolic issue, hypoxia, hyperthyroidism, neurologic disease, high dose medications, recreational drug intoxication or withdrawal, and exacerbation of primary psychiatric disorder.

10.1.3.2. Laboratory and imaging

- The specific laboratory investigations depend on the findings of the history and physical examination results. The recommendation is to do fasting blood sugar (FBC), CBC, blood film (BF) if there is fever, urine drug screen for substance abuse. Electroencephalogram (EEG) and magnetic resonance imaging (MRI) can be done if there are indications.

10.1.4. Treatment

10.1.4.1. ***Goals of treatment***

The goal of treatment in acutely disturbed patients is to

- ✓ Ensure safety,
- ✓ Calm down the patient as quickly as possible using the safest drugs available, and
- ✓ Identify and treat underlying causes.

10.1.4.2. General principles of management

- It is the priority of the management to ensure safety of the patient and other people.
- It is advisable to admit the patient on emergency basis for workup and stabilization, as well as to ensure safety of the patient and other vulnerable people.

10.1.4.3. Non-pharmacologic measures

- If necessary, it is advisable to restrain the patient without causing injuries.
- The procedure of restraint must be ordered by authorized clinician and must follow the protocol. It helps to talk to the patient in a firm but reassuring manner. Once admitted, carefully observe the patient's activities. Do not block exits and leave door to room open.
- Staff should maintain distance from potentially violent patients.
- It is advisable to adopt passive, non-confrontational posture and attitude, and allow the patient to ventilate his/her feelings.
- This is achieved by developing a therapeutic alliance with the patient and treating the patient as he/ she is expected to behave.
- It is not advisable to make challenging, provocative, or belligerent remarks.
- Do not turn your back on potentially violent patient; never underestimate the potential for violence.
- Safety of the patient should be ensured.

- Avoiding physical harm to the patient, keeping the environment safe to the patient and others are important considerations.
- The treating team should manage patient timely as soon as possible, check vital signs frequently after calming the patient, and keep the privacy and comfort of the patient. It is advisable to document and record all necessary interventions for the patient.
- Assessing and treating any underlying mental health problems and co-morbid medical conditions should be started as soon as possible.

The following are some important steps to be considered during assessment and the provision of non-pharmacologic interventions

- Identify any history of aggression or aggression trigger factors, including experience of abuse or trauma.
- Identify previous response to management of violence or aggression.
- Identify cognitive, language, communication and cultural factors that may increase the risk of violence or aggression in a child or young person.
- In case of children and young people with a history of violence or aggression, it is good to consider offering psychological help to develop greater self-control and techniques for self-soothing.
- Offer support and appropriate interventions, including psycho-education for patients and family.

10.1.4.4. Pharmacologic treatment

- The medications that can be used first line for sedation and behavioral control of patients who are acutely disturbed include Lorazepam, Diazepam and Haloperidol. All three drugs have preparations for parenteral use.
- Lorazepam can be given 1-2 mg IM, diazepam can be given 10-20 mg IV, and haloperidol 2-5 mg IM.

10.1.4.5. Precaution

- Combination of medications in one syringe is not recommended.
- Diazepam intravenous injection must be administered with care or given slowly if the cause of the acute disturbance is a medical condition. It may cause respiratory arrest. Never give chlorpromazine IV. It may lead to severe hypotension.
- Haloperidol IV should be avoided as it may cause cardiac arrest.
- Give the above drugs with caution for children and adolescents, old age, known medically ill patients, pregnant and breast-feeding women.

10.1.4.6. Specific treatment considerations

- If the agitation is associated with delirium and alcohol withdrawal or benzodiazepine withdrawal is not suspected, consider medical causes first in the emergency department. Common causes include hypoglycemia, hypoxia, head injury, or thyroid disease.
- Treat the underlying cause first before giving medications (best evidence is for oral Risperidone and oral Olanzapine).
- If the agitation is associated with delirium and this is likely due to alcohol or benzodiazepine withdrawal, or stimulant intoxication benzodiazepines are the first line treatment.
- If the agitation is because of a CNS depressant (like alcohol), protect the airway first. If medications are needed, first-generation antipsychotics like haloperidol are likely safer than benzodiazepines.
- If the agitation is associated with psychosis in a patient with a known psychiatric disorder, second-generation antipsychotics are preferred (best evidence for olanzapine or Risperidone).
- If the patient is taking a known psychiatric medication, consider dosing with this medication.
- If the cause of the agitation is unknown and there is no psychosis, treat like alcohol or benzodiazepine withdrawal.
- If the cause of the agitation is unknown and there is psychosis, treat as if the patient had a known psychiatric disorder.

Restraints are occasionally needed.

- ✓ If the agitation is severe and the patient is actively trying to hurt self or others.
- ✓ Restraints should be used as a last resort only and avoided if at all possible. If used, frequent reassessment and patient debriefing is necessary.
- ✓ Monitor vital signs, level of hydration, and level of consciousness at least every hour until there are no further concerns about their health status.
- ✓ Monitor every 15 to 30 minutes accordingly if the maximum dose has been exceeded, or the client appears to be sedated, has a pre-existing physical health problem, has experienced any complication as a result of any restrictive intervention.

10.1.4.7. Preventions

- Training stress coping mechanisms, educating about adherence to treatment, avoiding the use of psychoactive substances (like alcohol, khat, cigarrate, cannabis, cocaine, etc), avoidance of taking non prescribed narcotic drugs (like Pethidine, Morphine, Tramadol etc), and promoting lifestyle modifications which improve one's health are important preventive measures.

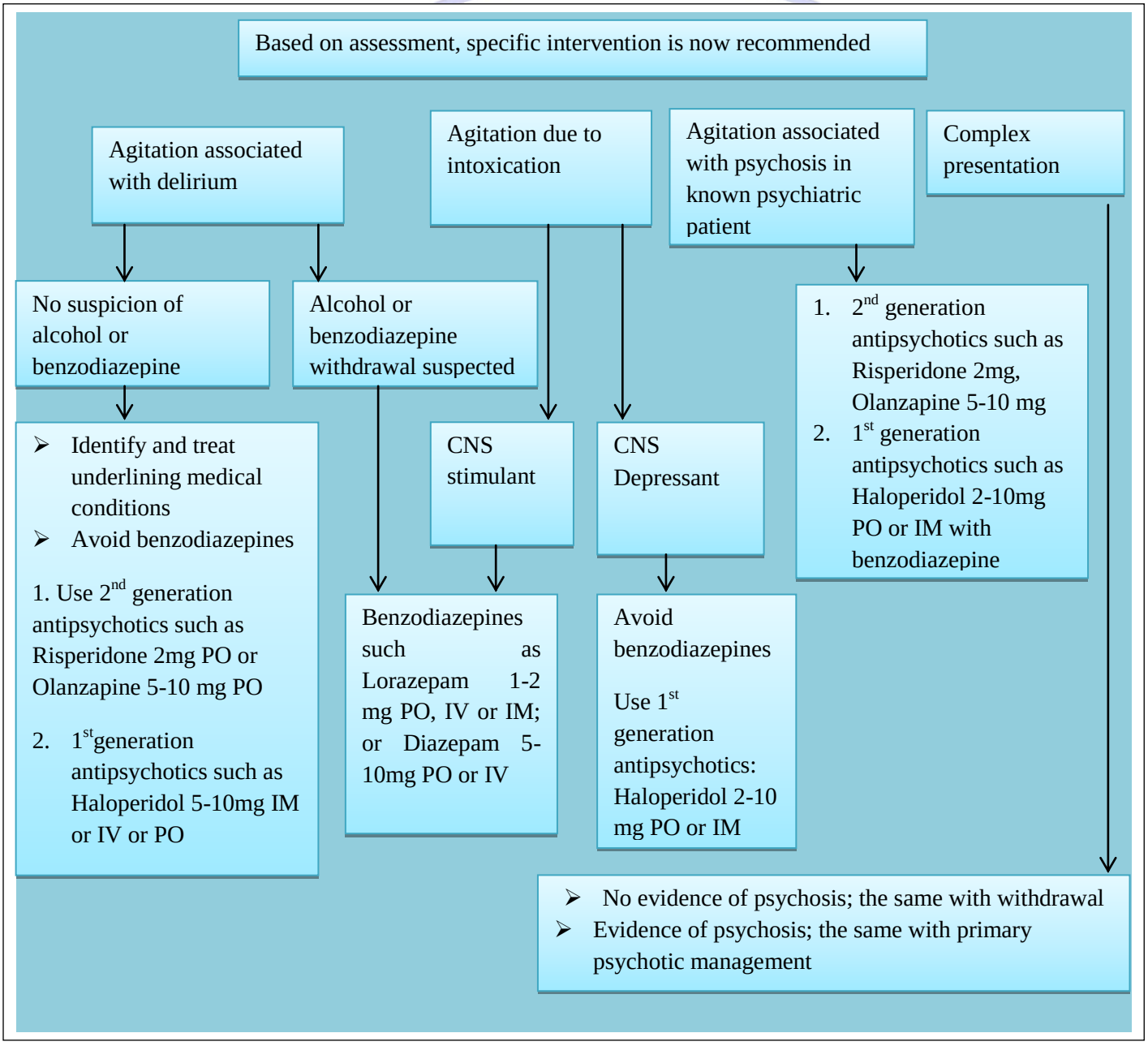


Figure 13: Algorithm for management of the acutely disturbed patient

10.2. Suicide or Self-Harm

10.2.1. Introduction

10.2.1.1. *Brief Description*

- Suicide is a multi-step process that includes suicidal ideation, suicide planning, suicide attempt, and suicide completion.
- It is sort of a deliberate self-harm that is described as the deliberate killing of oneself by a person and the attempt is defined as a non-fatal self-injurious behavior that is accompanied by evidence that the person meant to die. Suicidal ideation is thoughts of serving as the agent of one's own death. Suicidal ideation may vary in seriousness depending on the specificity of suicide plans and the degree of suicidal intent.
- Suicidal intent is a subjective expectation and desire for a self-destructive act to end in death.
- Lethality of suicidal behaviour is an objective danger to life associated with a suicide method or action. Note that lethality is distinct from and may not always coincide with an individual's expectation of what is medically dangerous.

10.2.1.2. Epidemiology

- Globally, an estimated 703,000 people died by suicide in 2019. The global age-standardized suicide rate was higher in males (12.6 per 100 000) than in females (5.4 per 100 000). So far no data pooled attempt to provide the real prevalence of suicide or self-harm in Ethiopia.

10.2.1.3. Causes and risk factors

- Having psychiatric disorders such as depressive disorders, psychotic disorders, dementia, delirium and personality disorders are considered as risk factors for suicide.
- Important risk factor includes having acute or chronic medical conditions such as cancer and HIV/AIDS.'At risk' mental status includes the presence of hopelessness, despair, agitation, shame, guilt or anger.
- Recent interpersonal crisis, especially rejection and humiliation increase the risk for suicide.
- The other risk factors are occurrence of recent suicide attempt, recent major loss or trauma or anniversary, alcohol intoxication or drug withdrawal state, chronic pain or illness, financial crisis or unemployment, lack of a social support network.

- Difficulty accessing help due to serviceavailability, lack of information, and lack of support or negative experiences with mental service providers also increases the risk.

10.2.2. Clinical characteristics

- Since suicide is associated with major depressive disorder, early warning signs of depression should alert the health professional to the need for further assessment of suicide risk.
- Some of these warning signs include
  - Depressed mood,
  - Markedly decreased interest or pleasure,
  - Significant weight loss when not dieting,
  - Insomnia or hypersomnia,
  - Psychomotor agitation or retardation, and
  - Feeling of worthlessness or excessive guilt.
- Assessment for suicidal behavior should include a complete psychiatric and medical history, with particular attention to the risk factors.
- The use of the modified SAD PERSONS scale is advisable to guide decision. (See annex 1 for modified SAD PERSONS scale).
- Physical examination should be guided by the history, but must include vital signs and neurological examination.

10.2.3. Investigation and Diagnostic tests

- Usually, there are no specific investigations for suicide but investigations can be done based on the type of measures used during suicide attempt.

10.2.4. Management of suicidal behavior

10.2.4.1. Goal of management

- The goal of management for patients at risk of suicide is to
  - Identify level of suicide risk and factors associated with suicidal behavior for the sake of early management intervention.

10.2.4.2. General principles of management

- Management for suicidal behavior has principles which include medical stabilization, reducing immediate risk and treatment planning, managing underlying factors and psychiatric disorders, and monitoring and follow-up.

- Medical stabilization at a hospital is the first priority for those who have tried suicide. For trauma management, contact the appropriate surgical or emergency medical service.
- Patients whose attempt involved drug ingestion should undergo decontamination and receive antidotesas indicated.
- Admission for further evaluation and initiation of therapy is nearly always indicatedfor patients with recent suicidal behaviour (e.g., suicide attempt) or imminent high risk of suicide (e.g., patients with moderate to severe suicidal ideation that includes a plan and intent).
- Factors that can place patients at high risk of suicide include:
    - Suicide attempt with a highly lethal method (e.g., firearm or hanging)
    - Suicide attempt that included steps to avoid detection
    - On-going suicidal ideation or disappointment that the suicide attempt was not successful
    - Inability to openly and honestly discuss the suicide attempt and what precipitated it
    - Inability to discuss safety planning (see 'Safety plan' below)
    - Lack of alternatives for adequate monitoring and treatment
    - Psychiatric disorders underlying the suicidal ideation and behaviours:
        - ✓ Depression
        - ✓ Anxiety disorders
        - ✓ Bipolar disorder
        - ✓ Personality disorders (e. g. borderline personality disorder)
        - ✓ Posttraumatic stress disorder
        - ✓ Psychotic disorders (e. g. schizophrenia)
        - ✓ Substance use disorders
    - Agitation
    - Impulsivity
    - Severe hopelessness
    - Poor social support

If Bed is not available for admission, doing the following helps

- Patients should be kept in an emergency room with all sources of potential harm removed by the nurses. If families are available, then they should be disclosed on the procedures and they can assist on this process. This is done at the emergency outpatient room.
- A staff member or nurse at OPD should be assigned to provide constant observation.
- The patient's belongings should be stored separately or searched for potential methods for self-harm.
- Cooperative family members may be present if the patient desires.
- Security staff may be necessary to detain patients who insist on leaving.
- Transfer of the patient should take place by ambulance, and the nurses assigned at the ambulance must be disclosed of the suicide risk.
- Efforts should be made to inform the patient's outpatient case team if already on follow up and case team clinicians about the impending hospitalization. This is done verbally or via referral form. Referrals should be short duration, **not to exceed 2 days**.
- Emergency Inpatient treatment should continue until the patient's safety has stabilized.

*Involuntary hospitalization:*If patients do not agree with plans for hospitalization, involuntary hospitalization may be necessary. However, the clinician should document clearly on the patient medical record and should consult the assigned or duty psychiatrist. Efforts should be initiated to contact family member with in 24 hour of admission. If the patient has no family support, then the higher clinical officer /medical director/ and social workers should be informed to facilitate social support and inform the hospital legal directorate or Police to minimize medico legal litigation.

*Outpatient care:*Patients in whom the risk of suicide is elevated but not imminent (eg, those with depression or alcohol abuse who express a desire to commit suicide but who do not have a specific plan or intent) need aggressive treatment that generally can be in an outpatient clinic.

Useful interventions include:

- Involving family members or people close to the patient to regularly monitor the patient until safety has further stabilized
- Provide patients and caregivers 24-hour access to clinical support in case of urgent need.

- Instruct family members that if the patient decompensates, the patient must return to the emergency department; if the patient refuses, the psychiatrist in charge or the higher clinical officer should be informed.
- Although patients may object to clinicians reaching out to other people for additional history or help in mitigating the risk of suicide, we maintain that safety trumps confidentiality. In addition, patient reluctance regarding clinical contact with family members is a therapeutic issue that should be assessed.
- Restricting access to all lethal means of suicide, particularly firearms and medications – Ask about the availability of firearms and medications, and make them temporarily inaccessible to the patient with the help of family members and the police.
- Communicating a commitment to help, and scheduling enough clinical contact such that the patient feels connected and supported.
- Identifying and avoiding triggers for relapse of suicidal ideation and warning signs.
- Educating patients and caregivers about the disinhibiting effects of alcohol and other drugs.
- Specifying coping strategies and healthy activities to manage or distract one-self from suicidal thoughts.
- Treating psychiatric disorders aggressively.

Safety plan: As part of supporting the patient's ability to avoid suicidal behaviour, clinicians should discuss a safety plan that specifies how patients can cope with recurrent suicidal urges in the future The safety plan is a widely used therapeutic tool. In addition, the extent to which patients can commit to stay safe and use the safety plan provides additional information about their risk for suicidal behaviour, and can thus aid the patient evaluation.

Patients who agree to adhere to a safety plan may still be at high risk; this agreement does not protect patients or clinicians, and is not a substitute for thorough evaluation, sound clinical judgment, and meaningful therapeutic interaction, particularly with impulsive patients.

Underlying factors and mental disorders: Once immediate safety has been ensured, clinicians should address underlying factors, including precipitating events, on-going life difficulties, and mental disorders. See precipitating events and on-going life difficulties and mental disorders.

Clinicians should ensure that patients receive appropriate psychiatric treatment**.** ***Patients discharged from inpatient psychiatric care are at high short-term risk***, particularly if there is a break in the continuity of care.

10.2.4.3. Non-pharmacological Management

- Different approaches of psychotherapy can be used, including cognitive-behavioural therapy (CBT), problem solving therapy, dialectical behavior therapy, or psychodynamic psychotherapy.

10.2.4.4. Pharmacological Treatment

- Most commonly patients with recurrent thought of suicide or suicide attempt are treated with anti-anxiety agents or antidepressants or combinations of anxiolytics and antidepressants. Less frequently they may be treated with antipsychotic medication or mood-stabilizing drugs.
- In many chronically suicidal patients, mood stabilizers are used to lessen the patient's tendency toward emotional over arousal and impulsivity.

Antianxiety Agents

Benzodiazepine is used to help a suicidal patient experiencing heightened levels of anxiety and agitation, a good general plan is to prescribe the drug at a dosage that provides **short-term relief** and to institute treatment that addresses the causes of the emotional difficulties.

Benzodiazepines	**Starting dose (mg/day)**	**Usual dose (mg/day)**	**Maximum dose (mg/day)**
Diazepam	5	5-15	30
Clonazepam	0.5	0.5-2	4
Lorazepam	1	1-8	12

Antidepressant Medications

There are three concernsin the use of antidepressants to treat suicidal patients.

*First, it is important to verify the diagnosis of depression.*Suicidality is not a sufficient criterion for diagnosing depressive illness. There is no firm evidence that antidepressant medication is helpful with suicidality per se and not justified to diagnose depressive disorder without using

adequate criteria according to DSM-5. It is advisable not to assume that suicidal thoughts or actions per se justify this diagnosis.

Second, if antidepressants are indicated, make sure the number of pills in the bottle makes up less than a lethal dose. For SSRIs, lethal dosing is not much of a problem—most individuals would need to take a number of months' supply to get into serious trouble. For tricyclic antidepressants, however, staying below lethal dose generally means administering 1- 2week prescription. Working with pharmacies to promote short prescription plan, and engaging familymembers or friends to help keep the patient supplied with a reasonable amount of medication helps. Most patients may hoard medication prescribed, increasing the risk that if they do overdose, the results will be fatal. Many patients who overdose do so impulsively. The person is angry or upset and often is consuming alcohol. There is very little lead time, sometimes just a matter of a few minutes, between when the person decides to overdose and ingests the medication.

Hence, it is advisable that the pharmacist involved in the treatment use a technique that involves packaging medication in individual wrappings. Un-wrapping each pill might interfere with the impulsivity of the moment and make the situation safer.

*Third, there is potentially troublesome aspect of prescribing antidepressants; particularly the SSRI class of medicines.*There is a possibility that these drugs may have an iatrogenic effect on suicidality in certain populations. Such certain populations warned by FDA include children, adolescents and adults aged 18 to 24 years, taking all antidepressant drugs (FDA 2007). However, the warning issued by 2007 did not advise against the prescription of antidepressants for approved indications, including depressive and anxiety disorders. The warning emphasized that patients 18 to 24 years of age should be informed about the risk of developing suicidality during initial antidepressant treatment (generally the first one to two months). Clinicians should monitor patients closely during initial antidepressant treatment. It is worth noting that depression and certain other serious psychiatric disorders are themselves associated with an increased risk of suicidality.

Table 8: starting and usual dose of antidepressants for the management of suicide

Antidepressants	Starting dose (mg/day)	Usual dose (mg/day)	Maximum dose (mg/day)
Fluoxetine	20	20-40	80
Sertraline	50-100	50-150	200
Amitriptyline	25-50	25-150	300
Imipramine	25-50	25-150	300

Antipsychotic Medications

Some antipsychotics, particularly the first-generation ones, in addition to overdose concerns, have a side-effect profile that can aggravate suicidality. Akathisia and akinesia are the 2 extrapyramidal symptoms that might put the patient to suicidality. Second-generation antipsychotics are less likely to produce akathisia and akinesia, lessening at least that risk of suicide. Clozapine can reduce suicidality in patients with schizophrenia. Furthermore, patientsreported improvement in depression and hopelessness symptoms. Olanzapine is also associated with a decreased risk of suicidal behaviors, although not perhaps as great as that for clozapine.

Table 9: General information of Antipsychotics medications for the management of suicide patients present with psychotic symptoms

Antipsychotics	Starting dose (mg/day)	Usual dose (mg/day)	Maximum dose (mg/day)	Route of administration
Haloperidol	5mg/ml	5-10mg/ml	20mg/ml	IM/IV
Haloperidol	1.5-5mg	1.5-10mg	20mg	PO
Chlorpromazine	25mg/ml	25-50mg/ml	100mg/ml	IM
Chlorpromazine	25-100mg	100-500mg	1000mg	PO
Thioridazine	25-100mg	100-300mg	800mg	PO
Trifluoperazine	1-5mg	5-10mg	20mg	PO

Fluphenazine Decanoate	12.5mg/ml/month	25-50mg/ml/month	100mg/ml/month	IM
Risperidone	2mg	2-6mg	8mg	PO
Olanzapine	5mg	5-10mg	20mg	PO

Table 10: Mood Stabilizers

Mood stabilizers	**Starting dose (mg/day)**	**Usual dose (mg/day)**	**Maximum dose (mg/day)**
Lithium Carbonate	300-600mg	600-1200mg	1800mg
Sodium Valproate	200-600mg	400-1000mg	2500mg
Carbamazepine	200-400mg	400-800mg	1800mg

Electroconvulsive therapy (ECT)

For severely depressed suicidal patients, electroconvulsive therapy frequently provides a rapid response that may be lifesaving in the short term and perhaps in the long term as well.

It is recommended that after acute treatment with ECT, maintenance treatment should continue with psychotropic medication or further ECT.

10.2.5. Prevention

Reducing suicidal immediate risk and maximizing patient safety

A person who has been identified as having a high risk of suicide should never be left alone. Until the mental health service arrives, the person should be confined in a secure location and under constant observation/supervision.

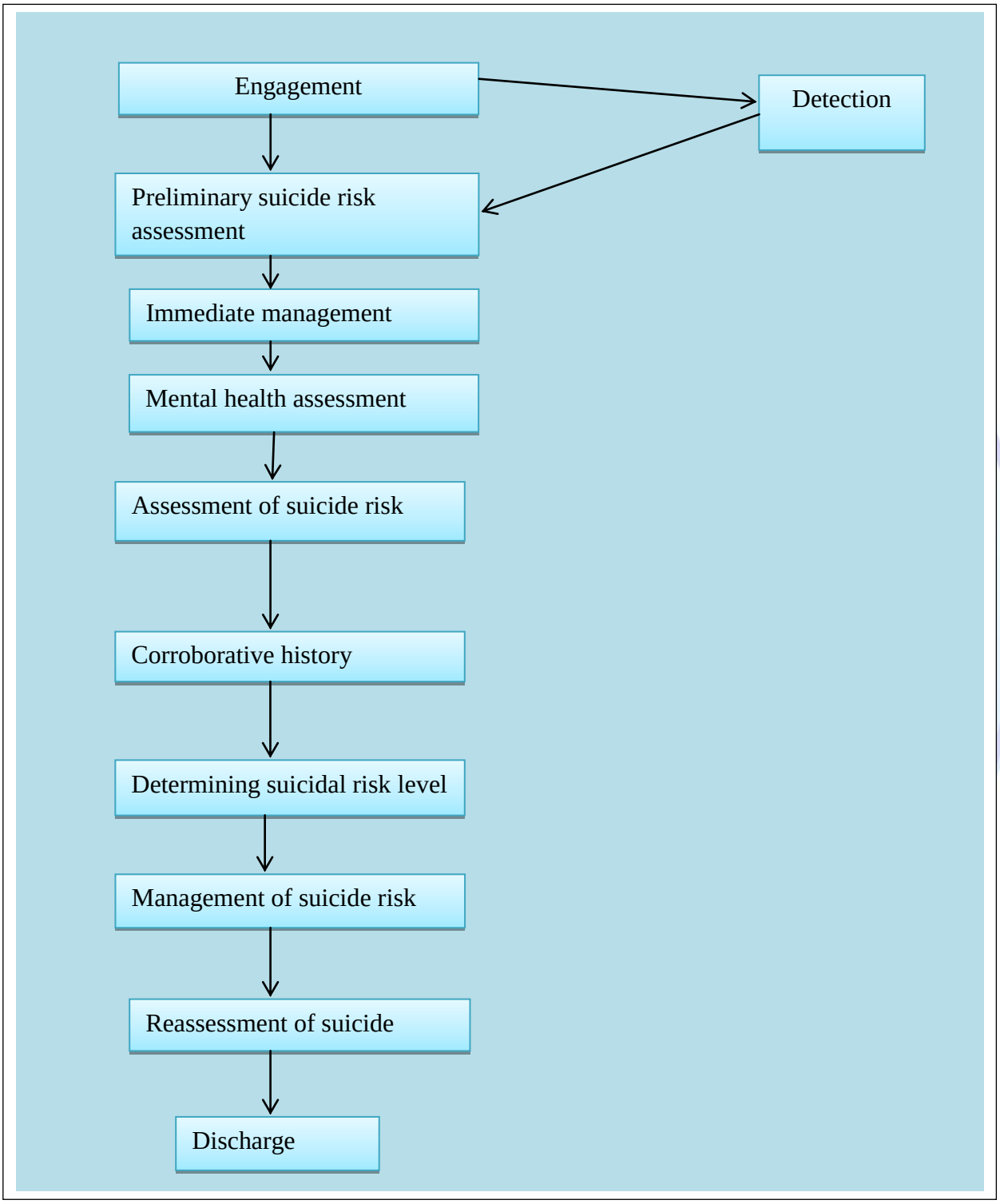


Figure 13: Algorithm for management of suicide (Adopted from NSW Health)

References

1. Quick Guide for Psychiatric Emergencies; 2018, ISBN : 978-3-319-58258-0
2. St. Paul hospital clinical practical guideline for psychiatry treatment, 2019
3. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, text revision. Washington DC, American Psychiatric Association, 2022.
4. Biftu BB, Dachew BA, Tiruneh BT, Guracho YD. Prevalence of suicidal ideation , suicidal attempt and completed suicide in Ethiopia : a systematic review and meta-analysis protocol. 2019;1–5.
5. WHO, Estimates GH. Suicide worldwide in 2019.
6. Emergencies P, Situations T. Kimberly D. Nordstrom Michael P. Wilson.
7. Brent DA, McMakin DL, Kennard BD, et al. Protecting adolescents from self-harm: a critical review of intervention studies. J Am Acad Child Adolesc Psychiatry 2013; 52:1260.
8. Girardi P, Tatarelli R, Lester D. Antidepressants and Suicide Risk : A Comprehensive Overview. 2010;2861–83.
9. American Psychiatric Association. Practice Guideline for the Assessment and Treatment of Patients with Suicidal Behaviors. 2003. https://psychiatryonline.org/guidelines (Accessed on December 04, 2017).
10. Jacobs DG, Baldessarini RJ, Horton L, Ph D, Pfeffer CR. Assessment and Treatment of Patients with Suicidal Behaviors. 2010;
11. NSW Department of Health 2004. Framework for Suicide Risk Assessment and Management. www.health.nsw.gov.au

CHAPTER ELEVEN

11.Drug Induced Movement Disorders and Other Adverse Effects of Medications

11.1. Neuroleptic Malignant Syndrome (NMS)

11.1.1. Introduction

11.1.1.1. Brief description

- Neuroleptic Malignant Syndrome (NMS) is a life-threatening condition linked to the use of dopamine-receptor antagonists or the abrupt discontinuation of dopaminergic medicines.
- Neuroleptic malignant syndrome has been linked to nearly every neuroleptic drug, but it is most typically connected with the high-potent typical antipsychotics such as haloperidol and fluphenazine.

11.1.1.2. Epidemiology

- Incidence rates of NMS range from 0.01% to 3.2% in patients taking antipsychotic medications. In several African nations, including Ethiopia, the incidence of NMS is unclear, and till the development of this guideline there has only been one case report published so far from Ethiopia.
- In terms of onset, 16 % of patients showed signs of NMS within 24 hours of starting a neuroleptic, 66 % within one week, and 96 % within 30 days. Neuroleptic malignant syndrome is uncommon after 30 days of taking a neuroleptic; however, NMS occurred after 30 days in 4% of patients.

11.1.1.3. Causes and risk factors

- Dopamine receptor blockage, which is most commonly caused by an antipsychotic drug, is the major cause of NMS. It is most commonly related with high-potency first-generation neuroleptics, but it can also be caused by other antipsychotics, antiemetics, tricyclic antidepressants, and lithium.

The following are risk factors for NMS:

- The use of high-potency and long-acting neuromuscular depot forms

- Parenteral administration of neuroleptics, higher titration rates, and high total dose of medication
- The use of numerous neuroleptics, or neuroleptic and lithium at the same time
- Abrupt withdrawal of dopaminergic drugs such as levodopa and amantadine, which is used to treat Parkinson's disease
- The use of antipsychotics in patients with catatonia
- Presence of agitation as a clinical feature
- Dehydration
- Restraint
- Iron deficiency

11.1.2. Clinical characteristics

- People with NMS usually acquire symptoms after one to three days of being exposed to an antipsychotic medicine. Prior to the beginning of NMS, nearly all case series of NMS patients have reported physical exhaustion and dehydration.
- Neuroleptic malignant syndrome presents with extreme elevations in temperature and generalized lead pipe rigidity which could be unresponsive to anti-Parkinsonian medications.
- There could be other features due to rigidity such as tremor, sialorrhea, akinesia, dystonia, trismus, myoclonus, dysarthria, dysphagia and rhabdomyolysis.
- Creatine kinase elevation of at least four times the upper limit of normal is commonly seen.
- NMS can also present with changes in mental status, characterized by altered consciousness ranging from stupor to coma.

11.1.3. Diagnosis and investigations

11.1.3.1. Diagnosis and differential diagnosis

- The diagnosis of NMS can be suspected by the temporal onset of characteristic symptoms and signs following treatment by antipsychotic medications. The diagnosis can be made based on the criteria given below.

