CHAPTER 15
MENTAL HEALTH CONDITIONS AND SUBSTANCE MISUSE

MENTAL HEALTH CONDITIONS

Precepts of the Mental Health Care Act No. 17 of 2002 include:

» All patients with mental illness and/or severe to profound intellectual disability should receive mental health care as either Voluntary, Assisted or Involuntary Mental Health Care Users.
» All registered medical practitioners, professional nurses, psychologists, occupational therapists (OTs), and social workers whose training includes mental health are designated Mental Health Care Practitioners.
» Mental health care practitioners and heads of health establishments at PHC and Hospital Adults level must be familiar with MHCA Forms 01 – 13A, 14, 17, 22, 25, 26, 27, and 48.
» The South African Police Service (SAPS) have an obligation to protect, apprehend, and assist people with mental illness with transfer, to and between health establishments.

Meaning of selected terminology used in this chapter:

» **Psychoeducation** (psychological education) involves informing a patient and their family or support system about their illness and providing problem solving, communication, and assertiveness skills training. The goals are to enable understanding, self-care, crisis management, suicide prevention, and relapse prevention. Information on aetiological factors, signs and symptoms, early signs of relapse, treatment options, need for adherence to treatment, and long-term course and outcome should be provided with consideration of the individual and their family's culture, beliefs, and coping mechanisms. Myths and misconceptions regarding the illness and its treatment are identified and managed in a person-centred manner. Advice on managing difficult behaviour and emergency situations is provided, and stigma is dispelled.

  Psychoeducation may require several individual, family, or group sessions, depending on the complexity of the illness and the understanding of the problem by the individual and their family / support system. Involvement of a registered counsellor, occupational therapist, and/or social worker is advised.

LoE:IVb[i]

» **Risk assessment** refers to a clinical judgement of the patient's potential for:
  - suicide or self-harm
  - aggression or violence towards others
  - being assaulted by others
  - high risk sexual behaviour

- severe self-neglect
- being exploited
- reputational damage
- non-adherence to treatment
- causing damage to property
- poor physical health

A risk assessment is performed by collecting information from the patient and relevant stakeholders which may include the person's family / support system, healthcare providers (including community health workers or social workers who have knowledge of the person's home), as well as past clinical and forensic history.

Close attention must be given to women in the perinatal period, people who care for others (e.g., parents, grandparents, teachers, and health and social care providers), and those with previous high-risk behaviour.

While the clinical judgement may not always be accurate, it should be justified by the available information. The clinical judgement serves to inform precautionary interventions, e.g. close clinical follow-up after hospital discharge with increased attention by the Ward-Based Outreach Team (WBOT), referral to social welfare / statutory services, advice regarding a protection order, and/or further psychoeducation.

A useful clinical guideline on how to conduct a risk assessment is available at: https://www.seslhd.health.nsw.gov.au/sites/default/files/documents/SESLHDGL%20082%20-%20%20Clinical%20Risk%20Assessment%20and%20Management%20-%20Mental%20Health2.pdf

LoE:IVb[ii]

15.1 AGGRESSIVE DISRUPTIVE BEHAVIOUR IN ADULTS

R45.1/45.4-8 + code(s) for underlying/comorbid condition(s)

DESCRIPTION

Agitation may escalate to overt aggression and often manifests with restlessness, pacing, and loud or demanding speech. Aggressive behaviour includes verbally abusive language, specific verbal threats, intimidating physical behaviour, and/or actual physical violence to self, others, or property. All agitation and aggression must be considered an emergency, and violence should be prevented wherever possible.

Causes for aggressive, disruptive behaviour include:

» **Physical:** acute medical illness, delirium and its causes (See section 20.8: Delirium with perceptual disturbances), epilepsy (pre-, intra-, and post-ictal), intracerebral lesions, traumatic brain injury.

» **Psychiatric:** psychosis, mania, agitated depression, neurocognitive disorders (e.g. dementias, old traumatic brain injury), developmental disorders (e.g. intellectual disability and autistic spectrum disorder), severe anxiety.
» **Substance misuse:** alcohol; cannabis; methaqualone (mandrax) intoxication or withdrawal; stimulant (cocaine, methamphetamine [tik], methcathinone [cat]) intoxication; benzodiazepine withdrawal.
» **Psychological factors:** high levels of impulsivity and antagonism, hypersensitivity to rejection or insult, poor frustration tolerance, and maladaptive coping skills may all contribute to aggression.
» **In pregnant women:** labour, obstetric complications, sepsis, organ failure as well as substances and mental disorders (See Primary Health Care [PHC] Standard Treatment Guidelines [STGs] and Essential Medicines List [EML], Chapter 6 Obstetrics and Gynaecology, section 6.9: Maternal mental health).

CAUTION

» **Do not assume that the aggression is due to mental illness or psychological factors.**
» Patients known with psychiatric conditions and/or intellectual disability often have co-morbid medical conditions, trauma, and substance misuse.

GENERAL MEASURES

» **Prepare, anticipate, and prevent**:
Be aware of high-risk patients e.g. those with previous violence, substance misuse, and State Patients on leave of absence. Have:
- a step-wise protocol to ensure safety of all patients and staff.
- clear roles for all staff members.
- a triage plan for early signs of aggression.
- available backup – hospital security and SAPS and EMS.
- a designated calming area – suitable for regular monitoring.

» **De-escalate and contain**:
- Be calm, confident, kind, and reassuring.
- Listen to the person.
- Maintain a submissive posture with open hands.
- Do NOT turn your back on the patient; avoid direct eye contact.
- Do NOT attempt to reason with the patient.
- Do NOT argue, confront delusions, or touch the patient.
- Set clear limits regarding behaviour.
- Take patient to quiet, calm area – do NOT leave unobserved.

» **Examine** for delirium, medical and other causes while calming the patient and after sedation.
» **Manual restraint:**
- May be necessary to administer medication.
- Manual restraint refers to interventions done with hands or bodies without the use of any device, to limit a user's movement of body or limb. It is sometimes called “holding”. Manual restraint must be respectful, controlled and kept to a

minimum. It should preferably be applied by personnel of the same sex as the patient.
- Report any injuries or death associated with the restraint to the Mental Health Review Board as well as the health facility quality assurance department.

LoE:IVb[iii]

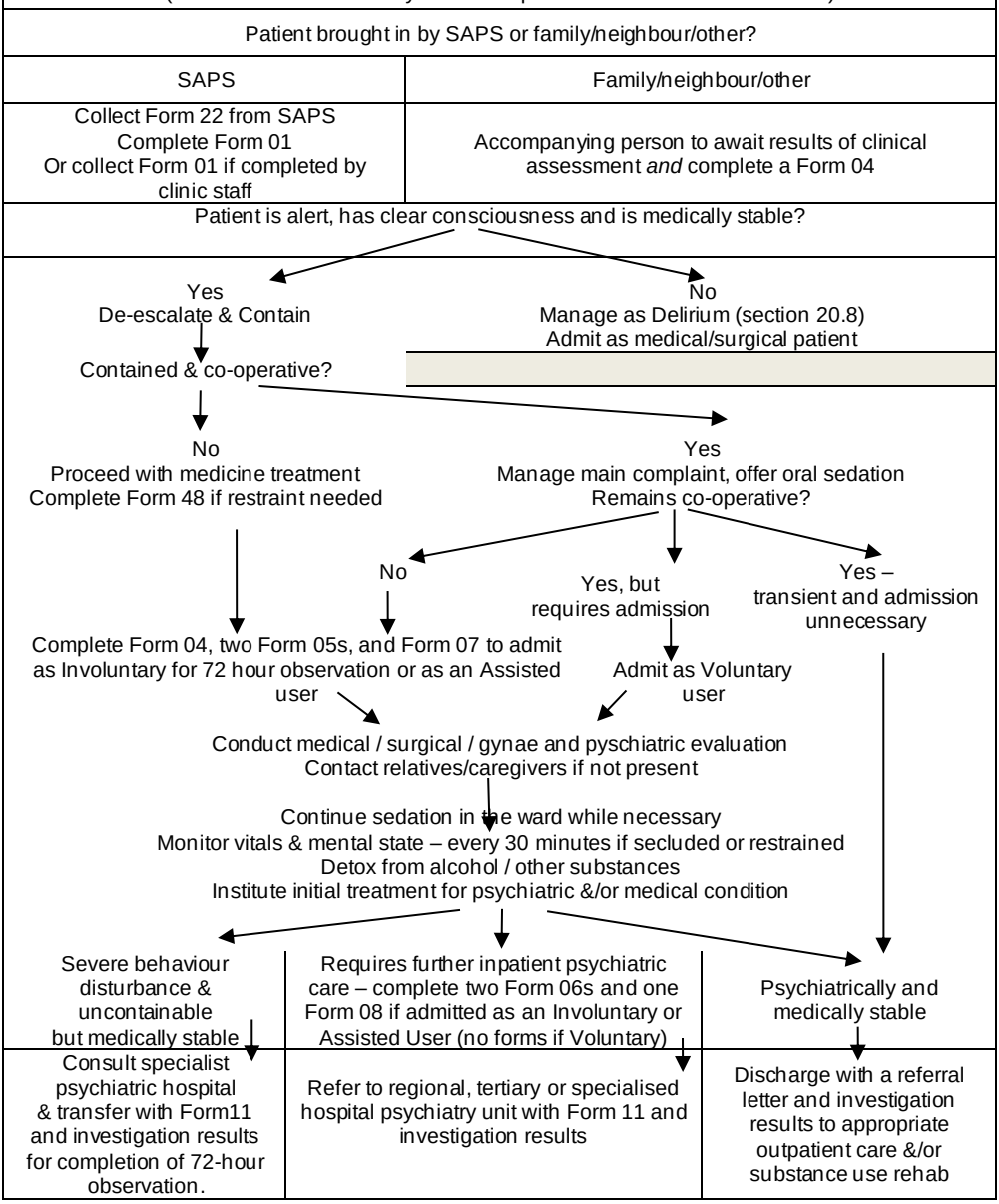
» **Mechanical restraint**:
- An emergency intervention in which an instrument or appliance is used to restrict movement of the body. See national policy guidelines on the use of mechanical restraint: https://www.knowledgehub.org.za/elibrary/policy-guidelines-seclusion-and-restraint-mental-health-care-users-2012

LoE:IVb[iv]

- Only use if absolutely necessary to protect the patient and others for as short a time as possible, and as prescribed by a doctor.
- Document the type, sites, and duration of any restraints used.
- 15-minute monitoring: vital signs, mental state, restraint sites, and reasons for use.
- For people managed under the MHCA, complete a MHCA Form 48 (restraint register) and submit to the Mental Health Review Board, together with a report of any injuries or death associated with the restraint as well as to the health facility quality assurance department.

- **Pregnant women:**
  - Never leave unattended.
  - Avoid excessive force; gently nurse mother in a supported semi-seated position (not supine or prone), in an armchair or large beanbag if available.
  - Use restraint sparingly and with care.
- **Counsel the family/friend/patient escort regarding:**
  - Possible causes for the behaviour.
  - Reasons for restraints if used.
  - Importance of their continued support of the patient post-discharge.

Figure 15.1: Aggressive and Disruptive Behaviour in Adults
District Hospital Casualty & Ward guideline
(For PHC & CHC Casualty – see Chapter 15.1 in PHC STGs and EML)



MEDICINE TREATMENT

The goal of rapid tranquilisation is to calm the patient so that risk to self or others is minimised and manage the underlying condition.

CAUTION

» Rapid tranquillisation may cause cardiovascular collapse, respiratory depression, acute dystonic reactions, and neuroleptic malignant syndrome.
» Pregnant women, elderly, intellectually disabled, and those with comorbid medical conditions and/or substance use are at highest risk of serious adverse drug reactions.
» Late pregnancy: neonatal sedation or extra-pyramidal side effects may occur.
» **Write out single prescriptions and review between each prescription.**
» **Allow at least 30 – 60 minutes between prescriptions.**
» **An emergency trolley, airway, bag, oxygen, and intravenous line must be available for use if needed.**

LoE:IVb[v]

» Monitor vital signs closely during and after medicine administration.
» Use the safest route of administration possible: The safest route of administration of benzodiazepines is oral followed by IM. IV route has the highest risk of respiratory depression and arrest.
» Do not use depot antipsychotic injections (e.g., flupenthixol decanoate or zuclopenthixol decanoate injections) for rapid tranquillisation.

Offer oral treatment:

If aggression is clearly caused by psychosis, or if pregnant, elderly/frail, or has significant risk for respiratory depression:

- Olanzapine, orodispersible tablet or IM, immediately:
  - Aggression clearly due to psychosis or if pregnant: 5–10 mg.
  - Elderly/frail, respiratory depression risk / medically unwell: 2.5–5 mg.
  - Repeat after 30–60 minutes if needed.

If cause of aggression unclear, non-pregnant, non-elderly/frail, and without significant risk for respiratory depression:

- Benzodiazepines, e.g.: *LoE:IIIb*[vi]
- Lorazepam, oral, 0.5–2 mg immediately.

OR *LoE:IVb*[vii]

- Clonazepam, oral, 0.5–2 mg immediately.

OR *LoE:IVb*[viii]

- Diazepam, oral, 5–10 mg immediately.

OR *LoE:IVb*[ix]

- Midazolam, oral or buccal, 7.5–15 mg immediately.

LoE:IIIb[x]

If there is an inadequate response to oral benzodiazepine (after 30–60 minutes), or where oral treatment is refused:

- Olanzapine, orodispersible tablet/IM, 5–10 mg immediately
  - Repeat after 30–60 minutes if needed.

Note: Repeated doses may result in excessive sedation

LoE:IVb[xi]

If there is an inadequate response to oral benzodiazepine with a history of intolerability to olanzapine (e.g. previous neuroleptic malignant syndrome):

- Lorazepam, IM, 0.5–2 mg immediately.

LoE:IIIb[xii]

OR

- Midazolam, IM, 7.5–15 mg immediately.

OR

LoE:IVb[xiii]

- Clonazepam, IM, 0.5–2 mg immediately.

Note:

» To avoid inappropriate repeat dosing, allow at least 30 minutes for the oral/IM medication to take effect.

LoE:IIIb[xiv]

» Repeated IM doses of benzodiazepines may result in toxicity owing to accumulation.

» Lorazepam IM has slower onset of sedation than midazolam IM (32 vs 18 minutes) and longer duration of sedation (217 vs 82 minutes).

» Clonazepam oral or IM may be used if longer duration of sedation is required. Onset of action may be 30-60 minutes, with predicted maximum effect after 1-4 hours. There is an increased risk of accumulation due to its long half-life (18-50 hours). Allow at least 12 hours between repeat doses.

LoE:IVb[xv]

LoE:IIb[xvi]

To continue tranquilisation under specialist supervision in psychiatric wards:

- Zuclopenthixol acetate, IM, 50–150 mg every 2–3 days (specialist/specialist consultation).
  - Start with 50mg in neuroleptic-naïve patients.
  - Maximum dose: 400 mg over a two-week period.

LoE:IVb[xvii]

If alcohol use is suspected:

ADD

- Thiamine, oral, 300 mg immediately and daily for 14 days.

LoE:IIIb[xviii]

Monitor the patient:

» Nurse in recovery position – prevent aspiration. Nurse pregnant women in supported semi-seated position if possible or left lateral position, and not supine.

» Monitor pulse, respiratory rate, blood pressure, temperature every 5–10 minutes for the first hour, and then every 30 minutes until the patient is ambulatory. Use pulse oximeter if available.
» Pregnant women: monitor fetal heart rate as well as mother's vital signs.
» Continue monitoring once ambulatory, assessing for risk of falls and further injury (especially elderly and frail), re-emergence of aggression, and abscondment.
» If patient absconds – request assistance from SAPS with a MHCA Form 25.

Manage acute complications:
» *Respiratory depression:* if respiratory rate drops to <12 breaths/minute, or oxygen saturation <90% - give oxygen; be prepared to ventilate.
» *Circulatory collapse*: See section 20.1: Cardiac arrest in adults.
» *Acute dystonia*: See PHC STGs and EML, section 16.2.1: Extra-pyramidal side effects.
» *Neuroleptic Malignant Syndrome:* See PHC STGs and EML, section 16.2.2: Neuroleptic malignant syndrome.

15.2 ANXIETY AND OBSESSIVE-COMPULSIVE DISORDERS

F40.0-2/F40.8-9/F41.0-3/F41.8-9/F42.0-9 + (F10.0-F19.9/R45.0-8/Z65.0-5/Z65.8-9/Z81.0-4/Z81.8)

DESCRIPTION

Anxiety is an emotional response to perceived or anticipated stress. It is diagnosed as a disorder when it is excessive or persistent and impacts daily functioning. Anxiety disorders often present with medically unexplained symptoms such as non-cardiac chest pain, abdominal discomfort, and neck and back muscle tension. However, anxiety symptoms may be caused by various medical conditions. In addition, medical conditions are commonly comorbid with anxiety disorders. They may exacerbate the symptoms, and the anxiety disorder may worsen the outcome of treatment of the medical condition.

Tobacco, alcohol, and other substance use are commonly associated with anxiety disorders. The substance use may be secondary to the disorder or causative or both. If caused by a substance, then an anxiety disorder due to the specific substance should be diagnosed.

Anxiety during pregnancy and the postnatal period may impact negatively on the mother's well-being and use of services, and is associated with poor psychological and neurodevelopmental outcomes in the child (See PHC STGs and EML, Chapter 6.9: Maternal mental health).

» **Psychological manifestations** of anxiety include panic symptoms, excessive worry, fear, mood changes, irritability, tearfulness, distress, and poor concentration.
» **Physical symptoms** include muscle tension, headache, abdominal cramps, nausea, palpitations, sweating, a choking feeling, shortness of breath, chest

pain, dizziness, numbness, and tingling of the hands and feet.

» **People with intellectual disability** may present with aggression, agitation, and demanding behaviour instead of anxiety.
» **Panic attacks** are abrupt surges of intense anxiety with prominent physical symptoms. They may occur in anxiety, mood, and psychotic disorders, and with alcohol and other substance misuse. They are a marker of increased severity of the primary disorder and may indicate a heightened risk of suicide.
» **Social phobia** (social anxiety disorder) is the fear of social interactions and usually starts in adolescence. Distorted thoughts are of perceived negative evaluation by others. Self-medication with alcohol or other substances is common and substance intoxication may be the presenting feature.
» **Obsessive thoughts and/or compulsive behaviour** are a core feature of obsessive compulsive disorder but may also occur in other disorders, particularly tic disorders, autistic spectrum, and psychotic disorders. Themes of the distorted thoughts and compulsions include hygiene (cleaning), security, symmetry, sexual and taboo topics, fears of causing harm, perceived physical defects, hair-pulling, or hoarding.

GENERAL MEASURES

Most patients can be treated as outpatients, but some may need to be admitted for diagnostic clarification, containment in extreme distress, or if at high risk of suicide.

» Maintain patience and an empathic attitude.
» Screen for and manage:
  - causative and comorbid medical illness, e.g. thyroid disease, hyperparathyroidism, phaeochromocytoma, vestibular dysfunctions, epilepsy, and cardiac conditions, hypertension, COPD, asthma, inflammatory bowel disease, GORD.
  - substance misuse, e.g. caffeine, nicotine, alcohol, analgesics, amphetamines and cocaine.
  - psychosocial stressors, especially in people with intellectual and other disabilities.
» Psychoeducate the patient and family (with patient's permission).
» Refer to registered counsellors and local support groups. Provide links to self-help literature, websites or groups, e.g. South African Depression and Anxiety Group (SADAG - www.sadag.org).

MEDICINE TREATMENT

Indicated where symptoms interfere with normal functions of daily living.

» Offer a choice of psychotherapy (if available) or medication and monitor response. Note: where there is concomitant drug/alcohol dependence or a comorbid major depressive episode, an antidepressant may be more appropriate than psychotherapy.
» Review every 2–4 weeks for 3 months, then 3–6 monthly.
» Partial response: combine medication with psychotherapy.
» If effective, continue for at least 12 months to prevent relapse.

- Selective serotonin reuptake inhibitor (SSRI), e.g.:
- Fluoxetine, oral.
  - Initiate at 20 mg alternate days for 2 weeks.
  - Increase to 20 mg daily after 2–4 weeks.
  - Delay dosage increase if increased agitation / panic symptoms occur.
  - If partial response, increase to 40 mg daily.

LoE:Ib[xix]

<u>If fluoxetine is poorly tolerated:</u>

- Alternative SSRI e.g.:
- Citalopram, oral.
  - Initiate at 10 mg daily for the 1st week.
  - Then increase to 20 mg daily.
  - If partial response, increase to 40 mg daily (except in cardiac disease or if >65 years of age).

LoE:Ib[xx]

CAUTION - SSRIs

SSRIs (e.g. fluoxetine, citalopram) may cause agitation initially. This typically resolves within 2-4 weeks.

LoE:IVb[xxi]

Ask about suicidal ideation in all patients, particularly adolescents and young adults (PHC STGs and EML, section 16.7: Suicide risk assessment).

If suicidal ideation present, refer before initiating SSRI.

Once started, monitor closely for clinical worsening, suicidality, or unusual changes in behaviour. Advise families and caregivers of the need for close observation and refer as required**.**

Note: Continue treatment for a minimum of 12 months. Consider slowly tapering and stopping treatment only if patient has had no/minimal symptoms and has been able to carry out routine daily activities.

Prolong treatment if any of the following are present:

» Previous episode/s of anxiety (extend treatment to at least 3 years).
» Any of the following: onset in adolescence, severe anxiety, suicidal attempt, sudden onset of symptoms, family history of bipolar disorder (extend treatment to at least 3 years).
» ≥3 previous episodes of anxiety (advise lifelong treatment).