The presence of criteria 1-7

1. Exposure to a dopamine antagonist or withdrawal of a dopamine agonist within the 72 hours preceding onset of symptoms
2. Hyperthermia on at least 2 occasions, of greater than 38°C
3. Rigidity
4. Mental status alteration, either reduced or fluctuating level of consciousness
5. Elevation of creatine kinase of at least 4 times the upper limit of normal
6. Sympathetic system lability with at least 2 of the following parameters:
    1. Blood pressure elevation, either systolic or diastolic, ≥ 25% above baseline
    2. Blood pressure fluctuation ≥ 20 mm Hg diastolic or 25 mm Hg systolic change occurring within 24 hours
    3. Diaphoresis
    4. Urinary incontinence
7. Hyper-metabolism, defined as heart rate increase ≥ 25% over baseline and respiratory rate increase ≥50% over baseline

Adopted from the International Multidisciplinary Panel of Experts Proposed Diagnostic Criteria for NMS (Using Delphi Method)

- Differential diagnosis is of prime importance because NMS is a diagnosis of exclusion. Neuroleptic malignant syndrome should be distinguished from:
    - Central nervous system infections
    - Inflammatory or autoimmune conditions
    - Status epilepticus
    - Subcortical structural lesions
    - Pheochromocytoma
    - Thyrotoxicosis

- Tetanus
- Heat stroke
- Serotonin syndrome
- Parkinsonian hyperthermia syndrome which follows abrupt discontinuation of dopamine agonists
- Alcohol or sedative withdrawal
- Malignant hyperthermia which occurs during anesthesia
- Hyperthermia associated with abuse of stimulants and hallucinogens
- Atropine poisoning from anticholinergics
- Malignant catatonia in patients with schizophrenia or a mood disorder

11.1.3.2. ***Laboratory and imaging***

- Patients with NMS may have leukocytosis, metabolic acidosis, hypoxia, decreased serum iron concentration, and elevations in serum muscle enzymes and catecholamines. The following laboratory and imaging tests are recommended:
  - Complete blood count (CBC)
  - Sedimentation rate (ESR)
  - Serum electrolytes
  - Serum urea and Creatinine
  - Serum transaminases
  - Creatine phosphokinase level
  - Urinalysis for myoglobinuria
  - Arterial or venous blood gas to screen for metabolic acidosis
  - Electroencephalogram (EEG)
  - CSF analysis (when indicated)
  - Brain magnetic resonance imaging (MRI) (when indicated)
  - Serum lithium level
  - Urine drug screen

11.1.4. Treatment of neuroleptic malignant syndrome (NMS)

11.1.4.1. Goals of treatment

Treatment for neuroleptic malignant syndrome has the following goals:

- Withdrawing the offending drug
- Providing supportive medical treatment
- Maintaining a stable cardio-respiratory system
- Reversing the hypo-dopaminergic state

11.1.4.2. General principles of treatment

- Neuroleptic malignant syndrome is a medical emergency that can result in substantial morbidity or death if not diagnosed and treated promptly. A multidisciplinary team approach should be followed in the treatment of NMS with possible involvement of psychiatrist, neurologist, internist, and emergency and critical care specialist when appropriate. The following measures should be taken:
  - The offending drug must be withdrawn immediately
  - Initiate supportive medical therapy
  - Maintain a stable cardiorespiratory system
  - Reverse the hypo-dopaminergic state

11.1.4.3. Non-pharmacologic treatment

Supportive medical therapy

- Supportive medical therapy is the mainstay of management of NMS. This includes rapid cooling as well as the correction of volume shortages and any electrolyte imbalances. Volume resuscitation should be aggressive, especially given that most patients with NMS are dehydrated in the acute phase of the illness. Recent reports suggest that alkalinized fluids or even bicarbonate loading may be of particular benefit in preventing renal failure.
- Due to chest wall rigidity, patients are at risk for cardiac dysrhythmias and respiratory failure. To maintain a stable cardiorespiratory system the use of mechanical ventilation, antiarrhythmic drugs, or pacemakers could be required. In such cases, the patient should be treated in an intensive care unit (ICU) facility.
- Intensive medical care should include close monitoring for consequences such as cardiorespiratory failure, renal failure, aspiration pneumonia, and coagulopathies, as well as cardiac, respiratory, and renal function support.

Electroconvulsive therapy (ECT)

- In refractory cases, electroconvulsive therapy (ECT) has been reported to be a successful treatment. Electroconvulsive therapy may be effective and should be strongly considered in the following instances:
  - If symptoms are refractory to supportive care and pharmacotherapy
  - If idiopathic malignant catatonia due to an underlying psychotic disorder cannot be excluded
  - If the patient has persistent residual catatonia and parkinsonism after resolution of the acute metabolic symptoms of NMS
- A typical ECT regimen for acute NMS would include six to 10 treatments with bilateral electrode placement. ECT is a relatively safe treatment in NMS, although use of succinylcholine during anesthesia should be carefully considered in patients with severe rhabdomyolysis to avoid the risk of hyperkalemia and cardiovascular complications.

11.1.4.4. Pharmacologic treatment

- There are reports that benzodiazepines, administered orally or parenterally, may ameliorate symptoms and hasten recovery in NMS, particularly in milder cases. Therefore, a trial of Lorazepam, starting with 1–2 mg parenteral, is a reasonable first-line intervention in patients with acute NMS, particularly in those with milder and primarily catatonic symptoms.
- Several dopaminergic drugs, including Bromocriptine may reverse Parkinsonism in NMS and have been reported in case reports and meta-analyses to reduce time to recovery and halve mortality rates when used alone or in combination with other treatments. The starting dose of Bromocriptine is 2.5 mg orally (or via nasogastric tube) two or three times a day, increased to a total daily dose of 45 mg if necessary. Bromocriptine can worsen psychosis and hypotension. It also may precipitate vomiting and thus should be used carefully in patients at risk of aspiration.
- Because of its efficacy in anesthetic-induced malignant hyperthermia, the muscle relaxant Dantrolene has been used in the treatment of NMS. Dantrolene may be useful only in cases of NMS with extreme temperature elevations, rigidity, and true hyper-metabolism.
- Generally, rapid reversal of the hyperthermia and rigidity is observed in patients treated with Dantrolene, but symptoms may return if treatment is discontinued prematurely. Dantrolene can be combined with benzodiazepines or dopamine agonists, but it should not be co-administered with calcium channel blockers, as cardiovascular collapse can occur. Typical

dosing of intravenous Dantrolene in the treatment of NMS is 1–2.5 mg/kg body weight administered initially, followed by 1 mg/kg every 6 hours. If rapid resolution of the fever and rigidity is observed, tapering or switching to oral Dantrolene after the first few days is possible. Side effects may include impairment of respiratory or hepatic function.

Resuming antipsychotic treatment after NMS

- Following recovery from an NMS episode, restarting antipsychotic therapy has been linked to a 30% chance of getting NMS again. However, most individuals who need antipsychotic medication can be treated safely if precautions are taken. The following measures should be taken:
  - Antipsychotic indications should be clearly documented
  - Alternative medications should be considered
  - Risk factors should be reduced
  - At least 2 weeks should pass after NMS recovery before re-challenge
  - Low doses of low-potency conventional antipsychotics or atypical antipsychotics should be initiated
  - Dose should be titrated gradually after a test dose
  - Patients should be closely monitored.

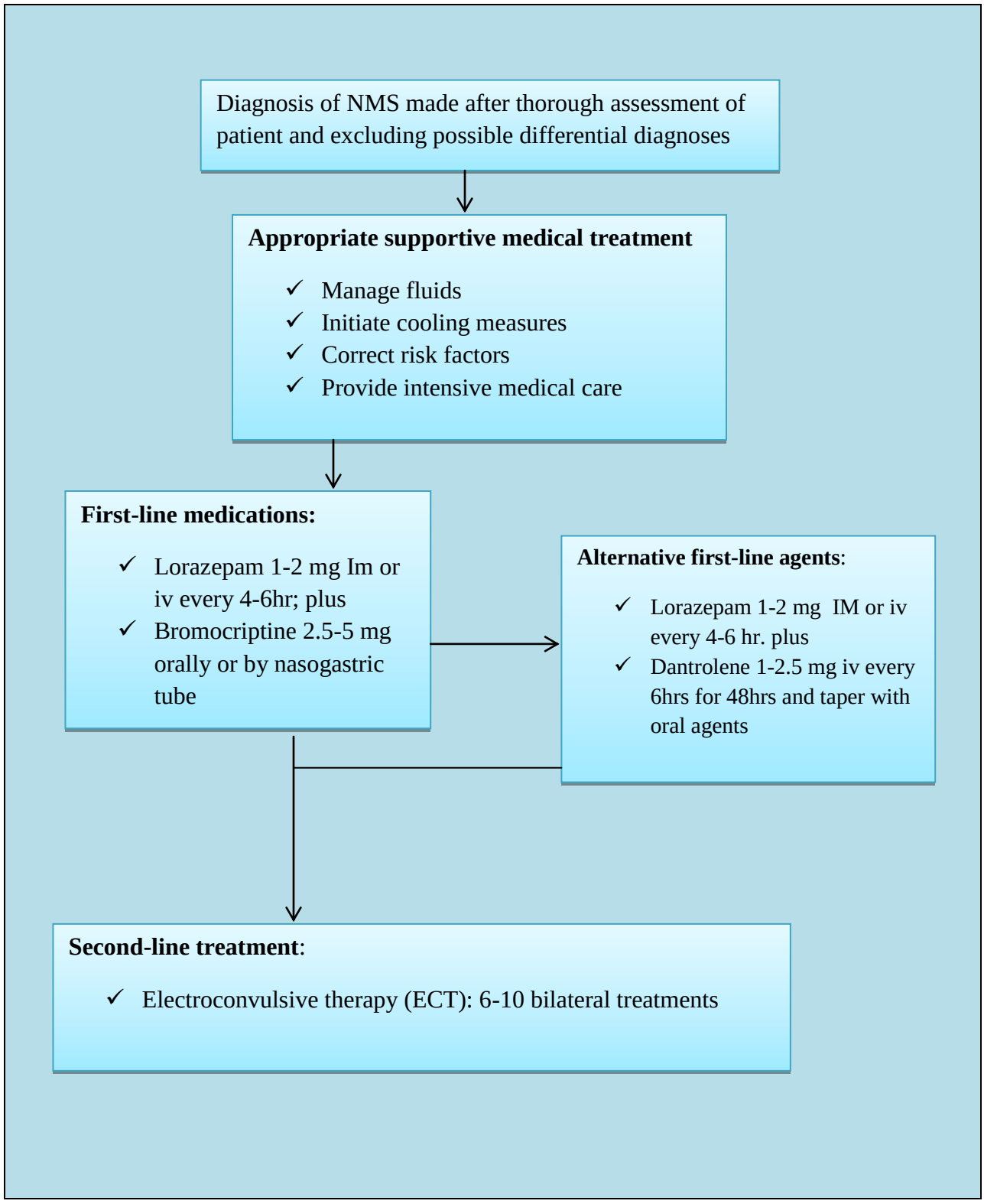


Figure 14: Algorithm for the treatment of neuroleptic malignant syndrome (NMS)

References

1. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, text revision. Washington DC, American Psychiatric Association, 2022.
2. Jeffrey R. Strawn, Paul E. Keck, Jr., Stanley N. Caroff. Neuroleptic Malignant Syndrome. *Am J Psychiatry 164:6, June 2007.*
3. Simon LV, Hashmi MF, Callahan AL. Neuroleptic Malignant Syndrome. [Updated 2021 Sep 19]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482282/.
4. Lang FU, Lang S, Becker T, Jäger M. Neuroleptic malignant syndrome or catatonia? Trying to solve the catatonic dilemma. Psychopharmacology (Berl). 2015 Jan;232(1):1-5. doi: 10.1007/s00213-014-3807-8. Epub 2014 Nov 20. PMID: 25407348.
5. Oruch R, Pryme IF, Engelsen BA, Lund A. Neuroleptic malignant syndrome: an easily overlooked neurologic emergency. Neuropsychiatr Dis Treat. 2017 Jan 16;13:161-175. doi: 10.2147/NDT.S118438. PMID: 28144147; PMCID: PMC5248946.
6. Fekadu A, Wakwoya A. Neuroleptic malignant syndrome: a case report. Ethiop Med J. 1999 Jul;37(3):195-8. PMID: 11957317.
7. Bristow MF, Kohen D. Neuroleptic malignant syndrome. Br J Hosp Med. 1996 Apr 17-30;55(8):517-20. PMID: 8732227.
8. Tormoehlen LM, Rusyniak DE. Neuroleptic malignant syndrome and serotonin syndrome. HandbClin Neurol. 2018;157:663-675. doi: 10.1016/B978-0-444-64074-1.00039-2. PMID: 30459031.
9. Castillo E, Rubin RT, Holsboer-Trachsler E. Clinical differentiation between lethal catatonia and neuroleptic malignant syndrome. Am J Psychiatry. 1989 Mar;146(3):324-8. doi: 10.1176/ajp.146.3.324. PMID: 2645794.
10. Park, J., Tan, J., Krzeminski, S., Hazeghazam, M., Bandlamuri, M., & Carlson, R. W. (2017). Malignant Catatonia Warrants Early Psychiatric-Critical Care Collaborative Management: Two Cases and Literature Review. *Case reports in critical care, 2017*, 1951965. https://doi.org/10.1155/2017/1951965

11. Sienaert P, van Harten P, Rhebergen D. The psychopharmacology of catatonia, neuroleptic malignant syndrome, akathisia, tardive dyskinesia, and dystonia. HandbClinNeurol. 2019;165:415-428. doi: 10.1016/B978-0-444-64012-3.00025-3. PMID: 31727227.
12. vanRensburg, R., &Decloedt, E. H. (2019). An Approach to the Pharmacotherapy of Neuroleptic Malignant Syndrome. *Psychopharmacology bulletin*, *49*(1), 84–91.
13. Ware MR, Feller DB, Hall KL. Neuroleptic Malignant Syndrome: Diagnosis and Management. Prim Care Companion CNS Disord. 2018 Jan 4;20(1):17r02185. doi: 10.4088/PCC.17r02185. PMID: 29325237.
14. Wijdicks E. (2019). Neuroleptic malignant syndrome - UpToDate. www.uptodate.com › contents › neuroleptic-malignant-syndrome.
15. Fink M. & Taylor M. (2003).Catatonia: A clinician's guide to diagnosis and treatment|Mental health ...Cambridge University Press ›.

11.2. Acute dystonia reaction

11.2.1. Introduction

11.2.1.1. Brief description

- Dystonic reactions are reversible extrapyramidal side effects that can occur after administration of antipsychotic, antidepressant and antiemetic drugs or after increases in the doses. Symptoms may begin immediately or can be delayed hours to days. Although a wide variety of medications can elicit symptoms, the typical antipsychotics are most often responsible.
- Dystonic reactions are characterized by abnormal and prolonged contraction of a specific group of muscles. The reactions may develop within a few days of starting or raising the dosage of a medication (e.g. a neuroleptic) or after reducing the dosages of a medication which was used to treat extrapyramidal symptoms. Sometimes the addition or withdrawal of a drug which has drug-drug interactions with antipsychotics could cause dystonic reactions by decrease of enzyme induction, or by causing enzyme inhibition. For example, carbamazepine is an enzyme inducer and its withdrawal could result in increase in serum levels of an antipsychotic such as haloperidol.
- Dystonic reactions affect muscles of the face, neck, trunk, pelvis, extremities, and even the larynx. They are characterized by intermittent spasmodic or sustained involuntary

contractions of the muscles. Although dystonic reactions are rarely life threatening, they often cause distress for patients and families, as well as aversions to subsequent treatment by antipsychotic medications.

11.2.1.2. Epidemiology

- The incidence of acute dystonic reactions varies according to individual susceptibility, drug identity, dose, and duration of therapy. The actual incidence of dystonic reactions is unknown, owing to misdiagnosis and underreporting. However, clinical practice shows that acute dystonia is not a rare condition, and an important cause of non-compliance to treatment using antipsychotic drugs.

11.2.1.3. *Causes and risk factors*

The causes and risk factors for acute drug-induced dystonia include the following:

- Family history of dystonia
- Recent history of cocaine or alcohol use
- Treatment with a potent dopamine D2 receptor antagonist (e.g. Fluphenazine, Haloperidol)
- Rapid escalation of dose of typical antipsychotics
- Young age
- Male sex
- Previous history of acute dystonia

11.2.2. Clinical features

- Acute, medication-induced dystonia can be detected in patients who exhibit abnormal posturing or muscular spasms within seven days of initiating drug treatment or following a quick rise in the dose of a medicine.
- About 50% of dystonia reactions occur within 48 hours of initiation of treatment, and 90% occur within 5 days.
- The commonly involved muscles are muscles of the eye (resulting in oculogyric crisis), the muscles of the neck (resulting in torticolis, anterocolis or retrocolis), the muscles of the jaw (resulting in trismus), the muscles of the trunk (resulting in opistotonus), as well as muscles of the head and limbs.

- There could be upper airway obstruction from pharyngeal muscle spasms or laryngospasm, which is rare but potentially life-threatening. Other severe presentations of acute dystonia may result in temporomandibular joint dislocation or oropharyngeal dysphagia.

11.2.3. Diagnosis and investigations

11.2.3.1. *Diagnosis and differential diagnosis*

- Diagnosis is suspected by the occurrence of the characteristic clinical features in a person who is on treatment by a drug which is known to cause dystonic reaction.
- Medication-induced acute dystonia must be distinguished from other similar neurologic conditions.

Important differential diagnoses to consider include:

- Tetanus
- Strychnine poisoning
- Carpopedal spasm following hyperventilation, hypocalcaemia and hypomagnesaemia
- Primary neurological causes such as Wilson's disease

- Clear description of association of symptoms with the use of medications with potential risk favors diagnosis of medication-induced acute dystonia. Improvements with dose decrease or discontinuation of the offending drug can be evidence of the diagnosis of medication-induced acute dystonia. Likewise, improvement of dystonic signs and symptoms after administration of the anticholinergic agent Trihexphenidyl (Benzhexol) can be used as evidence in favor of the diagnosis of medication-induced acute dystonia.

- Anticholinergic toxicity may be confused with dystonia. Do not administer anti-muscarinic agents in questionable cases. Oro-pharyngeal infections and upper airway obstruction may also have a presentation similar to acute drug-induced dystonia and they should be ruled out when suspected.

11.2.3.2. Laboratory and imaging

- The diagnosis is usually made by history and physical examination. A history of medication exposure is usually obtained. Even when a supporting history is not obtained, the clinical picture alone is enough to strongly suggest the diagnosis. A predictable, rapid resolution of symptoms following treatment with Trihexyphenidyl confirms the diagnosis. In most cases, laboratory and imaging tests are not needed.

11.2.4. Treatment

11.2.4.1. Goals of treatment

The goals of treatment for medication-induced acute dystonia are:

- To relieve the patient of the painful and distressing situation caused by the dystonic reaction
- To prevent serious complications such as laryngospasm, damage to the tongue, etc
- To identify and make changes regarding the offending drug (e.g., dose reduction, discontinuation, shift, etc)
- To sustain symptomatic relief and prevent similar reactions in the future

11.2.4.2. General principles of treatment

- When there is any doubt of differential diagnosis it is reasonable to treat as an acute dystonic reaction in the first instance, and investigate further if there is no response. In cases of suspected anticholinergic overdose, however, use of diazepam intravenously or an antihistamine may be preferred to administering anticholinergic agents.

11.2.4.3. Non-pharmacologic treatment

- Non-pharmacologic treatments are rarely are required in cases of acute dystonia.
  - Securing the airway is rarely necessary. However, urgent pharmacologic measures should be taken since laryngeal and pharyngeal dystonic reactions may place the patient at risk of imminent respiratory arrest.

11.2.4.4. Pharmacologic treatment

- Dystonia responds promptly to anticholinergic drugs and anticholinergics are the first-line treatment in mild to moderate cases.
  - The anticholinergic drugs Trihexyphenidyl and Benztropine are effective.
  - Most patients respond within 5-15 minutes of administration of anticholinergic drugs.
  - If there is no response after the first dose of an anticholinergic drug treatment, the dose can be repeated after 30 minutes of oral or sublingual administration.
- Trihexyphenidyl (Benzhexol) can be administered orally or by sublingual route at a dose of 2-5 mg. The dose can be repeated after 30 minutes if there is no response. Benztropine can be administered at a dose of 1-2 mg orally, intramuscularly or intravenously.

- Antihistamines can be used as alternatives to anticholinergic drugs as first-line. Diphenhydramine 1–2 mg/kg up to 100 mg by slow intravenous injection or promethazine, 25–50 mg intravenously or intramuscularly have been proved to be effective. Antihistamines may be a useful alternative for patients who have both dystonia and significant anticholinergic symptoms from antipsychotic drugs.
- Diazepam, 5–10 mg intravenously, has been used as second-line for the rare patient who does not completely responded to the more specific antidotes. In severe distress, or when there is risk for respiratory arrest due to laryngospasm, the use of intravenous diazepam is warranted as first line treatment. A patient in severe acute dystonia should be treated with diazepam intravenous 5-10 mg, which can be repeated after 10 minutes if no response.
- To prevent recurrence, Trihexyphenidyl or Benztropine should be taken orally twice daily for the next 2- 3 days once the patient has recovered from the acute dystonic reaction.
- After treatment of severe acute dystonia by intravenous diazepam, Trihexyphenidyl and benztropine can be given at the recommended doses twice daily for 2- 3 days. At the same time removal of the cause of the dystonia reaction should be made. This can be done by reducing the dose of the antipsychotic (or discontinuing or switching any other offending drug) which caused the dystonic reaction to levels below the dose causing dystonia.

11.2.4.5. Prevention

- Prevention of acute dystonia is the most important management. Dystonic reaction can be prevented by judicious use of antipsychotic drugs. Antipsychotic drugs with potential risk for acute dystonia should be initiated at lower doses. Dose escalation of the antipsychotic drug should be made by little amounts and less frequently. The best predictor of an acute dystonic reaction is a previous history of acute dystonia and patients should not be re-exposed to the same drug. It may be preferable to give those patients drugs with minimal risk for acute dystonia.
- Anti-emetics should be avoided in children, especially for short-term problems such as gastroenteritis. Instead, antihistamines such as promethazine should be considered.

- Drug-induced dystonia can be avoided by combining antipsychotic medicines with anticholinergic agents during the first four to seven days of treatment, or by starting treatment with atypical antipsychotics.

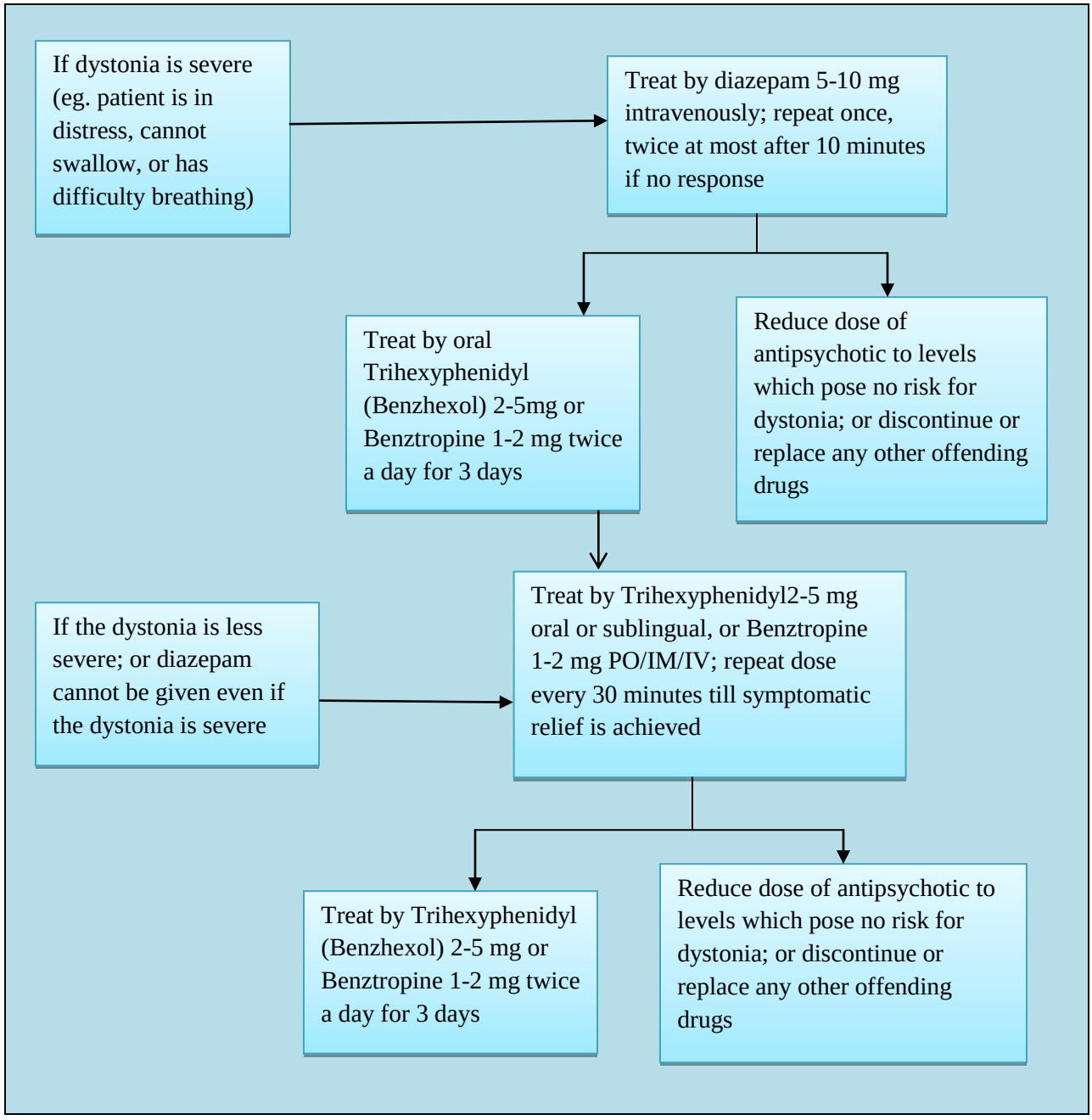


Figure 15: Algorithm for treatment of medication-induced acute dystonia

References

1. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, text revision. Washington DC, American Psychiatric Association, 2022.
2. Diane Campbell. The management of acute dystonic reactions. Aust Prescr 2001;24:19–20
3. Sadock, B. J., Sadock, V. A., & Ruiz, P. Kaplan & Sadock's synopsis of psychiatry: Behavioral sciences/clinical psychiatry (Eleventh edition). Philadelphia: Wolters Kluwer; 2015.
4. van Harten, P. N., Hoek, H. W., & Kahn, R. S. (1999). Acute dystonia induced by drug treatment. *Bmj*, *319*(7210), 623-626.
5. Rupniak, N. M. J., Jenner, P., & Marsden, C. D. (1986). Acute dystonia induced by neuroleptic drugs. *Psychopharmacology*, *88*(4), 403-419.
6. American Psychiatric Association (APA) (2013). Diagnostic and Statistical Manual of Psychiatric Disorders; 5th edition
7. Kanburoglu, M. K., Derinoz, O., Cizmeci, M. N., & Havali, C. (2013). Is acute dystonia an emergency? Sometimes, it really is!. *Pediatric Emergency Care*, *29*(3), 380-382.
8. Diane Campbell. The management of acute dystonic reactions. Aust Prescr 2001;24:19–20
9. J Michael Kowalski.Medication-Induced Dystonic Reactions. Medscape; Updated: Aug 10, 2020
10. Reccoppa, L., Welch, W. A., & Ware, M. R. (1990). Acute dystonia and fluoxetine. *The Journal of clinical psychiatry*.
11. Oyewole AO, Adelufosi AO, Abayomi O. Acute dystonic reaction as medical emergency: A report of two cases. Ann Med Health Sci Res 2013; 3:453-5.
12. Vena J, Dufel S, Paige T. Acute olanzapine-induced akathisia and dystonia in a patient discontinued from fluoxetine. The journal of emergency medicine. 2006 Apr 1;30(3):311-7.

13. Arana, G. W., Goff, D. C., Baldessarini, R. J., & Keepers, G. A. (1988). Efficacy of anticholinergic prophylaxis for neuroleptic-induced acute dystonia. *The American journal of psychiatry*.
14. Aguilar, E. J., Keshavan, M. S., Martínez-Quiles, M. D., Hernández, J., Gómez-Beneyto, M., & Schooler, N. R. (1994). Predictors of acute dystonia in first-episode psychotic patients. *The American journal of psychiatry*.

11.3. Tardive dyskinesia (TD)

11.3.1. Introduction

11.3.1.1. ***Brief description***

- Tardive dyskinesia (TD) is an involuntary movement syndrome that develops in people who are exposed to neuroleptic drugs.
- Tardive dyskinesia results controllable stiff, jerky motions of the face, perioral areas, the neck, the back and the extremities.
- It may manifest by blinking of the eyes, sticking out the tongue, or waving of the arms.
- Not everyone who takes an antipsychotic medication will develop TD. However, if it occurs, it is sometimes permanent.
- Extremely distressing and disabling TD reactions can occur to patients. The movements stop during sleep and are aggravated during wake hours and particularly during emotional disturbance.

11.3.1.2. ***Epidemiology***

- The estimated prevalence of TD among persistently neuroleptic treated individuals ranges from 15% to 32.4% ().
- In younger individuals the annual incidence is 4 to 5%. Although the incidence and prevalence of TD seems to be lower with second generation antipsychotics (SGAs), TD is still commonly seen in clinical practice. The prevalence of drug induced TD in Ethiopia ranges from 9.5% to 15.4% ().

11.3.1.3. Causes and risk factors

- Dopamine receptor blocking medicines, such as antipsychotics, have been identified as the cause of the illness. While data suggests that patients taking second-generation antipsychotics have a lower chance of developing TD than those taking first-generation antipsychotics, the

reduction is not as significant as thought previously. The risk factors for developing TD include the following:

- Aging
- Female sex
- Preexisting mood disorder
- Cognitive disturbance
- Alcohol or substance abuse
- Higher dose and longer use of antipsychotic drugs
- Treatment with typical antipsychotics
- Presence of negative symptoms in schizophrenia
- Use of lithium or antiparkinsonian medications
- "Organic" brain dysfunction, or damage
- Diabetes mellitus
- Seropositive for HIV
- Early extrapyramidal side effects

11.3.2. Clinical Characteristics

- Tardive dyskinesia (TD) is characterized by the occurrence of involuntary athetoid or choreiform movements lasting at least a few weeks.
- The disorder characteristically occurs in patients exposed to neuroleptic medications within a few months or years.
- In older persons, symptoms may develop after a shorter period of medication use.
- The abnormal movements generally include the tongue, lower face and jaw, the trunk and the extremities.
- Sometimes the abnormal movements may involve muscles of the pharynx and diaphragm.

The abnormal movements may appear after discontinuation, or change or reduction in dosage of neuroleptic medications;

- Such presentation is called neuroleptic withdrawal-emergent dyskinesia.
- Withdrawal-emergent dyskinesia is usually time-limited and lasts less than 4-8 weeks; therefore, if the dyskinesia persists beyond this period, the diagnosis of tardive dyskinesia can be considered.

11.3.3. Diagnosis and investigation

11.3.3.1. ***Diagnosis and differential diagnosis***

- Documentation differential diagnosis consideration is necessary to show that correct diagnosis of the disorder is made. Tardive dyskinesia must be distinguished from other neurologic conditions which have similar manifestations. Clear description of association of symptoms with the use of medications favors diagnosis of tardive dyskinesia. The following conditions should be considered and excluded as possible differential diagnoses:
  - Toxicity from hallucinogens
  - Conversion disorder
  - Compulsions
  - Dyskinesias secondary to drugs and substances (caffeine, chloroquine, estrogen, lithium, phenytoin)
  - Dyskinesias secondary to schizophrenia
  - Factitious disorder
  - Fahr syndrome
  - Hyperthyroidism
  - Hypoparathyroidism
  - Malingering
  - Meige syndrome
  - Polycythemia rubravera
  - Poorly fitting dentures
  - Spontaneous dyskinesias
  - Sydenham's chorea
  - Syphilis
  - Systemic lupus erythematosus
  - Wilson disease
  - Dementia in Parkinson's disease
  - Dementia in progressive supranuclear palsy

11.3.3.2. ***Laboratory and imaging***

- Unless clearly indicated by other concurrent conditions which necessitate laboratory and imaging studies as suggested by history and physical examination findings, laboratory and imaging studies are not helpful for diagnosis of the disorder. However, as part of comprehensive evaluation of the patient, complete medical history and physical examination (including neurologic examination) should be conducted. The decision about which laboratory or imaging investigation to choose depends on the findings of the history and physical examination.