LoE:IIIb[xxii]

<u>For short term use only in severe acute distress:</u>

- Benzodiazepines, e.g.:
- Diazepam, oral, 2.5–5 mg as a single dose.
  - Repeat 8 hourly, if required to a maximum of 30 mg daily (in divided doses).
  - Half the dose in the elderly or debilitated.
  - Duration of therapy: up to 2 weeks, taper off to zero within 6 weeks

LoE:IVb[xxiii]

- Commence definitive treatment with psychotherapy/SSRI treatment.

CAUTION - BENZODIAZEPINES

» Associated with cognitive impairment – reversible with short-term use and irreversible with long-term use.
» Elderly are at risk of over-sedation, falls and hip fractures.
» Dependence may occur after only a few weeks of treatment.
» Prescribe for as short a period of time as possible to achieve desired effect.
» Warn patient not to drive or operate machinery when used short-term.
» Avoid use in people at high risk of addiction, e.g. personality disorders and those with previous or other substance misuse.

LoE:IVb[xxiv]

PREGNANCY AND BREASTFEEDING

» SSRI treatment of depression in pregnancy is associated with improved symptoms in the mother and better emotional and psychological development of the child. Benefit is greater with increasing illness severity. Effect of SSRIs on anxiety in pregnancy is less clear.
» Lack of matched case-control studies mean harms of treatment are unclear.
» If stable on an SSRI, do not stop – discuss risk/benefit with mother.
» Index presentations: offer counselling, psychotherapy; discuss risk/benefit of SSRIs.
» Refer social worker to explore social and financial support systems.
» Avoid fluoxetine due to long half-life and relatively high concentration in breastmilk. Consider citalopram as alternative
» All antidepressants: possible increased risk of miscarriage, transient neonatal symptoms (jitteriness, irritability), and persistent pulmonary hypertension of the newborn.
» Avoid benzodiazepines – some association with neurodevelopmental delay in the child; neonatal sedation if used late in pregnancy.

LoE:IVb[xxv]

REFERRAL

» High suicide risk
» Severe symptoms with marked functional impairment
» Co-morbid severe psychiatric or medical conditions
» Poor response to treatment.

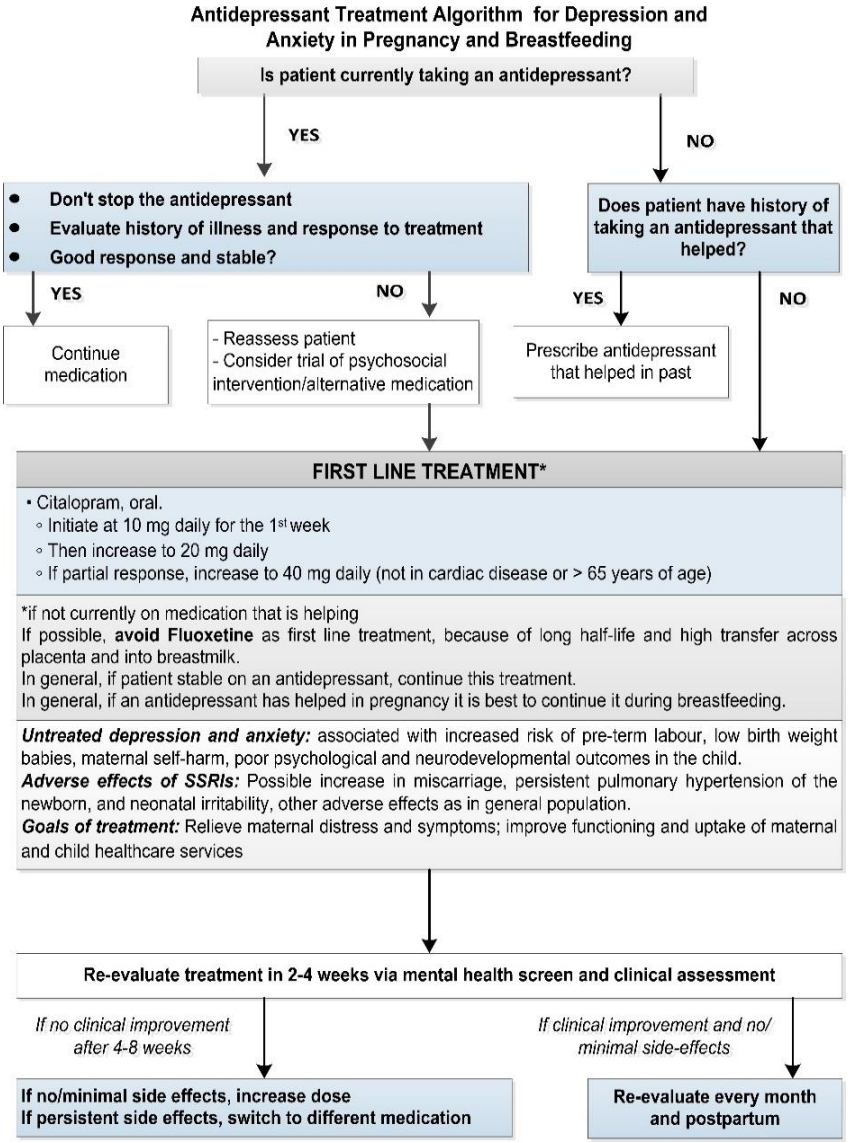


Figure 15.2: Antidepressant treatment algorithm for depression and anxiety in pregnancy and breastfeeding.
Adapted from the MCPAP for Moms Perinatal Depression Toolkit funded by the Massachusetts Department of Mental Health. Original Authors: Byatt N., Biebel K., Mittal L., Lundquist R., Freeman M., & Cohen L., Moore Simas T.

15.3 MOOD DISORDERS

15.3.1 DEPRESSIVE DISORDERS

F32.0-3/F32.8-9/F33.0-4/F33.8-9/F34.1 + (F10.0-F19.9/R45.0-8/Z65.0-5/Z65.8-9/Z81.0-4/Z81.8)

DESCRIPTION

Depressive disorders may occur as single or recurrent episodes, as a chronic, persistent low mood, or a combination of the two. Depressive disorders differ from bipolar disorder, in that there is no history of manic, hypomanic, or mixed episodes.

Depressive disorders cause significant impairment in social and occupational functioning, and may result in unemployment, poor self-care, neglect of dependent children, and suicide. They may be comorbid with, or secondary to, other medical illness or substance use. Depression impacts negatively on comorbid conditions, with increased pain, disability, and poorer treatment outcomes.

Depression is characterised by a low mood and/or a reduced capacity to enjoy life. However, it is often not recognised by the sufferer or clinician. It may be regarded as a normal emotional state or it may be unacceptable to the sufferer due to stigma. Thus, associated symptoms may be the presenting complaint rather than the low mood. Symptoms may also be masked in the interview setting. It is important to have a high degree of suspicion and to elicit symptoms, degree of impaired function, and suicide risk with care.

» In general, insomnia and loss of energy are the most common presenting complaints. In African cultures, somatic symptoms (bodily aches and pains) and rumination (‘thinking too much’) may predominate.
» The presence of mood, psychological, and cognitive symptoms help to differentiate between depression and normal sadness following a loss, or the loss of appetite and energy associated with a medical condition.
» Psychotic symptoms (delusions, hallucinations, or thought disorder) are usually mood congruent and indicate marked severity and a high risk to self or others.

Depression during pregnancy and the postnatal period is associated with preterm delivery, low-birth weight babies, poor maternal self-care, impaired mother-infant engagement, and poor psychological and neurodevelopmental outcomes in the child. Risk of negative impact is increased depending on severity (See PHC STGs and EML, Chapter 6.9: Maternal mental health).

GENERAL MEASURES

» Maintain an empathic and concerned attitude.
» Discuss uncertainty with a specialist at any point in the care pathway.
» Assess severity of the condition and suicide risk. See PHC STGs and EML section 16.7: Suicide risk assessment.
» Exclude and optimise treatment of underlying and/or comorbid medical conditions (e.g. hypothyroidism, anaemia, HIV/AIDS, TB, cancers, diabetes).

» Screen for, and manage, underlying or comorbid substance use, e.g. nicotine, alcohol, over the counter analgesics, benzodiazepines.
» Screen for bipolar disorder and comorbid psychiatric disorders – refer for specialist assessment.
» Explore and address psychosocial stressors:
  - Stress management / coping skills – refer to registered counsellors, social worker, and/or occupational therapy.
  - Relationship and family issues – refer to social worker, registered counsellors, Non-Governmental Organisation (NGO) counselling, e.g. FAMSA (www.famsa.org.za).
  - If abuse, intimate partner, or other violence is evident, refer to a social worker.
» Provide self-help literature, where available, and refer to local support groups, e.g. SADAG (www.sadag.org).

MEDICINE TREATMENT

» Offer choice of psychotherapy (if available) or medication.
» Antidepressants take 4–6 weeks to achieve their maximum effect. There is little evidence to support combination medicine treatment.
» Tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitors (SSRIs) are of equal efficacy.
» Electroconvulsive therapy (ECT) (specialist administered) is indicated under specific circumstances, e.g. severe depression, in pregnancy.
» The choice of therapy is guided by comorbid states, risk of overdose, and patient response.
» Refer to occupational therapy if available for vocational rehabilitation.

CAUTION - ANTIDEPRESSANTS

» SSRIs (e.g. fluoxetine, citalopram) may cause agitation and an increased suicide risk during the first 2–4 weeks.
» Once started, monitor closely for clinical worsening, suicidality, or unusual changes in behaviour. Advise families and caregivers of the need for close observation and refer as required.
» TCAs can be fatal in overdose. Prescription requires a risk assessment of the patient and others in their household, especially adolescents. See section 19.6.1: Tricyclic antidepressant poisoning.
» Avoid TCAs in the elderly and in patients with heart disease, urinary retention, glaucoma, and epilepsy.
» Do not prescribe antidepressants to a patient with bipolar disorder without consultation, as they may precipitate a manic episode.
» Be aware of interactions between antidepressants and other agents (e.g. other medicines, St John's Wort or traditional African medicine).

PREGNANCY AND BREASTFEEDING

» SSRI treatment of depression in pregnancy is associated with improved symptoms in the mother and better emotional and psychological development of the child. Benefit is greater with increasing illness severity. Effect of SSRIs in pregnancy on anxiety is less clear.
» Lack of matched case-control studies mean harms of treatment are unclear.
» If stable on an SSRI, do not stop – discuss risk/benefit with mother.
» Index presentations: offer counselling and psychotherapy; discuss risk/benefit of SSRIs.
» Refer social worker to explore social and financial support systems.
» Avoid fluoxetine due to long half-life and relatively high concentration in breastmilk. Consider citalopram as alternative.
» All antidepressants: possible increased risk of miscarriage, transient neonatal symptoms (jitteriness, irritability), and persistent pulmonary hypertension of the newborn.
» Avoid benzodiazepines – some association with neurodevelopmental delay in the child; neonatal sedation if used late in pregnancy.

LoE:IVb[xxvi]

- Selective serotonin reuptake inhibitor (SSRI), e.g.:
- Fluoxetine, oral.
  - Initiate at 20 mg alternate days for 2–4 weeks.
  - Thereafter, increase to 20 mg daily. Delay dosage increase if agitation/panic symptoms, suicidal ideation occur.
  - Reassess response after 4–6 weeks.
  - If partial response: increase to 40 mg daily and/or augment with psychotherapy.
  - If no response: consult with specialist (re-evaluate diagnosis, repeat general measures, prescribe alternative SSRI, psychotherapy, or ECT).

<u>If fluoxetine is poorly tolerated:</u>

- Alternative SSRI e.g.:
- Citalopram, oral.
  - Initiate at 10 mg daily for the 1st week.
  - Then increase to 20 mg daily. *LoE:Ib*[xxvii]
  - If partial response: increase to 40 mg daily (except in cardiac disease and >65 years) and/or augment with psychotherapy.
  - If no response: consult with specialist (re-evaluate diagnosis, repeat general measures, prescribe alternative SSRI, psychotherapy, or ECT).

<u>If a sedating antidepressant is required:</u>

- Amitriptyline, oral, at bedtime.
  - Initial dose: 25 mg per day.
  - Increase by 25 mg per day at 3–5 day intervals. *LoE:IVb*[xxviii]
  - Maximum dose: 150 mg per day.
  - If no response: discuss with specialist (re-evaluate diagnosis, repeat general measures, prescribe alternative SSRI, psychotherapy, or ECT).

Treatment duration
Continue for a minimum of 9 months. Consider stopping only if patient has had no/minimal symptoms and can carry out routine daily activities. Taper medicine slowly to avoid discontinuation symptoms; reinstitute if there is a recurrence.

Prolong treatment if:
» Concomitant generalised anxiety disorder (extend treatment to at least 1 year).
» Previous episode/s of depression (extend treatment to at least 3 years).
» Any of: severe depression, suicidal attempt, sudden onset of symptoms, family history of bipolar disorder (extend treatment to at least 3 years).
» If ≥3 episodes of depression, advise lifelong treatment. *LoE:IIb*[xxix]

REFERRAL
» Inadequate response to treatment.
» High suicide risk.
» Psychotic features.

15.3.2 BIPOLAR AND RELATED DISORDERS
F06.3/F30.0-2/F30.8-9/F31.0-9/F34.0/F34.8-9/F38.0/F39 + (F10.0-F19.9/R45.0-8/Z65.0-5/Z65.8-9/Z81.0-4/Z81.8)

DESCRIPTION
Bipolar disorder (BD) is a heterogenous illness, with high overlap in genetic risk with depression and schizophrenia. It usually follows a chronic, relapsing course, commonly starting in youth. The goal of care is euthymia and optimal functioning according to the person's ability.

BD may present with:
» an episode of depression, hypomania, mania or mixed mood symptoms.
» psychosis.
» treatment resistant depression and/or anxiety.
» consequences of disturbed behaviour and/or comorbid substance use.
» depression in women; men are more likely to present with disruptive behaviour.

Diagnostic requirements include, over the lifetime course:
» Bipolar I disorder (BD I): an episode of mania
» Bipolar II disorder (BD II): an episode of hypomania and depression.
» Other specified BD (BD OS): symptoms of BD plus clinical distress and/or functional impairment but full Diagnostic and Statistical Manual criteria are not met.
» BD due to another medical condition: direct physiological cause for the bipolar symptoms from another illness, e.g. right-sided cortical or sub-cortical lesions.

Bipolar disorder during pregnancy and the post-natal period is associated with pre-eclampsia, preterm delivery, and low-birth weight babies. Risk of relapse is high, especially postpartum. Psychotic episodes may be dangerous to mother, baby, or others (See PHC STGs and EML, Chapter 6.9: Maternal mental health).

GENERAL MEASURES

Assess and manage **in consultation with a psychiatrist.**
Risk to self and others is high in BD and unpredictable – repeated risk assessments and a biopsychosocial approach to care is recommended.

Acute management

» Mania, severe depression, and psychosis require urgent hospitalisation in a psychiatric unit, often as an Assisted or Involuntary MHCU.
» Investigate for causative medical conditions, medications, substances.
» Optimise management of comorbid medical illness and substance use.
» Stabilise the immediate mood; electroconvulsive therapy may be required.
» Commence long-term treatment strategy.
» Avoid premature discharge and ensure continuity of care post-discharge.

Long-term management

» Individualise management according to course of illness, cognitive functioning, insight and judgement, and social circumstances.
» Assertive nursing with adherence monitoring is required.
» Screen for and manage comorbid medical illness (thyroid disease, HIV/AIDS, cardiovascular and pulmonary disease, epilepsy, diabetes, obesity).
» Screen for, and manage, substance use.
» Psycho-educate patient, family, and carers on the nature of the illness, need for continued treatment, how to self-monitor, early signs of relapse, and need for structure and routine.
» Refer to support groups e.g. SADAG (www.SADAG.org) or South African Federation For Mental Health (www.SAFMH.org.za).
» Refer to occupational therapy, if available, for insight, motivation, and vocational rehabilitation.
» Delay important decisions until full recovery from an acute episode; a custodian/ curatorship / power of attorney may be required.
» Refer to social worker for placement in a residential home, day care, or sheltered employment/workshop as needed.

Women of childbearing potential (See PHC STGs and EML, Chapter 6.9: Maternal mental health).

» Advise family planning – psychoeducate regarding the need to plan pregnancy and comply with antenatal care.
» Manage pregnancy and postpartum period as there is a high-risk for adverse events.
» Select treatment options which are relatively safe in pregnancy.

MEDICINE TREATMENT

Treatment choice depends on course of illness; gender; comorbid medical conditions, substance use, or psychiatric conditions; and risk of non-adherence. Acute treatment should incorporate a long-term strategy. Combinations of medicines may be required, particularly in depression (See algorithms below).

Lithium is first-line option for long-term treatment:
» Response takes ± 1 week in mania and 6–8 weeks in depression
» Prevents manic episodes by up to 40-50% and depressive episodes by up to 20-30% and reduces aggression, self-harm, and suicide.

- Lithium, oral, usual dose range 200–600 mg at night, depending on desired blood levels.
  - Pre-treatment: check eGFR, TFTs, calcium, and ECG in patients with cardiovascular risk factors. Proceed if eGFR and ECG are normal, and any thyroid or parathyroid disease is treated.
  - Initial dose: 400 mg (200 mg in elderly or high risk for renal disease).
  - Measure plasma trough concentration (at least 12 hours after previous dose):
    - First measurement: After 5 days of treatment
    - Then 7 days after each dose change
    - Then at 1 month and 3 months of treatment
  - Document the number of hours since the last dose on the blood request form.
  - Lithium has a narrow therapeutic window. The therapeutic reference ranges are:
    - Acute mania: 0.8–1.0 mmol/L
    - Prevention of mania: 0.6–0.8 mmol/L
    - Prevention of depressive relapse: 0.4–0.8 mmol/L
  - Monitor lithium level and eGFR 6-monthly (3-monthly in elderly or medical comorbidity), and TSH and calcium annually.

CAUTION - LITHIUM

» Abrupt discontinuation may precipitate mania – taper slowly over 4 weeks.
» **Adverse effects** include nephrogenic diabetes insipidus, interstitial nephritis, chronic kidney disease; hypothyroidism; hyperparathyroidism; tremor.
» **Toxicity** occurs with levels >1.2 mmol/l (results in anorexia, nausea, diarrhoea, muscle weakness, drowsiness, ataxia, disorientation, seizures, coma, and death). Manage as for lithium poisoning (section 19.9.2: Lithium poisoning).
» Risk of toxicity is increased with change to a low salt diet, dehydration, drug-drug interactions (diuretics, ACE-inhibitors, NSAIDs).
» Therapeutic drug monitoring is essential when using lithium.
» Clinical toxicity may even occur within the therapeutic range.

If patient has depressive symptoms and lamotrigine is poorly tolerated or not effective:

- Quetiapine, oral, usual dose range 100–300 mg at night (specialist prescribed).
  - Titrate to clinical effect, e.g.: Day 1: 50 mg. Day 2: 100 mg. Day 3: 200 mg. Day 4: 300 mg.
  - In the elderly and patients with hepatic impairment: Start with 25 mg and titrate up more slowly according to clinical effect.

LoE:IIIb[xxx]

PREGNANCY AND BREASTFEEDING

Valproate:

» Contraindicated in women of childbearing potential due to high teratogenic risk (10%) and adverse neurodevelopmental outcomes (40%) with any pregnancy exposure. If no alternative, acknowledgment of risk must be signed: https://www.sahpra.org.za/wp-content/uploads/2020/08/6.28_Valproate_Annual_Risk_Acknowledgement_Form_Dec18_v1.pdf

LoE:IIIb[xxxi]

» If already on valproate: consult specialist and cross-titrate to an alternative medication if possible. Ensure folic acid supplementation (See PHC STGs and EML, section 16.6: Psychiatric patients – General monitoring and care).

» Avoid valproate in breastfeeding as there is insufficient evidence to be sure of safety and it may be associated with adverse neurodevelopmental outcomes.

LoE:IIIb[xxxii]

Lithium:

» 1st trimester exposure is associated with increased risk of congenital anomalies.

» Refer for a fetal anomaly ultrasound at 18–22 weeks gestation.

» Adjust dose with physiological changes of pregnancy according to blood levels: monitor levels monthly, then weekly after 36 weeks and postpartum.

» Monitor fluid balance during and after delivery.

» Neonatal complications: goitre, nephrogenic diabetes insipidus, cardiac arrhythmias, cardiac failure, hypotonia, and lethargy.

» Excreted in breast milk, risk to the infant is unknown but toxicity may occur: breastfeeding is not recommended.

LoE:IIIb[xxxiii]

Lamotrigine:

Increased hepatic clearance in pregnancy, but returns to normal post-partum; increase dose if necessary, according to clinical response and Figure 15.4 below.

May cause a rash in breastfed infant.

LoE:IIIb[xxxiv]

Antipsychotics:

» Considered safe, particularly quetiapine.

» They may increase the risk of gestational diabetes and obesity (especially olanzapine and clozapine).

» Clozapine: Do not stop in pregnancy due to risk of relapse of severe mental illness. Breastfeeding not recommended due to possible risk of agranulocytosis in the newborn.

Benzodiazepines: Avoid in pregnancy.

LoE:IVb[xxxv]

Use only very short-term for severe distress.

LoE:IVb[xxxvi]

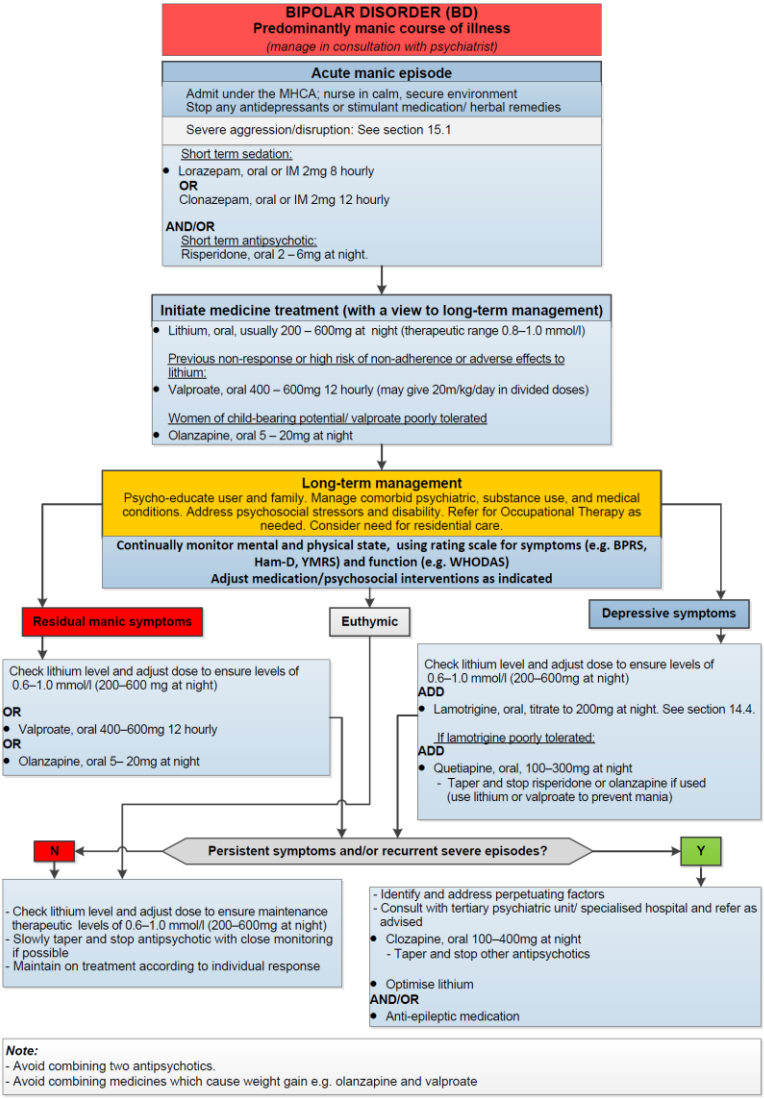


Figure 15.3: Algorithm for the management of bipolar disorder with predominantly manic course of illness *LoE:IIb*[xxxvii]

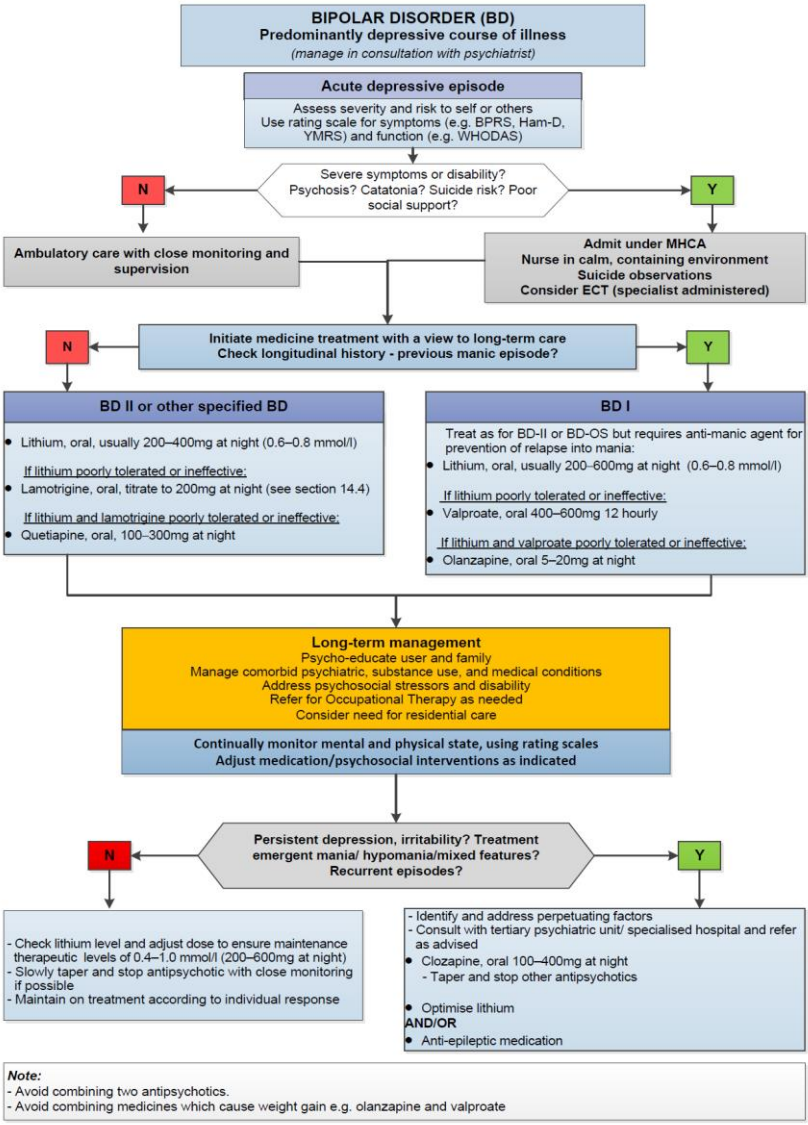


Figure 15.4: Algorithm for the management of bipolar disorder with predominantly depressive course of illness

LoE:IIb[xxxviii]

REFERRAL

All patients to be managed in consultation with a psychiatrist and to refer as advised, particularly if:

» High risk to self or others at any time.
» Rapid cycling (≥4 episodes despite treatment).
» Poor response to treatment with persistent depressive, manic, or mixed symptoms.

15.4 TRAUMA AND STRESS-RELATED DISORDERS

F43.0/F43.1/F43.2/F43.8-9 + (Z55-Z65)

DESCRIPTION

Acute stress and post-traumatic stress disorder arise in response to stressful events. The patient should have experienced the event as life threatening or as a physical threat to themselves or others, at which time they felt fear and helplessness.

A range of symptoms are associated with both of these conditions and include:

» re-experiencing of the event, e.g. flashbacks, dreams.
» avoidance of situations associated with the event.
» features of anxiety or increased arousal, e.g. hypervigilance, heightened startle response, and insomnia.

The conditions are symptomatically similar but differ with regard to the duration and time of onset of symptoms. The symptoms of acute stress disorder arise within 4 weeks of the event and last up to 4 weeks, whereas the symptoms of post-traumatic stress disorder last longer than 4 weeks and may arise more than 4 weeks after the traumatic incident.

GENERAL MEASURES

» Provide reassurance and support of patient and family.
» Assess risk to patient's safety: refer to police, social welfare and/or legal services as needed to ensure immediate safety.
» If patient has an ongoing/recent crisis: refer to social worker or registered counsellor for emotional containment and stress management.
» Psychotherapy, usually of a supportive / cognitive-behavioural nature.
» Trauma debriefing is not routinely recommended.

MEDICINE TREATMENT

Acute stress disorder:

Benzodiazepines may be useful in the immediate period following the traumatic event.

Prolonged use >1 week may be detrimental to adaptation, leading to higher rates of post-traumatic stress disorder.

For acute anxiety or agitation:

- Clonazepam, oral, 0.5–2 mg per day in 3 divided doses. *LoE:IVb*[xxxix]

For sleep disturbance: See section 15.6: Insomnia.

Post-traumatic stress-disorder:

- Selective serotonin reuptake inhibitors (SSRI), e.g.:
- Citalopram, oral, initial dose 20 mg daily. *LoE:IVb*[xl]

OR

- Fluoxetine, oral, initial dose 20 mg in the morning.

Note:

- A response to SSRI should be expected after 4–6 weeks.
- If there is no/partial response after 4–8 weeks, increase SSRI dose to 40 mg, if well tolerated.
- An adequate trial of treatment is 8–12 weeks, before an alternative treatment should be considered.
- Suicidal ideation may increase in the first few weeks of SSRI therapy. See PHC STGs and EML, 2023 – section 16.7: Suicide risk assessment.

PREGNANCY AND BREASTFEEDING

» Perinatal PTSD is associated with low birth weight babies and poor mother-baby interactions.
» Experiences in pregnancy and childbirth may be traumatic and exacerbate existing PTSD or trigger new onset PTSD.
» Women with a history of childhood adversity, sexual abuse, or other previous trauma are at risk of perinatal PTSD.
» Treatment of PTSD in pregnancy is the same as for non-pregnant women.
» Avoid fluoxetine due to long half-life and relatively high concentration in breastmilk. Consider citalopram as alternative.
» All antidepressants: possible increased risk of miscarriage, transient neonatal symptoms (jitteriness, irritability), and persistent pulmonary hypertension of the newborn. Assess and discuss risk/benefit profile with patient
» Avoid benzodiazepines – some association with neurodevelopmental delay in the child; neonatal sedation if used late in pregnancy.

LoE:IVb[xli]

REFERRAL

» Persistent symptoms.
» Inadequate response to treatment.
» Comorbid conditions.

15.5 PSYCHOTIC DISORDERS

DESCRIPTION

Psychosis is characterised by a loss of contact with reality. Psychotic disorders may present with:

» Delusions: Fixed beliefs which may manifest as disturbed speech content with persecutory, referential, grandiose, religiose, erotic, or bizarre themes.
» Hallucinations: Perceptual disturbances, e.g. auditory hallucinations, which are heard as voices distinct from the patients' thoughts.
» Disorganised thinking: Manifests as disordered flow of speech which impairs communication.
» Grossly disorganised or abnormal motor behaviour (including catatonia).
» Negative symptoms: reduced emotional expression, avolition, lack of speech, anhedonia, lack of social interaction.

Psychotic symptoms may occur in other psychiatric conditions (e.g. bipolar mania, major depression), medical conditions (e.g. certain types of epilepsy), or substance use (intoxication or withdrawal).

Psychosis is often accompanied by a lack of insight into the symptoms, poor judgement, and aggressive behaviour. The risk to self and others must always be assessed. It may be necessary to treat as an Assisted or Involuntary User under the MHCA.

15.5.1 ACUTE AND TRANSIENT PSYCHOTIC DISORDERS

F23.0-3/F23.8-9 + (F10.0-F19.9/R45.0-8/Z65.0-5/Z65.8-9/Z81.0-4/Z81.8)

DESCRIPTION

Sudden onset of ≥ 1 psychotic symptom (usually delusions, hallucinations, or disorganised thinking) which resolve spontaneously, usually within 1 month, with a full return to premorbid social or occupational functioning. Stressful events may precede the psychotic episode. Within 3 years, 40-50% will have a recurrent episode or develop schizophrenia or bipolar disorder.

LoE:IIb[xlii]

GENERAL MEASURES

Assess and manage in consultation with a psychiatrist.

» Assess risk to self and others.
» Exclude and treat medical causes of psychotic symptoms (e.g. delirium, dementia, epilepsy).
» Exclude and manage substance use (e.g. cannabis, alcohol, amphetamines, and cocaine).
» Assess and treat other mental illness, e.g. anxiety disorders (See section 15.2: anxiety and obsessive-compulsive disorders) and trauma and stress-related disorders (See section 15.4: Trauma and stress-related disorders).
» Refer to social worker, psychologist or counselling services to address psycho-social stressors.
» Active follow-up is needed: commence treatment for schizophrenia or bipolar disorder if these become evident. (See sections 15.3.2: Bipolar and related disorders and 15.5.2: Schizophrenia spectrum disorders).

MEDICINE TREATMENT

» Manage severe aggressive or disruptive behaviour (See section 15.1: Aggressive disruptive behaviour in adults).
» Treat according to underlying cause.

15.5.2 SCHIZOPHRENIA SPECTRUM DISORDERS

F20.0-6/F20.8-9/F22.0-9/F25.0-2/F25.8-9 + (F10.0-F19.9/R45.0-8/Z65.0-5/Z65.8-9/Z81.0-4/Z81.8)

DESCRIPTION

Schizophrenia is characterised by psychotic episodes which are severe, persistent, and accompanied by a marked deterioration in personal, social, and occupational functioning.

Whilst the presentation may be acute, the illness typically has a chronic, relapsing course with progressive cognitive and functional decline. Onset is usually in youth. Prognosis is worsened with delay in initial treatment, repeated episodes, and comorbid substance use. Comorbid metabolic syndrome and cardiovascular disease are common.

GENERAL MEASURES

» **Manage all patients in consultation with a psychiatrist.**
» Diagnostic certainty requires careful observation and re-evaluation over time.

Acute psychosis

» Assess risk to self and others.
» Clarify diagnosis.
» Manage within a multi-disciplinary team.
» Use shared decision-making in treatment process.
» Involve family and carers with patient's permission unless risk to self/others necessitates a breach of confidentiality.
» Provide psychoeducation to patient, family, and carers on the nature of the illness, need for continued treatment, how to self-monitor, early signs of relapse, and need for structure and routine.

Maintenance treatment

» Provide antipsychotic maintenance treatment to prevent relapse.
» Community-based nursing with adherence support, repeated risk assessment, and shared decision-making is required.
» Refer to occupational therapy for functional rehabilitation.
» Monitor psychiatric symptoms (use rating scales, e.g. BPRS or PANSS)
» Monitor extra-pyramidal side effects, weight, blood pressure, and glucose every 6 months.
» Adjust treatment according to response, adverse effects, and comorbidity.
» Provide lifestyle and dietary education; encourage exercise
» Treat comorbid mood disorders (section 15.3: Mood disorders)

» Treat comorbid hypertension (section 3.6: Hypertension), diabetes mellitus (section 8.5: Diabetes mellitus), and other medical conditions as needed
» Manage substance use – refer for rehab (South African National Council on Alcoholism and Drug Dependence [SANCA], Social Development)
» Poor adherence with recurrent episodes:
  - Check reasons – illness, medication, patient factors.
  - Poor response/ tolerability to medication – change to alternative antipsychotic.
  - Poor insight - try depot antipsychotic – start with test dose (half initial dose in algorithm below).
  - Address psychosocial factors, substance use.
» Refer to social worker for placement in a residential home, day care or sheltered employment/workshop as needed.

Women of childbearing potential: (See PHC STGs and EML, section 6.9: Maternal mental health).
» Advise family planning – psycho-educate regarding need to plan pregnancy and comply with antenatal care.
» If patient is a parent/guardian – support childcare; refer to social worker if impaired.
» Risk of psychotic relapse is high in pregnancy and postpartum including the first year post-delivery.
» In pregnancy: continue antipsychotic treatment; Monitor closely for weight gain, gestational diabetes, psychotic relapse, and/or substance use.

MEDICINE TREATMENT

Acute psychotic episode

» Treat severe aggression and disturbed behaviour (See section 15.1: Aggressive disruptive behaviour in adults).
» Initiate treatment with a view to long-term management.
» Assess risk factors for the development of tardive dyskinesia: age >50 years, female sex, prominent mood symptoms, cognitive or neurological disturbance e.g. intellectual disability, autistic spectrum, People living with HIV (PLHIV).
» In patients with high risk of tardive dyskinesia: Avoid haloperidol and antiparkinsonian medicines. Use chlorpromazine, risperidone or olanzapine at lowest doses needed to achieve desired effect. *LoE:IVb*[xliii]

Initiate treatment:

- Haloperidol, oral, 0.75–1.5 mg daily.
  - Increase to 5 mg daily if initial treatment tolerated and according to clinical response. *LoE:IVb*[xliv]

If good response/tolerability to haloperidol, or patient preference:

- Depot antipsychotic, e.g:
- Flupenthixol decanoate, IM, 10–40 mg every 4 weeks.

LoE:IVb[xlv]

- Initial dose: 10mg

OR

- Zuclopenthixol decanoate, IM, 100–400 mg every 4 weeks.
  - Initial dose: 100mg

LoE:III[xlvi]

<u>If poor response / poorly tolerated / high risk of tardive dyskinesia / extra-pyramidal side effects</u>:

- Risperidone, oral
  - Initial dose: 2–4 mg at night.
  - Assess efficacy after 4–6 weeks:
    - If a partial response is noted, increase the dosage.
    - If no response is noted, switch treatment.
  - Maximum dose: 6 mg daily.

LoE:IIb[xlvii]

OR

- Chlorpromazine, oral, 75–300 mg at night, but may be increased to 800mg a day in 2–3 divided doses according to clinical response.

LoE:IVb[xlviii]

<u>If poor response/tolerability to haloperidol, risperidone, and chlorpromazine:</u>

- Olanzapine, oral
  - Initial dose: 5 mg at night, increase to 10 mg at night.
  - Maximum dose: 20 mg at night.

LoE:IIb[xlix]

<u>If poor response/tolerability to olanzapine:</u>

- Clozapine, oral (specialist initiated, preferably as inpatient):
  - Initial dose: 12.5–25 mg at night.
  - Usual dose: 200–450 mg per day in 2 divided doses.
  - Maximum dose: 900 mg/day in 2 divided doses.

LoE:IVb[l]

CAUTION - CLOZAPINE

» May cause neutropenia (3% of cases) and agranulocytosis (0.8% of cases):
- Pre-treatment: Check that white cell count and absolute neutrophil count are normal.
- Monitor absolute neutrophil count regularly.
- Withdraw clozapine and review medication if neutrophils <1.0 x109/L (general population).

» Myocarditis: highest risk in first two months of treatment. Monitor pulse, blood pressure, temperature; advise patient to report any palpitations, shortness of breath, chest pain, fever immediately.

» Seizures: risk increased at doses >450 mg/day.
- Manage as for epilepsy (section 14.4: Epilepsy).
- Lamotrigine is preferred as it is weight neutral and does not interfere with clozapine metabolism.
- Avoid carbamazepine because of possible myelosuppression and enzyme induction.

» Constipation: avoid anticholinergics; may require laxatives; prolonged discomfort may indicate intestinal obstruction.

» Weight gain, diabetes, dyslipidaemia: Manage as per PHC STGs and EML, section 16.6: Psychiatric patients general monitoring and care; section 3.1: Ischaemic heart disease and atherosclerosis, prevention, and section 8.5.1: Type 2 diabetes mellitus.

LoE:IVb[li]

OR

If poor response to olanzapine and clozapine is not an option due to metabolic effects (weight gain, type 2 diabetes) or persistent negative symptoms are present: *LoE:IVb[lii]*

» Refer to tertiary and quaternary level care for amisulpride if excessive weight gain and/or type 2 diabetes, or persistent negative symptoms.

LoE:IVb[liii]

ADVERSE EFFECTS

Extrapyramidal adverse effects

Note: Anticholinergic medicines (e.g. orphenadrine) should not be added prophylactically to antipsychotics to prevent extrapyramidal side effects.

Acute dystonia: See the PHC STGs and EML, Section 16.2.1: Extra-pyramidal side effects.

Parkinsonism:

G21.0-1

- Anticholinergic agent, e.g.:
- Orphenadrine, oral, 50–150 mg daily according to individual response.
  - Usual dose: 50 mg 8 hourly.
  - Maximum dose: 150 mg daily.

- Use with caution in the elderly as it may cause confusion and urinary retention.
- Review antipsychotic treatment, and stop orphenadrine if medicine changed. *LoE:IVb*[liv]

Akathisia:
G25.8
A subjective unpleasant state of inner restlessness where there is a strong desire or compulsion to move:

- Propranolol, oral,
  - Start at 20 mg daily and titrate as needed up to 80 mg 8 hourly. *LoE:IIIb*[liv]
  - Monitor pulse and blood pressure.

Neuroleptic Malignant Syndrome:
See the PHC STGs and EML, Section 16.2.2: Neuroleptic malignant syndrome.

REFERRAL
All patients to be managed in consultation with a psychiatrist, refer as advised, particularly if:
» High risk to self or others at any time.
» If diagnosis is uncertain.
» Poor response to treatment.

15.6 INSOMNIA
G47.0/G47.9

DESCRIPTION
Insomnia may be an independent disorder or associated with comorbid conditions. Insomnia may persist despite successful treatment of the comorbidity and may necessitate separate treatment.
Patients presenting with insomnia may complain of difficulty falling asleep, frequent waking during the night, early-morning wakening, and daytime sleepiness.

GENERAL MEASURES
Treat the medical condition, psychiatric illness, substance use disorder or sleep disorder that may be precipitating or exacerbating the insomnia, if present.
Provide basic behavioural counselling about sleep hygiene and stimulus control as first step of treatment.
Cognitive behavioural therapy is the treatment of choice.

MEDICINE TREATMENT
If medication is needed:
Use the lowest effective dose.
Use intermittent dosing if possible (alternate night or less).

Sleep hygiene and stimulus control:

Maintain a regular sleep cycle (same time wake up in the morning, including week-ends).

Stimulus control:

- Keep the room quiet, dark, and at a comfortable temperature.
- Use the bed and bedroom only for sleeping and partner intimacy.

Limit intake of caffeine, nicotine, and alcohol, especially before bedtime.

Eat a light snack before bedtime and avoid eating large meals late at night.

Sleep restriction: avoid daytime naps.

Increase daily exercise (not late in the evening).

Practise anxiety management or relaxation techniques.

Go to bed only when tired. Sleep as much as needed to feel refreshed, not longer.

If unable to sleep despite attempting for more than 15–20 minutes, get out of bed and engage in a non-stimulating activity until tired (e.g. listen to soft music, read).

<u>If medication is needed to treat the insomnia:</u>

- Short-acting benzodiazepines, e.g.:
- Oxazepam, oral 7.5–30 mg at night.