- At onset of treatment, the minimal baseline workup should be done and documented. This may include:
  - Complete blood count (CBC), sedimentation rate (ESR), serum urea and creatinine, liver enzymes, VDRL and fasting blood sugar (FBS). When indicated, additional investigations can be done including urine drug screen, thyroid function tests (T3, T4, TSH), serum electrolytes, antinuclear antibody titer, and brain MRI.

11.3.4. Treatment

11.3.4.1. Goals of treatment

- The treatment goals for patients with tardive dyskinesia (TD) are:
  - Prevention and halting the progress of tardive dyskinesia symptoms and signs
  - Reducing TD symptoms and signs, and give symptomatic relief
  - Reducing further risk by switching to drugs with less risk of TD when antipsychotic medication use is a must

11.3.4.2. General principles of treatment

- Health education should be given to patient about the possibility of permanence of TD symptoms and about how to cope. At the same time giving the patient hope that there are treatment measures to stop progression of symptoms and possibly to reverse the symptoms of TD.
- The management of TD may take time and the patient should be given hope and realistic assurances continually.
- It is important to understand that improvement in symptoms may take months or years to occur.
- The most important principle of treatment of TD is removal of the causative drug. Measures to alleviate distress from TD symptoms should be taken to improve functional status and increase quality of life.
- In cases in which the use of antipsychotic is mandatory to control psychosis, the agent with least risk to cause TD should be administered. Throughout the course of TD treatment, the Abnormal Involuntary Movement Scale (AIMS) should be used to monitor changes in the severity of TD.

11.3.4.3. Non-pharmacologic

- Brain stimulation techniques can be used as non-pharmacologic measures. However, there is limited evidence for their effectiveness.

- The use of globus pallidus interna deep brain stimulation (GPi- DBS) has been suggested for treatment of TD. The evidence suggests GPi-DBS could be considered in cases where psychiatric symptoms are stabilized but TD symptoms are severe and distressing and not responsive to medical treatment. However, the availability of this treatment makes its use unlikely.

11.3.4.4. Pharmacologic treatment

- In some patients who develop tardive dyskinesia (TD) and do not have a psychotic disorder slow and gradual tapering of the medication can be attempted. However, the risk of worsening their mental health condition should be strongly considered; discussion with the patient and care givers is necessary to make such a decision.
- Patients must be warned that TD symptoms may worsen transiently as medication dosages are lowered (withdrawal emergent dyskinesias). In some cases, the signs of TD may take months or years to remit after stopping antipsychotic medication and may never completely resolve.

NB: The use of high doses of antipsychotic medication tomask TD is not recommended.

- In most patients with schizophrenia, however, stopping antipsychotic therapy is not an option for the treatment of TD due to the increased risk of relapse. In such cases, there are important measures to be taken:
  - If anticholinergic agents such as Trihexyphenidyl are co-prescribed with antipsychotic medication in a patient with TD, they should be withdrawn
  - Switching antipsychotic treatment to a second generation antipsychotic (SGA) with a lower D2 affinity, such as clozapine or Quetiapine
  - Vitamin E use does not lead to clinically important improvements in TD once it is established but may protect against deterioration of TD symptoms

The vesicular monoamine transporter-2 (VMAT-2) inhibitors

- The vesicular monoamine transporter 2 (VMAT-2) inhibitors exert their clinical action by depleting neurotransmitters such as dopamine in nerve terminals in the central nervous system. There are three VMAT2 inhibitor drugs commonly used in clinical practice. They are

Tetrabenazine, Deutetrabenazine and Valbenazine. Valbenazine has been approved for use in treatment of TD.

- There is good evidence of benefit for Valbenazine as a treatment for TD. There are recommendations for the use of Valbenazine as first-line treatment for TD; however, cost and availability issues preclude its use as first line treatment in the Ethiopian context.
- Valbenazine is initiated at oral dose of 40 mg once per day. After a week, the dose is increased to 80 mg oral dose once per day. There have been reports of ≥ 50% mean change in scores of the Abnormal Involuntary Movement Scale (AIMS) after two weeks of treatment using Valbenazine.
- Reports also showed sustained improvement in AIMS scores with continued treatment. There was decline in TD signs after treatment with Valbenazine was discontinued; this could mean that the treatment should continue to maintain symptom reduction.

11.3.4.5. Adverse effects of Valbenazine

The two most important adverse effects of Valbenazine are

- Somnolence and QT prolongation.
- Somnolence is the commonest adverse effect reported. Therefore, there are precautions that should be undertaken to manage these adverse effects.
- Due to somnolence, patients taking Valbenazine should not perform activities that require mental alertness such as operating machinery until they are sure that they tolerated it.
- To prevent QT prolongation and possible arrhythmia, baseline electrocardiograph (EKG) should be performed, and caution should be in place for those at risk.
- Avoid Valbenazine use in patients with congenital long QT syndrome or with arrhythmias associated with a prolonged QT interval.

11.3.4.6. Drug-drug interactions with Valbenazine

Table 11: Considerations for drug-drug interactions with Valbenazine

Factors	Dose adjustments for Valbenazine
Use of monoamine inhibitors (MAOIs) with Valbenazine (Examples include: isocarboxazid (Marplan, Validus Pharmaceuticals), phenelzine, selegiline)	Avoid concomitant use of Valbenazine with MAOIs

Use of strong CYP3A4 inducers with valbenazine (Examples include: rifampin, carbamazepine, phenytoin)	Avoid concomitant use with Valbenazine
Use of strong CYP3A4 inhibitors with valbenazine (Examples include: itraconazole, ketoconazole, clarithromycin)	Dose reduction to 40 mg/d of valbenazine recommended
Use of strong CYP2D6 inhibitors with valbenazine (Examples include: paroxetine, fluoxetine, quinidine)	Consider dose reduction of valbenazine based on tolerability

11.3.4.7. Use of Valbenazine in special populations

Pediatric age group: There are no controlled trials done to establish the efficacy and safety of use of Valbenazine in pediatric populations.

Geriatric patients: No dosage adjustments of Valbenazine are recommended in this population group.

Patients with hepatic impairment: In moderate to severe hepatic impairment, reduce the dose of Valbenazine to 40 mg/d.

Patients with renal impairment: Valbenazine has no primary renal metabolism. Therefore, no dosage adjustment is necessary for mild to moderate cases of renal impairment (Creatinine clearance 30-90 mL/min). However, valbenazine use is not recommended during severe renal impairment.

Pregnancy and lactation: There is limited data of safety during pregnancy. There is the possibility that Valbenazine use during pregnancy may cause harm to the fetus. Likewise, breastfeeding is not recommended during treatment with Valbenazine and until after 5 days after the last dose.

11.3.5. Other measures

- In patients failing to respond to more established alternative treatments for TD, such as switching to an SGA or prescribing VMAT-2 inhibitors, short-term treatment with vitamin

B6 may be considered. However, the dose and duration for optimal benefits while maintaining safety have not been established. There are inconclusive reports of benefit from benzodiazepines, particularly clonazepam; clinical experience also supports the benefit of clonazepam in combination with clozapine. However, the routine use of benzodiazepines could have potential adverse effects, and therefore, its use should be judicious.

11.3.6. Prevention

- Tardive dyskinesia (TD) is a relatively common and potentially disabling condition.
- The prevention and treatment of TD remain important concerns in current clinical practice. The prevention of TD is of primary importance, and clinicians should follow best practice guidance for the prescription of antipsychotic medication; this includes limiting prescription to specific indications, using the minimum effective dose, and minimizing the duration of therapy.
- TD is a very disabling clinical disorder that is often hard to manage and treat. Clinicians should be aware of the potential risk of developing TD in patients on long-term treatment with antipsychotics and should carefully assess patients to recognize TD for its prompt management. The baseline score of Abnormal Involuntary Movement Scale (AIMS) must be recorded and conducted periodically and documented to show any change in the intensity of the problem.

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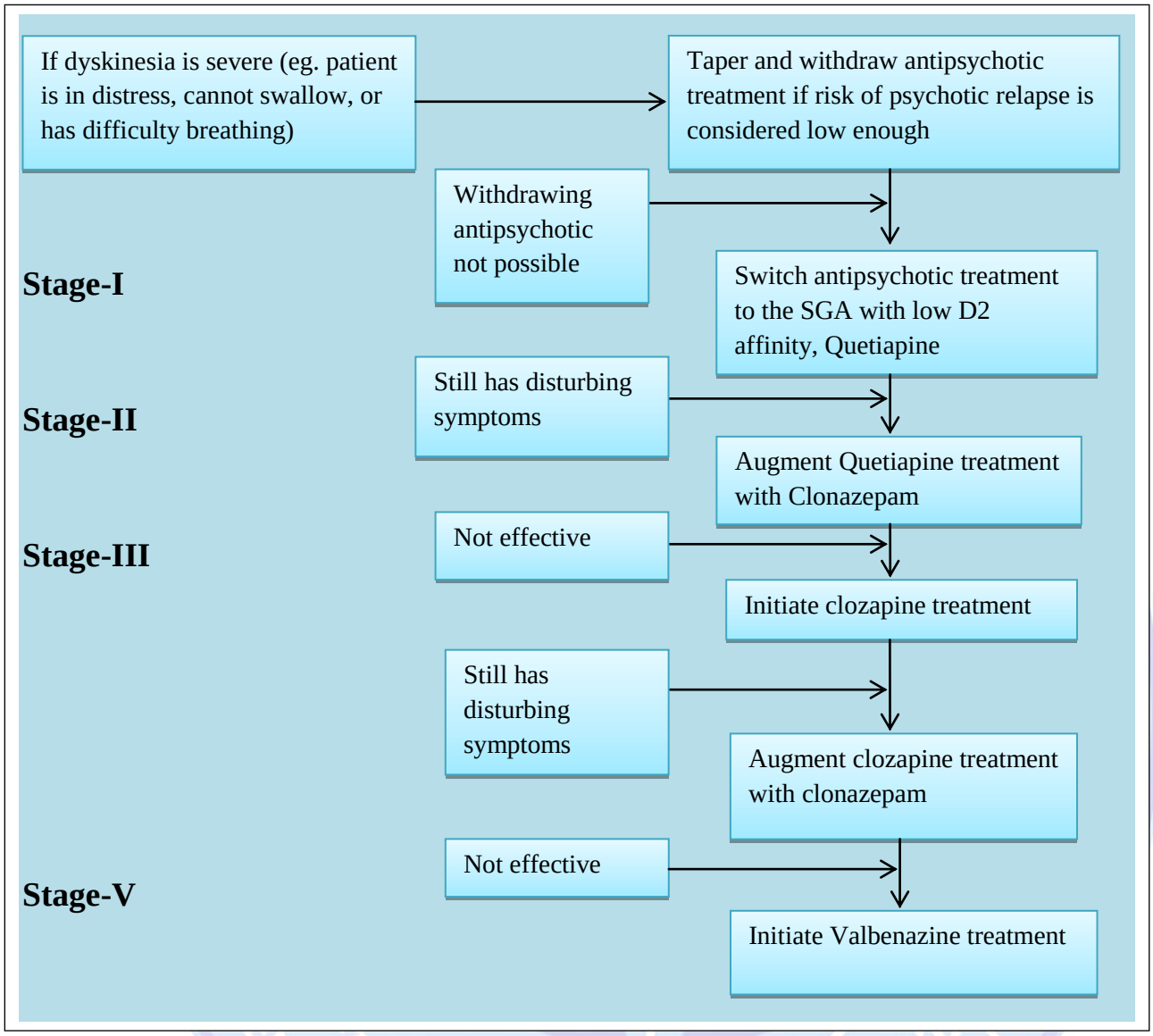


Figure 16: Algorithm for Treatment of Tardive Dyskinesia (TD)

References

1. De Leon, M. L., & Jankovic, J. Clinical features and management of classic tardive dyskinesia, tardive myoclonus, tardive tremor, and tardive tourettism. *NEUROLOGICAL DISEASE AND THERAPY*, 2004; *62*, 77-110.
2. Tardive Dyskinesia: Definition, Symptoms, Causes, Treatment
   WebMD › mental-health › tardive-dyskinesia (accessed on 12 February 2022).
3. Gerlach J, Casey DE. Tardive dyskinesia. ActaPsychiatricaScandinavica. 1988 Apr;77(4):369-78.
4. Dilip V. Jeste, Michael P. Caligiuri, Tardive Dyskinesia, *Schizophrenia Bulletin*, Volume 19, Issue 2, 1993, Pages 303–315, https://doi.org/10.1093/schbul/19.2.303
5. Kane JM, Smith JM. Tardive dyskinesia: prevalence and risk factors, 1959 to 1979. Archives of General Psychiatry. 1982 Apr 1;39(4):473-81.
6. Correll CU, Kane JM, Citrome LL. Epidemiology, Prevention, and Assessment of Tardive Dyskinesia and Advances in Treatment. J Clin Psychiatry. 2017 Sep/Oct;78(8):1136-1147. doi: 10.4088/JCP.tv17016ah4c. PMID: 29022654.
7. Widschwendter CG, Hofer A. Antipsychotic-induced tardive dyskinesia: update on epidemiology and management. CurrOpin Psychiatry. 2019 May;32(3):179-184. doi: 10.1097/YCO.0000000000000491. PMID: 30720484.
8. Solmi M, Pigato G, Kane JM, Correll CU. Clinical risk factors for the development of tardive dyskinesia. Journal of the Neurological Sciences. 2018 Jun 15;389:21-7.
9. Jeste DV, Caligiuri MP, Paulsen JS, Heaton RK, Lacro JP, Harris MJ, Bailey A, Fell RL, McAdams LA. Risk of tardive dyskinesia in older patients: a prospective longitudinal study of 266 outpatients. Archives of General Psychiatry. 1995 Sep 1;52(9):756-65.
10. Misgana, T., Yigzaw, N., &Asfaw, G. Drug-Induced Movement Disorders and Its Associated Factors Among Patients Attending Treatment at Public Hospitals in Eastern Ethiopia. *Neuropsychiatric disease and treatment*, 2020; *16*, 1987–1995. https://doi.org/10.2147/NDT.S261272
11. Taye, H., Awoke, T., &Ebrahim, J. Antipsychotic medication induced movement disorders: the case of Amanuel specialized mental hospital, Addis Ababa, Ethiopia. *Am J Psychiatry Neurosci*, 2014; *2*(5), 76-82.

12. Kumsa, A., Girma, S., Alemu, B., &Agenagnew, L. Psychotropic Medications-Induced Tardive Dyskinesia and Associated Factors Among Patients with Mental Illness in Ethiopia. *Clinical pharmacology: advances and applications*, 2020; *12*, 179–187. https://doi.org/10.2147/CPAA.S285585
13. Tilahun Abdeta, Daniel Tolessa, Wondale Tsega. Prevalence and associated factors of tardive dyskinesia among psychiatric patients on first-generation antipsychotics at Jimma University Specialized Hospital, psychiatric clinic, Ethiopia: Institutional based cross-sectional study. Journal of Psychiatry and Psychiatric Disorders 2019; 3: 179-190.
14. Cornett, E. M., Novitch, M., Kaye, A. D., Kata, V., & Kaye, A. M. Medication-induced tardive dyskinesia: a review and update. *Ochsner Journal*, 2017; *17*(2), 162-174.
15. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, text revision. Washington DC, American Psychiatric Association, 2022.
16. Lucia Ricciardi, Tamara Pringsheim, Thomas R.E. Barnes, Davide Martino, David Gardner, Gary Remington, Donald Addington, Francesca Morgante, Norman Poole, Alan Carson, and Mark Edwards. Treatment recommendations for Tardive Dyskinesia. The Canadian Journal of Psychiatry; 2019, Vol. 64(6) 388-399. DOI: 10.1177/0706743719828968
17. James Robert Brasic. Which conditions should be included in the differential diagnosis of tardive dyskinesia (TD)? Medscape (Updated 2018)
18. Sienaert P, van Harten P, Rhebergen D. The psychopharmacology of catatonia, neuroleptic malignant syndrome, akathisia, tardive dyskinesia, and dystonia. HandbClin Neurol. 2019;165:415-428. doi: 10.1016/B978-0-444-64012-3.00025-3. PMID: 31727227.

CHAPTER TWELVE

12.Epilepsy Management

12.1. Introduction

12.1.1. ***Brief description***

- Epilepsy is a chronic disorder characterized by recurrent unprovoked seizures. An epileptic seizure refers to transient occurrence of signs and/or symptoms due to abnormally excessive or synchronous neuronal activity in the brain. The epileptic seizure may be characterized by sensory, motor or autonomic phenomena with or without loss of consciousness.
- The term unprovoked implies the absence of a temporal or reversible factor that reduces the convulsive threshold and provokes a seizure at that moment. Seizures which occur in a setting of an acute illness or medical condition like high fever, hypoglycemia, etc. refer to acute symptomatic seizures.
- Epilepsy syndrome is a new addition to the current classification system and is defined as "a cluster of features incorporating seizure types, EEG, and imaging features that tend to occur together."

12.1.2. Epidemiology

- Epilepsy is a chronic non-communicable disease of the brain that affects people of all ages with almost 50 million individuals worldwide, making it one of the most common neurological diseases.
- Epilepsy affects about 80% of people in low- and middle-income nations. If properly diagnosed and treated, it is believed that up to 70% of persons with epilepsy could live seizure-free.
- People with epilepsy have a three-fold increased chance of dying prematurely than the general population. In low-income nations, three quarters of patients with epilepsy do not receive the therapy they require. People with epilepsy and their families face stigma and discrimination in many parts of the world.
- A door-to-door survey done in rural Ethiopia (n=61, 686) indicated the incidence of Epilepsy was 64 per 100,000 population; while in some areas like Zay society the prevalence of epilepsy was very high (29.5 per 1000 inhabitants). In 69 % of cases, generalized convulsive

seizures occurred, while partial seizures occurred in 20% and unclassifiable seizures occurred in 11%.

12.1.3. Causes and risk factors

- Epilepsy has six etiologic categories (structural, genetic, infectious, metabolic, immune, and unknown).
  - A structural etiology is determined when a structural abnormality is seen on neuroimaging and the abnormality is the probable cause of the seizures.
    - ✓ Structural etiologies include stroke, trauma, tumor, malformations of cortical development.
  - Genetic etiologies are determined if there is a known or presumed genetic mutation in which seizures are a core symptom of the disorder.
  - Infectious etiologies are the most common worldwide etiology.
    - ✓ Infectious etiologies include neuro-cysticercosis, HIV, cytomegalovirus, and cerebral toxoplasmosis.
- Factors that contribute to epilepsy syndrome include age of onset, remission, triggers, diurnal variation, intellectual and psychiatric dysfunction, EEG findings, imaging studies, family history, and genetics.
- Common precipitating factors for seizures include the following:
  - Flashing lights (resulting in reflex epilepsy)
  - Hyperventilation
  - Lower alertness, sleep itself and lack of enough sleep
  - Emotion
  - Physical stress
  - Special smells, sounds or sensations of touch
  - Alcohol
  - Hormonal changes, e.g., during menses
  - High fever
  - Dehydration/Over hydration

12.2. Clinical features

- It is necessary to determine the type of seizure in order to focus the diagnostic approach on a particular etiologic factor, to select the appropriate drug therapy, and to provide information regarding the prognosis.
- Epilepsy can be also classified into four main types.
  - (1) Focal
  - 2) Generalized
  - 3) Combined generalized and focal
  - 4) Unknown.

  - Focal epilepsy is a continuum of seizures, unifocal, and multifocal disorders that are confined to one hemisphere and can present with any type of focal seizure.It is diagnosed clinically but supported by an interictal EEG with focal epileptiform discharges.

  - Generalized epilepsy consists of many seizure types, and a patient can present with any type of generalized seizure, either motor or non-motor. Diagnosis is based on generalized spike-wave activity on EEG, and more importantly, clinical presentation.

  - Combined generalized and focal is a condition in which a patient has both focal and generalized seizures

  - In a situation where the clinician cannot categorize seizures as either for focal or generalized, the seizure is therefore referred to as unknown

- Symptoms of epilepsy can be categorized in to four phases. These are prodromal phase, aura phase, seizure (ictus) phase and post-ictal phase.

1. *Prodromal phase***:**This phase, which starts a few hours or even days before the actual seizure, should not be confused with the aura. Headache, irritability, insomnia, bad temper, depression, or increased activity in all the symptoms of prodromal phase.
2. *Aura phase*: An aura precedes the seizure by seconds or a few minutes. It marks the start of the seizure and the onset of the focal seizure. The symptoms are determined by where the focus is located. The aura's feelings are frequently hazy and incomprehensible, causing considerable terror. Strange epigastric sensations, hallucinatory experiences, foul odors, and other strange epigastric sensations may occur. The patient recalls the aura vividly, and while

he or she may not always be able to narrate it, he or she can attest to its presence before consciousness is lost.

3. *Seizure (ictus) phase*: Because most seizures result in a loss of consciousness, the patient is unable to provide any information regarding the ictus itself. We rely on eyewitnesses who witnessed the actual seizure for this. The patient has no recollection of having a seizure.The type of seizure, the duration of the seizure, the frequency of the seizure, the time of day or night the seizure occurs, and its relationship to sleep, the presence of an aura, the presence of a post-ictal phase, and the age of onset all influence seizure characteristics.
4. *Post- ictal phase*: This phase can be missing, brief, or lasts for several hours, if not days. A deep sleep is generally followed by headaches, fatigue, irritability, vomiting, confusion, muscular aches, or ataxia.Todd's paresis is a temporary paralysis of a section of the body that might last a few hours or days. When the dominant hemisphere of the brain is implicated, altered speech or aphasia can develop. Changed behavior and emotional outbursts are possible, and if they are disrupted, aggressive behavior is likely.

12.3. Diagnosis and investigations

12.3.1. Diagnosis and differential diagnosis

- Diagnosis is primarily clinical and depends on a good history and examination. Detailed clinical history from the patient, the family members and the eye witness (if available) about the event are very important for correct diagnosis.
    1. Presence of an aura, e.g. motor and/or sensory phenomenon, fear, abdominal discomfort, etc. may help to determine seizure type and localize the site of origin of seizure.
    2. Ictus/event could consist of unilateral or bilateral tonic clonic movements, sudden jerking, deviation of eyes and head, alteration or loss of consciousness, and may be associated with injuries, tongue bite or incontinence.
    3. Postictally the patient may have confusion, drowsiness, headache or weakness.
    4. Careful physical and neurological examinations are important in making a correct diagnosis.
- One should record pulse, blood pressure and look for subcutaneous nodules and examine heart, optic fundi and focal neurological signs.

- Investigations such as electroencephalogram (EEG) help in the diagnosis of seizures, while imaging procedures like computed tomography (CT) or magnetic resonance imaging (MRI) scan of the brain may reveal an underlying cause.
- A single seizure may occur for a number of reasons and is not necessarily diagnostic of epilepsy
- A diagnosis of epilepsy is established after any of the following situations:
    1. Two or more unprovoked or reflex seizures occurring with >24 h difference.
    2. A single unprovoked or reflex seizure with a probability of at least 60% of presenting a future seizure (similar range as the general risk of recurrence, after two unprovoked seizures that appear in the following 10 years).
    3. Diagnosed epileptic syndrome
- Differential diagnosis includes the following conditions:

1. *Syncope*

The pathogenesis of syncope is a consequence of a disruption of cerebral blood supply, whereas epilepsy is caused by an electrical discharge of the brain.

The distinction between syncope and epilepsy:

- ✓ The onset of syncope is usually not as sudden as that of epilepsy; the patient with syncope is frequently in the upright position at the time of its onset.
- ✓ Syncope is frequently accompanied by the premonitory symptoms of greyness/blackness of vision and dizziness.
- ✓ During syncope patients typically injure themselves less frequently than during epileptic seizures and recovery of consciousness takes place within seconds or minutes.
- ✓ Sphincter control is usually maintained during a syncopal event

In certain instances, syncope may be followed by clonic twitches; for example this is seen after vasovagal syncope, cough-syncope

2. *Pseudo-seizures (psychogenic seizures)*

Attacks are interpreted as a dissociative or conversion response to distress. A number of biographical, psychological, physiological, sociological, and financial factors including trauma

and neglect in earlier life, adverse life events in adulthood, personality pathology, and inadequate coping skills can predispose to, precipitate and perpetuate PNESs

Features that raise suspicion regarding the possibility of pseudo seizures include the following:

- Prolonged length of the actual seizure
- Lack of stereotyped seizure patterns; asynchronous movements of the extremities
- Atypical vocalization alternating movements of the head and pelvis.

3. *Transient ischemic attacks (TIAs)*

It is not uncommon that focal seizures are mistaken for TIAs. Whereas most epileptic seizures are characterized by predominantly 'positive' ictal features (e.g. excessive movement, sensory, visual, or auditory hallucinations), most transient ischemic attacks (TIAs) involve 'negative' features (e.g. weakness, loss of sensation, loss of speech).

Epileptic seizures are usually of shorter duration and there are also presences of a march of symptoms, and epileptiform activity on EEG.

4. *Movement disorders (paroxysmal dyskinesias)*

Paroxysmal dyskinesias are a group of rare hyperkinetic movement disorders characterized by brief intermittent dyskinesia movements.

5. *Migraine*

There are clinical similarities between migraine with visual aura and occipital epilepsy especially when these seizures are followed by a postictal headache

Migrainous auras are more likely to start in the center of the visual field, spread outwards over the course of minutes, and involve one hemi- field. Epileptic auras tend to start in the periphery and spread over the course of seconds.

12.3.2. Laboratory and imaging

Blood tests help establish a baseline and rule out the presence of infections and other abnormalities that may affect the choice of appropriate anticonvulsant medications and help to monitor the possible drug-induced side effects in the future.

- Do complete blood count (CBC), blood sugar, blood calcium and electrolyte levels, liver transaminases and kidney function tests (blood urea, creatinine, and urinalysis).
- Electroencephalogram (EEG) is a noninvasive and widely available investigation for evaluating an individual with suspected seizures.

Epilepsy cannot be diagnosed from an EEG alone. There must be a clinical description of episodes that are compatible with epilepsy. Routine EEG is useful for classification of seizure type and diagnosing the epilepsy syndrome.

There are better chances of detecting abnormalities if EEG is done soon after the seizure or within 48 hours. False negative interictal results occur in 50% of routine recordings. Repeating the recording reduces the false negative rate to 30%.

A normal EEG does not rule out diagnosis of epilepsy and also epileptiform discharges in the EEG may occasionally be seen among healthy adults without history of seizures.

- Video electroencephalogram (VEEG)

  It is used to investigate patients with difficult to control epilepsy. It may be performed in patients in whom psychogenic non-epileptiform events are suspected.

- Neuroimaging may include computed tomography (CT) scan or magnetic resonance imaging (MRI) scan of the brain. Neuroimaging is not mandatory for all patients with epilepsy.

Neuroimaging in epilepsy is useful in:

- ✓ Focal seizures
- ✓ Seizures suspected to be symptomatic in origin
- ✓ Difficult to control seizures (MRI using special epilepsy protocol)

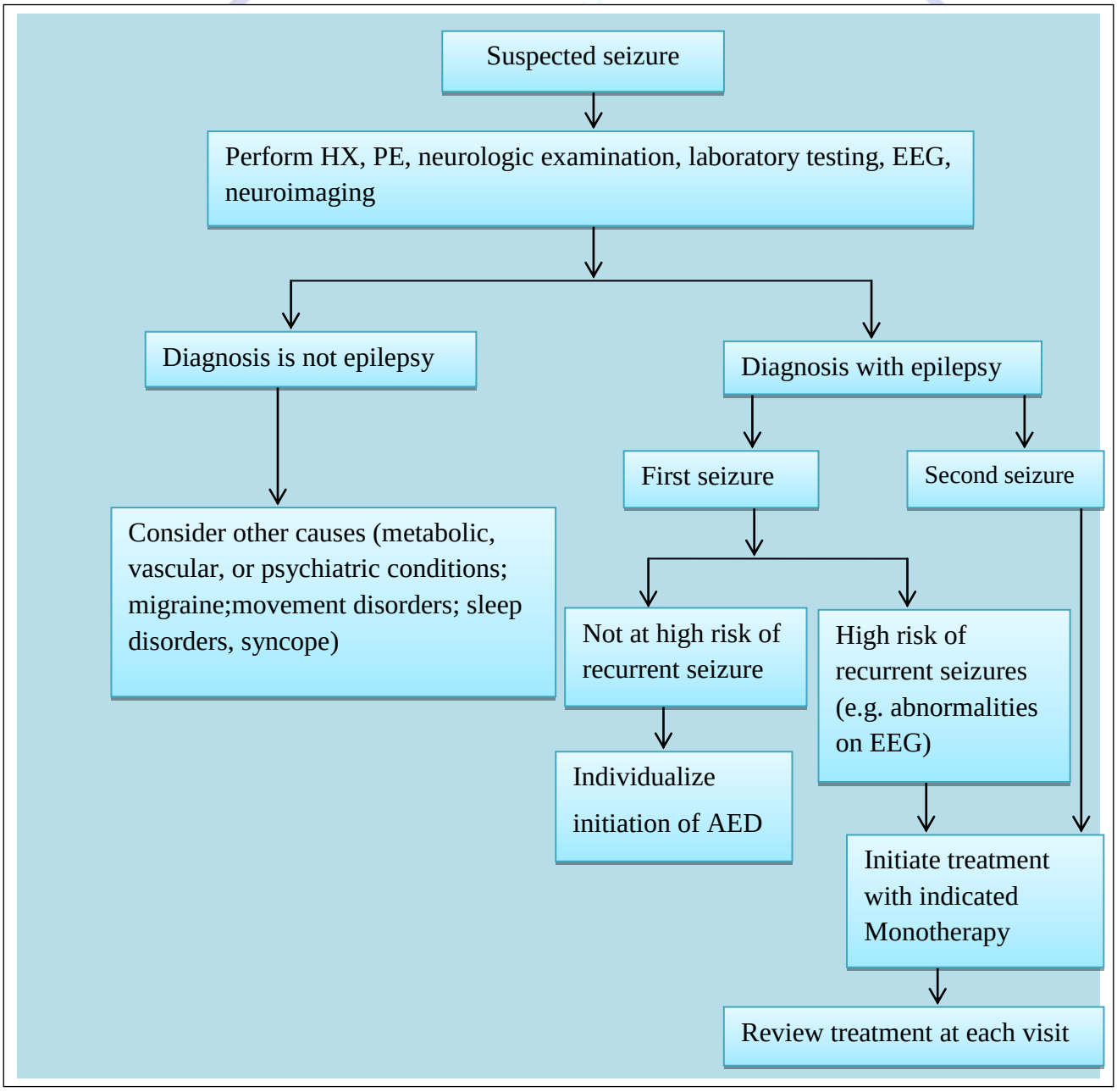
12.4. Treatment

12.4.1. Goals of treatment

- Conduct a thorough evaluation and confirm diagnosis
- Control seizures
- Ensure functioning and good quality of life
- Minimize adverse effects of antiepileptic drugs (AEDs)
- Prevent relapses

12.4.2. General principles of treatment

- The figure below summarizes the general principles of treatment for epilepsy:



12.4.3. Non-pharmacologic treatment

- Give psychoeducation about what epilepsy is and its causes and risk factors.
- Tell patients about the precipitating risk factors and the necessary precautions.
- Identify misconceptions and give corrective explanations and evidence.
- Advocate for functionality and normal life with appropriate precautions.
- Explain about the treatment and the importance of compliance.
- Work with patient and caregivers towards psychosocial support.

*12.4.4. **Pharmacological treatment***

- Antiepileptic drug (AED) therapy is the mainstay of treatment for most patients. The aim of treatment is to control seizures with the most appropriate AED without causing any significant side effects.
- Principles of AED treatment include:
  - Treatment should be started with a single conventional AED (monotherapy). The dose should be slowly built up until seizure control is achieved or side effects occur.
  - If the initial treatment is ineffective or poorly tolerated then monotherapy using another AED can be tried. The dose of the second drug is slowly increased until adequate or maximum tolerated dose is reached. The first drug is then tapered off slowly.
  - Combination therapy (polytherapy or adjunctive or “add-on” therapy) can be considered when two attempts at monotherapy with AEDs have not resulted in seizure freedom.
- *Treatment of the first unprovoked seizure may be considered under the following circumstances*:
  - Prolonged focal seizure
  - First seizure presenting as status epileptics.
  - Presence of neurological deficit, hemiparesis, intellectual disability, cerebral palsy, etc.
  - Family history of seizures among parents, siblings or children
  - Electroencephalogram abnormality
  - Abnormality on brain imaging (CT, MRI)

- When the patient might have had a seizure before. This may not have been recognized by the patient and may be brought out only by a careful history.