Short-term use of benzodiazepines of 14 days is recommended, as long-term use is often associated with dependence.

LoE:IIb[M]

REFERRAL

Patients with chronic insomnia.

15.7 DISCONTINUATION SYMPTOMS OF SEROTONIN REUPTAKE INHIBITORS

F19.3 + (Y49.2)

» Discontinuation symptoms are experienced due to receptor adaptation or receptor rebound after stopping of antidepressants. It can be avoided or reduced by slowly tapering the drug over at least 4 weeks.

» Symptoms include flu-like symptoms, 'shock-like" sensations, dizziness exacerbated by movement, insomnia, vivid dreaming and irritability, problems with concentration, and memory or movement disorders.

» It is managed by reintroduction of the SSRI and slower tapering of the dose.

» **Note:** Fluoxetine seldom causes discontinuation symptoms because of its long half-life.

15.8 SUBSTANCE USE DISORDERS

DESCRIPTION

Substance misuse is a general term which encompasses a range of substance use patterns including:

» Hazardous use – a risk of harmful consequences (social, mental, physical) to the user or others.
» Harmful use – the substance use causes harm to the user or others, and may be continuous or episodic (e.g. interpersonal violence after an alcohol binge).
» Dependence – characterised by a loss of self-regulation, repeated use despite harm, substance-induced mental illness, and withdrawal syndromes.

People with substance misuse present with related or comorbid health problems, e.g. to emergency rooms, infectious disease services (e.g. TB, HIV, Hepatitis, etc.); STD services; antenatal clinics; or mental health services.
Early identification and intervention of the substance use is advised to prevent further harm or dependence.

GENERAL MEASURES

» Screen for substance use disorders as a routine part of patient assessment, e.g. with WHO ASSIST[lvii]. The outcome of the screen should determine the level of intervention that is recommended– e.g. brief advice, a brief intervention (ASSIST linked brief intervention[lviii]) or referral to a local substance treatment programme (through a social worker or a registered NGO).
» Elective detoxification: plan in conjunction with a comprehensive substance treatment plan, co-ordinated by the Department of Social Development.
» Unplanned withdrawal: may occur during treatment for another medical condition or may be the presenting complaint. Provide brief intervention counselling and refer to a substance treatment programme.
» Injection drug use: counsel on harm reduction measures and refer to needle and syringe programmes, e.g. StepUp project[lix] (TB HIV Care), OUT, Anova[lx] and COSUP[lxi].

REFERRAL

» All patients treated for substance withdrawal should be referred to Social Services and/or a rehabilitation service for management of their substance use and aftercare.
» Discuss those with comorbid mental disorders with a psychiatrist; refer to specialist dual diagnosis services where available.
» Family and/or partners of people who use substances to registered counsellors and support groups (e.g., Al-anon family groups, https://www.alanon.org.za/)

15.8.1 ALCOHOL WITHDRAWAL

F10.3

GENERAL MEASURES

The following patients should be admitted for detoxification:
» past history of convulsions
» past history of psychosis
» suicidal ideation
» significant medical comorbidity such as heart failure and liver disease

» inadequate support at home
» history of withdrawal delirium
» >60 years of age
» pregnancy
» cognitive impairment
» previous failed community detoxification attempts

MEDICINE TREATMENT

Alcohol detoxification may be managed on an outpatient basis in most patients.

- Thiamine, oral, 300 mg daily for 14 days.

AND *LoE:IIb*[lxii]

- Diazepam, oral, 10 mg immediately.
  - Then 5 mg 6 hourly for 3 days.
  - Then 5 mg 12 hourly for 2 days.
  - Then 5 mg daily for 2 days.
  - Then stop.

Note: Higher doses may be needed in individual patients.

15.8.1.1 ALCOHOL WITHDRAWAL DELIRIUM (DELIRIUM TREMENS)

F10.4

DESCRIPTION

Delirium typically occurs 2–3 days following cessation of prolonged alcohol intake, reaching a peak at around 5 days. However, some withdrawal symptoms, such as tremor, may start within 12 hours.

» Typical clinical features include:
  - visual hallucinations
  - delusions
  - disorientation, fluctuating level of consciousness
  - agitation
  - tonic-clonic seizures – these do not generally need long term anticonvulsant therapy
  - tachycardia
  - hypertension
» It is important to consider alternative diagnoses, especially true in cases with an atypical presentation.
» Similar symptoms may occur following withdrawal from other sedative-hypnotic agents.
» Mortality varies from 1–5%.

GENERAL MEASURES

» For non-pharmacological management: See section 20.8: Delirium.
» Cardiac monitoring and oximetry should be used when administering large doses of benzodiazepines.
» Assess for infections and other comorbid conditions.
» Ensure adequate hydration. Overhydration is a common error made in this setting.
» Correct abnormalities of electrolytes.
» Provide nutritional support.
» Consider referring appropriate patients to a rehabilitation programme after recovery from delirium tremens.

MEDICINE TREATMENT

Administer medicine doses according to severity of symptoms. These patients may require high doses of benzodiazepines because of hepatic enzyme induction.

- Benzodiazepines, e.g.:
- Diazepam, slow IV (max rate <5 mg/minute), 10 mg (**Not IM**).
  - Repeat dose after 5–10 minutes if required.
  - If this dose is not sufficient, use 10 mg every 5–10 minutes for another 1–3 doses to a maximum of 50mg.

LoE:IVb[lxiii]

Where intravenous access is not possible:

- Clonazepam, IM, 2 mg as a single dose.
  - If no response, repeat dose after 60 minutes until patient is sedated.
  - Repeat dose regularly to maintain mild sedation. *LoE:IVb*

OR

- Lorazepam, IM, 1–4 mg every 30–60 minutes until patient is sedated.
  - Repeat dose regularly to maintain mild sedation. *LoE: IVb*

Once patient is sedated, i.e. light somnolence, maintain mild sedation with:

- Diazepam, oral, 5–20 mg.
  - Repeat dose regularly to maintain mild sedation. *LoE: IVb*

CAUTION

Benzodiazepines, especially diazepam IV, can cause respiratory depression. Monitor patients closely as benzodiazepines can exacerbate an abnormal mental state or mask important neurological signs of deterioration.

Note:

» Lorazepam IM has slower onset of sedation than midazolam IM (32 vs 18 minutes) and longer duration of sedation (217 vs 82 minutes).

» Clonazepam oral or IM may be used if longer duration of sedation is required. Onset of action may be 30-60 minutes, time to maximum concentration is 1-4 hours. Long half-life (18-50 hours) increases risk of accumulation. Allow at least 12 hours between repeat doses. *LoE:IIb*[lxiv]

When administering glucose-containing fluids:

- Thiamine, oral/IM, 300 mg daily.

Note:

» Neuroleptic medicines such as haloperidol are associated with a reduced seizure threshold and QTc prolongation.

» **It is preferable to increase the dose of benzodiazepines than to add haloperidol.**

LoE:IVb[lxv]

However, oral haloperidol may assist with managing hallucinations and agitation:

- Haloperidol, oral, 0.75–2.5 mg 12 hourly.
  - Maximum dose: 5mg per 24 hours.

LoE:IVb[lxvi]

Do NOT use olanzapine, IM in the management of alcohol withdrawal. Olanzapine, IM may increase risk of respiratory depression if combined with parenteral benzodiazepines particularly if alcohol has been consumed.

15.8.2 OPIATE (E.G. HEROIN, UNGA, WHOONGA, NYAOPE) WITHDRAWAL

F11.2/F11.8-9

DESCRIPTION

Opioid withdrawal is generally poorly tolerated, but not dangerous, except in very frail debilitated patients or during pregnancy, with an increased risk of miscarriage in the first trimester and of preterm delivery in the third trimester.

Signs and symptoms of opioid intoxication:

- Pinpoint pupils
- Clammy skin
- Respiratory depression
- Drowsiness
- Euphoria
- Hallucinations

Signs and symptoms of opioid withdrawal:

- Nausea / vomiting
- Gooseflesh
- Abdominal cramps
- Rhinorrhoea and lacrimation
- Myalgia
- Diarrhoea
- Restlessness / agitation

GENERAL MEASURES:

» The identification and evidence-based management of opioid dependence among patients who are admitted to hospital will increase their likelihood of completing their primary admission-related treatment. Sub-optimal management of opioid withdrawal will increase the likelihood of absconding from hospital.

» It is extremely important to counsel patients managed for opioid withdrawal upon discharge. Patients' opioid tolerance will be reduced after the down-tapering of methadone (or similar medication) during hospital stay. Upon discharge, patients should be advised to use opioids with caution due to their increased risk of accidental overdose. Opioid related overdose deaths must be prevented.

» Special considerations apply during pregnancy, consult an expert.

» Concomitant withdrawal from opioids and other "downer" drugs, like benzodiazepines or alcohol may complicate withdrawal, consult an expert.

MEDICINE TREATMENT

Monitor for objective signs of withdrawal using a rating scale like the objective opioid withdrawal scale (OOWS):
https://medicine.yale.edu/sbirt/OOWS_251773_284_5_v1.pdf

LoE:IVb[lxvii]

Mild withdrawal (OOWS <4)
May be managed on an outpatient basis.

Symptomatic treatment

- Diazepam, oral, 5–20 mg/day in 2–3 divided doses.
  - Taper off over 5–7 days.

For stomach cramps:
- Hyoscine butylbromide, oral, 20 mg 8 hourly as required.

For headaches:
- Paracetamol, oral, 500mg-1 g, 4–6 hourly as required (to a maximum of 4g in 24 hours).
  - Maximum dose: 15 mg/kg/dose. *LoE:IVb*[lxviii]

For muscle pains:
- NSAID, e.g.:
- Ibuprofen, oral 400 mg 8 hourly, with meals, as required.

LoE:IIb[lxix]

For diarrhoea:
- Loperamide, oral, 4 mg immediately.
  - Then 2 mg after each loose stool.
  - Maximum dose: 16 mg in 24 hours.

Moderate to severe withdrawal (OOWS ≥4)
Hospitalise patient.

Opioid assisted withdrawal:
» Goal is to safely alleviate withdrawal symptoms without causing intoxication or overdose.
» Symptomatic medication listed above may be used to reduce methadone requirements.

Day 1:
Wait for early evidence of withdrawal (OOWS ≥4), then:
- Methadone, oral, 5–10 mg.
  - If symptoms are still present after 2–-4 hours, give another 5–10 mg.
  - Repeat until objective withdrawal symptoms are adequately managed (OOWS <4).
  - The total 24-hour dose should not be more than 30 mg. Consult a person experienced in opioid withdrawal if >30 mg/day is required.

Day 2:
- Methadone, oral.
  - Repeat total dose of day 1 as a single dose or 2 divided doses.
  - Monitor for ongoing signs and symptoms of withdrawal.
  - If the signs and symptoms of withdrawal are still present on day 2, top-up doses of 5 mg may be given at 2–4 hourly intervals with a total daily dose of up to 30 mg. Consult a person experienced in opioid withdrawal if symptoms are not controlled on 30 mg/day.

Day 3 onwards:
- Methadone, oral.
  - Repeat total dose from the previous day (e.g. day 2) if top-ups were needed, and begin dose reductions on the following day (e.g. day 4).

- If no top-ups required on the previous day (e.g. day 2) and withdrawal symptoms are adequately controlled, begin dose reduction.
- Decrease dose by 10–20% per day over a period of 3–10 days.
- The withdrawal regimen may be shortened if the patient's withdrawal symptoms allow.

LoE:IVb[bxx]

If methadone is unavailable:

- Tramadol, oral, 200 mg 12 hourly for 14 days may attenuate withdrawal symptoms.

LoE:IIIb[bxxi]

Opioid poisoning
See section: 19.5.3. Opioid poisoning.

REFERRAL

» Patients with an opioid use disorder should be offered a referral to access opioid substitution therapy and/or other evidence-based treatment and support.
» Patients identified with current/recent history of intravenous drug use should be provided with sterile injecting equipment (1 ml insulin needles and alcohol swabs) upon discharge from hospital, as well as referral to a community- based needle and syringe programme (See details in section 15.8: Substance use disorders – General measures).

15.8.3 STIMULANT WITHDRAWAL, INCLUDING COCAINE AND AMPHETAMINE TYPE STIMULANTS (E.G. METHAMPHETAMINE/ TIK, METHCATHINONE/CAT)

F14.2/F15.2/F15.8-9

GENERAL MEASURES

These patients usually do not require admission.
Beware of depression and assess suicide risk.
Assess and monitor for psychosis.

MEDICINE TREATMENT

No substitute medication is available for detoxification.

For severe anxiety, irritability, or withdrawal-related insomnia:

- Benzodiazepines, short-term, e.g.:
- Diazepam, oral, 5–10 mg 8 hourly for 5–7 days.

15.8.4 METHAQUALONE (MANDRAX/WHITEPIPE) WITHDRAWAL

F19.2-4/F19.8-9

Withdrawal can be dangerous and may lead to seizures (see PHC STGs and EML, section 21.2.11: Seizures and status epilepticus) or delirium (see Adult Hospital STGs and EML, section 20.8: Delirium)
If withdrawal is symptomatic:

- Diazepam, oral, 5 mg 8 hourly.
  - Reduce over 3–5 days depending on clinical response.

15.8.5 CANNABIS WITHDRAWAL

F12.2

Withdrawal is rarely dangerous or poorly tolerated.
Assess for other accompanying psychiatric disorders e.g. mood or psychosis.

15.8.6 BENZODIAZEPINE WITHDRAWAL

F13.2

DESCRIPTION

Benzodiazepine addiction may occur after only a few weeks of use. Withdrawal symptoms may occur with abrupt dose reduction or cessation and include anxiety, nervousness, irritability, depersonalisation, delirium and seizures, increased sweating, sound sensitivity, nausea, difficulty concentrating, myoclonus, tremor, weakness, and fatigue.
Gradual tapering of the benzodiazepine is recommended to facilitate discontinuation.

GENERAL MEASURES

» The therapeutic relationship between client and doctor is extremely important in initiating dose reduction.
» Confirm benzodiazepine dependence – ascertain usage, history of previous withdrawal symptoms; a urine screen may be necessary.
» Establish full dosage of all benzodiazepines being taken, including those prescribed by other medical practitioners.
» Take time to explain negative impact of ongoing benzodiazepine use, benefits of stopping, and concepts like tolerance and withdrawal.
» Encourage the patient not to seek medication from other doctors.
» Evaluate and optimise management of comorbid substance use disorders, mental illness, and general health conditions.
» Avoid abrupt withdrawal of benzodiazepines; be prepared to take time. Negotiate each reduction with the patient. Individualise regular monitoring and motivation.
» Refer for substance use rehabilitation, e.g. SANCA (https://www.sancanational.info)
» Long-term follow-up with repeated motivation may be necessary to prevent relapse. *LoE:IIIb*[lxxii]

MEDICINE TREATMENT

» Replace short-acting benzodiazepine with an equivalent diazepam (long acting

benzodiazepine) dose.

» Patients may present with medicines that are unavailable in the public sector.

LoE:IVb[lxxiii]

Approximate equivalent doses to diazepam 5 mg are:

Alprazolam	0.25 mg
Bromazepam	1.5 mg
Clobazam	10 mg
Chlordiazepoxide	12.5 mg
Clonazepam	0.25–1 mg
Flunitrazepam	0.5 mg
Lorazepam	0.5 mg
Nitrazepam	5 mg
Oxazepam	15 mg
Temazepam	10 mg
Zolpidem	10 mg
Zopiclone	7.5 mg

Note:

» Medicines have only been included for comparison of estimated equivalent doses.

» Higher doses may be required for patients who are dependent on both alcohol and benzodiazepines. Inpatient assessment and initiation of benzodiazepine tapering may be warranted in these patients.

Reduction is done according to clinical response (See table below).

- Diazepam, oral.

Table 15.1: Dose reduction of diazepam-equivalent benzodiazepines

Daily diazepam-equivalent doses used	**Dose reduction recommendation**
> 50 mg/day	Reduce daily dose every 1–2 weeks by 10 mg/day until a daily dose of 50 mg is reached.
30-50 mg/day	Reduce every 1–2 weeks by 5 mg/day until a daily dose of 30 mg is reached.
20-29 mg/day	Reduce every 1–2 weeks by 2.5 mg/day until a daily dose of 20 mg is reached.
< 20 mg/day	Reduce every 1–2 weeks by 1.25 mg/day until stopped.

Note:

- If symptoms reappear, increase the dose by 2.5 or 5mg a day and then reduce dose using 2–4 week intervals.
- Do not prescribe more than one week's duration of medication at a time.

LoE:IIIb[lxxiv]

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Benzodiazepine detoxification: Baandrup L, Ebdrup BH, Rasmussen JØ, Lindschou J, Gluud C, Glenthøj BY. Pharmacological interventions for benzodiazepine discontinuation in chronic benzodiazepine users. Cochrane Database Syst Rev. 2018 Mar 15;3:CD011481. https://www.ncbi.nlm.nih.gov/pubmed/29543325

SOUTH AFRICAN ADULT HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 15: MENTAL HEALTH CONDITIONS AND SUBSTANCE MISUSE
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2020 -2023 REVIEW CYCLE)

The Adult Hospital Level (AHL) Mental Health Conditions and Substance Misuse chapter underwent detailed clinical editing resulting in editorial changes for clarity.

Medicine amendment recommendations, with supporting evidence and rationale are listed below.
Kindly review the medicine amendments in the context of the respective standard treatment guideline (STG) and supporting medicine reviews.

A: PROPOSED AMENDMENTS

SECTION	MEDICINE/MANAGEMENT	ADDED/DELETED/AMENDED/ NOT ADDED/ RETAINED
15.1 AGGRESSIVE DISRUPTIVE BEHAVIOUR IN ADULTS	Benzodiazepines, Oral: (e.g., Lorazepam, Clonazepam, Diazepam)	Retained
	Benzodiazepines, Oral or Buccal (e.g., Midazolam)	Retained
	Olanzapine, Oro-dispersible	Added
	Olanzapine, IM	Added
	Haloperidol, IM	Deleted
	Promethazine, IM	Deleted
	If previous intolerability to olanzapine (e.g., previous neuro-malignant syndrome): Benzodiazepines, IM (e.g., Lorazepam, Midazolam, Clonazepam, IM)	Added
	Under specialist care in psychiatric wards: Zuclopenthixol acetate, IM:	Retained *(Added low dose initiation in neuroleptic naïve patients.)*
	If alcohol use is suspected: Thiamine, Oral: Retained	Retained
	Inadequate response to oral benzodiazepine (after 30–60 minutes) or oral treatment refused: Lorazepam, IM	Deleted
	Inadequate response to oral benzodiazepine (after 30–60 minutes) or oral treatment refused: Midazolam, IM	Deleted
	Inadequate response to oral benzodiazepine (after 30–60 minutes) or oral treatment refused: Clonazepam, IM	Deleted
	Olanzapine, Oro-dispersible	Added
	Olanzapine, IM	Added
15.5.2 SCHIZOPHRENIA SPECTRUM DISORDERS	Haloperidol, Oral	Retained, with dosage range adjustment
	Depot antipsychotic, IM (e.g. Flupenthixol decanoate OR Zuclopenthixol decanoate)	Retained *(With downward adjustment of lower dose of zuclopenthixol to be equivalent to the lower dose of flupenthixol)*
	Risperidone, Oral	Retained
	Chlorpromazine, Oral	Retained
	Olanzapine, Oral	Retained with revision from specialist to doctor initiated
	Clozapine, Oral	Retained
15.6 INSOMNIA	**<u>If medication is needed to treat the insomnia:</u>** Short-acting benzodiazepines, oral (e.g.:Oxazepam)	*Retained (*with adjustment to starting dose of Oxazepam)
	Benzodiazepines, IV (e.g.: Diazepam)	Retained

SECTION	MEDICINE/MANAGEMENT	ADDED/DELETED/AMENDED/ NOT ADDED/ RETAINED
15.8.1 ALCOHOL WITHDRAWAL DELIRIUM (DELIRIUM TREMENS)	**Where IV access is not possible:** Clonazepam, IM	Retained
	Where IV access is not possible: Lorazepam, IM	Retained
	Once patient is sedated, i.e., light somnolence, maintain mild sedation with: Diazepam, Oral	Retained
	When administering glucose-containing fluids Thiamine, Oral/IM	Retained
	Severe agitation and restlessness persisting after adequate doses of benzodiazepines: Haloperidol, IM/IV	Deleted
	Management of hallucinations and agitation: Haloperidol, Oral	Added
	Management of hallucinations and agitation: Olanzapine, IM	Not added
15.8.2 OPIATE (e.g. HEROIN, UNGA, Whoonga, nyaope) WITHDRAWAL	**For Headaches:** Paracetamol, oral	Retained *(Dose range amended and maximum dose reiterated and aligned to AHL Chapter 25: Pain)*

MENTAL HEALTH CONDITIONS

In the introduction to the chapter a recommendation to consider the addition of registered counsellors, in the chapter, as mental health practitioners was accepted as this service is gradually rolling out in the public sector. Registered counsellors are now included in referral recommendations in the chapter.

An external comment was received, for all conditions, to include the psychoeducation of the patient's family regarding the condition, management (importance of adherence to medication and psychotherapy/counselling), as well as red flags to look out for when the patient is relapsing. It was motivated that by this intervention the potential for stigma will be reduced and conflict in families might be reduced offering the patient more. Furthermore, it was motivated that by promoting better supervision and adherence, risk to the patient and others, as well as relapse frequency can be reduced significantly potentially improving quality of life for the patient and family and preserving the patient's functionality and ability to contribute to society.