Choosing the appropriate antiepileptic drug

- Choice of AED should be individualized and should be based on factors such as seizure type, AED side-effect profile, presence of an epilepsy syndrome, other medications, co-morbidities, patient preference and cost. Single or twice-daily dose regimens improve AED treatment compliance.

Some examples of the impact of AED selection are:

- The presence of some generalized *seizure* types, e.g. typical absences and / or myoclonic jerks, may become more frequent and severe if treated with carbamazepine, phenytoin.

It is critical to match the correct AED with the correct seizure type (See table below).

Table 12:Common Seizure Disorders with Recommended First-Line and Alternative Therapy

Seizure Type	**First-line AEDs**	**Alternative agents(second- line AED)**	**Drugs to Avoid**
Focal	Carbamazepine, Phenytoin, Sodium Valproate	Phenobarbital Levetiracetam, Lamotrigine	
Generalized			
Tonic-clonic	Valproic acid Lamotrigine	Phenytoin Carbamazepine Phenobarbital	

Absence	Ethosuximide, valproate	Lamotrigine Clonazepam	Carbamazepine, phenytoin
Atypical Absence,Myoclonic, and Atonic Seizures	Valproic acid Lamotrigine	Clonazepam	Carbamazepine, phenytoin,

12.4.5. Monitoring the antiepileptic drug therapy

- The following tests may be carried out as necessary:
  - Complete blood count, liver enzymes and renal functions before starting AED
  - Calcium (Ca++), alkaline phosphatase (ALP) and other tests of bone metabolism every year for adults taking enzyme-inducing drug.
  - People with epilepsy should maintain a seizure diary and have regular follow-up. The first follow-up may be undertaken anytime within 2–4 weeks of initiation of treatment and subsequently at every 3–6 months, depending on the control of seizures and side effects(3) Lifestyle issues such as sleep, regular food intake, alcohol use, driving and pregnancy (if planned) should also be discussed.

Table 13: Dosing, Contraindications, and Adverse Effects for Common Antiepileptic Drugs

Antiepileptic drug	Initial dosage	Maximum dosage (may not be required for all patients)	Titration and administration	Adverse effects
Carbamazepine	400 mg daily	1,600mg daily	• Given two to four times daily • Increase dosage every two to three weeks until response is	Abnormal coordination, ataxia, blood dyscrasias, constipation, dizziness,

			reached • Target serum concentration: 4 to 12 mcg per mL	headache, hyponatraemia, metabolic bone disease, nausea, nystagmus, rash (human leukocyte antigen testing may be relevant), somnolence, vomiting
Lamotrigine	Specific dosing recommendations depend on other current antiepileptic drugs	Specific dosing recommendations depend on other current antiepileptic drugs	Specific dosing recommendations depend on other current antiepileptic drugs	Diplopia, dizziness, nausea, rash, tremor
Levetiracetam	500 to 1,000 mg daily	4,000 mg daily	• Given in two divided doses, increase every two weeks • Target serum concentration: 12 to 46 mcg per mL	Agitation, anxiety, depression, dizziness, fatigue, infection, irritability, rash, somnolence,
Phenobarbital	Children: 30 mg daily	Children: 150 mg daily	Given in two to three divided doses	Agitation, anxiety,

	Adults: 200 to 300 mg daily	Adults: 300 mg daily		ataxia, confusion, constipation, dizziness, drowsiness, hallucinations hyperkinesia, impaired judgment, insomnia, lethargy, nausea, vomiting
Phenytoin	3 to 5 mg per kg (200 to 400 mg) daily	600 mg daily	• Total serum concentration: 10 to 20 mcg per mL • Unbound drug concentration: 0.5 to 3 mcg per mL	Ataxia, blood dyscrasias, confusion, double vision, gingival hypertrophy, immunologic reaction, rash, slurred speech
Valproic acid	15 mg per kg (500 to 1,000 mg) daily	60 mg per kg (3,000 to 5,000 mg) daily	• Given once or twice daily, typically twice daily • Target serum concentration	Alopecia, dizziness, hyperammonemia, polycystic ovary syndrome, tremor,

			: 50 to 100 mcg per mL	weight gain
Clonazepam	Children: 0.05 mg per kg daily Adults: 1.5 mg daily	Children: 0.1 to 0.2 mg per kg daily Adults: 20 mg daily	• Given in three divided doses • Children: increase by 0.25 to 0.5 mg every three days to maintenance dosage of 0.1 to 0.2 mg per kg daily • Adults: Increase by 0.5 to 1 mg every three days until response is reached	Anorexia, ataxia, behavioral problems, constipation, dizziness, drowsiness

12.4.6. Drug-drug interactions

- The important points to remember about drug-drug interaction which involve AEDs are:
  - Certain AEDs such as Phenytoin, Phenobarbitone, Carbamazepine and Oxcarbazepine (OXC) induce hepatic enzymes and enhance the metabolism of lipid-soluble drugs. These interact with other AEDs, oral contraceptive pill (OCP) and oral anticoagulants.

- Valproate inhibits hepatic enzymes and slows down the metabolism of concomitant AEDs and other drugs having hepatic metabolism causing toxicity and requiring dose adjustments.
- Drug interactions become important while using AEDs with erythromycin, ciprofloxacin antitubercular drugs (e.g., isoniazid and rifampicin are enzyme inducers and also hepatotoxic), and antiretroviral drugs.

12.4.7. Considering stopping the antiepileptic drug

- Withdrawal in most cases after a seizure-free period of 2–3 years. The decision is mainly based on the type of epilepsy syndrome and cause of seizures and should be taken after discussion of the risks and benefits of withdrawal with the patient (PWE) and family.
- Antiepileptic drugs withdrawal should be avoided in certain epilepsy syndromes (e.g. juvenile myoclonic epilepsy) because of the higher risk of seizure relapse following AED withdrawal.
- Antiepileptic drugs are usually withdrawn gradually over several months (at least 3–6 months or longer). There is possibility of seizure recurrence during and after withdrawal.
- The tapering may be performed at a slower rate for benzodiazepines (6 months or longer).
- One drug at a time in those patients who are on multiple AEDs

12.4.8. Treatment refractory epilepsy

- Treatment refractory epilepsy (therapy resistant epilepsy) is defined as those in whom epilepsy is not controlled by two or more appropriate AEDs used in their optimal dosage. It is advisable to follow the following algorithm during the management of treatment-refractory epilepsy.

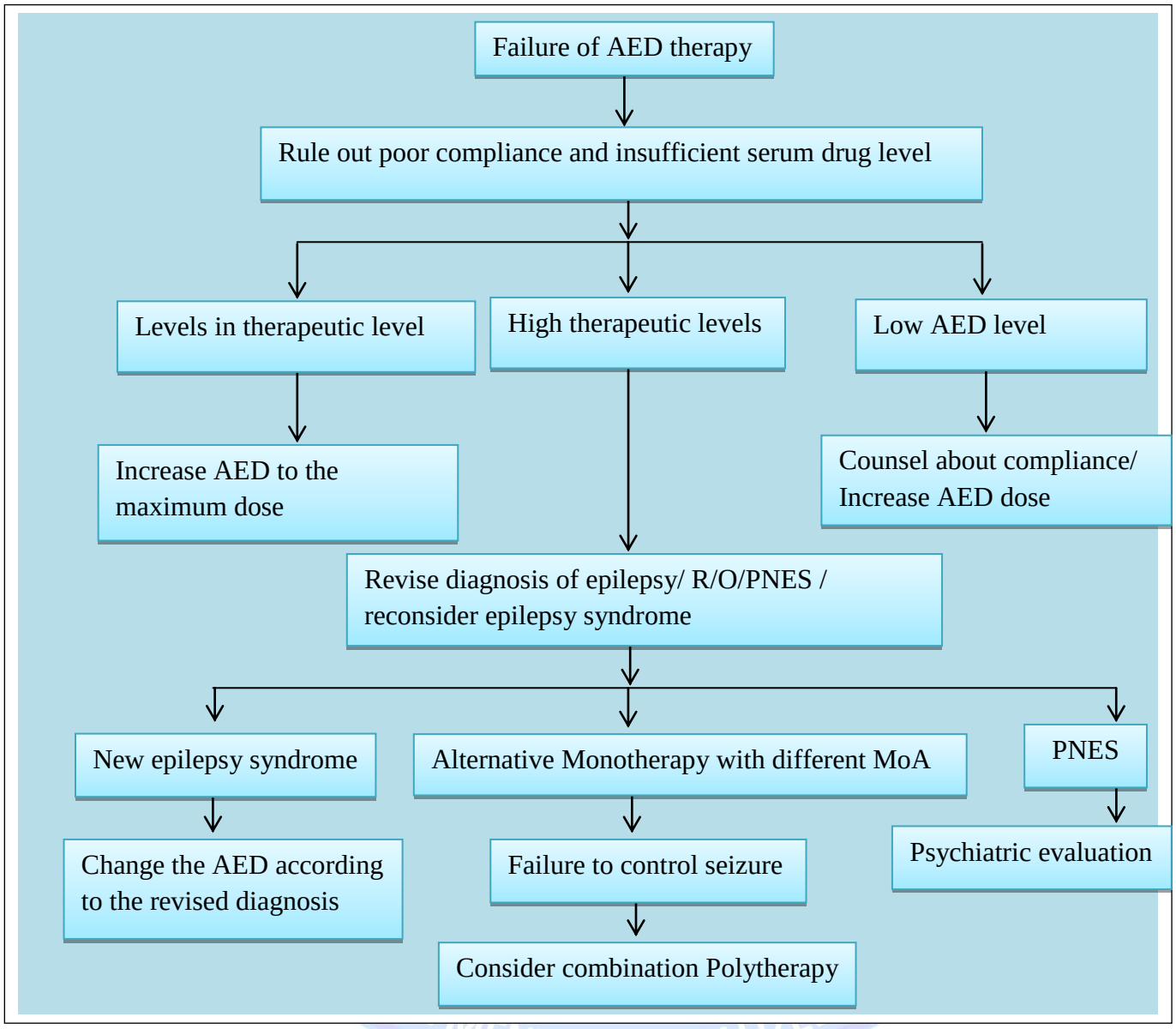


Figure 17: treatment algorism for Epilepsy

TREATMENT IN SPECIAL SITUATIONS

12.4.9. Special considerations

Women with epilepsy

- All women with epilepsy should be advised to plan their pregnancies. They should be cautioned that some AEDs may make OCPs ineffective. Barrier contraception is an alternative that can be considered.
- A universal recommendation for antenatal care includes prescription of 0.4 mg of folic acid daily. Women in developing countries may be at higher risk of folic acid deficiency owing to dietary inadequacy, infections, or concomitant use of other drugs; therefore, all women with epilepsy in the reproductive age group should be started on folic acid (5 mg/day) at the time of starting AED.
- The risk of major fetal malformations is approximately 5% compared to those without epilepsy, which is around 2–3%. The risk is further reduced when the mother is using monotherapy (a single AED) at low dose along with folic acid.
- Based on the currently available data, there is no superiority for one AED over the other with regard to fetal malformations. Nevertheless Valproate is contraindicated during pregnancy. Antiepileptic drugs should be continued in pregnancy.

Epilepsy and psychiatric disorders

Patients who have epilepsy have a higher incidence of psychiatric illness than the general population. Temporal-lobe epilepsy confers the highest rate of comorbidity.

Mood disorders

- Mood disorders are the most common psychiatric disorder comorbid with epilepsy. These disorders can present as an ictal aura in some cases.Interictal depression is the most commonly reported complaint in people with epilepsy with mood disorder.
- Taking a multidisciplinary team approach including full psychiatric and psychological evaluation in treating a mood disorder in a patient who has epilepsy might improve seizure and mood outcomes.
- Prompt treatment with antidepressant is indicated in PWE and comorbid depression. Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors are the drug of choice. Tricyclic antidepressants have proconvulsant properties; they are not prescribed in these patients.

- Some anti-seizure drugs (valproate, Lamotrigine and carbamazepine) appear to have mood stabilizing properties. In contrast, some AEDs, especially those that potentiate gamma-aminobutyric acid (GABA) neurotransmission (phenobarbital, topiramate, etc)have been reported to cause or exacerbate a depressed mood and should be avoided in patients with comorbid depression.

Psychosis

- The prevalence of psychosis is approximately 10% among persons who have epilepsy and is observed most often in patients who have complex partial seizures. Family history of epilepsy or psychosis, temporal lobe epilepsy, a long seizure history, and abnormalities in the limbic system, especially the hippocampus are some of the risk factors that predispose patients to psychosis.
- There are drugs that have been reported to provoke psychosis (levetiracetam, topiramate) may be less desirable in patients with psychosis history. Prescribe antipsychotics with caution because many of these agents have epileptogenic potential or can interfere with the hepatic metabolism of AEDs. Risperidone, and haloperidol have low potential for seizure induction whereas, chlorpromazine and clozapine are more likely to precipitate an ictal event

13.2.Status epileptics (SE)

- Status epilepticus (SE) is a serious medical condition with significant morbidity and mortality. Practical definition of SE is 5 min or more of continuous clinical and/or electro-graphic seizure activity or recurrent seizure activity without recovery (returning to baseline) between seizures.
- Status epilepticus requires emergent, targeted treatment to reduce patient morbidity and mortality.
- The etiologies of SE include:

  - Epileptic patients are the group at highest risk, especially if they fail to maintain inadequate anti-epileptic drug levels in the blood.

  - Prior trauma to the brain

- History of stroke
- Alcohol abuse
- Metabolic disease
- Hypoxia of the CNS which is also associated with a mortality rate of 60-70%
- Tumors of the brain
- Infections of the brain accompanied by fever, especially in children below 2 years who have no prior history of epilepsy

- Hyperglycemia, respiratory distress, metabolic acidosis and hyperpyrexia are metabolic complications of SE. While Cerebellar, cortical, and hippocampal damage can occur which manifest as chronic encephalopathy and brain atrophy.
- Continuation of the seizure activity may lead to more pathologic states such as hypotension, myocardial dysfunction, hypoglycemia, pulmonary edema. Gastrointestinal complications include stress ulcers and gastrointestinal hemorrhage, diarrhea, and paralytic ileus
- SE also produces lung injury, injury to the muscles and skeletal system, and renal injury secondary to the high level of circulating metabolic toxins resulting from the prolonged seizures. Therefore, early detection and treatment of complications is a crucial step in ensuring the best prognosis for SE.

Management of status epilepticus

- Status epilepticus requires emergency treatment that requires rapid and aggressive treatment to prevent neuronal damage, systemic complications and death. The principal goal of treatment is to urgently stop seizure activity.
- Treatment strategy includes:
  - Simultaneous assessment and management of airway, breathing, and circulation (obtain IV access, administer O2, and secure the airway as needed)
  - Seizure abortive drug treatment (i.e., benzodiazepine)
  - Screening for the underlying cause of SE, and immediate treatment of life-threatening causes of SE (e.g., meningitis, intracranial mass lesion)

- Once it is determined that SE is under control and vital signs are stable, specific diagnostic studies can be performed.
- The following are recommended next steps:
  - Lumbar puncture is generally needed if there is any suspicion of a central nervous system (CNS) infection
  - If the patient is currently treated with AEDs, a drug level should be checked and history obtained regarding compliance.
  - Brain imaging is required if the cause of SE suspected to be intracranial mass
  - Toxicology screen should be obtained, if there is no clear etiology for SE

The following algorithm summarizes the treatment approach for status epilepticus.

- 0-10min
- Stabilization Phase and initial
- Therapy phase

- Stabilize patient (airway, breathing, circulation)
  - ✓ Supplement O2 if needed
  - ✓ Obtain baseline vital signs, IV access (at least two), cardiac monitoring with pulse oximetry, fingerstick blood glucose level.
  - ✓ Labs: CBC, OFT, Electrolyte, ABG, AED levels, Toxicology screen

  Consider Thiamin and glucose
  - If blood glucose low(1 amp of 40% dextrose and start second IV with D5NS)
  - Give Thiamine if malnourished/alcoholic
- Neurologic examination

- Initial therapy

Diazepam 10mg IV over 2 minutes STAT, may repeat dose ONCE after 5 minutes

Seizure continue

- 10-60 min Second therapy phase

- ✓ Phenytoin 20mg/kg iv, 50mg/min OR
- ✓ Fosphenytoin 20 mg PE/kg IV, maximum rate of 150 mg PE/min,
- ✓ Needs EKG monitoring and BP checks during Loading Dose

- ✓ Phenytoin 10mg/kg iv, 50mg/min OR
- ✓ Fosphenytoin 10 mg PE/kg IV, maximum rate of 150 mg PE/min

If seizure continues admit to ICU, Intubation (if not already; Vasopressors (on standby)

- >60 min

Third therapy phase

Refractory status Epilepticus

- ✓ Phenobarbitone 20mg/KG IV 60mg/min

No response

Phenobarbitone 10mg/kg IV 60mg/min

Seizure continue

General anesthesia

Figure 18: Pharmacologic treatments of generalized tonic-clonic status epilepticus in adults

Important considerations:

- After initial therapy if seizure corrected or if the cause of seizure corrected, no need to add additional AED.
- Valproate can be used in a place of phenytoin in the second therapy in a patient who is already taking Valproate acid and maybe sub-therapeutic. Maintenance dose of AED should be started after 6 of the loading dose of AED.
- Heart rate or electrocardiogram monitoring is a recommendation during administration of phenytoin. The major advantage of Fosphenytoin is the relative absence of infusion site reactions compared with phenytoin, which can cause severe tissue injury after extravasation.
- Status epileptic that does not abate with benzodiazepines and two other anticonvulsant drugs is considered refractory. In this situation, treatment in the intensive care setting require intubation with continuous cardiovascular and electroencephalogram monitoring is indicated.

The following drugs can be used in general anesthesia:

- Ketamine
  - ✓ Loading dose: 3 mg/kg IV bolus
  - ✓ Continuous dosing: 3-10 mg/kg/hour
- Propofol
  - ✓ Loading dose: 2 mg/kg IV bolus
  - ✓ Continuous dosing: 30-200 mcg/kg/min
- Thiopental
  - ✓ Loading dose: 100-200 mg (adult)
  - ✓ Continuous dosing :3-5 mg/kg/h

With general anesthesia, maintain therapeutic level of phenytoin, phenobarbital or both. After seizure control, maintain continues infusion for 24hr.

References

1. Reséndiz-Aparicio JC, Pérez-García JC, Olivas-Peña E, García-Cuevas E, Roque-Villavicencio YL, Hernández-Hernández M, et al. Clinical guideline: definition and classification of epilepsy. Rev Mex Neurocienc. 2021;20(2):63–8.
2. Scott RA, Lhatoo SD, Sander JW. The treatment of epilepsy in developing countries: where do we go from here?.Bulletin of the World Health Organization. 2001; 79: 344-51.
3. Senanayake, N., &Román, G. C. (1993). Epidemiology of epilepsy in developing countries. Bulletin of the World Health Organization, 71(2), 247–258.
4. Tekle-Haimanot R, Forsgren L, Ekstedt J. Incidence of epilepsy in rural central Ethiopia. Epilepsia. 1997 May; 38(5):541-6. doi: 10.1111/j.1528-1157.1997.tb01138.x. PMID: 9184599.
5. Almu S, Tadesse Z, Cooper P, Hackett R. The prevalence of epilepsy in the Zay Society, Ethiopia--an area of high prevalence.Seizure. 2006 Apr; 15(3):211-3. doi: 10.1016/j.seizure.2006.01.004. Epub 2006 Feb 20. PMID: 16488161.
6. Worku D. Epilepsy in Ethiopia. Journal of the Neurological Sciences, 2013 Oct 15; 333:e5.
7. Pack AM. Epilepsy Overview and Revised Classification of Seizures and Epilepsies. Contin Lifelong Learn Neurol. 2019;25(2):306–21.
8. Roy MK DD, ABSTRACT. Indian Guidelines on Epilepsy Mrinal. Goodman Gilman's Pharmacol Basis Ther. 2013;1744–5.
9. Novak V. Epilepsy Treatment Introduction. Clin Ther. 2017;39(8):e105–6.
10. Bradley's Neurology in Clinical Practice_5th Ed. www.worldcat.org › title › bradleys-neurology-in-clinical-practice › oclc
11. Oishi M. [Differential diagnosis of epilepsy]. Nihon Rinsho. 2014;72(5):839–44.
12. Van der Meyden CH, Rodda JL. Epilepsy management at primary health care level. South African Med J. 2000;90(4 II):403–32.
13. Thomas S V. Management of epilepsy and pregnancy. J Postgrad Med. 2006;52(1):57–64.
14. Brophy GM, Bell R, Claassen J, Alldredge B, Bleck TP, Glauser T, et al. Guidelines for the evaluation and management of status epilepticus. Neurocrit Care. 2012;17(1):3–23.

15. Kälviäinen R. Status epilepticus treatment guidelines. Epilepsia. 2007;48(SUPPL. 8):99–102.
16. NewYork-Presbyterian Brooklyn Methodist Hospital ADULT Status Epilepticus Treatment Guideline. 2017;22–3. Available from: https://camls-us.org/wp-content/uploads/2017/10/1300-Status-Epilepticus-Guideline-Nouri.pdf
17. Dekker PA, World Health Organization. Epilepsy: A manual for medical and clinical officers in Africa. World Health Organization; 2002.
18. World Health Organization. (2019). Epilepsy: a public health imperative.
19. Epilepsy: Key facts. World Health Organization (WHO) 2022.https://www.who.int/news-room/fact-sheets/detail/epilepsy

CHAPTER THIRTEEN

14. Parkinson's Disease (PD)

14.1.Introduction

14.1.1. Brief description

- Parkinson's disease (PD) is a chronic, insidiously progressive neurodegenerative condition characterized by primarily motor symptomatology including bradykinesia, rest tremor, rigidity, and postural disturbances.
- It is also linked to a variety of non-motor symptoms, which, along with late-onset motor symptoms (such as postural instability and falls, gait freezing, speech and swallowing difficulties), are currently one of the most difficult challenges facing treating physicians when dealing with patients who have had the disease for a long time.

14.1.2. Epidemiology

- Parkinson's disease is a worldwide affliction, with an annual incidence rate of 4.5–19 per 100,000 people.
- The incidence of PD was 7 per 100,000 populations in Ethiopia. The incidence and prevalence of PD increases with advancing age, it is usually diagnosed in people over the age of 65 years.
- Early-onset Parkinson's disease is defined as the onset of Parkinsonian features before the age of 40 years. PD is twice as common in men as in women in most populations.

14.1.3. Causes and risk factors

- The pathological hallmark of PD is a loss of the pigmented, dopaminergic neurons of the substantianigra pars compacta in the brain, with the appearance of intracellular inclusions known as Lewy bodies.
- The pathogenic process in PD involves regions of the peripheral and central nervous system in addition to the dopaminergic neurons of the substantia nigra pars compacta (SNpc).
- Dopamine deficiency in the basal ganglia leads to classical Parkinsonian motor symptoms (bradykinesia, tremor, rigidity and later postural instability).

14.2.Clinical features

- Parkinson's disease is defined clinically by the presence of bradykinesia in combination with at least one more manifestation: muscular rigidity, rest tremor or postural instability.

- Clinical manifestations of PD may be classified into two groups: motor symptoms and non-motor symptoms.

- Motor symptoms start unilaterally

  - ✓ Tremor is the primary symptom for some patients; the tremor associated with PD typically takes the form of a rhythmic back and forth motion of the thumb and forefinger. This is sometimes called "pill rolling." Tremor usually begins in a hand, although sometimes a foot or the jaw is affected first.
  - ✓ Rigidity is the increased muscular resistance to passive range of motion, and it often has a "cogwheel" quality. When a limb is moved by the examiner, it resists, then gives way in small, step like movements as if it were being controlled by a cogwheel.
  - ✓ Bradykinesia is slowness of movement. This may well be the most disabling and distressing symptom of the disease because the patient cannot perform routine movements quickly.
  - ✓ Postural instability is impaired balance and coordination.A stooped posture may develop in which the patient's head is bowed and the shoulders are drooped. Patients may stop in midstride and "freeze" in place or they may walk with a series of quick, small steps as if hurrying forward to keep balance (festination).

- Other motor symptom includes hypomimia (expressionless face), dysarthria, dysphagia, decreased arm swing, shuffling gait, and difficulty rising from a chair, difficulties with turning in bed, micrographia (abnormally small handwriting). Some of these symptoms are components of the natural history of the disease, while others are related to dopaminergic therapy.

- Non-motor symptoms are seen in a large proportion of patients. Some of these non-motor symptoms can antedate the onset of cardinal motor symptoms by years.

- Non-motor symptoms include sleep disorders (for example, frequent waking, and rapid eye movement sleep behavior disorder (RBD), and day time somnolence), hyposmia(decreased sense of smell), disturbance in autonomic function (orthostatic hypotension, urogenital dysfunction, erectile dysfunction and constipation), cognitive impairment, mood disorders, dementia, hallucinations, fatigue and pain.

Table 14: Hoehn and Yahr Stage Parkinson's disease

Stage Disease	State
I	Unilateral involvement only, minimal or no functional impairment
II	Bilateral or midline involvement, without impairment of balance
III	First sign of impaired righting reflex, mild to moderate disability
IV	Fully developed, severely disabling disease; patient still able to walk and stand unassisted
V	Confinement to bed or wheelchair unless aided

14.3.Diagnosis and investigations

14.3.1. Diagnosis and differential diagnosis

- There are no practical diagnostic laboratory tests for PD, in clinical practice the diagnosis rests on the clinical features of the patients and by excluding other causes of parkinsonism and response to levodopa.
- Routine laboratory and neuroimaging studies are not helpful in the diagnosis of PD. When making the diagnosis of early PD, the clinician should be aware of a number of red flags suggesting a diagnosis other than Parkinson disease.
- Parkinson's disease constitutes only one of many different causes of parkinsonism. It is necessary to consider and differentiate idiopathic PD from the following conditions which could have parkinsonism as their manifestation:
    - Diffuse lewy body disease
    - Multiple system atrophy
    - Cortico-basal ganglionic degeneration
    - Progressive supranuclear palsy
    - Vascular parkinsonism
    - Drug-induced parkinsonism
    - Parkinsonism caused by toxins
    - Wilson's disease

- Huntington's disease
- Spinocerebellar ataxia
- And others

Table 15: "Red Flags" Suggesting a Diagnosis Other than Parkinson Disease

Red flags
• Rapid progression of gait impairment requiring regular use of wheelchair within 5 y of onset.
• Early bulbar dysfunction: severe dysphonia or dysarthria or severe dysphagia within first 5 y.
• Inspiratory respiratory dysfunction: inspiratory stridor or frequent inspiratory sighs.
• Severe autonomic failure within 5 y of disease onset. (a) Orthostatic hypotension (b) Severe urinary retention or urinary incontinence
• Recurrent (>1/y) falls because of impaired balance within 3 y of onset.
• Absence of any of the common non motor features of disease despite 5 yr disease duration. Including: sleep dysfunction, autonomic dysfunction, hyposmia, or psychiatric dysfunction.
• Unexplained pyramidal tract signs, excluding mild reflex asymmetry and isolated extensor plantar response.
• Bilateral symmetric Parkinsonism.

14.3.2. Laboratory and imaging

- The use of laboratory and imaging tests is not useful to diagnose PD. However, laboratory and imaging tests may be indicated to rule out other health conditions which may manifest with Parkinsonism or coexist with PD. The following laboratory and imaging tests could be conducted for a patient with PD:
  - Complete blood count (CBC), sedimentation rate (ESR), serum liver transaminases, blood urea and creatinine
  - Fasting blood sugar, lipid profile (LDL, HDL, triglycerides)
  - Brain magnetic resonance imaging (MRI)

- Based on findings of medical history, neurological and physical examination, other tests may also be conducted when clearly indicated.

14.4.Treatment

14.4.1. Goals of treatment

- Manage the disabling symptoms as they arise
- Encourage a healthy lifestyle
- Minimize adverse effects of medications and manage as they arise
- Help the patient and their family understand the disease

14.4.2. General principles of treatment

- The treatment options must be individualized and tailored to the needs of each individual patient.
- PD is best managed in a multidisciplinary setting, to obtain satisfactory results regarding the various disabling aspects of the disease.
- The treatment of Parkinson's disease begins with its motor symptoms; over time, dementia and depression typically appear and require their own treatments.

14.4.3. Non-pharmacological treatment

- Exercise is increasingly recognized as important in PD management. Exercising may increase your muscle strength, flexibility, and balance. Exercise can also improve patient well-being and reduce depression or anxiety.
- Parkinson's disease patient should maintain well balanced diet increase consumptions of water and fiber diet help to reduce constipation.
- People with Parkinson disease and their families need for psychological, financial, legal, or occupational support to improve quality of life.

14.4.4. Pharmacological treatment

- There is no proven definitive disease-modifying therapy for Parkinson's disease, but drugs are effective in symptom control. Medications are the most common therapy for PD. The goal is to correct the shortage of dopamine.
- Treatments may differ according to the patient's symptoms, age, and responses to specific drugs. It often takes time to find the best combination of drugs for each patient.

1. *Levodopa/carbidopa*

- Levodopa (L-dopa, L-3, 4-dihydroxyphenylalanine), the metabolic precursor of dopamine, is the single most effective agent for treating PD. It is first-line drug and considered as gold standard therapy and almost all patient require this particular treatment during the course of their illness.
- Levodopa is almost always given in combination with Carbidopa (inhibitor of aromaticL-amino acid decarboxylase), which protects levodopa from early conversion to dopamine outside your brain that markedly reduces its peripheral adverse effects, particularly nausea.
- As the disease progresses it is important to establish the dose that relieves the increasing symptoms. This usually requires increasing the frequency of dosing
- Available doses (10/100 mg, 25/100 mg and 50/250 mg)

❖ Adverse effects- Nausea, Orthostatic hypotension, dyskinesia, daytime sleepiness and edema.

2. *Dopamine-Receptor Agonists (Bromocriptine)*

- Dopamine agonists are also effective first-line drugs especially in younger patients. Dopamine agonist may be associated with less dyskinesia than Levodopa/Carbidopa.
- They last longer and may be used with levodopa to smooth the sometimes off-and-on effect of levodopa.
- Side effects include hallucinations, sleepiness, and behavioral problems that include pathological gambling, compulsive shopping and eating, hypersexuality, other impulse-control disorders and drug induced hallucinations (especially in elderly people with cognitive impairment), and therefore, they are better avoided in the high-risk groups.

3. *Anticholinergic Agents (Trihexyphenidyl)*

- They reduce tremor and rigidity but have no effects on bradykinesia and are better tolerated in younger patients.
- The adverse events associated with the muscarinic receptor antagonists result from their anticholinergic properties. Some of the common side effects are confusion, blurred vision, dry mouth, constipation, and urine retention.

When to start treatment?

- Deciding when to start drug therapy for Parkinson's disease should be individually tailored to a patient's symptoms, circumstances and comorbidities. Treatment is indicated when symptoms impact on quality of life.

14.4.5. *Complications related to pharmacological treatment*

Levodopa-related clinical fluctuations

- This drug related complications have various clinical presentations, and very often, the non-motor fluctuations precede and/or accompany the motor ones.
  - "Wearing-off" occurs during treatment. When "wearing-off" happens, the patient finds that levodopa effects begin to fade or wear off before the next dose. As a management for "wearing-off" give levodopa more frequently, possibly in smaller doses.
  - If the patient is experiencing a delayed or poor quality 'on' response, make sure the drug is not taken with a large amount of dietary protein and is taken 30 to 60 minutes before meals.
  - When fluctuations or 'on-off' attacks occur, instead of the usual rapid onset and four-hour duration of levodopa, unpredictable swings from normality to profound hypokinesia occur. As a management measure, do the following:
    - ✓ Ensure maximal absorption (take on empty stomach, treat constipation)
    - ✓ Give levodopa more frequently
    - ✓ Add a dopamine agonist
  - Abnormal involuntary movements or dyskinesias may occur during treatment such as:
    - ✓ Peak-dose dyskinesia, dominated by choreic movements and less frequently dystonic features during the "on" period, usually associated with high dopaminergic medication blood levels.
    - ✓ "Off" dystonia, usually associated with low dopaminergic medication blood levels that may manifest by painful foot inversion, may develop as "early-morning dystonia" that manifests on awakening before the first dose of levodopa.
    - ✓ Diphasic (biphasic) dyskinesia that usually manifests as choreic and/or dystonic movements during the time of increasing and decreasing levodopa levels.

- Dyskinesias are often not troubling to patients, so they do not always require a change of treatment. Disabling dyskinesias may require dose reduction at the risk of loss of efficacy.

14.4.6. Treatment of non-motor symptoms in Parkinson's disease

- Non-motor symptoms such as depression, constipation, and rapid eye movement (REM) sleep behavior disorder are increasingly recognized and may precede the diagnosis of PD by many years.
- Non-motor fluctuations are well recognized, and some may improve with optimization of dopaminergic therapies to improve wearing-off.

Table 16: Management Summary of common non-motor symptoms of Parkinson's disease

Symptom	Therapy	Comments
Depression	Consider Anti-depressant CBT	Optimized Dopaminergic Therapy SSRIs
Dementia	ChEIs **(e.g.** Rivastigmine)	May worsen tremor, GI/bladder AEs
Psychosis	Quetiapine Clozapine	Usually, first line Requires CBC monitoring
Postural hypotension		Reduce anti-hypertensives and otherpotential exacerbating drugs
Constipation	Probiotics and prebiotic fiber	Ensure good hydration Constipation may impact on medication absorption
Drooling		Anticholinergic may cause cognitive AEs
REM sleep behavior disorder	Clonazepam	

Reference

1. Stoker TB, Greenland JC, editors. Parkinson's Disease: Pathogenesis and Clinical Aspects [Internet]. Brisbane (AU): Codon Publications; 2018 Dec 21. Section II, Diagnosis and Management.

2. David P Moore. Textbook of Clinical Neuropsychiatry. 338 Euston Road, London NW1 3BH: Hodder Arnold Publications; 2008. Second edition
3. Joseph Jankovic and L Giselle Aguilar. Current approaches to the treatment of Parkinson's disease. Neuropsychiatr Dis Treat 2008; 4(4): 743- 757.
4. World Health Organization. Neurological disorders: public health challenges. World Health Organization; 2006.
5. Tekle-Haimanot R, Abebe M, Gebre-Mariam A, Forsgren L, Heijbel J, Holmgren G, Ekstedt J. Community-based study of neurological disorders in rural central Ethiopia. Neuroepidemiology. 1990;9(5):263-77.
6. Milanov I, Relja M, Bajenaru O, Kov N, Skorvanek M. Update on the Management of Parkinson ' s Disease for General Neurologists.2020.
7. Goldenberg MM, Mar M. Medical Management of Parkinson ' s Disease. P T. 2008;33(10).
8. Radhakrishnan DM, Goyal V. Parkinson ' s disease : A review. Neurology India 2018(March); 66(7): 26-35.
9. Robert Daroff, Joseph Jankovic, John Mazziotta, Scott Pomeroy.Bradley's Neurology in Clinical Practice. London: Elsevier; 2016.7th edition.
10. Jankovic J. Parkinson ' s disease : Clinical features and diagnosis. J Neurol Neurosurg Psychiatry 2008;79: 368–376. doi:10.1136/jnnp.2007.131045
11. Annabelle Sellbach and Peter Silburn. Management of Parkinson ' s disease. Aust Prescr 2012; 35: 183-8.
12. Julian Rodrigues. Parkinson's Disease: A General Practice Approach. Parkinson's Western Australia Inc 2014, 2017 (February).
13. Christopher Kobylecki. Update on the diagnosis and management of Parkinson' s disease. Clin Med (Lond) 2020 Jul; 20(4):393-398. doi: 10.7861/clinmed.2020-0220.

CHAPTER FIFTHEEN

15.Major and Mild Neurocognitive Disorders (NCDs)

15.1.Introduction

15.1.1. Brief description

- Major and mild neurocognitive disorders (NCDs) exist on a spectrum of cognitive functional impairment.
- Major NCD corresponds to the condition which previously was referred to as dementia. According to DSM-5, major neurocognitive disorder also known as "dementia" is defined as significant acquired cognitive impairment in one or more cognitive domains (eg, learning and memory, language, executive function, complex attention, perceptual-motor function, and social cognition) that represents a significant decline from baseline and interferes with independence in daily activities.

15.1.2. Epidemiology

- Globally, about 47 million people were living with dementia in 2015, and this number is projected to triple by 2050.
- A systematic review of studies from Sub-Saharan African countries showed that prevalence of dementia ranged from <1% to 10.1% in population-based studies and from <1% to 47.8% in hospital-based studies.
- Incidence data for dementia ranged from 8.7 to 21.8 cases per 1000 per year.
- Alzheimer disease was the most common form of the disease, representing 57.4 to 89.4 % of all cases, followed by vascular dementia 5.7 to 31.0% of cases, and the incidence of Alzheimer disease ranged from 9.5 to 11.5 per 1000 per year.

15.1.3. Causes and risk factors

The causes of NCD (dementia) can be either irreversible or reversible. Next is the list in each category.

Irreversible causes of NCD (dementia) include:

- Alzheimer's disease
- Frontotemporal dementia
- Vascular dementia

- Dementia with Lewy bodies
- Parkinson's dementia
- Huntington's disease
- Prion related dementia

Reversible causes of dementia include:

- Subdural hematoma
- Normal pressure hydrocephalus
- Intracranial tumors
- Central nervous system (CNS) infections (tubercular, fungal, HIV, neurosyphilis, protozoal, etc)
- Inflammatory (sarcoidosis, systemic lupus erythematosus, etc)
- Metabolic conditions (thyroid, pituitary, adrenal abnormalities, diabetes mellitus, etc)
- Electrolyte imbalance
- Organ failure (liver, renal, pulmonary)
- Nutritional deficiencies (vitamins A, B1, B6, B12, folate, iron)
- Depression
- Alcohol use disorder
- Heavy metal toxicity
- Medications and treatments (steroids, chemotherapy, radiotherapy, etc)
- Heart disease (arrhythmias, congestive heart failure, myocardial infarction)

Risk factors for NCD (dementia) include the following:

- Ageing
- Sex (female)
- Illiteracy/ lack of early education
- Environmental stress
- Vascular risk factors (hypertension, dyslipidemia)
- Lifestyle factors (Physical activity, cognitive activity, social activity and nutrition)
- Traumas/ accidents
- Inborn physical attributes
- Genetic influence

- Early-life deleterious conditions

15.2.Clinical features

The essential characteristic of NCDs is the occurrence of cognitive decline in one or more cognitive domains. Major and mild NCDs affect functioning of affected individuals due to the critical role of cognitive function in everyday life. The threshold for differentiating mild from major NCDs is based partly on the level of functional impairment.In major NCD there is a wide range of functional impairment. The specific functions that are compromised can help identify the cognitive domains affected. The affected cognitive domain could be one or more of the following:

- Complex attention
- Executive function
- Learning and memory
- Language
- Perceptual motor
- Social cognition

15.3.Diagnosis and investigations

15.3.1. Diagnosis and differential diagnosis

- Diagnosis of major and mild neurocognitive disorders (NCDs) should be made with fulfillment of the DSM-5 criteria for the disorders.
- The symptoms should be validated by both subjective and objective findings. Subjectively, a concern about cognitive deficits must be there on the side of the patient, knowledgeable informant or the clinician. Objectively, there should be detectable decline of performance on an objective assessment that falls below the expected level or that has been observed to decline over time. For objective assessment the clinician is expected to use brief cognitive tests such as the MINI-Mental State Examination.
- The clinician is expected to do intensive evaluation and workup to include the specific etiology which caused the NCD and document the evaluations and investigations conducted and their outcome.
- Searching for potential treatable or reversible causes for the NCDs is a critical part of the diagnostic process and its consideration and making the assessment must be clearly

documented. The criteria met during the initial diagnosis must be clearly documented and updated during each visit to show progress, as well as the essential workup for any specific causative condition.

- Risk assessment should include evaluation of suicidality, the potential for aggression, as well as evaluation of living conditions, safety of the environment, adequacy of supervision and evidence of neglect or abuse.
- Clear documentation of differential diagnosis is necessary. The differential diagnosis between normal cognitive function and mild NCD, as well as between mild and major NCDs is challenging.
- Careful history taking and objective assessment are critical for this distinction. A longitudinal evaluation using quantified assessments (such as the MINI-Mental State Examination) could be necessary.
- Both mild and major NCDs may be difficult to distinguish from a persistent delirium, which can also occur as comorbid condition. Careful assessment of attention and arousal will be helpful to differentiate NCDs from delirium. In NCDs, cognitive dysfunction occurs in clear sensorium, while sensorium is characteristically affected in delirium. It may be challenging to differentiate major depressive disorder (MDD) from mild NCD, and, to make matters worse, the two conditions may exist as comorbidities.
- Consistent specific cognitive deficits are characteristic of NCD, while non-specific or more variable cognitive performance is seen in MDD. Sometimes, treating the depression with repeated observation overtime may be required to make the differential diagnosis. A careful clarification of the individual's baseline status will help distinguish NCD from a specific learning disorder and other neurodevelopmental disorders.

15.3.2. Laboratory and imaging

- All the necessary baseline laboratory tests should be done for a patient with NCD. These may include complete blood count (CBC), sedimentation rate (ESR), liver transaminases, urea, creatinine, fasting blood sugar (FBS). Other tests could be indicated based on the results of the history and physical/ mental state examination.

Specific recommended tests for patients with NCD also are to be considered as justified. For all patients who have a clinical presentation consistent with Alzheimer disease only a basic set of

laboratory tests should be ordered to rule out causes of chronic metabolic encephalopathy producing chronic confusion and memory loss. These tests may include:

- Complete blood count (to rule out anemia)
- Thyroid stimulating hormone (to rule out hypothyroidism)
- Serum electrolytes (to rule out hyponatremia)
- Serum calcium (to rule out hypercalcemia)
- Serum fasting glucose (to rule out hyperglycemia)
- Serum vitamin B12 level

Brain magnetic resonance imaging (MRI) is recommended if one or more of the following criteria are present:

- Age < 60 years
- Rapid (e.g., over 1–2 months) unexplained decline in cognition or function
- Short duration of dementia (< 2 years)
- Recent and significant head trauma
- Unexplained neurologic symptoms (e.g., new onset of severe headache or seizures)
- History of cancer (especially types that metastasize to the brain)
- Use of anticoagulants or history of bleeding disorder
- History of urinary incontinence and gait disorder early in the course of dementia (as may be found in normal pressure hydrocephalus)
- Any new localizing sign (e.g., hemiparesis or a Babinski reflex)
- Unusual or atypical cognitive symptoms or presentation (e.g., progressive aphasia)
- Gait disturbance

15.4.Treatment

15.4.1. Goals of treatment

The goals of treatment for neurocognitive disorders (NCDs) are:

- Thorough evaluation to identify the underlying cause of the NCD
- Identify and treat reversible causes
- Identify and treat comorbid psychiatric and medical conditions

- Involving patients, families and caregivers in the management plan
- Provide appropriate psychotherapeutic measures
- Provide medications to improve cognitive function

15.4.2. General principles of treatment

- Thorough psychiatric, neurological, and other medical evaluation of the cause of the cognitive deficits and associated non-cognitive symptoms
- It is particularly critical to identify and treat other medical conditions, most notably delirium
- Ongoing periodic monitoring of the development and evolution of cognitive and non-cognitive psychiatric symptoms
- There should be routine follow-up at least every 3-6 months
- For patients with acute, complex, or potentially dangerous symptoms, or for administration of specific therapies more frequent visits as frequent as once or twice a week, or even admission could be necessary
- It is important to identify and treat co-occurring psychiatric and medical conditions
- Patients and families should be helped to anticipate future symptoms and the care likely to be required
- Important aspects of psychiatric management include educating patients and families about the illness, its treatment, and sources of additional care and support (eg., support groups, respite care, nursing homes, and other long-term care facilities)
- Because age may alter the absorption, distribution, metabolism, and elimination of many medications, elderly patients with NCD (dementia) may be more sensitive to their effects; therefore, care should be exercised to avoid such problems
- Precaution should be gauged particularly to the anticholinergic effects, orthostatic hypotension, sedation, and Parkinsonism
- Low starting doses, small increments in dose, and long intervals between dose increments are needed
- Because of the nature of the illness itself, it may be required to put a system in place that can enhance proper medication adherence

15.4.3. Non-pharmacologic treatment

- Psychotherapeutic measures could be helpful in the treatment of patients with NCDs. The recommended approaches include behavior-oriented, stimulation-oriented, and emotion-oriented.
- Behavioral-oriented treatments can help to identify the antecedents and consequences of problem behaviors. This allows reduction of the frequency of behaviors by directing changes in the environment that alter these antecedents and consequences.
- Stimulation-oriented treatments such as recreational activity, art therapy, and music therapy help to improve behavior, mood, and to a lesser extent, function.
- Emotion-oriented treatments such as supportive psychotherapy help address issues of loss in the early stages of NCD (dementia).

15.4.4. Pharmacologic treatment

Treatment of cognitive symptoms

- Cholinesterase inhibitors such as donepezil, rivastigmine and galantamine have modest benefits in 30-40% of patients for treatment of mild to moderate Alzheimer's disease. Those medications should be offered to patients after thorough discussion of their potential risks and benefits.
- Cholinesterase inhibitor medications should also be considered for patients with mild to moderate dementia associated with Parkinson's disease, as well as Lewy bodies. Memantine, a non-competitive N-methyl-D-aspartate (NMDA) antagonist, may provide modest benefits to patients with moderate to severe Alzheimer's disease and has fewer side-effects. However, availability and cost make the use of these medications difficult. The benefits of the medications compared to their cost should be realistically discussed with patients (or their families and caregivers). Sometimes, families could be desperate to help the patient and may push toward the use of the medications. Therefore, these medications have been included in the treatment of patients with NCD regardless of their availability in Ethiopia.

Treatment of psychosis and agitation

- Psychosis, aggression and agitation are common in patients with NCDs (dementia). Any underlying medical, psychiatric, environmental, or psychosocial conditions should be

addressed first. Antipsychotics may be necessary to control the symptoms with or without benzodiazepines. The use of antipsychotics and benzodiazepines should be re-evaluated and their benefit documented on an ongoing basis.

- Antipsychotics must be used with caution and at the lowest effective dose. The decision of which antipsychotic to use is based on the relationship between the side-effect profile and the characteristics of the individual patient. However, the use of low doses of haloperidol or Risperidone is recommended. Benzodiazepines could have a role in treating patients with prominent anxiety, or on as-needed basis for patients with infrequent episodes of agitation. If benzodiazepines have to be used Lorazepam is preferable to the long acting drugs (diazepam and clonazepam).

Treatment of depression

- Depression is common in patients with NCDs (dementia). Patients with depression should be evaluated for suicide risk. Depression may respond to improvements in the patient's living situation, or to stimulation-oriented treatments.
- An antidepressant must be given to treat clinically significant persistent depression. The choice among antidepressant agents is based on the side-effect profile of specific medications and the characteristics of the individual patient. Selective serotonin reuptake inhibitors (SSRIs) may be preferred because they appear to be better tolerated than other antidepressants.
- Antidepressant agents with substantial anticholinergic effects (eg., amitriptyline and imipramine) should be avoided. Unilateral electroconvulsive therapy (ECT) may be effective for patients who do not respond to medications.

Treatment of sleep disturbance

- Sleep disturbance is common in patients with NCD (dementia). Interventions include maintaining daytime activities and giving careful attention to sleep hygiene.
- Pharmacological interventions could be considered when other approaches have failed. If a patient also requires medication for other psychiatric condition, an agent with sedating properties given at bedtime, could be selected. For primarily treating the sleep

disturbance, benzodiazepines are not recommended for other than brief use. Diphenhydramine is not recommended because of its anticholinergic properties.

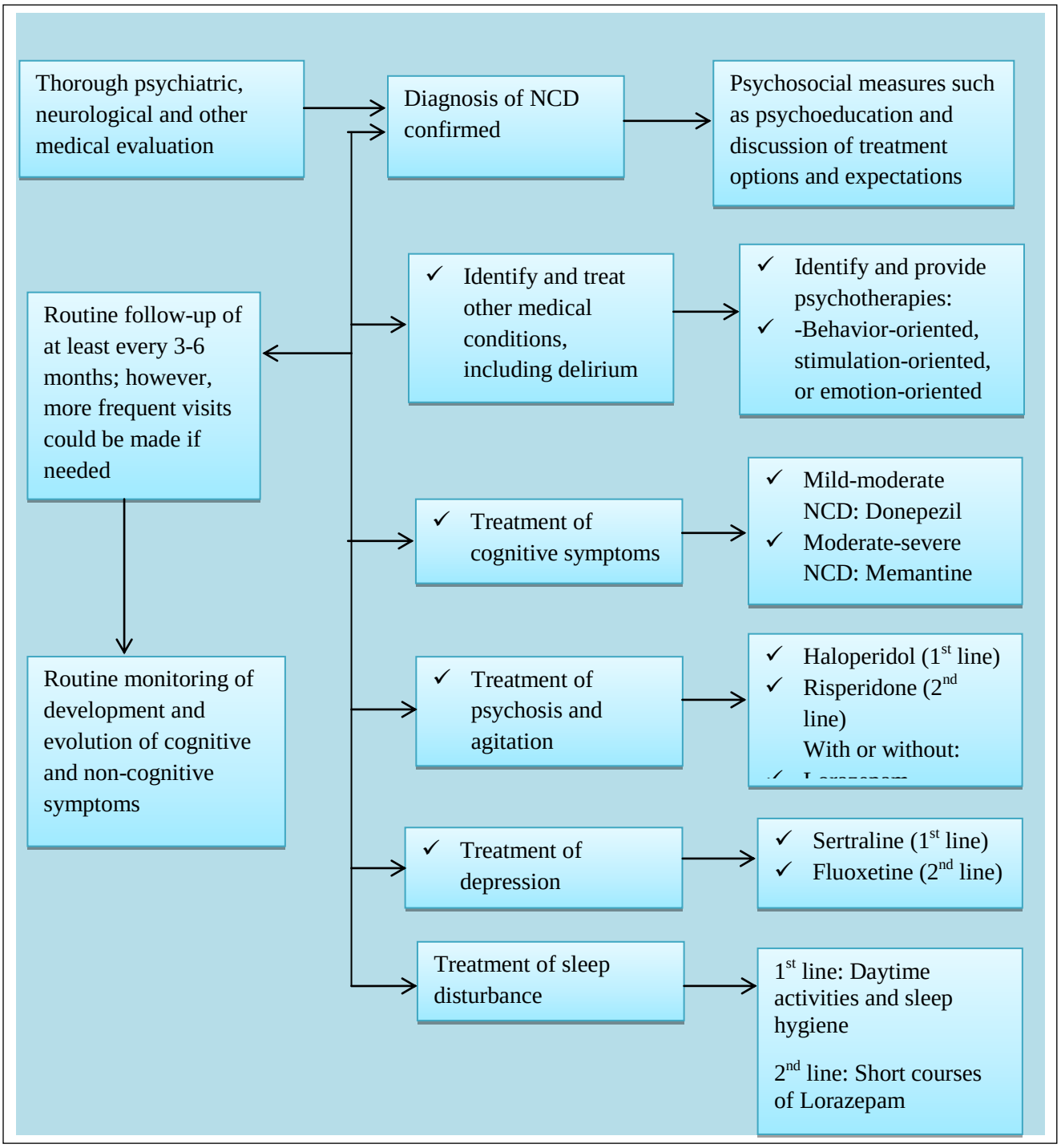


Figure 19: Algorithm for the treatment of neurocognitive disorders

Reference

2. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, text revision. Washington DC, American Psychiatric Association, 2022.
3. Practice Guideline for the Treatment of Alzheimer's disease and Other Dementias.American Psychiatric Association (APA), 2007.
4. Howard H. Feldman, Claudia Jacova, Alain Robillard, Angeles Garcia, Tiffany Chow, Michael Borrie, Hyman M. Schipper, Mervin Blair, Andrew Kertesz, Howard Chertkow. Diagnosis and treatment of dementia. CMAJ 2008;178(7):825-36
5. Gill Livingston, Andrew Sommerlad, VasilikiOrgeta, Sergi G Costafreda, Jonathan Huntley, David Ames et al. Dementia prevention, intervention, and care. The Lancet Commissions. www.thelancet.com. **Published online July 20, 2017**http://dx.doi.org/10.1016/S0140-6736(17)31363-6
6. Alain Lekoubou, Justin B Echouffo-Tcheugui and Andre P Kengne. Epidemiology of neurodegenerative diseases in sub-Saharan Africa: a systematic review. BMC Public Health 2014, 14:653. http://www.biomedcentral.com/1471-2458/14/653
7. Grover S, Somani A. Etiologies and risk factors for dementia. J GeriatrMent Health 2016;3:100-7.
8. Maria Cristina Polidori, GereonNelles, and LudgerPientka. Prevention of Dementia: Focus on Lifestyle. International Journal of Alzheimer's DiseaseVolume 2010, Article ID 393579, 9 pages doi:10.4061/2010/393579

CHAPTER SIXTEEN

16.Post-Traumatic Stress Disorder (PTSD)

16.1.Introduction

16.1.1. Brief description

- Post-traumatic stress disorder (PTSD) is characterized by the development of characteristic symptoms which occur following exposure to one or more traumatic events such as war, physical assault, sexual violence, being kidnapped, terrorist attack, torture, etc.
- The characteristic symptoms develop after exposure of the individual to traumatic events.
- Not all individuals exposed to traumatic events develop PTSD or its symptoms and signs.
- The disorder is characterized by symptoms of re-living the traumatic event through memories, nightmares or flashbacks. The re-living is associated with marked distress and the person attempts to avoid reminders of the traumatic event.
- In addition, the person develops negative sensations or emotions, as well as excessive excitability, which causes problems concentrating, sleeping, and so on.

16.1.2. Epidemiology

- About 8 million adults had PTSD during a given year worldwide
- Statistical estimates showed that PTSD is between 1% and 5% in the general population and between 3% and 58% for high-risk groups such as displaced people
- Prevalence rate of PTSD in developing countriesis higher compared with the developed ones
- In Ethiopian studies, the prevalence of PTSD among survivors of a landslide at Koshe in Addis Ababa was 37.3% and prevalence among internally displaced people (IDP) in South Ethiopia was 58.4%

16.1.3. Causes and risk Factors

- The causative and/or risk factors for developing PTSD include exposure to traumatic events including the following:
    - Experiencing or witnessing serious physical, emotional, or sexual abuse
    - Major accidents or illnesses, drug addiction
    - Major natural or man-made disasters, including war situations
    - Children and adults may experience PTSD symptoms after experiencing bullying by peers or mugging incidents

- After being exposed to traumatic events, the conditional probability of different people developing PTSD varies across cultural groups
- Pre-trauma factors which put a person at risk of developing PTSD include family history of mental illness and substance misuse history
- Post-trauma factors also put a person at risk of developing PTSD; one such factor is the lack of social support
- In Ethiopian studies, the risk factors identified for developing PTSD among survivors included:
    - Female sex
    - History of mental illness
    - Physical injury
    - Poor social support
    - High perceived life threats
    - Repeated displacement (among IDP)
    - Witnessing murder of a family member or a friend
    - Destruction of personal property

16.2.Clinical characteristics

- The clinical presentation of PTSD varies. In some patients, the predominating feature may be fear-based re-experiencing as well as emotional and behavioral symptoms.
- In others, anhedonia or dysphoric mood states and negative cognitions predominate.
- Arousal and reactive-externalizing symptoms predominate in another group of patients; dissociative symptoms predominate in still other groups.
- Different combinations of the listed presentations may occur in patients.
- In some patients the predominating feature may be an anxiety response that includes some form of re-experiencing of, or reactivity to the traumatic event.
- In others, a dissociative presentation can predominate; in still others, there can be a strong anger response in which reactivity is characterized by irritable or possibly aggressive responses.

The re-experiencing can be in form of recurrent, involuntary and intrusive recollections of the event; for example, distressing dreams that replay the traumatic event. Stimuli associated with

the trauma could be persistently avoided. For example, the patient may avoid thoughts, memories, feelings or talking about the traumatic event. Patients may also have heightened sensitivity to potential threats. Loss of concentration, sleep difficulties, and becoming quick-tempered may also occur.

Some features may be associated with the occurrence of PTSD symptoms. Developmental regression such as loss of language in young children, auditory pseudo-hallucination such as having the sensory experience of hearing one's thought spoken, as well as paranoid ideations can be present.

16.3.Diagnosis and investigations

16.3.1. *Diagnosis and differential diagnosis*

- Diagnosis of post-traumatic stress disorder (PTSD) or should be made with fulfillment of the DSM criteria for the disorder. The criteria met during the initial diagnosis must be clearly documented and updated during each visit to hospital to show progress.
- Documentation of consideration of differential diagnosis is necessary to show that clear diagnosis of PTSD has been made. PTSD must be differentiated from adjustment disorders. The diagnosis of adjustment disorders can be used when the diagnosis of PTSD or ASD has been ruled out.
- Acute stress disorder is distinguished from PTSD because the duration of symptoms in acute stress disorder is between 3 days and one month, while the duration of symptoms in PTSD is more than one month.
- Post-traumatic stress disorder should be differentiated from obsessive-compulsive disorder (OCD). In OCD the recurrent intrusive thoughts meet the definition of an obsession, and are not related to experiencing a traumatic event.
- Anxiety disorders are also a potential group of disorders for differential diagnosis with PTSD. However, the arousal and dissociative symptoms of panic disorder are not associated with specific traumatic event. The worry and irritability of generalized anxiety disorder (GAD) are not associated with specific traumatic event, either. The other differential diagnostic category is dissociative disorders.

- Dissociative amnesia, dissociative identity disorder and depersonalization, as well as de-realization may occur after trauma may confuse with dissociative disorders. However, full criteria should be met for the diagnosis of PTSD to be made.
- Psychosis could be another differential diagnostic challenge. Flashbacks in PTSD can often be confused with illusions, hallucinations and other perceptual disturbances that occur in disorders which often present with psychosis (such as schizophrenia, brief psychotic disorder and other psychiatric manifestations of psychosis, depression, bipolar disorders, delirium, etc).
- Detailed history is needed to distinguish these symptoms to avoid misdiagnosis.

16.3.2. *Laboratory and imaging*

- Laboratory and imaging studies are not helpful for diagnosis of post-traumatic stress disorder. However, as part of comprehensive evaluation of the patient, complete medical history and physical examination are part of any psychiatric evaluation; the findings of the history and physical examination will reveal to the clinician about which laboratory and imaging studies to consider based on the age, sex and medical condition of the patient.
- At onset of treatment, the minimal baseline workup should be done and documented. The minimal baseline workup may include complete blood count (CBC), sedimentation rate (ESR), liver enzymes, urea and creatinine, fasting blood sugar and, in female patients of reproductive age urine HCG.

16.4.Treatment

16.4.1. Goals of treatment

- To not further traumatize the patient
- To assure the safety of the patient
- To give symptomatic relief to the patient
- To help the patient cope better
- To fully control symptoms of PTSD in the long-term

16.4.2. General principles of management

- Evidence does not support the wide spread use of early intervention with psychological strategies for the prevention of PTSD. Debriefing of all trauma victims is not recommended, rather, screening and treating appropriate individuals is preferred. There is little evidence

supporting the use of pharmacotherapy for the prevention of PTSD, with most studies suggesting no preventive benefits.

- Psychological therapies for PTSD generally include education about the disorder and its treatment, as well as exposure to cues relating to the traumatic event. Psychotherapy has demonstrated significant efficacy.
- Care for patients with post-traumatic stress disorder (PTSD) should be given within a safe environment. Ensuring safety is the first step in the management of patients who have faced recent trauma. Additionally, ensuring that patients have basic needs for example food, shelter, sanitation should be the priority.
- Insensitive or premature exploration of recent life-threatening events or losses can be counterproductive, leading the patient to avoid medical care. Therefore, it is necessary to be sensitive and non-judgmental during interview. Privacy and confidentiality should be assured. Not pushing or coercing the patient to tell their stories in relation to the trauma is very important. The clinician should pay attention to the basic needs of the patient and become advocate to the patient.
- After it has been determined that the traumatically exposed individual is able to tolerate more extensive evaluation, it is important to obtain a detailed history of the exposure and the patient's early responses to the trauma as well as the responses of significant others. This history can provide important information for treatment and prognosis.
- As with all psychiatric patients, for patients exposed to trauma it is crucial to assess the risk for suicide and nonlethal self-injurious behavior as well as the risk for harm to others. Hospitalization is generally indicated for patients who are considered to pose a serious threat of harm to themselves or others. If such patients refuse admission, they may be hospitalized involuntarily when their condition meets applicable criteria for emergency detention or involuntary hospitalization. Severely ill patients who lack adequate social support outside a hospital setting should also be considered for hospital admission.
- The therapeutic alliance is important and at times challenging to establish with patients who have experienced traumatic events. Attention to the clinician-patient interaction is important, even in settings such as emergency departments where the clinician may have only a single contact with the patient. A positive experience may also make the patient more receptive to

future evaluation or follow-up. Evaluation and treatment should always be conducted with sensitivity and in a safe environment that facilitates the development of trust.

- Providing optimal treatment for patients with PTSD may require a team approach involving the coordinated effort of several clinicians. Patients may have a wide variety of comorbid psychiatric and/or physical disorders that need to be addressed. Family intervention or coordination of support services is often needed. One team member must assume the primary overall responsibility for the patient's treatment. This individual serves as the coordinator of the treatment plan, advocates for the appropriate level of care, oversees the family involvement, makes decisions regarding which potential treatment modalities are useful and which should be discontinued, helps assess the effects of medications, and monitors the patient's safety. A psychiatrist is best positioned for such a role.
- Monitoring the patient's status for the emergence of changes in destructive impulses toward self or others is especially crucial. Emergence of new symptoms, significant deterioration in functional status, or significant periods without response to treatment may suggest a need for diagnostic reevaluation. For persons who seek care after traumatic events, it is helpful to provide education concerning the natural course of and interventions for PTSD as well as for the broad range of normal stress-related reactions.

16.4.3. Non-pharmacologic treatment

- Studies show evidence of the efficacy of several cognitive behavioral therapy (CBT) approaches for the management of chronic PTSD compared with wait-list or usual care control groups.
- There was evidence that individual trauma focused cognitive behavioral therapy (TF-CBT), eye-movement desensitization and reprocessing (EMDR), stress management, and group TF-CBT were effective. Prolonged exposure (PE) was found to be as effective as other active treatments (e.g., CBT or EMDR). Imaginal exposure appears to be as effective as in vivo exposure.
- Dialectical behavior therapy (DBT), which was developed to reduce self-harm behavior in patients with borderline personality disorder, was shown to be useful in patients with PTSD. When used as a pretreatment, DBT reduced self-harm behaviors allowing over half of patients to become suitable candidates for PTSD treatment. Studies also suggest that

cognitive behavioral therapy (CBT) is useful for fear-based PTSD, while this treatment approach may require an additional treatment module in complex PTSD.

- The role of combining psychotherapy and medication, such as selective serotonin reuptake inhibitors (SSRIs) requires further study as results are inconsistent. Adjunctive propranolol with trauma reactivation therapy was found to help prevent reconsolidation of the traumatic memory and thus decreased physiological responses and PTSD symptoms during subsequent follow-up in randomized and open trials.
- In summary, psychotherapy is an effective first-line option for the treatment of PTSD. Effective approaches include TF-CBT, EMDR, PE, and stress management therapy. The recommendation and initiation of a particular psychotherapeutic modality should be done with due consideration of the availability of expertise and conducive conditions for its implementation.