The committee supported adding a note regarding either counselling or psychoeducation of the family to all conditions, with a slight variation in phrasing depending on the condition. Furthermore, the meaning of the selected terminology of psychoeducation[1] was added to the introduction of the chapter to ensure that the definition is understood throughout the chapter and to promote investment in time in ensuring that the patient's family and friends have a clear understanding of the patient's condition.

A description of risk assessment was also provided citing and adapting Australian Guidance[2] as there are currently no South African standardised guidance tools available for risk assessment. The decision to include risk assessment in the introduction was reached by the committee in response to an external comment to include risk of reputation to patient under the bipolar and related disorders STG which was not accepted by the committee because risk to reputation is only one aspect of risk to self (along with risk to job, finances, property and relationships), all of which would be better suited for inclusion in a national clinical programme guideline, outside the scope of the STGs.

[1] Definition (Psychoeducation): Sarkhel S, Singh OP, Arora M. Clinical Practice Guidelines for Psychoeducation in Psychiatric Disorders General Principles of Psychoeducation. Indian J Psychiatry. 2020 Jan;62(Suppl 2):S319-S323. doi: 10.4103/psychiatry.IndianJPsychiatry_780_19. Epub 2020 Jan 17. PMID: 32055073; PMCID: PMC7001357

[2] Definition (Risk Assessment): New South Wales Government. SESLHDGL/082 Clinical Risk Assessment and Management. 2022/04 Version 7.2

A comment to mention palliative care in the chapter was not accepted; as the chapter covers mental health conditions in all patient populations (e.g., general medical, emergencies, obstetrics & gynecology, surgical, palliative care and poisoning). The committee recommended, as is current practice in the STGs, that other chapters where appropriate are cross-referenced to mental health conditions so that mental health conditions are integrated into the general healthcare process.

An external commentator raised that dementia is not covered in sufficient detail in the mental health conditions chapter. Dementia is covered in the PHC Chapter 15 Central Nervous System (CNS).

Links to training material was removed in the chapter because training manuals are no longer available, as confirmed by the national mental health directorate, and as raised by an external commentator the interactive links in the chapter are no longer valid. The reason is that civilians cannot provide training to the SAPS. Relevant mental health training is to be incorporated into standard SAPS training.

The STG was updated as follows:

Precepts of the Mental Health Care Act No. 17 of 2002 include:

» All patients with mental illness and/or severe to profound intellectual disability should receive mental health care as either Voluntary, Assisted or Involuntary Mental Health Care Users.
» All registered medical practitioners, professional nurses, psychologists, occupational therapists (OTs), and social workers whose training includes mental health are designated Mental Health Care Practitioners.
» Mental health care practitioners and heads of health establishments at PHC and Hospital Adults level must be familiar with MHCA Forms 01 – 13A, 14, 17, 22, 25, 26, 27, and 48.
» The South African Police Service (SAPS) have an obligation to protect, apprehend, and assist people with mental illness with transfer, to and between health establishments.

Meaning of selected terminology used in this chapter:

» **Psychoeducation** (psychological education) involves informing a patient and their family or support system about their illness and providing problem solving, communication, and assertiveness skills training. The goals are to enable understanding, self-care, crisis management, suicide prevention, and relapse prevention. Information on aetiological factors, signs and symptoms, early signs of relapse, treatment options, need for adherence to treatment, and long-term course and outcome should be provided with consideration of the individual and their family's culture, beliefs, and coping mechanisms. Myths and misconceptions regarding the illness and its treatment are identified and managed in a person-centred manner. Advice on managing difficult behaviour and emergency situations is provided, and is stigma dispelled.

  Psychoeducation may require several individual, family, or group sessions, depending on the complexity of the illness and the understanding of the problem by the individual and their family / support system. Involvement of a registered counsellor, occupational therapist, and/or social worker is advised.

» **Risk assessment** refers to a clinical judgement of the patient's potential for:
  - suicide or self-harm
  - aggression or violence towards others
  - being assaulted by others
  - high risk sexual behaviour
  - severe self-neglect
  - being exploited
  - reputational damage
  - non-adherence to treatment
  - causing damage to property
  - poor physical health

  A risk assessment is performed by collecting information from the patient and relevant stakeholders which may include the person's family / support system, healthcare providers (including community health workers or social workers who have knowledge of the person's home), as well as past clinical and forensic history.

  Close attention must be given to women in the perinatal period, people who care for others (e.g., parents, grandparents, teachers, health and social care providers), and those with previous high-risk behaviour.

  While the clinical judgement may not always be accurate, it should be justified by the available information. The clinical judgement serves to inform precautionary interventions, e.g. close clinical follow-up after hospital discharge with increased attention by the Ward-Based Outreach Team (WBOT), referral to social welfare / statutory services, advice regarding a protection order, and/or further psychoeducation.

  A useful clinical guideline on how to conduct a risk assessment is available at: https://www.seslhd.health.nsw.gov.au/sites/default/files/documents/SESLHDGL%20082%20-

%20%20Clinical%20Risk%20Assessment%20and%20Management%20-%20Mental%20Health2.pdf

~~**A training manual is available from**~~
~~https://www.who.int/mental_health/policy/en/training_guidelines_for_south_african_policy.pdf~~

15.1 AGGRESSIVE DISRUPTIVE BEHAVIOUR IN ADULTS

Description

An editorial comment for the cross-reference to the PHC STGs Maternal Mental Health section to be labelled was accepted. A full cross reference to the appropriate section is now provided.

The STG was updated as follows:

DESCRIPTION
Agitation may escalate to overt aggression and often manifests with restlessness, pacing, and loud or demanding speech. Aggressive behaviour includes verbally abusive language, specific verbal threats, intimidating physical behaviour, and/or actual physical violence to self, others, or property. All agitation and aggression must be considered an emergency, and violence should be prevented wherever possible.
~~Multiple c~~Causes for aggressive, disruptive behaviour include:

- **Physical:** acute medical illness, delirium and its causes (See section 20.8: Delirium), epilepsy (pre-, intra-, and post-ictal), intracerebral lesions, traumatic brain injury.
- **Psychiatric:** psychosis, mania, agitated depression, neurocognitive disorders (e.g. dementias, old traumatic brain injury), developmental disorders (e.g. intellectual disability and autistic spectrum disorder), severe anxiety.
- **Substance misuse:** alcohol; cannabis; methaqualone (mandrax) intoxication or withdrawal; stimulant (cocaine, methamphetamine [tik], methcathinone [cat]) intoxication; benzodiazepine withdrawal.
- **Psychological factors:** high levels of impulsivity and antagonism, hypersensitivity to rejection or insult, poor frustration tolerance, and maladaptive coping skills may all contribute to aggression.
- **In pregnant women:** In pregnant women: labour, obstetric complications, sepsis, organ failure as well as substances and mental disorders (See Primary Health Care [PHC] Standard Treatment Guidelines [STGs] and Essential Medicines List [EML], Chapter 6 Obstetrics and Gynaecology, section 6.9: Maternal mental health).

General Measures

Definitions of manual and mechanical restraint are provided in line with World Health Organization[3] and National Department of Health Policy[4].

Under general measures an external commentator raised that when patients feel they are not listened to, it leads to aggressive behavior, and therefore an important handling principle is to listen to the patient. The STG was updated to include the importance of listening to the patient.

An external comment was received suggesting that for the section on manual and mechanical restraints it would be important and in line with NDOH policy[5] to inform and educate the family of aggressive patients that were restrained regarding the reasons for the patient's restraints. It was highlighted that this could assist with the traumatic nature of restraints for the patient and family, as well as serve to reduce the number of complaints received from the family which could potentially reduce the burden of redress meetings and medico-legal cases. The STG was updated to include a new point to counsel family/ friend/ escort on reasons for restraints.

The STG wording was updated in line with the following external comment received for mechanical restraints i.e., that MHCA 48 would only be completed and sent to the Mental Health Review Board if the restrained patient is in fact a Mental Health Care User under the Mental Health Care Act (MHCA). For example, delirious patients would also be

[3] Strategies to end seclusion and restraint. WHO Quality Rights Specialized training. Course guide. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO. Available from: https://apps.who.int/iris/bitstream/handle/10665/329605/9789241516754-eng.pdf

[4] National Department of Health. Policy Guidelines on Seclusion and Restraint of Mental Health Care Users. 2012. Available from: https://www.knowledgehub.org.za/elibrary/policy-guidelines-seclusion-and-restraint-mental-health-care-users-2012

[5] National Department of Health. Policy Guidelines on Seclusion and Restraint of Mental Health Care Users 2012. https://www.knowledgehub.org.za/elibrary/policy-guidelines-seclusion-and-restraint-mental-health-care-users-2012

restrained, but they would be excluded from the MHCA due to their condition and restraining them would not warrant the completion of MHCA 48, though restraints still need to be documented and the patients need to be monitored.

An external comment for the section on manual and mechanical restraints that it would be important for any injuries or death that occurred associated with restraining a patient to be reported in writing to the Mental Health Review Board; was accepted. Additionally, a note for reporting to the health facility quality assurance was also added in line with standard reporting mechanisms. An external comment to include prescription of mechanical restraint by a medical doctor was accepted.

For pregnant woman an external comment for pregnant women to be lowered into a semi-seated position on a large bean bag if available and avoiding excessive force was accepted, for appropriate comfort of patient and child.

The STG was updated as follows:

GENERAL MEASURES

» **Prepare, anticipate, and prevent**:
Be aware of ~~high risk~~ high-risk patients e.g. those with previous violence, substance misuse, and State Patients on leave of absence. Have:
- a step-wise protocol to ensure safety of all patients and staff.
- clear roles for all staff members.
- a triage plan for early signs of aggression.
- available backup – hospital security and SAPS and EMS.
- a designated calming area – suitable for regular monitoring.

» **De-escalate and contain**:
- Be calm, confident, kind, and reassuring.
- Listen to the person.
- Maintain a submissive posture with open hands.
- Do NOT turn your back on the patient; avoid direct eye contact.
- Do NOT attempt to reason with the patient.
- Do NOT argue, confront delusions, or touch the patient.
- Set clear limits regarding behaviour.
- Take patient to quiet, calm area – do NOT leave unobserved.

» **Examine** for delirium, medical and other causes while calming the patient and after sedation.

» **Manual restraint:**
- May be necessary to administer medication.
- Manual restraint refers to interventions done with hands or bodies without the use of any device, to limit a user's movement of body or limb. It is sometimes called "holding". Manual restraint must be respectful, controlled and kept to a minimum. It should preferably be applied by personnel of the same sex as the patient.
- Report any injuries or death associated with the restraint to the Mental Health Review Board as well as the health facility quality assurance department.

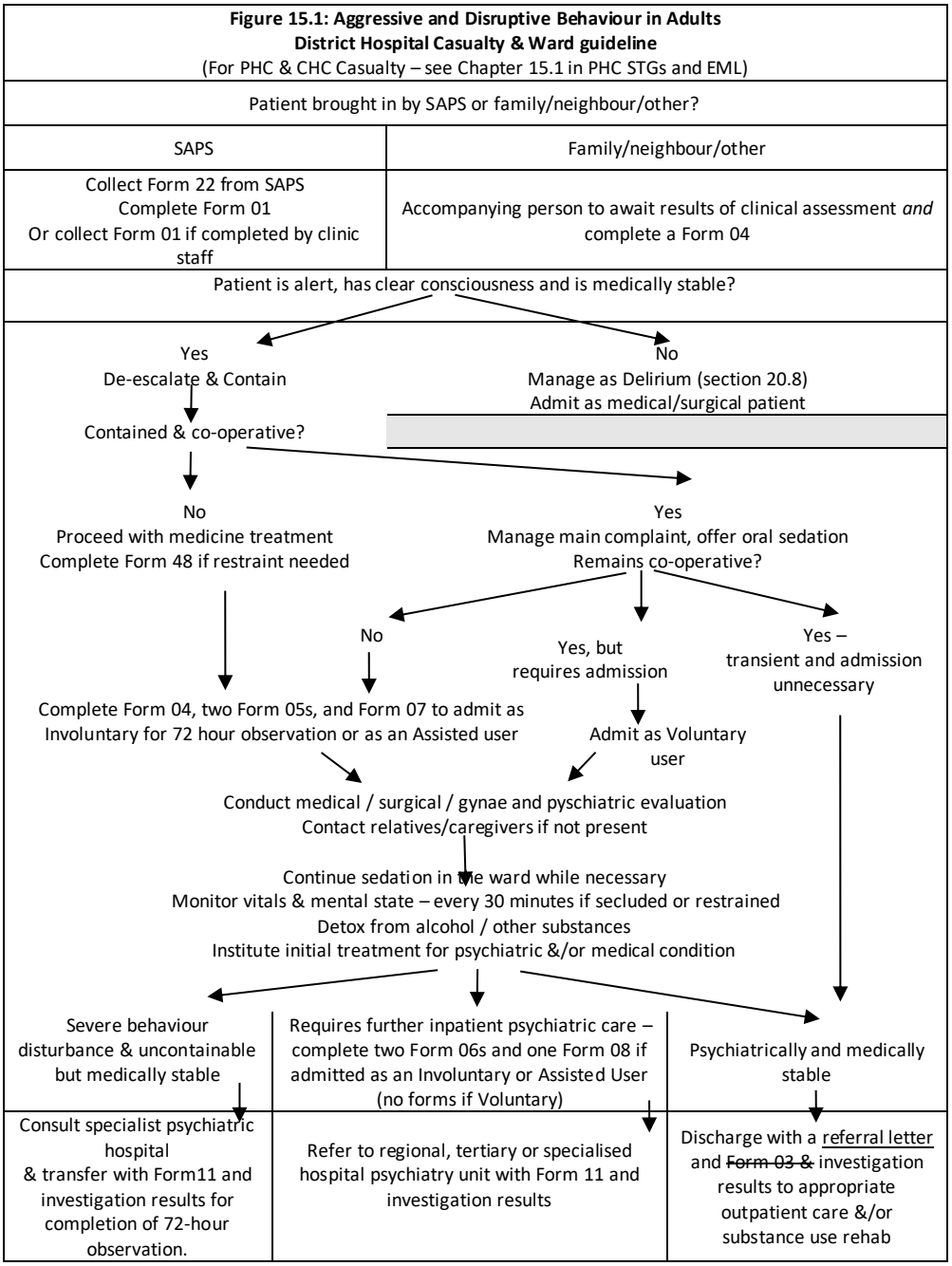
» **Mechanical restraint**:
- An emergency intervention in which an instrument or appliance is used to restrict movement of the body. See national policy guidelines on the use of mechanical restraint: https://www.knowledgehub.org.za/elibrary/policy-guidelines-seclusion-and-restraint-mental-health-care-users-2012
- Only use if absolutely necessary to protect the patient and others for as short a time as possible, and as prescribed by a doctor.
- Document the type, sites and duration of any restraints used.
- 15-minute monitoring: vital signs, mental state, restraint sites, and reasons for use.
- For people managed under the MHCA, ~~C~~complete a MHCA Form 48 (restraint register) and submit to the Mental Health Review Board, together with a report of any injuries or death associated with the restraint as well as to the health facility quality assurance department.
- .

» **Pregnant women:**
- Never leave unattended.
- Avoid excessive force; gently nurse mother in a supported semi-seated position (not supine or prone), in an armchair or large beanbag if available.
- Use restraint sparingly and with care.

» **Counsel the family/ friend/ patient escort regarding:**
- Possible causes for the behaviour.
- Reasons for restraints if used.
- Importance of their continued support of the patient post-discharge.

For the aggressive and disruptive behavior in adults district hospital casualty and ward guideline algorithm an external comment was received highlighting that an amendment was required for the section on discharge for "Transient disturbance". A Form 01 had been completed for patients on this part of the flow chart which indicates that discharge takes place on the form itself not on a Form 03. This leg of the flow chart does not include the filling of Forms 4, 2x 05 and 07. The algorithm was therefore amended for referral letter to replace form 03; to correctly match instruction in the earlier sections of the algorithm. Other minor editorial changes were made to the algorithm.

The algorithm was updated as follows.



Rapid Tranquillisation

Benzodiazepines, Oral: (e.g., Lorazepam, Clonazepam, Diazepam)[6,7,8]: *Retained*

[6] Benzodiazepines: Zaman H, Sampson SJ, Beck AL, Sharma T, Clay FJ, Spyridi S, Zhao S, Gillies D. Benzodiazepines for psychosis-induced aggression or agitation. Cochrane Database Syst Rev. 2017 Dec 8;12:CD003079. https://www.ncbi.nlm.nih.gov/pubmed/29219171

[7] Lorazepam, oral (dose range): Taylor, David; Paton, Carol; Kapur, Shitij. The Maudsley Prescribing Guidelines, Twelfth Edition. London: CRC Press; 2015

[8] Lorazepam, oral (dose range): South African Medicines Formulary. 124th Edition. Division of Clinical Pharmacology. University of Cape Town. 202216.

Benzodiazepines, Oral or Buccal (e.g., Midazolam)[9,10,11]: *Retained*
Olanzapine, Oro-dispersible: *Added*
Olanzapine, IM: *Added*
Haloperidol, IM: *Deleted*
Promethazine, IM: *Deleted*

Haloperidol injection was not available in the South African market. Haloperidol IM is included in the therapeutic interchange database for aggressive disruptive behaviour. Olanzapine oro-dispersable and Olanzapine, IM were reviewed for the management of aggressive disruptive behaviour in adults.

Refer to the medicine review - Olanzapine for aggression in adults, 14 March 2024, below:

Olanzapine for agression_PHC-Adults

Recommendation: Considering that parenteral haloperidol supply has been erratic in South Africa, the PHC/Adult Hospital Level Committee suggest using olanzapine, oral, oro-dispersible or parenteral formulations.
Rationale: The very low certainty evidence suggests olanzapine may be superior to lorazepam and to the combination of haloperidol and promethazine in reduction of agitated or aggressive behaviour. There appears to be no difference in achieving sedation.
Level of Evidence: Very low certainty evidence
Review indicator: New evidence of benefit or harm

If previous intolerability to olanzapine (e.g., previous neuro-malignant syndrome) administer parenteral benzodiazepine:
Benzodiazepines, IM (e.g., Lorazepam, Midazolam, Clonazepam, IM, 0.5–2 mg)[12,13]: *Added*

Under specialist care in psychiatric wards:
Zuclopenthixol acetate, IM[14]: *Retained (*Added low dose initiation in neuroleptic naïve patients.)

If alcohol use is suspected:
Thiamine, Oral[15,16]: *Retained*

Inadequate response to oral benzodiazepine (after 30–60 minutes) or oral treatment refused:
Lorazepam, IM: *Deleted*
Midazolam, IM: *Deleted*
Clonazepam, IM: *Deleted*
Olanzapine, Oro-*dispersible:* *Added*
Olanzapine, IM: *Added*

For rapid tranquilization, olanzapine, orodispersible route of administration was clarified as the preferred route of administration as 1st line therapy.

[9] Midazolam, buccal: Taylor D, Okocha C, Paton C, Smith S, Connolly A. Buccal midazolam for agitation on psychiatric intensive care wards.Int J Psychiatry ClinPract.2008;12(4):309-11. http://www.ncbi.nlm.nih.gov/pubmed/24937720
[10] Midazolam, buccal: National Department of Health, Essential Drugs Programme: Primary Health Care STGs and EML, 2018. http://www.health.gov.za/
[11] Midazolam, oral: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.
[12] Lorazepam, IM: Alexander J, Tharyan P, Adams C, John T, Mol C, Philip J. Rapid tranquillisation of violent or agitated patients in a psychiatric emergency setting. Pragmatic randomised trial of intramuscular lorazepam v. haloperidol plus promethazine. Br J Psychiatry. 2004 Jul;185:63-9. http://www.ncbi.nlm.nih.gov/pubmed/15231557
[13] Lorazepam, IM (dose range): Taylor, David; Paton, Carol; Kapur, Shitij. The Maudsley Prescribing Guidelines, Tenth Edition. London: CRC Press; 2009.
[14] Zuclopenthixol acetate, IM: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022
[15] Taylor DM, Barnes TRE, Young AH. The Maudsley Prescribing Guidelines in Psychiatry. 13th ed: WILEY Blackwell; 2018.
[16] Lingford-Hughes AR, Welch S, Peters L, Nutt DJ; British Association for Psychopharmacology, Expert Reviewers Group. BAP updated guidelines: evidence-based guidelines for the pharmacological management of substance abuse, harmful use, addiction and comorbidity: recommendations from BAP. J Psychopharmacol. 2012 Jul;26(7):899-952. doi: 10.1177/0269881112444324. Epub 2012 May 23. PMID: 22628390

An external comment for an editorial revision on how the dose and formulation of olanzapine oral/IM is represented in the STG was accepted with reference to the NDOH medicine review[17].

A note was added to the STG indicating that depot neuroleptics have no place in managing the acutely aggressive patient.

The STG was revised as follows:

MEDICINE TREATMENT– ~~Rapid Tranquillisation~~

The goal of rapid tranquilisation is to calm the patient so that risk to self or others is minimised and manage the underlying condition.

CAUTION

» Rapid tranquillisation may cause cardiovascular collapse, respiratory depression, acute dystonic reactions, and neuroleptic malignant syndrome.
» Pregnant women, elderly, intellectually disabled, and those with comorbid medical conditions and/or substance use are at highest risk of serious adverse drug reactions.
» Late pregnancy: neonatal sedation or extra-pyramidal side effects may occur.
» **Write out single prescriptions and review between each prescription.**
» **Allow at least 30 – 60 minutes between prescriptions.**
» **An emergency trolley, airway, bag, oxygen, and intravenous line must be available for use if needed.**

» Monitor vital signs closely during and after medicine administration.
» Use the safest route of administration possible: The safest route of administration of benzodiazepines is oral followed by IM. IV route has the highest risk of respiratory depression and arrest.