16.4.4. Pharmacologic treatment

- Pharmacological interventions that have good evidence for efficacy in treating PTSD include the selective serotonin reuptake inhibitors such as sertraline and fluoxetine. The SSRIs should be considered first-line pharmacologic agents. The tricyclinc antidepressants such as amitriptyline were also found to be beneficial for the treatment of PTSD with evidence. The other medications for which there is evidence include the noradrenergic and specific serotonergic antidepressants (NaSSAs) such as mirtazapine.

- Pharmacologic agents are indicated for PTSD patients with severe symptoms of co-morbidities such as depression, and to those with high risk of suicide; in such cases, antidepressants should always be considered. The use of atypical antipsychotics such as risperidone and quetiapine has limited evidence and it is better avoided as solo therapy considering the risk of using antipsychotic medications for PTSD. Atypical antipsychotics could, however, be helpful in patients with psychotic symptoms; besides, atypical antipsychotics could help to augment SSRIs or TCAs during treatment of PTSD.

- Response to treatment can be monitored using the Clinical Global Impressions Scale. The Clinical Global Impressions Scale-Severity Item (CGI-S) should be scored at baseline, and the Clinical Global Impressions Scale-Improvement Item (CGI-I) should be scored at 12 and

24 weeks to see response. The usual duration of treatment trial of 12 weeks is not adequate for PTSD; therefore, treatment should continue for 24 weeks.

- In summary pharmacotherapeutic approaches for PTSD should begin with one of the first-line options, which include SSRIs such as sertraline or fluoxetine. If response to optimal doses (50-200 mg/day of sertraline or 20-60 mg/day of fluoxetine) is inadequate or the agent is not tolerated, therapy should be switched to another first line drug, or to a second line agent. Patients with PTSD may make few gains during treatment, and it is important to preserve even small gains achieved with initial therapy. Therefore, if there is significant (but not adequate) response at 12 weeks of treatment, augmentation with other agents such as atypical antipsychotic drugs may be important early in treatment.
- Patients who do not respond to multiple courses of therapy are considered to have treatment-refractory illness. In such patients it is important to reassess the diagnosis and consider comorbid medical and psychiatric conditions that may be affecting response to the

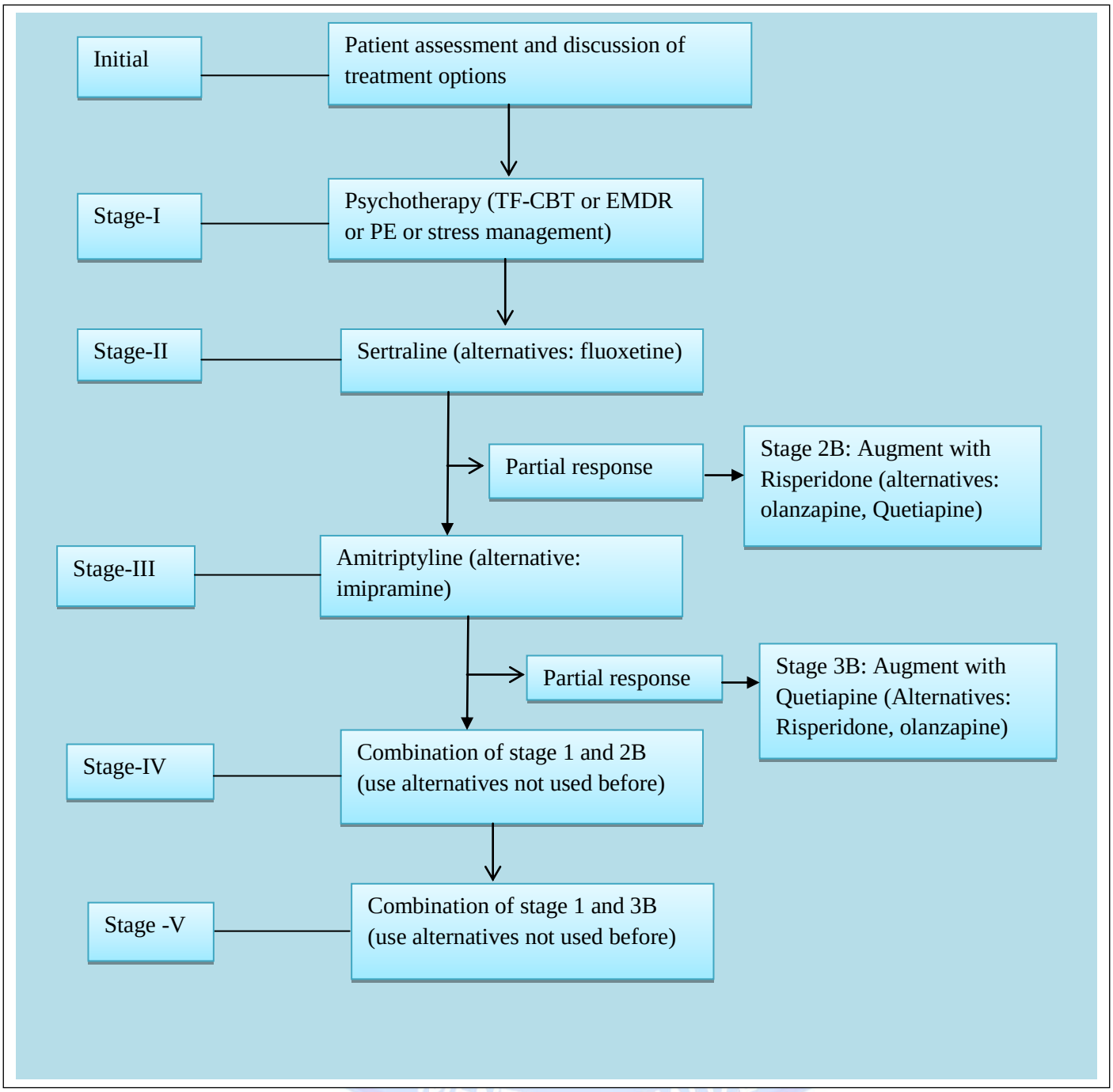


Figure 20: Algorithm for the treatment of PTSD

References

1. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, text revision. Washington DC, American Psychiatric Association, 2022.

2. Martin A Katzman, Pierre Bleau, Pierre Blier, PratapChokka, Kevin Kjernisted, Michael Van Ameringen. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. BMC Psychiatry 2014, 14 (Suppl 1):S1 http://www.biomedcentral.com/1471-244X/14/S1/S1
3. Asnakew S, Shumet S, Ginbare W, *et al*. Prevalence of post-traumatic stress disorder and associated factors among Koshe landslide survivors, Addis Ababa, Ethiopia: a community-based, crosssectional study. *BMJ Open* 2019;9:e028550. doi:10.1136/ bmjopen-2018-028550
4. Hg L, Heather Graham L. How Common is PTSD? National Center for PTSD. 2015.:1. National Center for PTSD. 2015:1.
5. Norris FH, Murphy AD, Baker CK, *et al*. Epidemiology of trauma and posttraumatic stress disorder in Mexico. *J AbnormPsychol*2003;112:646–56.
6. Keane TM, Marshall AD, Taft CT. Posttraumatic stress disorder: etiology, epidemiology, and treatment outcome. *Annu Rev ClinPsychol*2006;2:161–97.
7. DerebeMadoro, HabtamuKerebih, YoditHabtamu, Meseret G/tsadik, HirbayeMokona, AlemayehuMolla, TirusewWondie, KalkidanYohannes. Post-Traumatic Stress Disorder and Associated Factors Among Internally Displaced People in South Ethiopia: A Cross-Sectional Study. Neuropsychiatric Disease and Treatment 2020:16 2317–2326
8. Steel Z, Chey T, Silove D, Marnane C, Bryant RA, Van Ommeren M. Association of torture and other potentially traumatic events with mental health outcomes among populations exposed to mass conflict and displacement: a systematic review and meta-analysis. *JAMA*. 2009;302(5):537–549. doi:10.1001/jama.20 09.113218
9. Delirium: Prevention, diagnosis and management. National Institute for Health and Care Excellence (NICE, 2018). www.nice.org.uk/guidance/ng116
10. Williams T, Phillips NJ, Stein DJ, Ipser JC. Pharmacotherapy for post-traumatic stress disorder (PTSD). Cochrane Database of Systematic Reviews 2022, Issue 3. Art. No.: CD002795. DOI: 10.1002/14651858.CD002795.pub3.

CHAPTER SEVENTEEN

17.Substance Related Disorders

17.1.Introduction

- Substance-related disorders encompass 10 separate classes of drugs: alcohol, caffeine, cannabis, hallucinogens (with separate categories for phencyclidine [or similarly acting arylcyclohexylamines] and other hallucinogens), inhalants, opioids, sedatives/ hypnotics/ anxiolytics, stimulants (amphetamine-type substances, cocaine, and other stimulants), tobacco, and other (or unknown) substances.
- All drugs that are taken in excess have in common the ability to directly activate the brain reward systems, which are involved in the reinforcement of behaviors and establishment of memories. Instead of achieving reward system activation through adaptive behaviors, these substances produce such an intense activation of the reward system that normal activities may be neglected.
- The pharmacological mechanisms by which each class of drugs produces reward are different, but the drugs typically activate the system and produce feelings of pleasure, often referred to as a "high."

17.1.1. Brief description

- The essential feature of a substance use disorder is a cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues using the substance despite significant substance-related problems.
- The diagnosis of a substance use disorder can be applied to all 10 substance classes included in the definition except caffeine.
- An important characteristic of substance use disorders is an underlying change in brain circuits that may persist beyond detoxification, particularly in individuals with severe disorders.
- The behavioral effects of these brain changes may be exhibited in the repeated relapses and intense drug craving when the individuals are exposed to drug-related stimuli. Overall, the diagnosis of a substance use disorder is based on a pathological pattern of behaviors related to use of the substance.

17.1.2. Epidemiology

- Studies showed that there is widespread use of alcohol and khat among the general population in Ethiopia.
- The studies also showed that use of illicit drugs was limited to at-risk populations. Prevalence of hazardous use of alcohol was found to be 3%, and alcohol dependence was 1.5%.
- The prevalence of khat consumption varied from 0.3% to 64.7% (Fekadu et al 2007). In a study conducted among university students, the lifetime use of each substance includes alcohol (68.2%), khat (53.6%), cigarettes (46.1%), and illicit drugs (23.3%) (Shegute and Wasihun, 2021).
- Among university instructors, studies show marked lifetime prevalence of substance use; the lifetime prevalence of khat chewing, alcohol use, and smoking cigarette was 51.6, 81.3, and 17.3%, respectively.
- The prevalence of substance uses disorder among users was 36.9% (Gizaw et al 2022).
- The national prevalence for Ethiopia showed to be 1.86% for alcohol use disorder, 5% for khat use disorder, and 0.5% for drug use (includes opioids, cannabis). (EMHS 2020-2025).

17.1.3. Causes and risk factors

- Someone with family history of substance use disorder has a higher risk to develop the disorder; this shows the role of genetic factors.
- Environmental factors also play significant role. People who have experienced physical, emotional or sexual abuse or trauma are more likely to develop a substance use disorder.
- Others who have friends who use, or those subjected to peer pressure, may also be at a greater risk (children more than older adults). Risk factors related to relationships include parents who use drugs and alcohol or who suffer from mental illness, child abuse and maltreatment, and inadequate supervision.
- Community risk factors include neighborhood poverty and violence. Social risk factors can include norms and laws favorable to substance use, as well as racism and a lack of economic opportunity.
- People with an existing mental health condition like depression, PTSD and ADHD are also more likely to develop a substance use disorder as a way of coping with the emotions and anxieties that these disorders cause.

17.2.Clinical features

- One category of substance-related disorders is substance use disorder. Impaired control over substance use is the defining characteristic of substance use disorder for any given substance. This can be expressed by the fact that the individual may take the substance in larger amounts or over a longer period than was originally intended.
- In addition, the individual may express a persistent desire to cut down or regulate substance use and may report multiple unsuccessful efforts to decrease or discontinue use.
- The individual may also spend a great deal of time obtaining the substance, using the substance, or recovering from its effects.
- The individual can feel craving for the substance involved, which is manifested by an intense desire or urge for the drug.
- The other defining characteristic of substance use disorders is social and occupational dysfunction. In this case, recurrent substance use may result in a failure to fulfill major role obligations at work, school, or home.
- The individual may continue substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance.
- Important social, occupational, or recreational activities may be given up or reduced because of substance use. In this case, the individual may withdraw from family activities and hobbies in order to use the substance.
- There could be risky use of substances. In this regard, there could be recurrent substance use in situations in which it is physically hazardous. The individual may also continue substance use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
- Substance use disorder can manifest with the existence of pharmacological changes in the individual, such as tolerance and withdrawal. Tolerance is signaled by requiring a markedly increased dose of the substance to achieve the desired effect or a markedly reduced effect when the usual dose is consumed.
- Withdrawal is a syndrome that occurs when blood or tissue concentrations of a substance decline in an individual who had maintained prolonged, heavy use of the substance. After developing withdrawal symptoms, the individual is likely to consume the substance to

relieve the symptoms. (seen DSM-5) Each substance has a distinct set of symptoms during withdrawal.

- The second category of substance-related disorders is substance-induced disorder.
  - Substance-induced disorders include substance intoxication,
  - Substance withdrawal, and
  - Substance/medication-induced mental disorders (e.g. substance-induced psychotic disorder, substance-induced depressive disorder).

- ***Physical examination***

- General physical assessment should be done including neurological exam.
- This will ascertain the patient's general health and identify any medical or psychiatric disorders of immediate concern.
- Vital signs including temperature, pulse, respiration and blood pressure should be routine part of the physical examination.
- Vital signs are important indicators and should be monitored throughout the detoxification as well.
- Neurologic examination should be conducted routinely for every patient suspected of substance-related disorders.
- Assessment for physical, sensory or cognitive disabilities should be part of the physical examination.
- Physical examination in substance users may reveal evidence of needle or track marks, nasal septal perforation, liver damage, HIV-related infections, genital infections, and other illnesses.

17.3.Diagnosis and investigation

17.3.1. Diagnosis and differential diagnosis

- Pertinent history and mental status examination must be done during initial evaluation.
- Biomedical evaluation should include general health history. Such history may include the patient's medical and surgical history, the presence of any psychiatric or medical conditions, any known medication allergies, and the presence of any history of seizures.
- Mental status examination should assess whether the patient is oriented, alert, and cooperative.

- It should also assess if thoughts are coherent, and if there are signs of psychosis or destructive thoughts. Patterns of substance consumption should routinely be part of the assessment. This may include when the patient last used the substances concerned, and the amount and frequency of the use.
- Past substance abuse treatments or detoxification must be part of the history, including the course and number of previous withdrawals, as well as any complications that may have occurred.
- Psychosocial evaluation should include demographic features, living conditions (including checking whether the patient is homeless or living in a shelter, the living condition, whether there are significant others in the home, and whether they can safely supervise the patient), risk to violence or suicide, the presence of dependent children (Is the patient able to care for children, provide adequate child care, and ensure the safety of children), and legal status (Is the patient a legal resident? Are there pending legal matters? Is treatment court ordered?)

17.3.2. Differential diagnosis

- The differential diagnostic considerations could vary and they depend on the specific type of substance-related disorder.

17.3.3. Laboratory and imaging

- Biochemical markers are not adequate screening or assessment instruments when used alone. They should be used to support a more comprehensive assessment. Common uses of this biochemical markers are-

✓ In the initial screening setting to support or refute other information that leads to proper diagnosis, assessment, and management.

✓ For forensic purposes (e.g., evaluating a driver after an automobile accident).

✓ Laboratory tests are useful to track progress. For instance, serial measures of MCV or ultrasound of the liver can be used to see improvement in person who has AUD.

- <u>Urine drug screens</u>

✓ Testing for drugs of abuse can be performed on multiple types of samples including urine, blood, breath, hair, saliva, and sweat.

- ✓ Urine testing is most widely used because it is noninvasive, simple to obtain, and yields a detectable concentration of most drugs.
- ✓ Urine drug screens vary widely in their methods of detection, sensitivity and specificity, expense, and availability.
- ✓ Clinicians should be aware of which drugs are screened for by the laboratory they use, the relative time window of detection, and whether cross reactivity with other interfering substances may alter outcomes.
- ✓ Many laboratories perform more specific confirmation testing on positive screening tests, which can largely eliminate false positives.
- ✓ Urine testing should at a minimum test for the presence of benzodiazepines, barbiturates, cocaine, amphetamines, cannabis and opioids.

- Gammaglutamyltransferase (GGT)

- ✓ Gamma-glutamyl-transferase (GGT) has been measured in serum for many years as a marker for liver damage among alcohol abusers. More recently, GGT has been advocated as a measure of cumulative alcohol use. Sensitivity of the test is in the 60 to 70 percent range and specificity is in the 40 to 50 percent range.
- ✓ In general, both sensitivity and specificity are lower in females than males.
- ✓ GGT does correlate with alcohol intake but often requires heavy drinking (more than six drinks per day) to elevate it, and only about half of individuals will show elevations.
- ✓ The half-life of elevated serum GGT after the onset of abstinence is said to be 2 to 3 weeks with alcoholic liver disease.
- ✓ Chlorpromazine, phenobarbital, and acetaminophen can all raise serum GGT levels.
- ✓ GGT is limited by its expense and its relatively low specificity, which sometimes leads to false positive evaluations.
- ✓ GGT is helpful as a motivational enhancer in patients with a high degree of denial during detoxification.
- ✓ Evidence of liver damage, as measured by the GGT, provides patients with objective feedback concerning the consequences of their alcohol use and thus plays a very important role in enhancing motivation.
- ✓ In any form of hepatitis, GGT may be elevated, indicating damage to liver cells. Therefore, GGT elevation does not automatically mean liver damage from alcohol use,

although this is certainly one of the most common reasons for elevated GGT levels in patients who are hospitalized.

- ✓ The use of GGT levels along with carbohydrate deficient transferrin (CDT) levels is a relatively sensitive and specific indicator of alcohol use.

- Carbohydrate deficient transferrin (CDT)

- ✓ Carbohydrate deficient transferrin (CDT) has been developed as a marker of cumulative alcohol consumption.
- ✓ Sensitivities appear to be in the 70 to 80 percent range, and specificities of greater than 90 percent have been found. Sensitivity and specificity are somewhat lower among females than males.
- ✓ Most therapeutic drugs or drugs of abuse do not appear to affect CDT levels. When CDT and GGT levels are combined, sensitivity and specificity rise to more than 90 percent (Anton 2001

- Mean corpuscular volume (MCV)

- ✓ Erythrocyte size often is part of a complete blood count; therefore, it is widely available to clinicians. Sensitivity and specificity are in the 30 to 50 percent range.
- ✓ Caution should be exercised when interpreting an elevated MCV in relation to drinking behavior.
- ✓ This lab test should be considered complementary to other biological markers that are more specific and sensitive, such as GGT or CDT.

17.4.Treatment

17.4.1. Goals of treatment

- Treatment for substance-related disorders has the following objectives:

  - To provide safe and humane withdrawal from substances
  - To foster the patient's entry into long term treatment and recovery

17.4.2. General principles of management

- Substance use disorders are brain disorders and not evidence of moral weaknesses. Substance use disorders are treatable, and there is hope for recovery.
- Patients are treated in a nonjudgmental and supportive manner.

- Service planning is completed in partnership with the patient and his or her social support network.
- All health professionals involved in the care of the patient will have to maximize opportunities to promote rehabilitation and maintenance activities, as well as to link the patient to appropriate substance abuse treatment immediately after the detoxification phase.
- Active involvement of the family and other support systems while respecting the patient's rights to privacy and confidentiality is encouraged. Patients are treated with due consideration for individual background, culture, preferences, disability status, vulnerabilities, and strengths.
- Evaluating and addressing psychosocial and biomedical issues of patients entering detoxification are important. Health professionals should screen for medical problems that may put the client at risk for a medical crisis during detoxification.
- Regarding co-occurring medical conditions the initial consultation should include an evaluation of the expected signs, symptoms, and severity of the withdrawal.
- During detoxification any significant deviation from the expected course of withdrawal should be observed closely.
- Detoxification should begin as the patient is being medically stabilized. Psychological factors, co-occurring psychiatric disorders, social supports and environmental factors critically influence success and sustainability of abstinence from substance use.

17.4.3. Non-pharmacologic treatment

Detoxification

- Detoxification is a process consisting of three essential components which should be available to all people seeking treatment:
  - ✓ Evaluation,
  - ✓ Stabilization and
  - ✓ Fostering patient readiness for entry into comprehensive treatment.
- Detoxification can take place in a wide variety of settings and at a number of levels of intensity within these settings. Placement should be appropriate to the patient's needs.

- All persons requiring treatment for substance use disorders should receive necessary treatment after detoxification.
- A successful detoxification process can be measured, in part, by whether an individual who is substance dependent enters and remains in some form of substance abuse treatment/rehabilitation after detoxification.
- The first consideration for evaluation is medical conditions and complications. The presence of infectious illnesses, chronic illnesses requiring intensive or specialized treatment, pregnancy, and chronic pain should be evaluated.
- The other consideration for evaluation is the level of motivation (readiness to change). This involves the degree to which the client acknowledges that substance use behaviors are a problem and is willing to confront them honestly. Relapse history and potential is another important issue that should be evaluated.
- Historical relapse patterns, periods of abstinence, and predictors of abstinence; client awareness of relapse triggers and craving are important considerations in this regard. Frequency, amount, and duration of substance use, chronicity of problems, and indicators of abuse or dependence need to be assessed.
- Developmental and cognitive issues such as ability to participate in confrontational treatment settings, and benefit from cognitive interventions and group therapy are important considerations. Finally, the degree of support from family and significant others, as well as the presence of substance free friends, and involvement in support groups need to be assessed.
- Stabilization involves physical detoxification. This involves specific treatment regimens for specific substances and provides guidance on the medical, nursing, and social services aspects of these treatments.
- Treatment and maintenance activities are offered in a variety of settings. These include substance abuse treatment centers, as well as settings operating for other purposes, including mental health centers, prisons, and community corrections facilities.
- Stabilization can be followed by fostering patient readiness for entry into comprehensive treatment. This can be achieved through motivational enhancement interventions and continued support.

17.4.4. Pharmacologic treatment

- Medications can be used to facilitate withdrawal during detoxification or to prevent life threatening conditions during withdrawal from some substances.
- Alcohol and sedatives/hypnotics and anxiolytic substances could have life-threatening withdrawal reactions and withdrawal needs to be medically assisted to prevent them.
- Medications can also be used as replacement therapy to sustain abstinence in case of methadone replacement for opioid substances.
- Medications are also applicable to sustain abstinence in motivated individuals such as the use of disulfiram and naltrexone in alcohol use disorders and nicotine replacement therapies in the case of nicotine use disorders.
- Medications can be used to treat comorbid psychiatric disorders such as depression.

17.4.4.1. Alcohol withdrawal

17.4.4.1.1. Signs and symptoms of withdrawal

- The signs and symptoms of acute alcohol withdrawal generally start 6 to 24 hours after the patient took his last drink. Alcohol withdrawal may begin when the patient still has significant blood alcohol concentrations. The signs and symptoms may include the following:

  - ✓ Restlessness, irritability, anxiety, agitation
  - ✓ Anorexia (lack of appetite), nausea, vomiting
  - ✓ Tremor (shakiness), elevated heart rate, increased blood pressure
  - ✓ Insomnia, intense dreaming, nightmares
  - ✓ Poor concentration, impaired memory and judgment
  - ✓ Increased sensitivity to sound, light, and tactile sensations
  - ✓ Hallucinations (auditory, visual, or tactile)
  - ✓ Delusions, usually of paranoid or persecutory varieties
  - ✓ Grand mal seizures

- Mild alcohol withdrawal generally consists of anxiety, irritability, difficulty sleeping, and decreased appetite.
- Severe alcohol withdrawal usually is characterized by obvious trembling of the hands and arms, sweating, elevation of pulse (above 100) and blood pressure (greater than 140/90),

nausea (sometimes with vomiting), and hypersensitivity to noises (which seem louder than usual) and light (which appears brighter than usual).

- Brief periods of auditory and visual hallucinations also may occur.
- A fever greater than 101° F also may be seen, though care should be taken to determine whether the fever is the result of an infection.
- Seizures and true delirium tremens represent the most extreme forms of severe alcohol withdrawal.
- The use of a standardized clinical rating instrument for withdrawal such as the CIWAAr is valuable because it guides the clinician through multiple domains of alcohol withdrawal and allows for semi quantitative assessment of nausea, tremor, autonomic hyperactivity, anxiety, agitation, perceptual disturbances, headache, and disorientation.
- Age, general health, nutritional factors, and possible co-occurring medical or psychiatric conditions all appear to play a role in increasing the severity of the symptoms of alcohol withdrawal.
- The most useful clinical factors to assess the likelihood and the extent of a current withdrawal is the patient's last withdrawal and the number of previous withdrawals (treated or untreated) experienced, with three or four being a particularly significant number for the appearance of severe withdrawal reactions unless adequate medical care is provided. This assumption that this phenomenon will manifest itself, which has been referred to as the "kindling hypothesis," is well established in the research literature (Booth and Blow 1993; Wojnar et al. 1999).
- Medical complications of alcohol withdrawal with fatal consequences include seizures; delirium tremens (severe delirium with trembling); and dysregulation of body temperature, pulse, and blood pressure are outcomes in severe alcohol dependence. Other medical complications of alcohol include infections, hypoglycemia, gastrointestinal bleeding, undetected trauma, hepatic failure, dilated cardiomyopathy, pancreatitis, and encephalopathy.
- The suspicion of impending complications or their appearance will require hospitalization of the client and possible intensive care unit level of management. Consultation with internists specializing in infectious disease, pulmonary care, and hepatology could be necessary.

17.4.4.1.2. Treatment of alcohol withdrawal

- Deciding on whether to use medical management for the treatment of alcohol withdrawal requires that patients be separated into three groups. The first and most obvious group comprises those clients who have had a previous history of the most extreme forms of withdrawal, that of seizures and/or delirium.
- The medication treatment of this group in early abstinence, whether or not they have had the initiation of withdrawal symptoms, should proceed as quickly as possible.
- The second group of patients requiring immediate medication treatment includes those patients who are already in withdrawal and demonstrating moderate symptoms of withdrawal.
- The third group of patients includes those who may still be intoxicated and therefore have not had time to develop withdrawal symptoms or who have, at the time of admission, been abstinent for a few hours and have not developed signs or symptoms of withdrawal.
- A decision regarding medication for this group should be in part based on age, number of years of alcohol dependence, and the number of previously treated or untreated severe withdrawal episodes (three or four appears to be a significant threshold in predicting future serious withdrawal).
- If there is an opportunity to observe the patient in the emergency department of the clinic or similar setting over the next 6 to 8 hours, then it is possible to delay a decision regarding treatment and periodically reevaluate a client of this category.
- If this is not possible, then the return of the patient to a setting in which there is some supervision by family, significant others, or in a social detoxification program is desirable.
- In some circumstances, no treatment may be safer than treatment with medication has shown that benzodiazepines confer protection against alcohol withdrawal seizures and thus patients with previous seizures should be treated early.
- Depending upon the clinical setting and the patient circumstances, there are several acceptable regimens for treating alcohol withdrawal that make use of benzodiazepines. These drugs remain the medication class of choice for treating alcohol withdrawal.

- The early recognition of alcohol withdrawal and prompt administration of a suitable benzodiazepine usually will prevent the withdrawal reaction from proceeding to serious consequences.
- Patients suspected of alcohol withdrawal should be seen promptly by a clinician who has experience in diagnosing and managing alcohol withdrawal.

Benzodiazepines

- Benzodiazepines remain the medication class of choice for treating alcohol withdrawal.
- Administration of a slowly metabolized benzodiazepine, frequently intravenously, but sometimes orally, may be carried out every 1 to 2 hours until significant clinical improvement occurs (such as reducing the CIWAAr score to 10 or less) or the patient becomes sedated (**Refer annex 2**).
- Patients at grave risk for the most severe complications of alcohol withdrawal or who are already experiencing severe withdrawal should be hospitalized and can be treated with this regimen.
- In general, patients with severe withdrawal may receive 20mg of diazepam or 100mg of Chlordiazepoxide every 2 to 3 hours until improvement or sedation prevails.
- Over sedation, ataxia (lack of muscular coordination), and confusion, particularly in elderly patients, may occur with this protocol.
- The treatment staff should closely monitor hemodynamic (blood pressure and pulse) and respiratory features.
- They should particularly be prepared to detect and rapidly treat apnea (no breathing) with assisted ventilation.
- Having experienced staff with adequate time to frequently monitor the patient and provide intravenous medication is necessary.
- Symptom triggered therapy using the CIWAAr or similar alcohol withdrawal rating scales, medical personnel can be trained to recognize signs and symptoms of alcohol withdrawal, make a rating, and based on that rating administer benzodiazepines to their patients only when signs and symptoms reach a particular threshold score.
- Typical routine of administration of symptom triggered therapy is as follows: Administer 50mg of Chlordiazepoxideor 10mg of diazepam for CIWAAr>9 and reassess in 1 hour.

- Continue administering 50mg Chlordiazepoxide or 10mg of diazepam every hour until CIWAAr is <10.
- Patients with a history of withdrawal seizures should receive scheduled doses of a long acting benzodiazepine (e.g., diazepam 20mg every 8 hours for 3 days) regardless of CIWAAr score, and should receive additional doses if indicated by elevated CIWAAr score.

- Medication is omitted if the patient is sleeping soundly, showing signs of over sedation, or exhibiting marked ataxia. Under or overmedication with this regimen can occur depending on benzodiazepine tolerance; the presence of chronic cigarette smoking, which induces benzodiazepine metabolism; liver function; age; and the presence of co-occurring medical or psychiatric conditions. It is important to enforce strict limitations on driving automobiles, climbing, or operating hazardous machinery.
- Symptom triggered therapy requires monitoring and decision making by a clinician. Tapering doses should be gradual. Before beginning any tapering regimen, the patient must be fully stabilized; that is, all signs and symptoms of withdrawal must be improved. Without proper stabilization no tapering scheme will succeed. Once the patient has been stabilized, oral benzodiazepines can be administered on a predetermined dosing schedule for several days and gradually tapered over time. Benzodiazepines' potential interactions with alcohol can lead to coma and respiratory suppression, and motor incoordination.

Barbiturates

- Barbiturates have been used for nearly a century for the treatment of alcohol withdrawal. Most barbiturates, other than phenobarbital, have fallen into disfavor because of severe lethal interactions with alcohol. Barbiturates are highly addictive.
- In clinical practice, phenobarbital is effective both for the treatment of alcohol withdrawal and sedative hypnotic withdrawal although few controlled trials have been conducted with it.
- Phenobarbital has a long half-life and may rapidly accumulate. Overdoses with phenobarbital also can be fatal. Members of the consensus panel recommend its use only in highly supervised settings.

Anticonvulsants

- Anticonvulsants have been used in Europe for a quarter of a century for the treatment of alcohol withdrawal.
- Carbamazepine has been shown in at least three trials to be as effective as various benzodiazepines in mild to moderate alcohol withdrawal.
- Although less well studied, Sodium Valproate also has been shown to be effective.
- Carbamazepine and Sodium Valproate have limitations in that they only have been studied in mild to moderate withdrawal, can on rare occasions have serious hepatic and bone marrow toxicities, interact with several other classes of medication, and are only available in oral forms. They are not, however, controlled substances, are not abused, and as previously noted, carbamazepine may have the propensity to reduce some of the indices of drinking behavior immediately in the post withdrawal treatment of outpatients.
- Newer drugs such as Tiagabine, oxcarbazepine, and gabapentin do not appear to have these liabilities, but sufficient studies have not been done to confirm their effectiveness and safety.