- ~~In pregnancy, the frail and elderly, or where respiratory depression is a concern, use a short-acting benzodiazepine at the lowest dose.~~

- ~~The safest route of administration of benzodiazepines is oral followed by IM with the IV route having the highest risk of respiratory depression and arrest. Use the safest route possible.~~
- ~~Monitor vital signs closely during and after administration. Use haloperidol instead of benzodiazepines in patients with respiratory insufficiency.~~

~~Where aggression is clearly caused by psychosis haloperidol and promethazine may be used as 1st line treatment and not benzodiazepines.~~

- Do not use depot antipsychotic injections (e.g., flupenthixol decanoate or zuclopenthixol decanoate injections) for rapid tranquillisation.

Offer oral treatment:

If aggression is clearly caused by psychosis, or if pregnant, elderly/frail, or has significant risk for respiratory depression:

- Olanzapine, orodispersible tablet or IM, immediately:
  - Aggression clearly due to psychosis or if pregnant: 5–10 mg.
  - Elderly/frail, respiratory depression risk / medically unwell: 2.5–5 mg.
  - Repeat after 30–60 minutes if needed.

If cause of aggression unclear, non-pregnant, non-elderly/frail, and without significant risk for respiratory depression:

- Benzodiazepines, e.g.:
- Lorazepam, oral, 0.5–2 mg immediately.

OR

- Clonazepam, oral, 0.5–2 mg immediately.

OR

- Diazepam, oral, 5–10 mg immediately.

OR

- Midazolam, oral or buccal, 7.5–15 mg immediately.

[17] Olanzapine, oral/oral dispersible tablet/IM/: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Olanzapine for Aggressive / disruptive behaviour, 29 September 2022. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

If there is an inadequate response to oral benzodiazepine (after 30–60 minutes) or where oral treatment is refused~~, administer parenteral or oro-dispersible benzodiazepine treatment:~~

~~• Lorazepam, IM, 0.5–2 mg, immediately.~~

~~**OR**~~

~~Midazolam, IM, 7.5–15 mg immediately.~~

~~**OR**~~

~~Clonazepam, IM, 0.5–2 mg, immediately.~~

~~**Note:**~~

~~• To avoid inappropriate repeat dosing allow at least 30 minutes for the oral/IM medication to take effect.~~

~~• Repeated IM doses of benzodiazepines may result in toxicity owing to accumulation.~~

~~• Lorazepam IM has slower onset of sedation than midazolam IM (32 vs 18 minutes) and longer duration of sedation (217 vs 82 minutes).~~

~~• Clonazepam oral or IM may be used if longer duration of sedation is required. Onset of action may be 30-60 minutes, time to maximum concentration is 1-4 hours. Long half-life (18-50 hours) increases risk of accumulation. Allow at least 12 hours between repeat doses.~~

- Olanzapine, orodispersible tablet/ IM, 5–10 mg immediately ~~orodispersible tablet or IM~~
  - Repeat after 30–60 minutes if needed.

Note: Repeated doses may result in excessive sedation

If there is an inadequate response to oral benzodiazepine with a history of intolerability to olanzapine (e.g. previous neuroleptic malignant syndrome):

- Lorazepam, IM, 0.5–2 mg, immediately.

OR

Midazolam, IM, 7.5–15 mg immediately.

OR

Clonazepam, IM, 0.5–2 mg, immediately.

Note:

» To avoid inappropriate repeat dosing, allow at least 30 minutes for the oral/IM medication to take effect.

» Repeated IM doses of benzodiazepines may result in toxicity owing to accumulation.

» Lorazepam IM has slower onset of sedation than midazolam IM (32 vs 18 minutes) and longer duration of sedation (217 vs 82 minutes).

Clonazepam oral or IM may be used if longer duration of sedation is required. Onset of action may be 30-60 minutes, with predicted maximum effect after 1-4 hours. There is an increased risk of accumulation due to its long half-life (18-50 hours. Allow at least 12 hours between repeat doses.

To continue tranquilisation under specialist ~~care~~ supervision in psychiatric wards:

- Zuclopenthixol acetate, IM, 50–150 mg every 2–3 days (specialist/specialist consultation).
  - Start with 50mg in neuroleptic-naïve patients.

Maximum dose: 400 mg over a two-week period

Under “manage acute complications” drop in respiratory rate was specified as < 12 breaths/minute and an editorial update was affected revising the cross references from the 2018 to revised 2023 primary health care mental health conditions chapter.

The STG was updated as follows:

Manage acute complications:

» *Respiratory depression:* if respiratory rate drops to <12 breaths/minute, or oxygen saturation <90% - give oxygen; be prepared to ventilate.

» *Circulatory collapse*: See section 20.1: Cardiac arrest in adults.

» *Acute dystonia*: See PHC STGs and EML, ~~2018~~ section 16.2.1: Extra-pyramidal side effects.

» *Neuroleptic Malignant Syndrome:* See ~~the~~ PHC STGs and EML, ~~2018~~, section 16.2.2: Neuroleptic malignant syndrome.

An external commentator queried if passive aggressive behavior (and/or negativistic behavior) should be included in the aggressive disruptive behavior STG. Negativistic behavior was not included as the treatment is non-medical (e.g., do not raise voice with the patient), and the STG is intended to cover overt aggression requiring pharmacological treatment. Negativistic behavior can be very provocative for health care providers and needs to be handled well, without becoming aggressive towards or belittling of the patient. The committee considered the addition of management of negativistic behavior more appropriate to include in a national clinical practice guideline.

15.2 ANXIETY AND OBSESSIVE-COMPULSIVE DISORDERS

In this section an external comment that anxiety is also common among patients at the end of life and that it does require good symptom management and the involvement of a palliative care team was not accepted because anxiety is common in multiple medical situations with end of life being one of them. The committee recommended instead that management of a person's anxiety should be mentioned in other chapters where appropriate, and cross referenced to mental health chapter if required.

An external recommendation to consider the addition of registered counsellors, in the chapter, as mental health practitioners was accepted as this service is gradually rolling out in the public sector. Registered counsellors are now included in referral recommendations in the anxiety and obsessive-compulsive disorders STG.

The STG was updated as follows:

GENERAL MEASURES

Most patients can be treated as outpatients, but some may need to be admitted for diagnostic clarification, containment in extreme distress, or at high risk of suicide.

» Maintain patience and an empathic attitude.
» Screen for and manage:
  - causative and comorbid medical illness, e.g. thyroid disease, hyperparathyroidism, phaeochromocytoma, vestibular dysfunctions, epilepsy, and cardiac conditions, hypertension, COPD, asthma, inflammatory bowel disease, GORD.
  - substance misuse, e.g. caffeine, nicotine, alcohol, analgesics, amphetamines and cocaine
  - psychosocial stressors, especially in people with intellectual and other disabilities.
» Psychoeducate the patient and family (with patient's permission).
» Refer to registered counsellors and local support groups. Provide links to self-help literature, websites or groups, e.g. South African Depression and Anxiety Group (SADAG - www.sadag.org).

A detailed external comment was received from a group of medical experts to make the following augmented and adapted revisions, with references* in the STG caution box for pregnancy and breastfeeding:

» SSRI treatment of depression in pregnancy is associated with improved symptoms in the mother and better emotional and psychological development of the child. Benefit is greater in severe illness.
» Lack of matched case-control studies mean harms of treatment are unclear.
» If stable on an SSRI, do not stop, abrupt discontinuation is associated with depressive relapse – discuss the risk of untreated illness vs, the risk of medication in pregnancy with mother.
» Index presentations: offer counselling on social support, physical activity, sleep, psychotherapy, especially therapies with an interpersonal component; discuss risk/benefit of SSRIs. Explore referrals for socio-economic supports.
  - For moderate to severe illness consider SSRI's as first line treatment together with psychotherapy.
» All antidepressants: there are small possible increased risks of small for gestational age, preterm delivery and spontaneous miscarriage, as well as persistent pulmonary hypertension of the newborn. However, these outcomes have also been shown to be associated respectively with perinatal depression itself; and mode of delivery - rather than drug exposure per se. There is no consistent information to support specific teratogenic risks nor to support negative long term developmental outcomes in exposed offspring.
» Medication withdrawal or poor neonatal adaption syndrome (jitteriness, irritability) may occur in up to 30% of exposed babies around birth, typically mild and resolving within 1-2 days. Tapering of maternal dose towards the end of pregnancy is not advised – this does not improve neonatal outcomes and places the mother at significant psychiatric risk. Breastfeeding may help to ease any potential serotonin withdrawal symptoms for the infant in the early postpartum period.
» Data suggest that, for moderate to severe symptoms, psychotherapy alone may not be sufficient, and augmentation with pharmacotherapy ought to be considered. Medication should be titrated to the lowest effective therapeutic does, with a goal of full symptom remission.
» Avoid benzodiazepines – some association with neurodevelopmental delay in the child; neonatal sedation if used late in pregnancy. Benzodiazepines should be restricted to emergency settings or in acute clinical scenarios i.e., rapid tranquilisation of an aggressive patient.
» Eglonyl (sulpiride) is an antipsychotic that increases milk supply and can cause drowsiness and other distressing side-effects. It's not effective as an antidepressant on its own.

*

- Andersen JT et al. Exposure to selective serotonin re-uptake inhibitors in early pregnancy and the risk of miscarriage. Obstet Gynecol 2014;124(4):655–61.
- Andrade C. Antidepressant exposure during pregnancy and risk of autism in the offspring, 1: meta-review of meta-analyses. J Clin Psychiatry 2017;78(8): e1047–51.
  Boukhris T et al. Antidepressant use during pregnancy and the risk of autism spectrum disorder in children. JAMA Pediatr 2016; 170(2):117–24.
  Castro VM et al. Absence of evidence for increase in risk for autism or attention-deficit hyperactivity disorder following antidepressant exposure during pregnancy: a replication study. Transl Psychiatry 2016;6:e708.
- Croen LA et al., 2020. A network meta-analysis of the effects of psychotherapies, pharmacotherapies and their combination in the treatment of adult depression. World Psychiatry, 19(1), pp.92-107Kimmel, M.C., Cox, E et al 2018. Pharmacologic treatment of perinatal depression. Obstetrics and Gynecology Clinics, 45(3), pp.419-440.
- Huybrechts et al. Antidepressant use in pregnancy and the risk of cardiac defects. N Engl J Med 2014;370(25):2397–407
- Huybrechts et al. Preterm birth and antidepressant medication use during pregnancy: a systematic review and meta-analysis. PLoS One 2014;9(3):e92778.
- Lauren A et al. (2022) Pregnancy outcomes and anxiety in nulliparous women, The Journal of Maternal-Fetal & Neonatal Medicine, 35:25, 8681-8690, DOI: 10.1080/14767058.2021.1998441
- Lebin LG, Novick AM. Selective Serotonin Reuptake Inhibitors (SSRIs) in Pregnancy: An Updated Review on Risks to Mother, Fetus, and Child. Curr Psychiatry Rep. 2022 Nov;24(11):687-695. doi: 10.1007/s11920-022-01372-x. Epub 2022 Oct 1. PMID: 36181572.
- Kieviet N et al. The use of psychotropic medication during pregnancy: how about the newborn? Neuropsychiatr Dis Treat 2013;9: 1257–66
- Nulman et al. Neurodevelopment of children prenatally exposed to selective reuptake inhibitor antidepressants: Toronto sibling study. J Clin Psychiatry 2015;76(7):e842–7.
  Rai D et al. Parental depression, maternal antidepressant use during pregnancy, and the risk of autism spectrum disorders: population based case-control study. BMJ 2013;346:f2059.
  Santucci et al. Impact of prenatal exposure to se-rotonin reuptake inhibitors or maternal major depressive disorder on infant developmental outcomes. J Clin Psychiatry 2014;75(10):1088–95.
- Sujan et al. Associations of maternal antidepressant use during the first trimester of pregnancy with preterm birth, small for gesta-tional age, autism spectrum disorder, and attention-deficit/hyperactivity disorder in offspring. JAMA 2017;317(15):1553–62.
  Wisner et al. Risk-benefit decision making for treatment of depression during pregnancy. Am J Psychiatry 2000;157(12):1933–40.
- Womersley K, et al. What are the risks associated with different Selective Serotonin Re-uptake Inhibitors (SSRIs) to treat depression and anxiety in pregnancy? An evaluation of current evidence. Psychiatr Danub. 2017 Sep;29(Suppl 3):629-644. PMID: 28953843.

The external comment was not accepted as it was considered to be too detailed for the purposes of the STGs; as STGs are not clinical practice guidelines. The Committee noted that some of the dosing titration suggestions are included under different disorders in the STGs. The risk vs benefit comments should ideally be phrased for implementation on how to practice as part of a clinical practice guideline. Additionally, sulpiride would require consideration for inclusion through a full medicine review in an STG, which can be considered for the next review cycle of the mental health chapters.

For these reasons the committee instead recommends and highlights the importance for advocacy for a National Department of Health Mental Health Clinical Programme Guideline to align to the STGs and outline items outside the scope of the STGs.

The pregnany and breastfeeding caution box was not amended, as above but revised with referral to a social worker to explore social and financial support systems for the patient for better socieoecomic support. A reference for SSRI treatment was added to the pregnancy and breastfeeding box.[18]

The STG was updated as follows:

PREGNANCY AND BREASTFEEDING

» SSRI treatment of depression in pregnancy is associated with improved symptoms in the mother and better emotional and psychological development of the child. Benefit is greater with increasing illness severity. Effect of SSRIs on anxiety in pregnancy is less clear.
» Lack of matched case-control studies mean harms of treatment are unclear.
» If stable on an SSRI, do not stop – discuss risk/benefit with mother.
» Index presentations: offer counselling, psychotherapy; discuss risk/benefit of SSRIs.
» Refer social worker to explore social and financial support systems.
» Avoid fluoxetine due to long half-life and relatively high concentration in breastmilk. Consider citalopram as alternative
» All antidepressants: possible increased risk of miscarriage, transient neonatal symptoms (jitteriness, irritability), and persistent pulmonary hypertension of the newborn.
» Avoid benzodiazepines – some association with neurodevelopmental delay in the child; neonatal sedation if used late in pregnancy.

15.3.1 DEPRESSIVE DISORDERS

An external comment to update the reference year for the PHC STGs and EML from 2018 to 2023 for section 16.7: Suicide risk assessment was accepted.

An external recommendation to consider the addition of registered counsellors, in the chapter, as mental health practitioners was accepted as this service is gradually rolling out in the public sector. Counselling and occupational therapy also now included.

An external comment to add vocational rehabilitation under referral was not accepted for the referral section of the STG as the referral section is for next level of care rather than for allied health interventions. The recommendation was instead added under the medicine treatment section of the STG.

The STG was updated as follows:

[18] Sertraline, oral (perinatal anxiety and depression): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Sertraline for Perinatal Anxiety and Depression, March 2020. http://www.health.gov.za/

GENERAL MEASURES

» Maintain an empathic and concerned attitude.
» Discuss uncertainty with a specialist at any point in the care pathway.
» Assess severity of the condition and suicide risk. See PHC STGs and EML, ~~2018~~ section 16.7: Suicide risk assessment.
» Exclude and optimise treatment of underlying and/or comorbid medical conditions (e.g. hypothyroidism, anaemia, HIV/AIDS, TB, cancers, diabetes).
» Screen for and manage underlying or comorbid substance use, e.g. nicotine, alcohol, over the counter analgesics, benzodiazepines.
» Screen for bipolar disorder and comorbid psychiatric disorders – refer for specialist assessment.
» Explore and address psychosocial stressors:
  - Stress management / coping skills – refer to registered counsellors, social worker, ~~for counselling~~ and /or occupational therapy.
  - Relationship and family issues – refer to social worker, registered counsellors, Non-Governmental Organisation (NGO) ~~for~~ counselling, e.g. FAMSA (www.famsa.org.za).
  - If abuse, intimate partner, or other violence is evident, ~~R~~ refer to a social worker ~~if abuse is evident~~.
» Provide self-help literature, where available, and refer to local support groups, e.g. SADAG (www.sadag.org).

MEDICINE TREATMENT

» Offer choice of psychotherapy (if available) or medication.
» Antidepressants take 4–6 weeks to achieve their maximum effect. There is little evidence to support combination medicine treatment.
» Tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitors (SSRIs) are of equal efficacy.
» Electroconvulsive therapy (ECT) (specialist administered) is indicated under specific circumstances, e.g. severe depression, in pregnancy.
» The choice of therapy is guided by comorbid states, risk of overdose, and patient response.
» Refer to occupational therapy if available for vocational rehabilitation.

As discussed under 15.2 anxiety and obsessive-compulsive disorders a detailed external comment received from a group of medical experts to make revisions, with references, in the STG caution box for pregnancy and breastfeeding was not accepted as it is outside the scope of the STG and more in line with a clinical practice guideline.

The pregnancy and breastfeeding caution box was not amended as above but revised with referral to a social worker to explore social and financial support systems for the patient for better socioeconomic support. A reference for SSRI treatment was added to the pregnancy and breastfeeding box.[19]

The STG was updated as follows:

PREGNANCY AND BREASTFEEDING

» SSRI treatment of depression in pregnancy is associated with improved symptoms in the mother and better emotional and psychological development of the child. Benefit is greater with increasing illness severity. Effect of SSRIs in pregnancy on anxiety is less clear.
» Lack of matched case-control studies mean harms of treatment are unclear.
» If stable on an SSRI, do not stop – discuss risk/benefit with mother.
» Index presentations: offer counselling~~,~~ and psychotherapy; discuss risk/benefit of SSRIs.
» Refer social worker to explore social and financial support systems.
» Avoid fluoxetine due to long half-life and relatively high concentration in breastmilk. Consider citalopram as alternative.
» All antidepressants: possible increased risk of miscarriage, transient neonatal symptoms (jitteriness, irritability), and persistent pulmonary hypertension of the newborn.

Avoid benzodiazepines – some association with neurodevelopmental delay in the child; neonatal sedation if used late in pregnancy

15.3.2 BIPOLAR AND RELATED DISORDERS

An external comment to add risk to reputation of patient under bipolar and related disorders was not accepted for the bipolar and related disorders STG because risk to reputation is one aspect of risk to self (along with risk to job, finances, property and relationships), all of which would be better suited to inclusion in a national clinical programme guideline, outside the scope of the STGs. The committee recommended instead to describe risk assessment in detail with reference to a tool for risk assessment; now included in the introduction to the chapter citing and adapting Australian Guidance[20] as there are currently no South African standardised guidance tools available for risk assessment.

[19] Sertraline, oral (perinatal anxiety and depression): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Sertraline for Perinatal Anxiety and Depression, March 2020. http://www.health.gov.za/

[20] Definition (Risk Assessment): New South Wales Government. SESLHDGL/082 Clinical Risk Assessment and Management. 2022/04 Version 7.2

Obesity was added under long-term management for screening and managing co-morbid related illnesses[21].

An external comment to refer to social worker and occupational therapist for placement in a residential home, sheltered employment/protected employment/workshop as needed (noting that occupational therapist's input is equally important because the functional capacity of the patient must be factored in and occupational therapist's scope is vocational rehabilitation) was accepted also including social workers because while the occupational therapists input is needed, the application process is the social workers responsibility.

The STG was amended as follows:

Long-term management

» Individualise management according to course of illness, cognitive functioning, insight and judgement, and social circumstances.
» Assertive nursing with adherence monitoring is required.
» Screen for and manage comorbid medical illness (thyroid disease, HIV/AIDS, cardiovascular and pulmonary disease, epilepsy, diabetes, obesity).
» Screen for and manage substance use.
» Psycho-educate patient, family, and carers on the nature of the illness, need for continued treatment, how to self-monitor, early signs of relapse, and need for structure and routine.
» Refer to support groups e.g. SADAG (www.SADAG.org) or South African Federation For Mental Health (www.SAFMH.org.za).
» Refer to occupational therapy if available for insight, motivation, and vocational rehabilitation.
» Delay important decisions until full recovery from an acute episode; a custodian / curatorship / power of attorney may be required.
» Refer to social worker for placement in a residential home, day care or sheltered employment/workshop as needed.

Editorial updates were made to the STG as follows, including correction of upper level of lithium dose to match suggested algorithm dosing:

- Lithium, oral, usual dose range 200–~~8~~600 mg at night depending on desired blood levels.
  - Pre-treatment: check eGFR, TFTs, calcium, and ECG in patients with cardiovascular risk factors. Proceed if eGFR~~,~~ and ECG are normal and any thyroid or parathyroid disease is treated.
  - ~~Start with~~ Initiate dose: 400 mg (200 mg in elderly or high risk for renal disease).
  - ~~Trough (12 hours after night dose)~~ Measure plasma trough concentration (at least 12 hours after previous dose):
    - First measurement: After 5 days of treatment
    - Then 7 days after each dose change
    - Then at 1 month and 3 months of treatment
  - Document the number of hours since the last dose on the blood request form.
  - ~~level after 5 days, then 7 days after each dose change, then at 1 month and 3 months.~~
  - Lithium has a narrow therapeutic window. The therapeutic reference ranges are ~~is 0.8–1.0 mmol/L in acute mania, 0.6–0.8 mmol/l for prevention of mania and 0.4–0.8 mmol/l for prevention of depressive relapse~~.:
    - Acute mania: 0.8–1.0 mmol/L
    - Prevention of mania: 0.6–0.8 mmol/L
    - Prevention of depressive relapse: 0.4–0.8 mmol/L
  - Monitor lithium level and eGFR 6-monthly (3-monthly in elderly or medical comorbidity); TSH and calcium annually.

An external comment to include referral to a dietitian in the caution box for all patients on lithium was not accepted as the committee felt that it was not necessary in every case and a dietician is included in management of comorbid medical illness included under long term management in the STG.

A heading was added for the indication of quetiapine, and an editorial correction to ensure the titration example for quetiapine matches the maximum dose of quetiapine.

The STG was updated as follows:

[21] Tully A, Smyth S, Conway Y, Geddes J, Devane D, Kelly JP, Jordan F. Interventions for the management of obesity in people with bipolar disorder. Cochrane Database of Systematic Reviews 2020, Issue 7. Art. No.: CD013006. DOI: 10.1002/14651858.CD013006.pub2

If patient has depressive symptoms and lamotrigine is poorly tolerated or not effective:

- Quetiapine, oral, usual dose range 100–300 mg at night (specialist prescribed).
  - Titrate to clinical effect, e.g.: Day 1: 50 mg. Day 2: 100 mg. Day 3: 200 mg. Day 4: ~~300~~400 mg.
  - In the elderly and patients with hepatic impairment: Start with 25 mg and titrate up more slowly according to clinical effect.

Editorial amendments as suggested by a group of external commentators on the use of medicines in pregnancy and breastfeeding were supported for inclusion in the chapter as they provided further clarity.

Monitoring in women in the "reproductive age-group" section and wording was used to include any time during pregnancy and pre-conception. The committee noted as per an external comment that clozapine can be used during pregnancy and if stopped in patients with treatment-resistant schizophrenia can result in a serious relapse with no alternatives available. Therefore, the recommendation that Clozapine is not recommended due to risk of agranulocytosis was removed and reworded to "Do not stop in pregnancy due to risk of relapse of severe mental illness. Breastfeeding not recommended due to possible risk of agranulocytosis in the newborn.[22]

An external comment that all people with bipolar disorder should be managed in conjunction with a specialist was not accepted as delivery in a specialist centre should be addressed in the obstetric guidelines, and needs to be discussed with NDOH maternal and child health programme for feasibility.

An external comment that slow cross-titration, for women already on valproate, especially in the first trimester may increase exposure to the foetus was not accepted for amendment as the word 'rapidly' would need to be defined, and may not be suitable in every case, and the STG now suggests the cross titration to be conducted in consultation with a specialist to also prevent a relapse of symptom. Wording to ensure folic acid supplementation is now included in line with the adult hospital level neurological disorders chapter[23,24].

An external commentator raised that first trimester lithium exposure is associated with increased risk of congenital cardiac anomalies. i.e. Ebstein's anomaly (Downward displacement of the tricuspid valve which can be surgically corrected after birth – 1 in 1000 births) and therefore a Fetal anomaly ultrasound at 18–22 weeks gestation is recommended. The committee acknowledged that first trimester lithium use is associated with increased risk of a range of major malformations compared to women with bipolar disorder not on lithium[25]. Lithium exposure during the first trimester was associated with an increased risk of major malformations (pooled prevalence 7·4% [95% CI 4·0–10·7] vs 4·3% [3·7–4·8]; pooled aOR 1·71, 95% CI 1·07–2·72) but for major cardiac malformations the difference was not significant (2·1% [0·5–3·7] vs 1·6% [1·0–2·1]; pooled aOR 1·54, 95% CI 0·64–3·70)[25]. Therefore, the original wording was retained because although the risk is low this may be overwhelming for patients to hear and they may want to switch therapy which may increase the risk of relapse. The ERC acknowledged pharmacological treatment association with a range of anomalies, and therefore it would not be possible to go into detail in the STGs. The information would be more appropriate for a clinical guideline.

An external commentator also recommended adjustment of dose of lithium with physiological changes of pregnancy with monitoring levels monthly, then weekly after 36 weeks. The external commentator also suggested, with evidence[26], that adjusting dose to maintain lithium levels at the higher end of the therapeutic range to minimise the risk of postpartum psychosis; and that lithium levels must be carefully monitored around the time of delivery and that fluid balance should be monitored and maintained during delivery. The committee did not accept the comment regarding levels at which lithium should be maintained as this is likely to be variable depending on the predominant course of illness (algorithms provided in the chapter), access to monitoring, and medical comorbid ities. The evidence[26] provided by the external commentator is a narrative review, with no methodology and no clear analysis to recommend

22 Beex-Oosterhuis MM, Van Gool AR, Heerdink ER, van Kesteren C, van Marum RJ. Clozapine Treatment During Pregnancy and the Postpartum Period: A Systematic Literature Review. J Clin Psychiatry. 2021 Dec 14;83(1):21r13952. doi: 10.4088/JCP.21r13952. PMID: 34905664.

23 Adults: National Department of Health: Essential Drugs Programme. Adult Hospital level STGs and EML.

24 Folic acid, oral (supplementation in pregnant women on valproic acid): South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022

25 Munk-Olsen T, Liu X, Viktorin A, Brown HK, Di Florio A, D'Onofrio BM, Gomes T, Howard LM, Khalifeh H, Krohn H, Larsson H, Lichtenstein P, Taylor CL, Van Kamp I, Wesseloo R, Meltzer-Brody S, Vigod SN, Bergink V. Maternal and infant outcomes associated with lithium use in pregnancy: an international collaborative meta-analysis of six cohort studies. Lancet Psychiatry. 2018 Aug;5(8):644-652. https://www.ncbi.nlm.nih.gov/pubmed/29929874

26 Poels EMP, Bijma HH, Galbally M, Bergink V. Lithium during pregnancy and after delivery: a review. Int J Bipolar Disord. 2018 Dec 2;6(1):26. doi: 10.1186/s40345-018-0135-7. PMID: 30506447; PMCID: PMC6274637.

specific lithium levels in pregnancy. The external comment to monitor fluid balance around delivery was accepted and added.

The link to the South African Health Products Regulatory Authority (SAHPRA) valproate assessment of risk form was checked and updated and risk estimates of adverse effects for valproate included[27].

The STG was updated as follows:

PREGNANCY AND BREASTFEEDING

Valproate:

» Contraindicated in women of childbearing potential due to high teratogenic risk (10%) and adverse neurodevelopmental outcomes (40%) with any pregnancy exposure. If no alternative, ~~the~~ acknowledgment of risk ~~form~~ must be signed
» If already on valproate: consult specialist and cross-titrate to an alternative medication if possible ~~(consult specialist if required).~~ Ensure folic acid supplementation. (See PHC STGs and EML, section 16.6: Psychiatric patients – General monitoring and care).
» ~~Not recommended/Avoid~~ valproate in breastfeeding as there is insufficient evidence to be sure of safety and it may be associated with adverse
neurodevelopmental outcomes.

Lithium:

» 1st trimester exposure is associated with increased risk of congenital anomalies.
» Refer for a fetal anomaly ultrasound at 18–22 weeks gestation.
» Adjust dose with physiological changes of pregnancy according to blood levels: monitor levels monthly, then weekly after 36 weeks and postpartum.
» Monitor fluid balance during and after delivery.
» Neonatal complications: goitre, nephrogenic diabetes insipidus, cardiac arrhythmias, cardiac failure, hypotonia, and lethargy.
» Excreted in breast milk, risk to the infant is unknown but toxicity may occur:
breastfeeding is not recommended.

Lamotrigine: Increased hepatic clearance in pregnancy, but returns to normal post-partum; increase dose if necessary, according to clinical response and Figure 15.4 below. May cause a rash in breastfed infant.

Antipsychotics:

» Considered safest, particularly quetiapine. They may lincreased the risk of gestational diabetes and obesity (highestrisk with especially olanzapine, and clozapine).
Clozapine: ~~d~~ Do not stop in pregnancy due to risk of relapse of severe mental illness. Breastfeeding not recommended due to possible risk of agranulocytosis in the newborn. ~~Clozapine is not recommended due to risk of agranulocytosis.~~

Benzodiazepines: Avoid in pregnancy.
Use only very short-term for severe distress

Specialist prescribing for olanzapine and quetiapine were removed from the STG to allow continued prescribing by doctors at lower levels of care. Editorial edits were made to the following two algorithms.

[27] Valproic acid – caution in pregnancy: European Medicines Agency - Pharmacovigilance Risk Assessment Committee. Assessment report EMA/198940/2018 - valproate exposure in pregnancy, 8 February 2018. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Valproate_2017_31/Position_provided_by_CMDh/WC500250221.pdf.
Valproic acid – caution in pregnancy: Meador K, Reynolds MW, Crean S, Fahrbach K, Probst C. Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. Epilepsy Res. 2008 Sep;81(1):1-13. https://www.ncbi.nlm.nih.gov/pubmed/18565732.

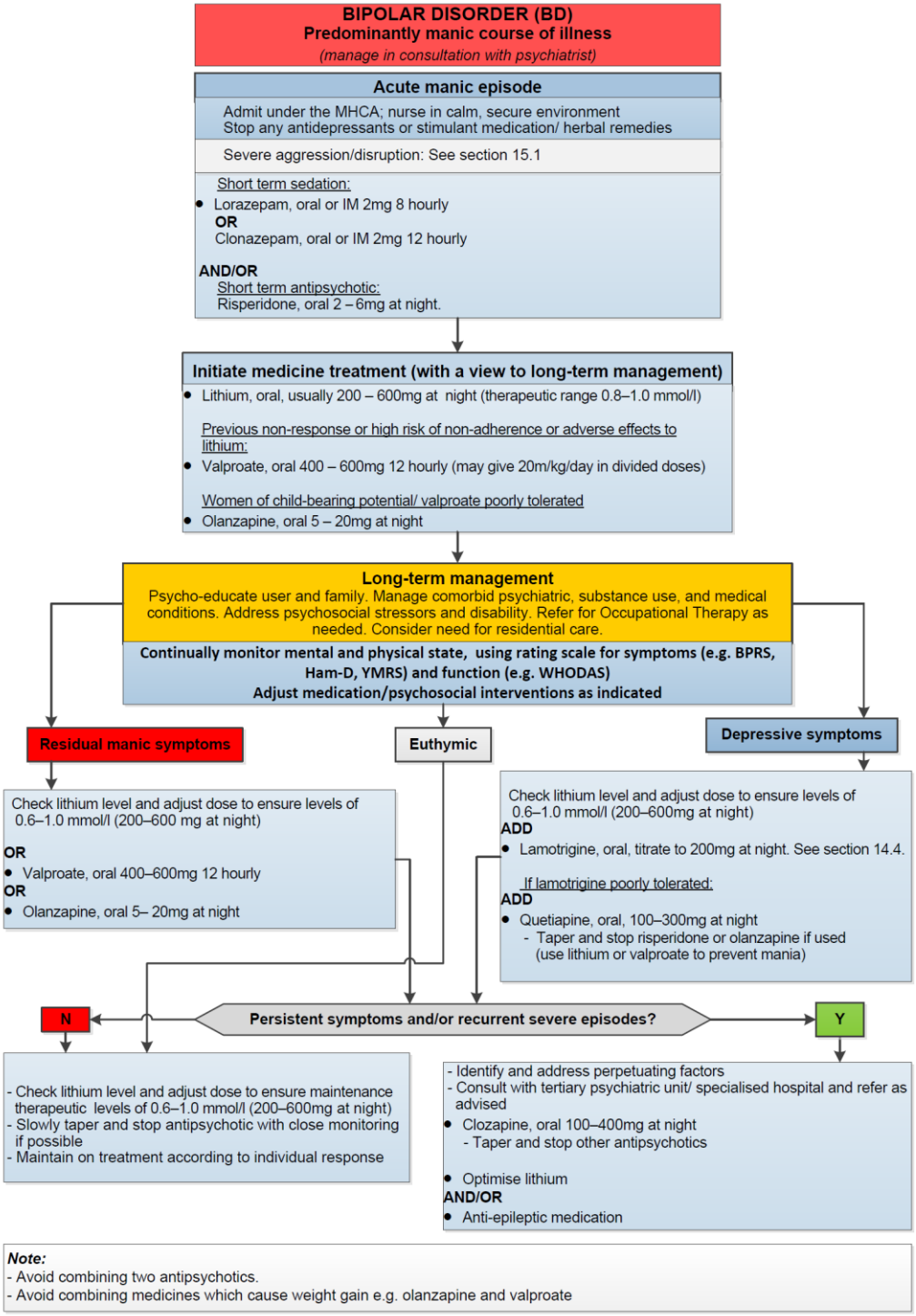


Figure 15.3: Algorithm for the management of bipolar disorder with predominantly manic course of illness

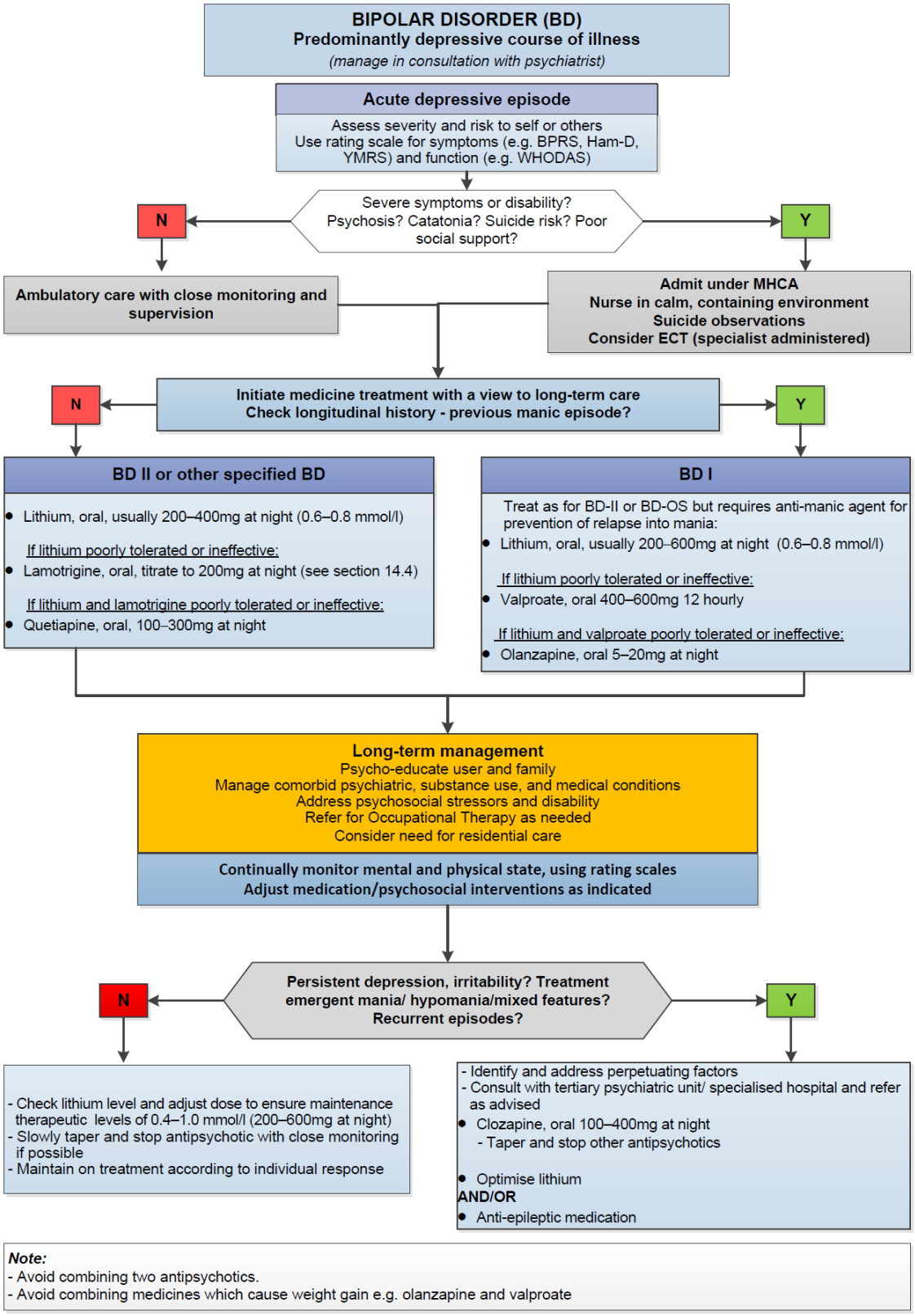


Figure 15.4: Algorithm for the management of bipolar disorder with predominantly depressive course of illness

Clarification of ≥4 episodes, for rapid cycling, was provided as per DSM-V definition for a referral.

The STG was updated as follows:

REFERRAL

All patients to be managed in consultation with a psychiatrist and to refer as advised~~,~~ and to particularly if:

» High risk to self or others at any time.
» Rapid cycling (≥4 ~~repeated~~ episodes despite treatment).
» Poor response to treatment with persistent depressive, manic, or mixed symptoms.

15.4 TRAUMA AND STRESS-RELATED DISORDERS

An external comment to delete the sentence "Child abuse and trauma histories (including traumatic birth experience) and trauma experiences within pregnancy are associated with gestational and postnatal PTSD" was accepted as the information is repeated in the caution box for pregnancy and breastfeeding which was added to the STG (see below).

DESCRIPTION

Acute stress and post-traumatic stress disorder arise in response to stressful events. The patient should have experienced the event as life threatening or as a physical threat to themselves or others, at which time they felt fear and helplessness.

A range of symptoms are associated with both of these conditions and include:

» re-experiencing of the event, e.g. flashbacks, dreams.
» avoidance of situations associated with the event.
» features of anxiety or increased arousal, e.g. hypervigilance, heightened startle response, and insomnia.

The conditions are symptomatically similar but differ with regard to the duration and time of onset of symptoms. The symptoms of acute stress disorder arise within 4 weeks of the event and last up to 4 weeks, whereas the symptoms of post-traumatic stress disorder last longer than 4 weeks~~,~~ and may arise more than 4 weeks after the traumatic incident.

~~Child abuse and trauma histories (including traumatic birth experience) and trauma experiences within pregnancy are associated with gestational and postnatal PTSD.~~

Under general measures an external commentator recommended adding "*If the crisis is still ongoing currently, provide emotional containment and counselling on how to manage the crisis. This may include referral to access police, social work and/or legal services. If the crisis is very recent, provide emotional containment, as well as normalization of and psycho-education on symptoms and their management, e.g., advise on the importance of engaging with thought and feelings towards making sense and feeling safer again.* The Committee recommended that referral to a social worker or registered counsellor for emotional containment and stress management for ongoing /recent crisis be added. The detail suggested for the content of counselling was considered to be outside the scope of the STGs and was not included.

The STG was updated as follows:

GENERAL MEASURES

Provide ~~R~~ reassurance and support of patient and family.
Assess risk to patient's safety: refer to police, social welfare and/or legal services as needed to ensure immediate safety.
If patient has an ongoing/recent crisis: refer to social worker or registered counsellor for emotional containment and stress management.
Psychotherapy, usually of a supportive / cognitive-behavioural nature.
Trauma debriefing is not routinely recommended.

For the post-traumatic stress-disorder (PTSD) subsection an external commentator suggested that complex PTSD be mentioned given the severity and chronicity of trauma experiences in South Africa. The committee noted that there

is no evidence-based treatment available for complex PTSD and any addition would only be descriptive; and therefore would be more appropriate for a clinical programme guideline. Additionally, the STG includes ICD 10 codes and inclusion of complex PTSD can be considered when ICD 11 is operationalized.

For PTSD, very low dose antipsychotics for symptom attenuation in severe cases was raised for inclusion by an external commentator, with no supporting evidence. The Committee acknowledged that a full evidence-based motivation for addition of very low dose antipsychotics to the EML for the indication of symptom attenuation in severe PTSD cases would require a full evidence-based medicine review and motivation and should be considered in the next review cycle.

A caution box was added with supporting evidence[28,29,30,31] to the STG as suggested by an external commentator to reiterate PTSD in pregnancy, and align to the box on pregnancy and breastfeeding on SRRIs in section 15.3.1 depressive disorders. Prevalence of PTSD as suggested by the commentator was not added because the Committee considered it to be outside the scope of the STGs, with limited references for South Africa.

The STG was updated as follows:

PREGNANCY AND BREASTFEEDING

» Perinatal PTSD is associated with low birth weight babies and poor mother-baby interactions.
» Experiences in pregnancy and childbirth may be traumatic and exacerbate existing PTSD or trigger new onset PTSD.
» Women with a history of childhood adversity, sexual abuse, or other previous trauma are at risk of perinatal PTSD.
» Treatment of PTSD in pregnancy is the same as for non-pregnant women.
» Avoid fluoxetine due to long half-life and relatively high concentration in breastmilk. Consider citalopram as alternative.
» All antidepressants: possible increased risk of miscarriage, transient neonatal symptoms (jitteriness, irritability), and persistent pulmonary hypertension of the newborn. Assess and discuss risk/benefit profile with patient.
» Avoid benzodiazepines – some association with neurodevelopmental delay in the child; neonatal sedation if used late in pregnancy.

15.5 PSYCHOTIC DISORDERS

An external comment was received to add aggressive behaviour and self-harm or harm to others as part of the list of presentation of psychosis under the description section of the STG. The committee raised that the current list refers to defining features of psychosis where aggressive/ high risk behaviour is non-specific. Therefore, aggressive behaviour was included under description but not as part of the list of defining features of psychosis.

The STG was updated as follows:

DESCRIPTION

Psychosis is characterised by a loss of contact with reality. Psychotic disorders may present with:

» Delusions: Fixed beliefs which may manifest as disturbed speech content with persecutory, referential, grandiose, religiose, erotic, or bizarre themes
» Hallucinations: Perceptual disturbances, e.g. auditory hallucinations, which are heard as voices distinct from the patients' thoughts.
» Disorganised thinking: Manifests as disordered flow of speech which impairs communication.
» Grossly disorganised or abnormal motor behaviour (including catatonia).
» Negative symptoms: reduced emotional expression, avolition, lack of speech, anhedonia, lack of social interaction.