Other agents

- Beta blockers and alpha adrenergic agonists such as clonidine have been used in the treatment of alcohol withdrawal. They do not prevent seizures or delirium and have only modest benefits for ameliorating symptoms of withdrawal. However, some patients will have tachycardia and hypertension that will not be controlled by benzodiazepines, and beta blockers and alpha adrenergic agonists can be of use in these patients.
- Calcium channel antagonists will also ameliorate some symptoms of alcohol withdrawal. As with beta blockers and clonidine,calcium channel antagonists should be considered adjunctive therapy primarily to manage extreme hypertension during withdrawal.

Antipsychotics

- Antipsychotics have long been used to control extreme agitation, hallucinations, delusions, and delirium during alcohol withdrawal.
- Older, low potency drugs such as chlorpromazine generally are avoided since they can reduce the seizure threshold.
- High potency drugs such as haloperidol also can reduce the seizure threshold, but less commonly.
- Haloperidol and related agents are available for oral, intramuscular, and intravenous administration. Clinicians should note that since antipsychotics can lower the seizure threshold, their use during alcohol withdrawal should be under taken with great care and close supervision of the patient is required.

Relapse prevention agents

- Relapse prevention agents such as naltrexone and acamprosate are under consideration as additional therapies during late withdrawal treatment, although they are not effective for alcohol detoxification. Since one third to one half of outpatients detoxifying with benzodiazepines will either drink or leave treatment prematurely, naltrexone and acamprosatemaybe valuable in assisting in reducing the probability of the individual drinking during late detoxification.
- High dose naltrexone therapy has been associated with some liver toxicity, but this has not been reported in individuals taking therapeutic doses. Acamprosate may produce diarrhea and this may be already present in some individuals in alcohol withdrawal. Thus far no well controlled studies have been conducted to provide guidelines as to when these medications should be introduced during detoxification or whether it would be better to wait until the early phase of rehabilitation.
- However, insufficient information has been accumulated on these drugs, and therefore they are not recommended for use in clinical patient settings. Their use in alcohol withdrawal should be considered experimental and premature for the present.

Management of Delirium and Seizures

- Delirium and seizures are the two most pathologic responses seen in alcohol withdrawal. The major goal of medical management is to avoid seizures and delirium tremens (DTs)

with aggressive use of the primary detoxification drug (e.g., higher doses of a benzodiazepine).

Delirium tremens (DTs)

- Prevention is essential where DTs are concerned.
- DTs do not develop suddenly but instead progress from earlier withdrawal symptoms.
- Properly administered symptom triggered medication approaches will prevent DTs. It can be challenging clinically to differentiate impending DTs versus benzodiazepine toxicity on day 3 of detoxification. When in doubt, in most cases it is safer to overmedicate than to under treat and allow DTs to develop; death and disability may result from DTs or seizures without medical care. Flumazenil is an antagonist that can be used to reverse benzodiazepine overdose.
- For patients with a history of DTs or seizures, early benzodiazepine treatment is indicated at the first clinical contact setting (e.g., doctor's office, clinic, urgent care, emergency department).
- Patients with severe withdrawal symptoms, multiple past detoxifications (more than three), and co-occurring unstable medical and psychiatric conditions should be managed similarly.
- Once an initial clinical screening and assessment have been made, and the diagnosis is reasonably certain, medication should be given. Giving the patient a benzodiazepine should not be delayed by waiting for the return of laboratory studies, transportation problems, or the availability of a hospital bed.
- Early thiamine and multivitamin administration also should be done at this time. Once full DTs have developed, they tend to run their course despite medication management, and there is little evidence in the medical literature to suggest that any medication treatment can immediately abort DTs.
- Patients presenting in severe DTs should have emergency medical transport to a qualified emergency department and generally will require hospitalization.
- If the DTs are severe, patients may need to be placed in an intensive care unit (ICU), and in such settings continuous monitoring of cardiac rhythm, pulse, blood pressure, oxygen

saturation, temperature, and respiration rates begins with the emergency medical system and continues in the emergency department and ICU.

- Early care will depend on medical and surgical complications and may involve protocols from advanced cardiac life support (ACLS) and/or advanced trauma life support.
- Correction of fluids and electrolytes (salts in the blood), hyperthermia (high fever), and hypertension are vital.
- Loading doses of IV diazepam or Lorazepam are recommended, as are IV thiamine (prior to IV glucose) and multiple vitamins.
- The physician should consider intramuscular or intravenous haloperidol to treat agitation and hallucinations.
- Nursing care is vital, with particular attention to medication administration, patient comfort, soft restraints, and frequent contact with orienting responses and clarification of environmental misperceptions.

Withdrawal seizures

- Alcohol withdrawal seizures represent another management challenge, since no large scale clinical studies have been conducted to establish firmly best treatment practices.
- The majority of alcohol withdrawal seizures occur within the first 48 hours after cessation or reduction of alcohol, with peak incidence around 24 hours.
- Most alcohol withdrawal seizures are singular, but if more than one occurs they tend to be within several hours of each other.
- While alcohol withdrawal seizures can occur several days out, a higher index of suspicion for other causes is prudent. Someone experiencing an alcohol withdrawal seizure is at greater risk for progressing to DTs, whereas it is extremely unlikely that a patient already in DTs will also then experience a seizure.
- The occurrence of an alcohol withdrawal seizure happens quickly, usually without warning to the individual experiencing the seizure or anyone around him.
- Predicting who will have a seizure during alcohol withdrawal cannot be accomplished with any great certainty. There are some factors that clearly increase the risk of a seizure, but even in individuals with all of these factors, most patients will not have a seizure. Out

of 100 people experiencing alcohol withdrawal only two or three of them will have a seizure.

- The best single predictor of a future alcohol withdrawal seizure is a previous alcohol withdrawal seizure. Individuals who have had three or more documented withdrawal episodes in the past are much more likely to have a seizure regardless of other factors including age, gender, or overall medical health.
- In patients who seize, evaluation of electrolyte disturbances, central nervous system (CNS) trauma, and consideration of sedative hypnotic withdrawal should be reviewed.
- Patients who have had a single witnessed orsuspected alcohol withdrawal seizure shouldbe immediately given a benzodiazepine, preferably with IV administration.
- The study by D'Onofrio and colleagues (1999) indicated that a single dose of 1mg of IV Lorazepam reduced recurrent seizure risk, reduced rates of return to emergency departments, and lowered hospitalization rates.
- However, hospitalization for further detoxification treatment is strongly advised to monitor and ameliorate other withdrawal symptoms, reduce suffering, and stabilize the patient for rehabilitation treatment.

Patient care and comfort

- Interpersonal support and hygienic care along with adequate nutrition should be provided. Staff assisting patients in detoxification should provide whatever assistance is necessary to help get patients cleaned up after entering the facility and bathed thoroughly as soon as they have been medically stabilized.
- Attention to the treatment of scabies, body lice, and other skin conditions should be given. Screening for tuberculosis should be done. Dental and oral care should be made available.
- The patient should be screened for physical trauma, including bruises and lacerations. Tetanus immunization may be necessary. Patients with an altered mental status or altered level of consciousness should be seen in emergency departments, evaluated, and possibly hospitalized.

- Staff should continue to observe patients for head injuries after admission because some head injuries, such as subdural hematomas, may not immediately be evident and cost considerations may preclude obtaining a brain scan in some settings.

Recommended schedule for detoxification using benzodiazepines

- There are three types of regimens for detoxification of alcohol using benzodiazepines.
  - The first is fixed tapering dose regimen (FTDR). With FTDR, patients are given a fixed dose of a benzodiazepine. Because this regimen is not adjusted based on the severity of withdrawal symptoms, it is best suited for people with mild symptoms recovering in outpatient rehab settings.
  - The second type is symptom triggered regimen (STR). STR is often used in an inpatient treatment program where symptoms can be monitored by medical staff. This method provides a scale in which patient rates the pain associated with withdrawal symptoms. The medication dosage is based on the answers they provide – unbearable symptoms warrant higher doses, whereas minor symptoms involve lower doses.
  - The third type of regimen is loading dose regimen (LDR). A LDR involves the use of long-acting benzodiazepine. These types of medications usually stay in the body for several days and reduce the risk of seizures during detox. LDR is commonly used in inpatient rehab so treatment providers can monitor a patient's vitals and withdrawal symptoms.
- A symptom-triggered regimen may be preferred in most cases of alcohol withdrawal syndrome because it results in the administration of less dosages of medication and shorter duration of treatment and reduces the risk of under medicating or overmedicating a patient since the drug is dosed and administered depending upon the severity of withdrawal symptoms as assessed by the rating scales.
- Benzodiazepines can be administered by using fixed-schedule or symptom-triggered regimens with or without loading. The Clinical Institute Withdrawal of Alcohol Scale, Revised (CIWA-Ar) has been validated and is used for medication administration in symptom-triggered therapy. In this approach, medication is given only when the CIWA-Ar score is higher than 8 points. The efficacy profile is better with symptom-triggered therapy than with fixed-schedule dosing in patients admitted for detoxification but not necessarily for the treatment of DT.
- Intravenous administration of drugs allows immediate assessment of treatment adequacy compared with the lag time associated with absorption of oral medications. This is a particularly useful factor when using symptom-triggered therapy. Typically, a loading dose is given to achieve light sedation, followed by maintenance medication. The amount of medication required to achieve an adequate loading dose varies with the severity of withdrawal.

- Lorazepam can be administered intravenously, intramuscularly, or orally. Lorazepam provides a long duration of seizure control because of its slow redistribution. It may have decreased risk of sedation among those with liver disease because of its short half-life and absence of active metabolites. The dosing is 1-4 mg IV every 5-15 minutes until adequate control of agitation is achieved. This will be 30 minutes if the tablet form is used.
- Large and rapid doses of Lorazepam may cause cardiovascular toxicity due to propylene glycol.
- Total dosing of intravenous Lorazepam should not routinely exceed 20 mg/h or 50 mg in 8 hours.After stabilization, give tapering dose of Lorazepam at scheduled intervals.
- Lorazepam 2 mg q6h x4 doses, then 1 mg q6h x8 doses After that taper by 1 mg every day. Monitor between dosing intervals on CIWA and provide additional medication if score >8-10.
- Diazepam can be administered intravenously, orally, or per rectum. Diazepam rapidly controls agitation because of its rapid distribution secondary to its high lipid solubility.
- However, it has a long duration of action. Its active metabolites help smooth the course of withdrawal and limit breakthrough symptoms; however, prolonged sedation is a risk.
- Diazepam is initially given at a dose of 5 mg IV. The drug is repeated at 5-20 mg per dose every 5-15 minutes until adequate control of agitation is achieved. This will be30 to 60 minutes for tablet form. After agitation is controlled, an hourly dose is given as needed to maintain light somnolence.
- Total dosing of intravenous diazepam should not routinely exceed 100 mg/h or 250 mg in 8 hours. After stabilization, give tapering dose of diazepam at scheduled intervals.
- Diazepam 10 mg q6h x4 doses, then 5 mg q6h x8 doses. After that, taper by 5 mg every day. Monitor between dosing intervals on CIWA and provide additional medication if score >8-10.
- In cases not responding to massive doses of benzodiazepines, intravenous infusion of Propofol or intravenous boluses of barbiturates (phenobarbital and pentobarbital) should be added as second-line GABA modulators.

17.4.4.2. Nicotine

- Nicotine addiction in the form of cigarette smoking accounts for more deaths each year than AIDS, alcohol, cocaine, heroin, homicide, suicide, motor vehicle crashes, and fires combined.
- Smokers are at increased risk for several medical problems, including myocardial infarction, coronary artery disease, hypertension, stroke, peripheral vascular disease, chronic obstructive lung disease, chronic bronchitis, and several types of cancer (lung, stomach, head and neck, and bladder).
- Other problems associated with nicotine addiction include gastro esophageal reflux disease and gastric ulcerations, cataracts, and premature wrinkling of the skin.

- There also appears to be an anti-estrogen effect (suppression of an important hormone) that may lead to early development of osteoporosis in women.
- Nicotine binds to nicotinic acetylcholine receptors in the brain and has the direct ability to stimulate the release of dopamine in the nucleus accumbens area. The nucleus accumbens has long been considered the "reward center" in the brain. This increase in dopamine is similar to what occurs when patients use stimulants and is felt to be an essential element in the reward process of addiction.
- As many as 90 percent of patients entering treatment for substance abuse are current nicotine users (Perine and Schare 1999). There has long been controversy in the field of addiction medicine as to how best to handle the problem of nicotine dependence inpatients seeking treatment for other types of substance abuse.
- Traditionally, it has been argued that patients would find that trying to stop smoking while also contending with other (more pressing) addiction problems would be too difficult and distracting in early abstinence. However, others argue that nicotine dependence is a lethal disease and that physicians have the responsibility to intervene in this addiction with the same aggressiveness they show toward other addictive substances. This pro intervention position has received increasing attention from clinicians, in as much as it is now understood that alcohol consumption is associated with increased nicotine usage (Henningfield et al. 1984). Gulliver and colleagues (1995) have demonstrated that theurge to smoke is correlated with the urge to drink, and others have shown that continued nicotine dependence may be a relapse trigger for resumption of drinking.
- The concern that smoking cessation may precipitate relapse to other substances of abuse has not been supported in the literature.Treatment programs that have attempted to treat nicotine dependence in conjunction with other drugs of addiction have met with limited success (Bobo and Davis 1993; Burling et al. 1991; Hurt et al. 1994) and have generated increased interest in smoking cessation as a part of a patient's overall substance abuse treatment (Sees and Clark 1993).
- One study reported that forcing unmotivated patients (or patients who did not consider smoking a problem) to quit was counter therapeutic (Trudeau et al. 1995). Moreover, it has traditionally been accepted that nicotine detoxification concurrent with detoxification from other substances makes the undertaking more difficult.

Nicotine withdrawal

- Abrupt cessation of nicotine use after prolonged heavy use, or reduction in the amount of nicotine used, followed within 24 hours by 4 or more of the following signs which cause significant distress or functional impairment: dysphoric or depressed mood;insomnia;irritability, frustration, or anger;anxiety;difficulty concentrating; restlessness;decreased heart rate;and increased appetite or weight gain.
- There are no major medical complications precipitated by nicotine withdrawal itself, however. To better understand a patient's level of nicotine dependence, providers can assess biochemical markers including nicotine, cotinine, and carbon monoxide.
- Nicotine and its metabolite cotinine can be measured in urine, blood, or saliva. Cotinine continues to be present in bodily fluids for up to 7 days after cessation.
- Clinicians should use caution when interpreting the meaning of nicotine and cotinine assays, as they are not specific to tobacco derived nicotine and may indicate the patient's compliance with nicotine replacement therapy rather than smoking.

1.4.4.2.1: Managing nicotine use disorder

Applying the "5 A's" of brief intervention is recommended. The "5 A's" are listed below.

1. Ask about tobacco use. Identify and document tobacco use status for every patient at every visit.
2. Advise to quit. In a clear, strong, and personalized manner urge every tobacco user to quit.
3. Assess willingness to make a quit attempt. Is the tobacco user willing to make a quit attempt at this time?
4. Assist in quit attempt. For the patient willing to make a quit attempt, use counseling and pharmacotherapy to help him or her quit.
5. Arrange follow up. Schedule follow up contact, preferably within the first week after the quit date (Source: Fiore et al. 2000 a, p. 26).

Most smokers attempt cessation on an outpatient basis and without any assistance from professionals. However, if a patient decides that she or he wants help with smoking cessation, it is important for the clinician to present a supportive and nonjudgmental attitude and develop a therapeutic alliance with the patient. It must be emphasized that nicotine dependence is a chronic

relapsing disorder and that patients often make several attempts at quitting before succeeding. The clinician has the responsibility of providing pharmaceutical treatment, education about common problems associated with cessation, and emotional support to patients attempting to quit. Discussing nicotine withdrawal symptoms can often help allay patient concerns.

Management of nicotine withdrawal without medications

About one third of current smokers attempt to quit smoking each year and more than 90 percent of these try to do so without any formal nicotine cessation treatment. Most smokers will make several attempts, on their own, to quit and ultimately, only about 50 percent are successful over a lifetime. While some smokers are able to quit on their own, others may require intervention in the form of behavioral treatment and/or pharmacotherapy. There are insufficient data available to determine who will benefit most from a particular type of treatment. Some patients may prefer to stop smoking without the use of medication.

1.4.4.2.2: Management of nicotine withdrawal with medications

It is recommended that all smokers who want to quit should be offered active medication that has been approved for assisting in smoking cessation unless there is a medical contraindication (Fiore et al. 2000 a). Nicotine replacement therapy (NRT) can be provided in this regard. Nicotine gum, transdermal patches, nicotine nasal spray, and nicotine inhaler have been approved for use. Nicotine gum and nicotine transdermal patch are now available over the counter. After the acute withdrawal period, patients are then weaned off the medication until they become nicotine free. There are several medications that can be used to help patients quit smoking.

Nicotine replacement therapy (NRT): NRT is the remedial administration of nicotine to the body by means other than tobacco, for quitting tobacco use.Common forms of NRT and available dosage are provided below.

Table 16: Available NRT for the management of *nicotine withdrawal*

Forms	How it works	Available dosage
Nicotine gum	Delivers nicotine through the lining of the mouth	2mg, 4 mg
Nicotine patch	Delivers nicotine through skin	• 24 hour delivery systems 7mg, 14mg, 21mg • 16 hour delivery systems 5mg, 10mg, 15mg
Nicotine lozenge	Delivers nicotine through the lining of the mouth	2mg, 4 mg
Nicotine nasal spray	Delivers nicotine through the lining of the nose	0.5 mg nicotine in 50 µl aqueous nicotine solution
Nicotine inhaler	Delivers nicotine to the oral mucosa, not the lung	10 mg catridge delivers 4mg inhaled nicotine vapor

- Using NRT is a safe alternative to cigarettes; the patient will take in less nicotine and at a much slower rate than when smoking. In addition, there will be no high concentration arterial bolus of nicotine characteristic of cigarette smoking. Overall nicotine dose is about 1/3 to ½ that is found in cigarettes. No toxic tar and gas phase when applied.
- Common contraindications include pregnancy, bbreast-feeding,under 18's, acute myocardial infarction, unstable angina, severe cardiac arrhythmias, and recent cerebrovascular accident. Caution is needed in conditions including diabetes mellitus, hyperthyroidism, peripheral

vascular disease, hypertension, stable angina, coronary heart disease, renal or hepatic impairment, and cancer of the adrenal glands.

- Bupropion: Bupropion SR (sustained release) Originally used as anti-depressant, can also be used to help adults quit smoking. It can affect the levels of neurotransmitters affecting the urge to smoke. Bupropion can be used as an alternative to NRT. It can also lessen some withdrawal symptoms (anxiety irritability and depression). It is available in 150 mg sustained release tablet. It can be used in the following schedule: Day 1- 3, 150mg (1 tablet) daily; Day 4-6, 150 mg twice daily; Day 7 (quit day) – 150mg twice daily for 12 weeks. Contraindications include pregnancy, breastfeeding, concomitant with medications or medical conditions known to lower the seizure threshold, and severe hepatic cirrhosis.
- Other medications that can be used to help patients quit nicotine include varenicline, clonidine, nortriptyline, and cyticine. Their use is reserved as second line to be used if NRT or bupropion are not available or cannot be given.

Recommended schedule for NRTs

- Nicotine gum can be chewed slowly until the individual notices a “peppery” taste. Then individual should stop chewing and move gum between cheek and gum.
- Chewed and parked between cheek and jaw one piece every 1-2 hours. The dose can be determined based either on the number of cigarettes smoked per day (cpd) (1 cigarettecontains approximately 1 mg of nicotine, although the content varies in each brand), or on the time to first cigarette of the day. Based on cpd, 4mg gum is chewed at one time if the cpd is >20; the 2mg gum will be chewed if cpd is ≤20. Based on time to first cigarette of the day, the 4mg gum is chewed if the time is ≤30 minutes; the 2mg will be chewed if the time is >30 minutes. Initial dosing is 1-2 pieces every 1-2 hours (10-12 pieces/day). Taper the dose as tolerated. Up to 12 weeks of treatment needed with no more than 24 pieces to be used per day. Adverse effects may include hiccups, sore mouth, jaw ache, and stomach irritation.
- Nicotine patch can be used one patch each day. A new patch should be placed on a part of the body between the neck and waist.
- A new spot each day should be chosen to lessen skin irritation. Dosing for nicotine patch involves 42 mg/day if >40 cpd; 28-35 mg/day if 21-39 cpd; 14-21 mg/day if 10-20 cpd; and

14 mg/day if <10 cpd. Dose can be adjust based on withdrawal symptoms, urges, and comfort. After 4 weeks of abstinence, taper every 2 weeks in 7-14 mg steps as tolerated. The duration of treatment can be 8-12 weeks. Adverse effects include skin irritation, allergy, vivid dreams and sleep disturbances.

1.4.4.3: Stimulants

- Cocaine and amphetamines (such as methamphetamine) are the most frequently abused central nervous system stimulants. These agents are intensely rewarding and are self administered by laboratory animals to the point of death. Individuals dependent on stimulants experience profound loss of control over stimulant intake; presumably in response to the stimulation and disruption of endogenous reward centers (Dackis and O'Brien 2001).
- Addicts often use stimulants in a binge pattern that is followed by periods of withdrawal. It is not clear whether cravings occur predominantly during stimulant withdrawal or after these symptoms have largely disappeared.
- Stimulants are associated with withdrawal symptoms that differ markedly from those seen with opioids, alcohol, and sedative dependence.
- While most clinicians believe that alcohol and heroin withdrawal should be treated aggressively with detoxification, there has been little emphasis on treating symptoms of stimulant withdrawal.
- Consequently, no medications have been developed for this purpose. This situation is understandable because stimulant withdrawal usually does not involve medical danger or intense patient discomfort. However, if stimulant withdrawal predicts poor outcome, it may be a reasonable target for clinical interventions. An often overlooked but potentially lethal "medical danger" during stimulant withdrawal is the risk of a profound dysphoria (depression, negative thoughts and feelings) that may include suicidal ideas or attempts. This may be, in part, a physiological response to cocaine or amphetamine withdrawal and, in part, a reaction to individuals' acute realization of the devastating psychosocial consequences after a binge ends. While both cocaine and amphetamine users may experience depression during withdrawal, the period of depression experienced by amphetamine users is more prolonged and may be more intense.

- Amphetamine users, in particular, should be monitored closely during detoxification for signs of suicidality and treated for depression if appropriate. Although the literature on cocaine withdrawal is controversial, reasonable consensus supports the constellation of symptoms depicted (Coffey et al. 2000; Cottler et al. 1993).
- These symptoms often disappear after several days of stimulant abstinence but can persist for 3 to 4 weeks (Coffey et al. 2000). In addition, since individuals addicted to stimulants often fail to achieve abstinence, withdrawal symptoms can be a persistent component of active addiction. In addition, individuals addicted to stimulants may experience impairment in hedonic function that has been ascribed to stimulant induced disruptions of endogenous reward centers (Dackis and O'Brien 2002).
- Research on animals has found that exposure to high doses of methamphetamine results in changes to both the dopaminergic and serotonergic systems of the brain (Nordahl et al. 2005) and dopamine abnormalities among animals and humans who had been ingesting cocaine (Schuckit 2000).

Medical complications of stimulant use

- Central nervous system stimulants exert most of their toxic effects through vasoconstriction (constriction of the blood vessels). Consequently, a number of medical conditions can arise from ischemia.
- Myocardial (heart muscle) infarction and stroke are widely recognized complications of stimulant use.
- However, other problems such as spontaneous abortion, bowel necrosis (tissue death), and renal (kidney) infarction also have been reported from cocaine induced vasoconstriction.
- Cardiac arrhythmias also are common. Other medical problems that are associated with stimulant dependence include dental disease, neuropsychiatric abnormalities, and movement disturbances/disorders.

1.4.4.3.1: Stimulant withdrawal symptoms

- Stimulant withdrawal symptoms include:

- Depression, hypersomnia (or insomnia), fatigue, anxiety, irritability, poor concentration, psychomotor retardation, increased appetite, paranoia, and drug craving. (Source: Consensus Panelist Robert Malcolm, M.D.)

- Stimulant withdrawal is not usually associated with medical complications. However, patients with recent cocaine use can experience persistent cardiac complications, including
  - Prolonged QTc interval and vulnerability for arrhythmia and myocardial infarction (Chakko and Myerburg 1995).
  - Some conditions and many drugs (LAAM, other opioids, and even antibiotics) can cause the interval to lengthen and this can result in cardiac rhythm disturbances. Anterior chest pain or cardiac symptoms should therefore be fully evaluated in these individuals.
  - Seizures also may be a complication of stimulant abuse and can occur during detoxification. Persistent headaches could represent a subdural, subarachnoid, or intracerebral bleed and should be appropriately evaluated.
  - It also should be emphasized that people who abuse stimulants usually become addicted to other substances, such as alcohol, sedatives, or opioids, and therefore can experience any of the complications ascribed to detoxification from these substances. Covert use of other substances should be suspected and assessed with urine toxicology.

1.4.4.3.2: Management of stimulant use disorder

Management of withdrawal without medications

- The most effective means of treating stimulant withdrawal involves establishing a period of abstinence from these agents.
- Access to brief hospitalization, a level of care previously available for those who abuse stimulants, has been largely eliminated by managed care initiatives. In its place, intensive outpatient treatment can assist the patient to cease use long enough for withdrawal symptoms to abate entirely.

Management of withdrawal with medications

- Since stimulant withdrawal is not associated with severe physical symptoms, adjunctive medications are seldom required.
- These patients often are sleep deprived and might be unable to benefit from therapeutic activities during the first 24 to 36 hours of abstinence. They often are hungry and in need of large meal portions initially as their food intake may have been inadequate during active addiction.
- Stimulant users also may be irritable and care should be taken to avoid needless confrontation during the initial withdrawal phase.
- Headaches often are reported and can be treated symptomatically. On occasion, patients undergoing withdrawal from cocaine or amphetamines report insomnia and may benefit from diphenhydramine 50 to 100mg, trazodone 75 to 200mg, or hydroxyzine 25 to 50mg at bedtime.
- Benzodiazepines should be avoided unless required for concomitant alcohol or sedative detoxification. As stimulant withdrawal symptoms wane, patients are best treated with an active rehabilitative approach that combines entry into substance abuse treatment with support, education, and changes in lifestyle.Antidepressants, such as selective serotonin reuptake inhibitors, can be prescribed for the depression that often accompanies methamphetamine or other amphetamine withdrawal.

17.4.4.3. Cannabis

- Marijuana and hashish are the two forms of cannabis. These substances containthe active ingredient THC (delta9tetrahydrocannabinol) and are forms of cannabis commonly used today.
- The field of addiction medicine has given considerable attention to the question of whether there is a specific withdrawal syndrome associated with cessation from prolonged THC use. In the past, many have stated that there is no acute abstinence syndrome that develops in people who abruptly discontinue THC.
- More recently this has been called into question and most experts now believe that a THC - specific withdrawal syndrome does occur in some patients who are heavy users (Budney et al. 2001).

- Both animal and human studies indicate that a withdrawal syndrome starts within 24 hours of cessation and may last for up to a week. The amount of THC that one needs to ingest in order to experience withdrawal is unknown. It can be assumed, however, that heavier consumption is more likely to be associated with withdrawal symptoms.
- The most frequently seen symptoms of THC withdrawal are anxiety, restlessness and irritability, sleep disturbance, and change in appetite (usually anorexia). Other symptoms of withdrawal are less frequently seen and appear to include tremor, diaphoresis, tachycardia, and GI disturbances, including nausea, vomiting, and diarrhea. Cognitive difficulties including depression also have been reported and may persist but usually improve with time.
- There are no medical complications of withdrawal from THC, and medication is generally not required to manage withdrawal.

1.4.4.4.1: Management of cannabis use disorder

- Clinicians may see a variety of the symptoms mentioned above, but these generally require no immediate medication during the detoxification period and usually are self limiting.
- However, the clinician should be aware of the potential for more persistent problems. Screening the patient for suicidal ideation or other mental health problems is warranted.
- Benzodiazepines and other addictive medications should be avoided. The patient should be encouraged to maintain abstinence from THC as well as other addictive substances. Some patients will require a substance free, supportive environment to achieve and maintain abstinence.
- Clinicians should educate all patients about the effects of withdrawal, validate their complaints, and reassure them that their symptoms will likely improve with time. Symptomatic relief may be provided in order to increase the patient's comfort.

17.4.4.4. Opioids

- Opioids are highly addictive, and their chronic use leads to withdrawal symptoms that, although not medically dangerous, can be highly unpleasant and produce intense discomfort.

- All opioids (e.g., heroin, morphine, hydromorphone, oxycodone, codeine, and methadone) produce similar effects by interacting with endogenous opioid receptors. Opioid intoxication causes euphoria, analgesia and calmness.
- Intoxication also results in signs and symptoms including bradycardia, hypotension, hypothermia, sedation, meiosis, hypokinesis, slurred speech, andhead nodding.

Opioid withdrawal symptoms

- All opioid agents produce similar withdrawal signs and symptoms with some variance in severity, time of onset, and duration ofsymptomatology, depending on the agent used, the duration of use, the daily dose, and the interval between doses.
- For instance, heroin withdrawal typically begins 8 to 12 hours after the last heroin dose and subsides within a period of 3 to 5 days.
- Methadone withdrawal typically begins 36 to 48 hours after the last dose, peaksafter about 3 days, and gradually subsides over a period of 3 weeks or longer.
- Physiological, genetic, and psychological factors can significantly affect intoxication and withdrawal severity. The signs and symptoms of opioid withdrawal include tachycardia, hypertension, hyperthermia, insomnia, Mydriasis, hyperreflexia,diaphoresis, piloerection, increased respiratory rate, lacrimation, yawning,rhinorrhea, andmuscle spasms. It also results in abdominal cramps, nausea, vomiting, diarrhea,bone and muscle pain, andanxiety.
- The clinician uses intoxication and withdrawal measures as guides to avoid under or overmedicating patients during medically supervised detoxification; the number and intensity of signs determine the severity of opioid withdrawal.
- It is important to appreciate that untreated opioid withdrawal gradually builds in severity of signs and symptoms and then diminishes in a self-limited manner. Repeated assessments should be made during detoxification to determine whether symptoms areimproving or worsening. Repeated assessments also should address the effectiveness ofpharmacological interventions.
- Detoxification strategies should aim to establish control over the opioid withdrawal syndrome after which, dose reductions can be made gradually.
- Medical complications associated with opioidwithdrawal can develop and should be quickly identified and treated.

- Unlike alcohol andsedative withdrawal, uncomplicated opioidwithdrawal is not life-threatening. Rarely,severe gastrointestinal symptoms produced byopioid withdrawal, such as vomiting or diarrhea, can lead to dehydration or electrolyte imbalance.
- Most individuals can be treatedwith oral fluids, especially fluids containingelectrolytes, and some might require intravenous therapies.
- In addition, underlying cardiac illness could be made worse in the presence of the autonomic arousal that is characteristic of opioid withdrawal.
- Fever may be present during opioid withdrawal and typically will respond to detoxification. Other causes of fever should be evaluated, particularly with intravenous users.
- The Clinical Opioid Withdrawal Scale (COWS) is recommended for use to assess the opioid withdrawal symptoms and signs. (See annex 3)

The Clinical Opiate Withdrawal Scale (COWS) is an 11-item scale designed to be administered by a clinician. This tool can be used in both inpatient and outpatient settings to reproducibly rate common signs and symptoms of opiate withdrawal and monitor these symptoms over time. The summed score for the complete scale can be used to help clinicians determine the stage or severity of opiate withdrawal and assess the level of physical dependence on opioids. Practitioners sometimes express concern about the objectivity of the items in the COWS; however, the symptoms of opioid withdrawal have been likened to a severe influenza infection (e.g., nausea, vomiting, sweating, joint aches, agitation, tremor), and patients should not exceed the lowest score in most categories without exhibiting some observable sign or symptom of withdrawal.

17.4.4.4.1. Management of opioid withdrawal

Management of withdrawal without medications

- It is not recommended that clinicians attempt to manage significant opioid withdrawal symptoms without the effective detoxification agents. Even mild levels of opioid use commonly produce uncomfortable levels of withdrawal symptomatology.
- Management of this syndrome without medications can produce needless suffering in a population that tends to have limited tolerance for physical pain.

Management of withdrawal with medications

- The management of opioid withdrawal with medications is most commonly achieved through the use of methadone (in addition to adjunctive medications for nausea, vomiting, diarrhea, and stomach cramps).
- Methadone is the most frequently used agent approved for detoxification by the Food and Drug Administration (FDA), and a new medication, Buprenorphine, has been approved for use.
- Methadone can be used for detoxification from heroin and all opioid agonists.
- Another commonly used agent is clonidine (Gold et al. 1984), an adrenergic agonist that relieves most opioid withdrawal symptoms without producing opioid intoxication or drug reward.
- However, clonidine detoxification is less effective against many opioid withdrawal symptoms.
- Additional opioid agonists could be used theoretically for detoxification but would have to be administered "off label," because the FDA has approved only methadone for this purpose.
- Detoxification is indicated for treatmentseeking persons who display signs and symptoms sufficient to warrant treatment with medications and for whom maintenance is declined or for some reason is not indicated or practical.
- In addition, individuals dependent on opioids sometimes are hospitalized for other health problems and may require hospital-based detoxification even though they are not seeking substance abuse treatment. Such patients also can be maintained on methadone during the course of hospitalization for any condition other than opioid addiction. On the other hand, some persons may not have used sufficient amounts of opioids to develop withdrawal symptoms, and for others sufficient time may have elapsed since their last dose to extinguish withdrawal and eliminate the need for detoxification.
- Care should be taken to avoid giving methadone to newly admitted patients with signs of opioid intoxication, since overdose could result.
- Note that methadone stabilization is the treatment of choice for patients who are pregnant and opioid dependent.
- Clonidine was originally marketed and approved for the treatment of high blood pressure but also has been used for opioid detoxification since 1978.

- While clonidine is not FDA approved for treatment of opioid withdrawal, it is widely used "off label" for this purpose (Alling 1992) because the research literature substantiates its effectiveness for this condition.
- The main advantage of clonidine over methadone in the treatment of opioid withdrawal is that clonidine does not produce opioid intoxication and is not reinforcing. Nevertheless, patients addicted to opioids generally prefer methadone over clonidine detoxification. Although clonidine alleviates some symptoms of opioid withdrawal, it usually is relatively ineffective for insomnia,muscle aches, and drug craving. Completion rates for opioid detoxification using clonidine have been low (ranging from 20 to 40 percent); those patients who complete the procedure are more likely to be dependent on opioids other than heroin and report lower levels of subjective withdrawal symptoms than those who do not complete (Strobbe et al. 2003).
- Inpatient treatment, if available, can provide additional support, medical supervision, and rehabilitative treatment that serve as disincentives to relapse.

Patient care and comfort

- Opioid detoxification, when properly conducted, usually can be concluded without significant patient discomfort.
- Aside from the compassionate goal of preventing unnecessary suffering, appropriate opioid detoxification strengthens the therapeutic alliance between the patient and clinician and prevents patients from leaving treatment prematurely.
- Discomfort also can indicate that too low a dose of the detoxification agent is being administered. Mere symptomatic treatment is not a substitute for reversing opioid withdrawal and care should be taken to avoid masking symptoms that would better respond to detoxification.
- Nevertheless, patients receiving adequate detoxification doses still may complain of symptoms that can be treated with adjunctivemedications.
- Insomnia can be treated with diphenhydramine 50 to 100mg, trazodone 75 to 200mg, or hydroxyzine 25 to 50mg at bedtime.

- Benzodiazepines should be avoided unless required for concomitant alcohol or sedative detoxification. Headache, muscle aches, and bone pain can be managed with Acetaminophen (Paracetamol), aspirin, or ibuprofen as needed.
- Abdominal cramps are rare when the detoxification dose is sufficient but can be ameliorated with dicyclomine 10 to 20mg every 6 hours. Antacid suspension can be administered for epigastric complaints and bismuth subcarbonate 30 cc can be given every 2 to 3 hours for diarrhea.
- Constipation, a frequent complaint during methadone maintenance, usually can be managed with milk of magnesia at 30 cc daily. Opioid dependence, particularly intravenous heroin dependence, is associated with a number of medical conditions. For this reason, a complete physical examination, review of systems, and laboratory evaluation (when indicated) should be conducted.
- The patient should be screened for tuberculosis as well as for commonly encountered medical complications. These include HIV/AIDS, viral hepatitis (especially B and C), other sexually transmitted diseases, and opportunistic infections. Injection sites should be examined for infection or abscess and patients should be queried about night sweats, chills, nutritional intake, diarrhea and gastrointestinal distress, fever, and cough. History or evidence of trauma also should be elicited as part of a comprehensive assessment upon which a full treatment plan will be based.
- In general, patients should be ambulatory and able to participate in rehabilitative activities during detoxification. However, during the first 24 hours they may require bed rest or reduced activity.

17.4.4.4.2. Methadone replacement therapy schedule

- Methadone is an opioid, like heroin or opium.
- Methadone maintenance treatment has been used to treat opioid dependence since the 1950s. The opioid dependent patient takes a daily dose of methadone as a liquid or pill. This reduces their withdrawal symptoms and cravings for opioids. Methadone is addictive, like other opioids.
- However, being on methadone is not the same as being dependent on illegal opioids such as heroin:

- It is safer for the patient to take methadone under medical supervision than it is to take heroin of unknown purity.
- Methadone is taken orally. Heroin is often injected, which can lead to HIV transmission if needles and syringes are shared.
- People are heroin dependent often spend most of their time trying to obtain and use heroin. This can involve criminal activity such as stealing. Patients in methadone do not needto do this. Instead, they can undertake productive activities such as education, employment and parenting.

- Methadone maintenance therapy (MMT) has known advantages. There has been a great deal of research on MMT. This research has found that MMT significantly reduces drug injecting; because it reduces drug injecting, MMT reduces HIV transmission; MMT significantly reduces the death rate associated with opioid dependence; MMT reduces criminal activity by opioid users; and methadone doses of greater than 60mg are most effective.
- Methadone is a synthetic opioid agonist. This means it produces effects in the body in the same way as heroin, morphine and other opioids. It is taken orally as a tablet or syrup.
- When an opioid dependent person takes methadone, it relieves withdrawal symptoms and opioid cravings; at a maintenance dose, it does not induce euphoria.
- Onset of effects occurs 30 minutes after swallowing and peak effects are felt approximately three hours after swallowing. At first, the half-life (the length of time for which effects are felt) of methadone is approximately 15 hours; however, with repeated dosing, the half-life extends to approximately 24 hours. It can take between 3 and 10 days for the amount of methadone in the patient's system to stabilize.
- Most people beginning MMT experience few side effects. However, there are some side effects of methadone, including:

  - Disturbed sleep
  - Nausea and vomiting
  - Constipation
  - Dry mouth
  - Increased perspiration
  - Sexual dysfunction

- Menstrual irregularities in women
- Weight gain

- Drug interactions: Interactions between methadone and other drugs can lead to overdose or death. Drugs that depress the respiratory system (e.g. benzodiazepines) increase the effects of methadone. Drugs that affect metabolism can induce methadone withdrawal symptoms.

  - The HIV medications **Nevirapine** and **Efavirenz** increase metabolism of methadone, causing opioid withdrawal. Some protease inhibitors (PIs) may have the same effect, especially when associated to a small boosting dose of ritonavir.
  - The tuberculosis medication **rifampicin** increases metabolism of methadone and reduces the half-life of methadone.

- Patients receiving these medications, or other medications with potential serious interactions, in combination with methadone should be monitored for signs of withdrawal or intoxication, and their methadone dose adjusted accordingly.
- Patients in methadone maintenance treatment can become tolerant to the pain-relieving effects of opioids. In the event that an MMT patient requires pain relief, non-opioid analgesics such as Paracetamol can be given. If methadone patients are provided with opioid analgesics, they may require higher than normal doses to experience pain relief.
- Indications: Methadone maintenance treatment is indicated for patients who are dependent on opioids or have a history of opioid dependence. In closed settings, it is important to remember that patients not currently physically dependent on opioids can benefit from the relapse prevention effects of methadone maintenance treatment.
- Patients must also be able to give informed consent for methadone maintenance treatment.
- Contraindications: Patients with severe liver disease should not be prescribed methadone maintenance treatment as methadone may precipitate hepatic encephalopathy.
- Patients who are intolerant of methadone or ingredients in methadone formulations should not be prescribed methadone.
- Risk: The major risk associated with methadone is overdose. Overdose is a particular concern in the initial stages of MMT and when methadone is used in combination with other depressant drugs. Methadone overdose may not be obvious for three to four hours after

ingestion. Patients should be closely monitored during the first week of treatment for signs of overdose, including:

- Pinpoint pupils
- Nausea and vomiting
- Dizziness
- Excess sedation
- Slurred speech
- Snoring
- Slow pulse and shallow breathing
- Frothing at the mouth
- Unconscious and unable to be roused

- Overdose is more likely to occur if the patient is using other drugs that depress the central nervous system e.g. alcohol, benzodiazepines or opioids.
- Patients should be informed of the risks of using these drugs in combination with methadone. In case of overdose, naloxone should be administered.
- This reverses the effects of methadone. Because methadone has a long half-life, it is necessary to provide a prolonged infusion or multiple doses of naloxone over several hours. Patients who have overdosed should be transferred to a hospital and monitored for at least four hours.
- Dosing: The first dose of methadone given to a patient is low. The size of the dose is gradually increased until the **maintenance dose** is reached. The maintenance dose is the amount of methadone the patient requires to prevent opioid withdrawal symptoms, but does not induce euphoria.
- The first dose of methadone should be between 10-30mg. Patients who have recently used opioids can be given a first dose at the higher end of this range. The first dose given to a patient who has not recently used opioids should be no greater than 10-20mg. When determining the size of the first dose, keep in mind that deaths from methadone overdose in the first two weeks of treatment have occurred at doses as low as 40-60mg per day.
- Observe the patient 3-4 hours after the first dose has been taken. If the patient is showing signs of overdose, continue to monitor the patient at fifteen minute intervals. If the patient enters a coma, administer naloxone as a prolonged infusion.
- Provide the same dose daily for three days. The patient will experience increasing effects from the same dose over this time. After the first three days, assess the patient's withdrawal

symptoms. If the patient is experiencing withdrawal, increase the dose by 5-10mg every three days. Dose increases should not be greater than 20mg per week.

- Monitor the patient for signs of withdrawal and intoxication and adjust the methadone dose accordingly to find the patient's maintenance dose. This process may take several weeks. The maintenance dose will usually be between 60-120mg, but may be higher or lower, depending on the patient's history of opioid use.
- Managing of dosing: Patients in methadone maintenance treatment must be dosed once every day. Methadone dosing must be strictly managed in order to minimize *diversion.* Diversion refers to patients giving or selling their methadone to others for other's use:
    - A patient may deliberately not swallow, or swallow and then vomit, their dose in order to sell it or give it to another resident
    - A patient may be forced by another resident to give their dose away
- A well-managed program can minimize the risk of diversion by having clear dosing procedures. Dosing should be conducted by nurses or other health professionals under the supervision of nurses.
- Treatment review: At regular periods, the patient and prescribing doctor should meet for a treatment review. The following should be discussed at a treatment review:
    - Suitability of the current methadone dose, withdrawal symptoms and side effects, requests for dose increases
    - Other medications the patient is taking
    - Physical and psychological health
    - Current drug use, including signs of injecting drug use
    - Review of treatment goals
- At the commencement of MMT, treatment review should occur weekly. After two months in treatment, the frequency of treatment reviews can be reduced to once every four to six weeks.
- Patients who are using illicit drugs, are suspected of diverting their methadone dose, or have recently had their dose increased or decreased should attend treatment review meetings weekly.
- Duration of treatment: There is no set rule for how long someone should stay in methadone maintenance treatment. However, it is well known that the longer a patient remains in

treatment, the better the outcome. Generally, patients should be encouraged to remain in methadone maintenance treatment for long term.

17.4.4.4.3. Benzodiazepines and other sedative hypnotics

- Patients intoxicated with sedative/hypnotics appear similar to individuals intoxicated with alcohol. Slurred speech, ataxia, and poor physical coordination are prominent.
- If benzodiazepines are used alone, breath and blood alcohol levels should be zero. It should be remembered that benzodiazepines, when ingested alone, intentionally, or accidentally in overdose, rarely lead to death by themselves. Unfortunately, most individuals who ingest benzodiazepines also may be using alcohol, other sedative/hypnotics, or other drugs of abuse, which in combination with benzodiazepines could be fatal if not managed appropriately.
- Management of benzodiazepines and other sedative/hypnotics in overdose is in part supported with particular attention to ventilation. Additionally, removal of the benzodiazepine from the gastrointestinal tract using lavage and a cathartic is generally carried out, particularly if the overdose is recent.
- Flumazenil is a competitive antagonist that acts at the benzodiazepine receptor. It can reverse the sedative and overdose effects of benzodiazepines but not of alcohol or other sedative-/hypnotics.
- The medication is administered via IV by slow push (2 to 3 minutes) and dosage varies, depending on whether one is treating sedation reversal or overdose coma reversal. Clinicians should be aware that in chronic benzodiazepine users who are physically dependent, flumazenil may induce seizures, high blood pressure, and delirium. So patients who are comatose from benzodiazepines and are benzodiazepine dependent may move quickly from coma to acute benzodiazepine withdrawal symptoms when flumazenil is administered.
- Assessing the potential or actual severity of a benzodiazepine and other sedative/hypnotic abstinence syndrome is based primarily on clinical information obtained from the patient, significant others, and physical assessment. Confirmation of length of benzodiazepine treatment with significant others, local pharmacies, and treating physicians is useful.
- Specific name of medication, dose, and duration of therapy are vital. The presence or absence of alcohol use is also important to know, as with the use of other sedative/-hypnotics, such as medications for sleep.

- The existence of co-occurring psychiatric disorders such as panic disorder also are important factors and should be investigated. Cigarette smoking tends to induce the metabolism of some benzodiazepines and this can be a factor in scheduling a taper. Physical assessment, with particular attention to mental status, and neurologic exams are important. Determination of vital signs also provides guidance.
- A urine drug screen may confirm the presence of benzodiazepines but otherwise will not be particularly helpful.
- Medical complications of withdrawal from benzodiazepines include problems similar to those seen in alcohol withdrawal.
- Seizures are particularly worrisome and may occur without being preceded by other evidence of withdrawal. As in alcohol withdrawal, seizures and delirium represent the most extreme pathology seen. Anecdotal reports appearing in the literature also have described distortions in taste, smell, and other perceptions. Since many individuals who take benzodiazepines have underlying anxiety disorders, it often is difficult during periods of withdrawal to determine whether symptomatology is related to withdrawal or the emergence of panic attack symptoms.
- Elderly patients who are being withdrawn from benzodiazepine are at risk for falls and myocardial infarctions. Delirium without marked autonomic hyperactivity also may be seen in the elderly.
- The management of benzodiazepine withdrawal is not recommended without medical supervision. All benzodiazepines should be tapered rather than stopped abruptly, regardless of dose or duration of use unless it is a matter of use for only a few days (Ashton2002).

17.4.4.4.4. Management of withdrawal from benzodiazepines and other sedative hypnotics

Management of withdrawal with medications

- From the limited number of controlled trials that can provide guidance in the management of benzodiazepine or other sedative withdrawal (see Rickels and colleagues (1999) and Eickelberg and Mayo Smith (1998), recommended approaches can be followed.
- For long acting benzodiazepines, begin with a slow taper of the benzodiazepine that the patient is already taking. This can be conducted over weeks or perhaps even months.
- For a patient with history of serious loss of control, sometimes switching to another benzodiazepine is therapeutic.

- The other approach is switching the patient to another benzodiazepine with a long half-life; Chlordiazepoxide and clonazepam are recommended. Recurring assessment is necessary, particularly around times of dosage reductions.
- Pregnant patients will need to be detoxified slowly and in consultation with an obstetrician. Provide patient education, and provide alternative cognitive and behavioral techniques for anxiety reduction and sleep enhancement during detoxification (Spiegel 1999).
- Use of anticonvulsants such as carbamazepine and valproate, as well as antidepressants such as imipramine is advocated during withdrawal (Dickinson etal. 2003). Rickels and colleagues (1999).
- The use of anticonvulsants is probably best reserved as an adjunctive medicine to the long--acting benzodiazepine or phenobarbital.
- For patients with major autonomic symptoms during withdrawal that cannot be controlled bythe primary treating agent, consideration of the use of a low dose of clonidine or propranolol may be helpful.
- Preparing patients and starting detoxification during a period of low external stressors, with patient commitment to tapering, and a plan to manage underlying anxiety disorders, also are important in detoxification. A flexible detoxification schedule is advised. During periods of increased withdrawal symptoms, dosage should be stabilized or even increased for a period of days.
- Frequent in person or phone contact with the patient is vital. Patients being detoxified in the outpatient setting may need to be seen several times per week, especially at times of dosage reductions.

17.4.4.4.5. Management of Poly-drug Abuse: An Integrated Approach

- One of the most significant changes in detoxification services in recent years has been the increase in the number of patients requiring detoxification from more than one substance.

Co-occurring disorders

- Those who are users of multiple illicit substances are more likely to experience psychiatric disorders, and the risk is highest among those who use opiates and benzodiazepines and/or alcohol.
- Depression is more common among those who abuse a combination of these substances, and women are at higher risk than men. Among those patients who are positive for depression,

the risk of suicide is high. Marsden and colleagues' 2000 study of 1,075 clients entering treatment showed that 29 % reported suicidal ideation in the past 3 months.

- During acute intoxication and withdrawal, it is important to provide an environment that minimizes the opportunities for suicide attempts.
- Intoxication with alcohol, cocaine or amphetamines may be associated with increased risk of violence.
- Symptoms associated with this increased risk for violence include hallucinations, paranoia, anxiety, and depression. As a precaution, all patients who are intoxicated should be considered potentially violent (Miller et al. 1994). With the patient's consent, a review of the patient's mental health history with the patient and family is useful in identifying co-occurring psychiatric conditions.
- Diagnosis of co-occurring substance related disorders and mental conditions is difficult during acute intoxication and withdrawal because it often is impossible to be precise until the clinical picture allows for the full assessment of both the effects of substance use and of the symptoms of mental disorders. As the individual moves from severe to moderate withdrawal symptoms, attention to differential diagnosis of substance use disorders and other psychiatric disorders becomes a priority.
- It is important that during the detoxification process, the patient avoid substituting one addiction for another. Consuming excessive amounts of caffeine or sugar cane compromise the process and lead to relapse. Fresh fruits, vegetables, and other whole foods can contribute to the individual's health and wellness.
- Gastrointestinal disturbances (i.e., nausea, vomiting, and diarrhea) may accompany the first phase of detoxification. Such disturbances can worsen dehydration and may disturb blood chemistry balance, which in turn can lead to mental status changes, neurological or heart problems, and other potentially dangerous medical conditions.
- Patients with gastrointestinal disturbances may only be able to tolerate clear liquids. When solid foods are tolerated, balanced meals consisting of low fat foods, with an increased intake of protein (meat, dairy products, legumes), complex carbohydrates (whole grain bread and cereals), and dietary fiber are recommended.
- Patients undergoing detoxification may also experience constipation. Increasing the fiber content of the diet will help to alleviate this discomfort.

Chronic relapse

- A patient who recently relapsed after period of extended abstinence may feel especially hopeless and vulnerable (an abstinence violation effect). In this situation, clinicians can acknowledge progress that had been made prior to relapse and reassure the patient that the internal gains from past recovery work have not all been lost (despite the feeling at the moment that they have), perhaps reframing the severity of emotional pain as an indicator of how important recovery is to the patient.

Strategies for engaging and retaining patients in detoxification

- It is essential to keep patients who enter detoxification from "falling through the cracks".
- Successful providers acknowledge and show respect for the patient's pain, needs, and joys, and validate the patient's fears, ambivalence, expectation of recovery, and positive life changes.
- It is essential that all clinicians who have contact with patients in withdrawal continually offer hope and the expectation of recovery. An atmosphere that conveys comfort, relaxation, cleanliness, availability of medical attention, and security is beneficial to patients experiencing the discomforts of the withdrawal process. Throughout the detoxification experience, detoxification staff should be unified in their message that detoxification is only the beginning of the substance abuse treatment process and that rehabilitation and maintenance activities are critical to sustained recovery.

Educate the patient on the withdrawal process

- During withdrawal, it is useful to provide information on the typical withdrawal process based on the particular drug of abuse.
- Usually withdrawal includes symptoms that are the opposite of the effects of the particular drug. This rebound effect can cause anxiety and concern for patients. Providing information about the common withdrawal symptoms of the specific drugs of abuse may reduce discomfort and the likelihood that the individual will leave detoxification services prematurely.

- Settings that routinely encounter individuals in withdrawal should have written materials available on drug effects and withdrawal from specific drugs, and has staffs that are well versed in the signs and symptoms of withdrawal. Providers should be alert to drug seeking behaviors, including bringing alcohol or other drugs into the facility. It is important to note, however, that personnel should be respectful in their efforts to maintain a drug free environment. It is important to explain to patients (prior to treatment) and visitors why substances are not allowed in the facility.

17.4.4.4.6. Enhancing motivation

- Motivational enhancements are particularly well suited to accomplishing the detoxification services goal of promoting initiation in rehabilitation and maintenance activities. Use of these techniques in the detoxification setting increases the likelihood that patients will seek treatment by helping them understand the adverse consequences of continued substance use. The following approach is recommended to follow during motivational enhancement counseling:

  - Focus on the patient's strengths
  - Show respect for a patient's decisions and autonomy; respect should be maintained at all times, even when the patient is intoxicated
  - Avoid confrontation
  - Individualize treatment
  - Do not use labels that depersonalize the patient, such as "addict" or "alcoholic."
  - Empathize with the patient, making an attempt to understand the patient's perspective and accept his or her feelings
  - Accept treatment goals that involve small steps toward ultimate goals
  - Assist the patient in developing an awareness of discrepancies between her or his goals or values and current behavior
  - Listen reflectively to the patient's immediate concerns and ask open-ended questions

- If the patient places considerable value on her or his relationships with significant others, success is more likely (Longabaugh et al. 1993).
- Tailoring motivational intervention to stages of change is important. Perhaps the most well-known and empirically validated model of "readiness to change" that has been applied to substance abuse is the trans-theoretical model, also known as the stages of change model.
- According to the model, a client is considered to be in one of five stages of readiness to change his substance abusing behavior, each stage being progressively closer to sustained recovery. Those stages are pre-contemplation, contemplation, preparation, action, and maintenance.
- The model assumes that individuals may move back and forth between different stages over time individual's level of motivation is definitely not a permanent characteristic. Rather, motivation to change can be influenced by others, including detoxification treatment staff. In general, the basic concept is to try to move patients to the next stage of change. The clinician needs to identify any potential obstacles that might hinder the patient's progress through the stages of change.

17.4.4.5. Evaluation for rehabilitation needs

- To make appropriate recommendations for ongoing treatment and recovery activities, detoxification staff needs to determine the individual characteristics of clients and their environments that are likely to influence the level of care, setting, and specialized services needed for recovery.
- Factors needed to make a placement decision based on six dimensions:
    - Acute intoxication and/or withdrawal potential
    - Biomedical conditions and complications
    - Emotional, behavioral, or cognitive conditions or complications
    - Readiness to change
    - Relapse, continued use, or continued problem potential
    - Recovery/living environment

- Due to the limited time patients stay in detoxification settings, it is challenging for programs to conduct a complete assessment of the rehabilitation needs of the individual.

17.4.4.6. Co-occurring psychiatric disorders

- Other psychiatric symptoms that are likely to complicate the treatment of the substance use disorder and require treatment themselves, concerns about safety in certain settings (note that assessment for co-occurring disorders should include a determination of any psychiatric medications that the patient may be taking for the condition).
- Current domestic violence that affects the safety of the living environment, co-occurring posttraumatic stress disorder or trauma history that might complicate rehabilitation.
- Prior successful and unsuccessful rehabilitation experiences might influence decision about type of setting indicated at the present time.

Reference

1. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, text revision. Washington DC, American Psychiatric Association, 2022.
2. Nathanael J McKeown,Nathanael J McKeown, Patrick L West.Withdrawal Syndromes Treatment & Management. Medscape Oct 18, 2020.
3. Carol Galbicsek. Benzodiazepines in treating alcoholism. Alcohol Rehab Guide; February 25, 2022.
4. Ankur Sachdeva, Mina Chandra, Smita N. Deshpande. A Comparative Study of Fixed Tapering Dose Regimen versus Symptom-triggered Regimen of Lorazepam for Alcohol Detoxification. *Alcohol and Alcoholism*, Volume 49, Issue 3, May/June 2014, Pages 287–291, https://doi.org/10.1093/alcalc/agt181
5. Stead LF, et al. Nicotine replacement therapy for smoking cessation. Cochrane Database of Systematic Reviews 2008
6. Tobacco Advisory Group of the Royal College of Physicians 2000.

7. World Health Organization (WHO). Methadone maintenance treatment. Clinical Guidelines for Withdrawal Management and Treatment of Drug Dependence in Closed Setting, 2009.
8. AbebawFekadu, AtalayAlem, and Charlotte Hanlon. Alcohol and drug abuse in Ethiopia: Past, present and future. African Journal of Drug and Alcohol Studies, 2007; 6(1).
9. TewodrosShegute and YaredWasihun. Prevalence of Substance Use in University Students, Ethiopia. Substance Abuse: Research and Treatment 2021; Volume 15: 1–16.
10. Abraham TamiratGizaw ,DemumaAmdisa and YohannesKebedeLemu. Predictors of substance use among Jimma University instructors, Southwest Ethiopia. Substance Abuse Treatment, Prevention, and Policy 2020; 15:2.
11. SAMHSA (Substance Abuse and Mental Health Services Administration). www.samhsa.gov.
12. Rehab After Work: Outpatient Treatment Centers. Risk factors for substance use disorders. Updated Aug 16, 2018.
13. Wesson, D. R., & Ling, W. (2003). The Clinical Opiate Withdrawal Scale (COWS). J Psychoactive Drugs, 35(2), 253–9.

Annexes

Annex 1: The modified SAD PERSONS scale

The score is calculated from 10 yes/no questions, with one point for each affirmative answer except where indicated as 2 points:

- S: Male sex
- A: Age 15-29 years, or >58 years (2 points)
- D: Depression or hopelessness
- P: Previous attempt
- E: Excess alcohol or substance use
- R: Rational thinking loss eg. psychosis or organic disease (2 points)
- S: Single (eg. divorced or widowed)
- O: Organized plan or serious attempt (2 points)
- N: No social supports
- S: Stated future attempt (2 points)

The score is then mapped onto a risk assessment scale as follows:

- 0-5: May be safe to discharge (depending upon circumstances)
- 6-8: Probably requires psychiatric consultation
- >8: Probably requires hospital admission

Annex 2: ALCOHOL CIWAAR SULLIVAN ET AL. 1989

Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar) Patient:_____ Date: _____ Time: _____ (24 hour clock, midnight = 00:00)	
Pulse or heart rate, taken for one minute:_____ Blood pressure:_____	
NAUSEA AND VOMITING -- Ask "Do you feel sick to your stomach? Have you vomited?" Observation. 0 no nausea and no vomiting 1 mild nausea with no vomiting 2 3 4 intermittent nausea with dry heaves 5 6 7 constant nausea, frequent dry heaves and vomiting	TACTILE DISTURBANCES -- Ask "Have you any itching, pins and needles sensations, any burning, any numbness, or do you feel bugs crawling on or under your skin?" Observation. 0 none 1 very mild itching, pins and needles, burning or numbness 2 mild itching, pins and needles, burning or numbness 3 moderate itching, pins and needles, burning or numbness 4 moderately severe hallucinations 5 severe hallucinations 6

	extremely severe hallucinations 7 continuous hallucinations
TREMOR -- Arms extended and fingers spread apart. Observation. 0 no tremor 1 not visible, but can be felt fingertip to fingertip 2 3 4 moderate, with patient's arms extended 5 6 7 severe, even with arms not extended	AUDITORY DISTURBANCES -- Ask "Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?" Observation. 0 not present 1 very mild harshness or ability to frighten 2 mild harshness or ability to frighten 3 moderate harshness or ability to frighten 4 moderately severe hallucinations 5 severe hallucinations 6 extremely severe hallucinations 7 continuous hallucinations
PAROXYSMAL SWEATS -- Observation. 0 no sweat visible 1 barely perceptible sweating, palms moist 2 3 4 beads of sweat obvious on forehead 5 6 7 drenching sweats	VISUAL DISTURBANCES -- Ask "Does the light appear to be too bright? Is its color different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know are not there?" Observation. 0 not present 1 very mild sensitivity 2 mild sensitivity 3 moderate sensitivity 4 moderately severe hallucinations 5 severe hallucinations 6 extremely severe hallucinations 7 continuous hallucinations
ANXIETY -- Ask "Do you feel nervous?" Observation. 0 no anxiety, at ease 1 mild anxious 2 3 4 moderately anxious, or guarded, so anxiety is inferred 5 6 7 equivalent to acute panic states as seen in severe delirium or acute schizophrenic reactions	HEADACHE, FULLNESS IN HEAD -- Ask "Does your head feel different? Does it feel like there is a band around your head?" Do not rate for dizziness or lightheadedness. Otherwise, rate severity. 0 not present 1 very mild 2 mild 3 moderate 4 moderately severe 5 severe 6 very severe 7 extremely severe
AGITATION -- Observation. 0 normal activity 1 somewhat more than normal activity 2 3 4 moderately fidgety and restless 5 6 7 paces back and forth during most of the interview, or constantly thrashes about	ORIENTATION AND CLOUDING OF SENSORIUM -- Ask "What day is this? Where are you? Who am I?" 0 oriented and can do serial additions 1 cannot do serial additions or is uncertain about date 2 disoriented for date by no more than 2 calendar days 3 disoriented for date by more than 2 calendar days 4 disoriented for place/or person
	Total CIWA-Ar Score _____ Rater's Initials _____ Maximum Possible Score 67

The CIWA-Ar is not copyrighted and may be reproduced freely. This assessment for monitoring withdrawal symptoms requires approximately 5 minutes to administer. The maximum score is 67 (see instrument). Patients scoring less than 10 do not usually need additional medication for withdrawal.
Sullivan, J.T.; Sykora, K.; Schneiderman, J.; Naranjo, C.A.; and Sellers, E.M. Assessment of alcohol withdrawal: The revised Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-Ar). British Journal of Addiction 84:1353-1357, 1989.

Annex 3:The Clinical Opiate Withdrawal Scale (COWS)

For each item, circle the number that best describes the patient' s signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.

Patient's name ……..	
Date …….	
Time ……..	
Reason for the assessment ……	
Resting Pulse Rate: …… beats/minute. Measured after patient is sitting or lying for one minute 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120	**GI Upset**: over last 1/2 hour 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting
Sweating: over past 1/2 hour not accounted for by room temperature or patient activity. 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	**Tremor**: observation of outstretched hands 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching

Restlessness: Observation during assessment 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 unable to sit still for more than a few seconds	**Yawning**: Observation during assessment 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute
Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	**Anxiety or Irritability** 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable or anxious 4 patient so irritable or anxious that participation in the assessment is difficult
Bone or Joint aches: if patient was having pain previously, only the additional component attributed to opiates withdrawal is scored 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	**Gooseflesh skin** 0 skin is smooth 3 piloerrection of skin can be felt or hairs standing up on arms 5 prominent piloerrection
Runny nose or tearing: Not accounted for by cold -symptoms or allergies 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	**Total Score** ……. The total score is the sum of all 11 items Initials of person completing assessment: …… …….

Score: 5- 12 = mild; 1 3-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal This version may be copied and used clinically.
Source: Wesson, D. R., & Ling, W. (2003). The Clinical Opiate Withdrawal Scale (COWS). J Psychoactive Drugs, 35(2), 253–9.