Psychotic symptoms may occur in other psychiatric conditions (e.g. bipolar mania, major depression), medical conditions (e.g. certain types of epilepsy), or substance use (intoxication or withdrawal).

Psychosis is often accompanied by a lack of insight into the symptoms ~~and~~ poor judgement, and aggressive behaviour. The risk to self and others must always be assessed. It may be necessary to treat as an Assisted or Involuntary User under the MHCA.

28 Pregnancy and breast feeding: Cook N, Ayers S, Horsch A. Maternal posttraumatic stress disorder during the perinatal period and child outcomes: A systematic review. J Affect Disord. 2018 Jan 1;225:18-31. doi:10.1016/j.jad.2017.07.045. Epub 2017 Jul 27. PMID: 28777972.
29 Pregnancy and breast feeding: Laifer LM, O'Hara MW, DiLillo D, Brock RL. Risk for trauma-related distress following difficult childbirth: Trajectories of traumatic intrusions across 2 years postpartum. Arch Womens Ment Health. 2023 Apr;26(2):191-200. doi: 10.1007/s00737-023-01296-2. Epub 2023 Jan 31. PMID: 36719513; PMCID: PMC10083078.
30 Pregnancy and breast feeding: Dozio E, Feldman M, Bizouerne C, Drain E, Laroche Joubert M, Mansouri M, Moro MR, Ouss L. The Transgenerational Transmission of Trauma: The Effects of Maternal PTSD in Mother-Infant Interactions. Front Psychiatry. 2020 Nov 30;11:480690. doi: 10.3389/fpsyt.2020.480690. PMID: 33329072; PMCID: PMC7733963.
31 Pregnancy and breast feeding: Cirino NH, Knapp JM. Perinatal Posttraumatic Stress Disorder: A Review of Risk Factors, Diagnosis, and Treatment. Obstet Gynecol Surv. 2019 Jun;74(6):369-376. doi: 10.1097/OGX.0000000000000680. PMID: 31216046.

15.5.1 ACUTE AND TRANSIENT PSYCHOTIC DISORDERS

An external comment to add referral to occupational therapist was not accepted as the evidence for occupational therapy in acute and transient psychotic disorders is not clear and the committee expressed concern for burdening services if not indicated. Referral to an occupational therapist is now included for schizophrenia spectrum disorders (see 15.5.2 schizophrenia spectrum disorders below).

15.5.2 SCHIZOPHRENIA SPECTRUM DISORDERS

An external comment to add referral to occupational therapist was not accepted for acute and transient psychotic disorders (see 15.5.1 acute and transient psychotic disorders above) as the evidence for occupational therapy in acute and transient psychotic disorders is not clear and the committee expressed concern for burdening services if not indicated. Referral to an occupational therapist was instead included for schizophrenia spectrum disorders.

The STG was updated as follows:

Maintenance treatment

» Provide antipsychotic maintenance treatment to prevent relapse.
» Community-based nursing with adherence support, repeated risk assessment, and shared decision-making is required.
» Refer to occupational therapy for functional rehabilitation.
» Monitor psychiatric symptoms (use rating scales, e.g. BPRS or PANSS)
» Monitor extra-pyramidal side effects, weight, blood pressure, and glucose every 6 months.
» Monitor extra-pyramidal side effects, weight, BP and glucose 6-monthly
» Adjust treatment according to response, adverse effects, and comorbidity.
» Provide lifestyle and dietary education; encourage exercise
» Treat comorbid mood disorders (section 15.3: Mood disorders)
» Treat comorbid hypertension (section 3.6: Hypertension), diabetes mellitus (section 8.5: Diabetes mellitus), and other medical conditions as needed
» Manage substance use – refer for rehab (South African National Council on Alcoholism and Drug Dependence [SANCA], Social Development)
» Poor adherence with recurrent episodes:
  - Check reasons – illness, medication, patient factors.
  - Poor response/ tolerability to medication – change to alternative antipsychotic.
  - Poor insight - try depot antipsychotic – start with test dose (half initial dose in algorithm below).
  - Address psychosocial factors, substance use.
» Refer to social worker for placement in a residential home, day care or sheltered employment/workshop as needed.

Monitoring in women in reproductive age-group was updated in line with the caution in pregnancy and breastfeeding section 15.3.2 bipolar and related disorders section. The committee noted as per an external comment that clozapine can be used during pregnancy[32] and if stopped in patients with treatment-resistant schizophrenia can result in a serious relapse with no alternatives available.

The STG was updated as follows:

Women ~~in reproductive age-group~~ of childbearing potential: (See PHC STGs and EML, section 6.9: Maternal mental health).

» Advise family planning – psycho-educate regarding need to plan pregnancy and comply with antenatal care.
» If patient is a parent/guardian– support childcare; refer to social worker if impaired.
» Risk of psychotic relapse is high in pregnancy and postpartum including the first year post-delivery.

In pregnancy: ~~C~~continue antipsychotic treatment.; Monitor closely for weight gain, gestational diabetes, psychotic relapse, substance use. ~~All are considered safe except clozapine – only use if benefit outweighs risk.~~

32 Beex-Oosterhuis MM, Van Gool AR, Heerdink ER, van Kesteren C, van Marum RJ. Clozapine Treatment During Pregnancy and the Postpartum Period: A Systematic Literature Review. J Clin Psychiatry. 2021 Dec 14;83(1):21r13952. doi: 10.4088/JCP.21r13952. PMID: 34905664.

Medicine Treatment

An editorial change was made to the STG replacing HIV positive with PLHIV.

MEDICINE TREATMENT

Acute psychotic episode

» Treat severe aggression and disturbed behaviour (See section 15.1: Aggressive disruptive behaviour in adults).
» Initiate treatment with a view to long-term management.
» Assess risk factors for the development of tardive dyskinesia: (age >50 years, female sex, prominent mood symptoms, cognitive or neurological disturbance e.g. intellectual disability, autistic spectrum, ~~HIV positive~~ People living with HIV (PLHIV).):
» In patients with high risk of tardive dyskinesia: avoid haloperidol and antiparkinsonian medicines~~;~~. ~~u~~Use chlorpromazine, risperidone or olanzapine at lowest doses ~~possible~~ needed to achieve desired effect.

Haloperidol, Oral[33]: *Retained, with dosage range adjustment*
Depot antipsychotic, IM (e.g Flupenthixol decanoate OR Zuclopenthixol decanoate)[34]: *Retained (With downward adjustment of lower dose of zuclopenthixol to be equivalent to the lower dose of flupenthixol)*
Risperidone, Oral[35,36]: *Retained*

Haloperidol IM was not available in South Africa. Oral haloperidol as a, 1.5mg scored tablet, is available locally. However, the 0.5mg haloperidol capsule is being discontinued in South Africa[37]. The recommendation to initiate treatment, in an acute psychotic episode, with oral haloperidol was retained, but with the lower and upper end of the dosage range adjusted to accommodate available strength and formulation.

Chlorpromazine, Oral[38]: *Retained* (with maximum doses and guidance on divided doses provided)
Olanzapine, Oral,[39,40,41,42,43]: *Retained (as doctor prescribed and not specialist initiated)*
Clozapine, Oral[44,45,46]: *Retained*

Refer to the medicine review 'Olanzapine, oral for schizophrenia-Adult review_13June2019':

Olanzapine^J oral for schizophrenia-Adult r

33 Haloperidol: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.
34 Flupenthixol decanoate, IM & Zuclopenthixol decanoate, IM: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 202216.
35 Risperidone, oral::Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet. 2009 Jan 3;373(9657):31-41. http://www.ncbi.nlm.nih.gov/pubmed/19058842
36 Risperidone, oral: Crespo-Facorro B, Pérez-Iglesias R, Mata I, Ramirez-Bonilla M, Martínez-Garcia O, Pardo-Garcia G, Caseiro O, Pelayo-Terán JM, Vázquez-Barquero JL. Effectiveness of haloperidol, risperidone and olanzapine in the treatment of first-episode non-affective psychosis: results of a randomized, flexible-dose, open-label 1-year follow-up comparison. J Psychopharmacol.2011 Jun;25(6):744-54. http://www.ncbi.nlm.nih.gov/pubmed/21292922
37 Correspondence: Pfizer Pharmaceuticals: Re: Discontinuation of SERENACE 0,5mg Capsules
38 Chlorpromazine, oral: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.
39 Olanzapine, oral: Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, Samara M, Barbui C, Engel RR, Geddes JR, Kissling W, Stapf MP, Lässig B, Salanti G, Davis JM. Comparative efficacy and tolerability of antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet. 2013 Sep 14;382(9896):951-62. https://www.ncbi.nlm.nih.gov/pubmed/23810019
40 Olanzapine, oral: Krause M, Zhu Y, Huhn M, Schneider-Thoma J, Bighelli I, Nikolakopoulou A, Leucht S. Antipsychotic drugs for patients with schizophrenia and predominant or prominent negative symptoms: a systematic review and meta-analysis. Eur Arch Psychiatry Clin Neurosci. 2018 Oct;268(7):625-639. https://www.ncbi.nlm.nih.gov/pubmed/29368205
41 Olanzapine, oral: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Olanzapine, oral for schizophrenia and related disorders, June 2019. http://www.health.gov.za/
42 Orphenadrine, oral: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.
43 Olanzapine, oral: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Olanzapine, oral for schizophrenia and related disorders, June 2019. http://www.health.gov.za/
44 FDA Drug Safety Communication: FDA modifies monitoring for neutropenia associated with schizophrenia medicine clozapine, 2015. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-modifies-monitoring-neutropenia-associated-schizophrenia-medicine
45 Clozapine, oral (caution): Taylor, David; Paton, Carol; Kapur, Shitij. The Maudsley Prescribing Guidelines, Twelfth Edition. London: CRC Press; 2015.
46 Clozapine, oral (caution): South African Medicines Formulary. 142th Edition. Division of Clinical Pharmacology. University of Cape Town. 202216.

Recommendation

Based on the evidence review, the Adult Hospital Level Committee recommends that olanzapine be used as 2nd or 3rd line treatment according to clinical judgement following haloperidol, risperidone and /or chlorpromazine in patients with schizophrenia, prior to consideration of clozapine (for treatment resistance in general) or amisulpiride (for treatment resistant negative symptoms).

Rationale: Evidence suggests that olanzapine is more efficacious than haloperidol and chlorpromazine; and more efficacious than risperidone in select patients. Choice of treatment is also dependant on adverse effects – extra-pyramidal effects greater with haloperidol; metabolic risk associated with clozapine and olanzapine and clozapine has the additional risk of agranulocytosis, and may convey a higher risk of seizures. **Level of Evidence: II, network meta-analysis and systematic reviews of RCTs of low-moderate quality.**

NEMLC MEETING OF 11 JULY 2019:

NEMLC accepted the proposal as recommended by the Adult Hospital Level Committee (see above).

Olanzapine, oral, revised to doctor initiated prescription rather than specialist-initiated prescription, with proposal for eventual removal of chlorpromazine from the treatment algorithm.

Refer to evidence summary:

Chlorpromazine in Schiz_PHC-Adults_Rev

While no direct comparisons between olanzapine and chlorpromazine were found, a good quality network meta-analysis by Leucht et al., 2013,[47] found that, vs placebo:

- olanzapine ranked higher in efficacy than chlorpromazine, measured as a reduction of the PANSS score (SMD -0.59, 95% CI -0.65 to -0.53 for olanzapine vs SMD -0.38, 95% CI -0.54 to -0.23 for chlorpromazine)
- olanzapine appears to have better or similar acceptability and tolerability than chlorpromazine"
    - discontinuation of medicine occurred less with olanzapine than with chlorpromazine
    - weight gain was similar for both medications, as was increased prolactin
    - extra-pyramidal side effects occurred with chlorpromazine but not with olanzapine
    - sedation may be more with chlorpromazine than with olanzapine

At October 2022 tender prices,[48] olanzapine is considerably cheaper than chlorpromazine at equivalent doses:

Medicine Pack	Price	Standard dose	Cost per month
Chlorpromazine; 100mg; Tablet; 56 Tablets	R78.90	300mg per day	R118.35
Olanzapine; 10mg; Tablet; 28 Tablets	R22.43	10mg at night	R22.43

Conclusion

There is no cost, efficacy, or tolerability advantage of chlorpromazine in the treatment of schizophrenia if olanzapine is widely available.

Proposal

To alter prescribing level of olanzapine in schizophrenia to doctor initiated and to remove chlorpromazine from the treatment algorithm. However, chlorpromazine to remain on national tender to allow for supply adjustment of olanzapine.

Level of Evidence: Moderate Certainty Evidence: Meta-Analysis: IIb

The STG was revised as follows:

[47] Leucht S, Cipriani A, Spineli L, Mavridis D, Örey D, Richter F, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: A multiple-treatments meta-analysis. Lancet. 2013;382(9896):951–62. DOI:10.1016/S0140-6736(13)60733-3

[48] NDOH Tenders, available from https://www.health.gov.za/tenders/ (accessed 23 October 2022)

Initiate treatment:

- Haloperidol, oral, 0.75–1.5 mg daily.
    - Increase to 5 mg daily if initial treatment tolerated and according to clinical response.

If good response/tolerability to haloperidol, or patient preference:

- Depot antipsychotic, e.g:
- Flupenthixol decanoate, IM, 10–40 mg every 4 weeks.
    - Initial dose: 10mg

OR

Zuclopenthixol decanoate, IM, ~~2~~100–400 mg every 4 weeks.

- Initial dose: 100mg

If poor response/ poorly tolerated/ high risk of tardive dyskinesia/ extra-pyramidal side effects:

- Risperidone, oral
    - Initial dose: 2–4 mg at night.
    - ~~Maximum dose: 6 mg daily.~~
    - Assess efficacy after 4–6 weeks:
        - If a partial response is noted, ~~optimise~~ increase the dosage.
        - If no response is noted, switch treatment.
    - Maximum dose: 6 mg daily.

OR

- Chlorpromazine, oral, 75–300 mg daily at night, but may be increased to 800mg a day in 2–3 divided doses according to clinical response.

If poor response/tolerability to haloperidol and risperidone, ~~or~~ and chlorpromazine:

- Olanzapine, oral ~~(specialist initiated).~~
    - Initial dose: 5 mg at night, increase to 10 mg at night.
    - Maximum dose: 20 mg at night.

If poor response/ tolerability to olanzapine:

- Clozapine, oral (specialist initiated, preferably as inpatient):
    - Initial dose: 12.5–25 mg at night.
    - Usual dose: 200–450 mg per day in 2 divided doses.
    - Maximum dose: 900 mg/day in in 2 divided doses.

An external comment to include under neuroleptic malignant syndrome a specific section for pregnancy and breast feeding and the need to continue antipsychotics was accepted but not included under neuroleptic malignant syndrome but under 'women in the reproductive age group' for this STG as described above.

15.6 INSOMNIA

If medication is needed to treat the insomnia:

Short-acting benzodiazepines, e.g.Oxazepam: *Retained (*with adjustment to starting dose of Oxazepam)

The starting dose of oxazepam was lowered to 7.5mg from 15mg. SAMF recommends starting at 5 mg. Since only a 15mg and 30mg scored oxazepam tablet is available on tender, 15mg was offered as a starting dose. It was confirmed that the tablets are scored. Therefore, for ease of dosing the starting dose was adjusted down to 7.5mg.

The STG was updated as follows:

If medication is needed to treat the insomnia:
- Short-acting benzodiazepines, e.g.:
- Oxazepam, oral ~~15~~ 7.5–30 mg at night.

Short-term use of benzodiazepines of 14 days is recommended, as long-term use is often associated with dependence

15.8. SUBSTANCE USE DISORDERS

An external comment for substance use disorders to refer family and/or partners of substance users also for support and counselling (e.g. support groups like Al-Anon) was accepted. The committee agreed that management of substance use disorders can be improved and recurrent relapse reduced, by improving support of substance user and reducing enabling behavior. A link to Al-anon has been added under the referral section of the STG.

An editorial revision was made to the STG numbering; now updated to section 15.8. Substance Use Disorders.

The STG was updated as follows:

REFERRAL
» All patients treated for substance withdrawal should be referred to Social Services and/or a rehabilitation service for management of their substance use and aftercare.
» Discuss those with comorbid severe mental disorders ~~services~~ with a psychiatrist; refer to specialist dual diagnosis services where available.
» Family and/or partners of people who use substances to registered counsellors and support groups (e.g., Al-anon family groups, https://www.alanon.org.za/)

15.8.1 ALCOHOL WITHDRAWAL

An editorial revision was made to the STG numbering; now updated to section 15.8.1 Alcohol Withdrawal.

15.8.1.1 ALCOHOL WITHDRAWAL DELIRIUM (DELIRIUM TREMENS)

An editorial revision was made to the STG numbering; now updated to section 15.8.1.1 Alcohol Withdrawal Delirium (Delirium tremens).

The following editorial revision was made to the STG.

GENERAL MEASURES
» See section 20.8: Delirium ~~with perceptual disturbances~~ for non-pharmacological management.

Benzodiazepines, IV (e.g.: Diazepam): *Retained*

Where intravenous access is not possible:
Clonazepam, IM: *Retained*
Lorazepam, IM: *Retained*

Once patient is sedated, i.e., light somnolence, maintain mild sedation with:
Diazepam, Oral: *Retained*

When administering glucose-containing fluids:
Thiamine, Oral/IM: *Retained*

Severe agitation and restlessness persisting after adequate doses of benzodiazepines:
Haloperidol, IM/IV: *Deleted*

Haloperidol IM is included in the therapeutic interchange database for this indication.

Management of hallucinations and agitation:
Haloperidol, Oral: *Added*
Olanzapine, IM: *Not added*

A slow flow rate for IV diazepam administration is now provided, with clarification on number of doses and maximum dose[49].

Olanzapine, IM should not be used in the management of alcohol withdrawal as it may increase risk of respiratory depression if combined with parenteral benzodiazepines. This is of particular concern if alcohol has been consumed.[50] Therefore, Olanzapine, IM not added to the STG.

The STG was updated as follows:

MEDICINE TREATMENT
Administer medicine doses according to severity of symptoms. These patients may require high doses of benzodiazepines because of hepatic enzyme induction.

- Benzodiazepines, e.g.:
  - Diazepam, slow IV (max rate <5 mg/minute), 10 mg (Not IM).
  - Repeat dose after 5–10 minutes if required.
  - If this dose is not sufficient, use 10 mg every 5–10 minutes for another 1–3 doses to a maximum of 50mg.

Where intravenous access is not possible:
- Clonazepam, IM, 2 mg as a single dose.
  - If no response, repeat dose after 60 minutes until patient is sedated.
  - Repeat dose regularly to maintain mild sedation.

OR
- Lorazepam, IM, 1–4 mg every 30–60 minutes until patient is sedated.
  - Repeat dose regularly to maintain mild sedation.

Once patient is sedated, i.e. light somnolence, maintain mild sedation with:
- Diazepam, oral, 5–20 mg.
  - Repeat dose regularly to maintain mild sedation.

CAUTION

Benzodiazepines, especially diazepam IV, can cause respiratory depression.
Monitor patients closely as benzodiazepines can exacerbate an abnormal mental state or mask important neurological signs of deterioration.

Note:
» Lorazepam IM has slower onset of sedation than midazolam IM (32 vs 18 minutes) and longer duration of sedation (217 vs 82 minutes).
» Clonazepam oral or IM may be used if longer duration of sedation is required. Onset of action may be 30-60 minutes, time to maximum concentration is 1-4 hours. Long half-life (18-50 hours) increases risk of accumulation. Allow at least 12 hours between repeat doses.

~~See the note regarding benzodiazepines in section 15.2: Confusional states/delirium.~~

[49] South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[50] Taylor DM, Barnes TRE, Young AH. The Maudsley Prescribing Guidelines in Psychiatry. 13th ed: WILEY Blackwell; 2018.

When administering glucose-containing fluids:
Thiamine, oral/IM, 300 mg daily.

NOTE:

» Neuroleptic medicines such as haloperidol, are associated with a reduced seizure threshold and QTc prolongation. ~~Consider only for severe agitation and restlessness persisting after adequate doses of benzodiazepines~~**.**

» It is preferable to increase the dose of benzodiazepines than to add haloperidol.

However, oral haloperidol may assist with managing hallucinations and agitation:
~~Haloperidol, IV/IM, 0.5–5 mg.~~

- ~~Repeat after 4–8 hours as required to a maximum of 20 mg daily.~~

~~Once patient has responded and is able to take oral medication:~~
Haloperidol, oral, 0.75–2.5 mg 12 hourly

- Maximum dose: 5mg per 24 hours

Do NOT use olanzapine, IM in the management of alcohol withdrawal. Olanzapine, IM may increase risk of respiratory depression if combined with parenteral benzodiazepines particularly if alcohol has been consumed.

15.8.2 OPIATE (E.G. HEROIN, UNGA, WHOONGA, NYAOPE) WITHDRAWAL

An editorial revision was made to the STG numbering; now updated to section 15.8.2 Opiate (E.G. Heroin, Unga, Whoonga, Nyaope) Withdrawal.

For headaches:
Paracetamol[51]: *Retained* (*Dose range amended and maximum dose reiterated and aligned to AHL Chapter 25: Pain)*

15.8.3 STIMULANT WITHDRAWAL, INCLUDING COCAINE AND AMPHETAMINE TYPE STIMULANTS (E.G. METHAMPHETAMINE/ TIK, METHCATHINONE/CAT)

An editorial revision was made to the STG numbering; now updated to section 15.8.3 Stimulant Withdrawal, Including Cocaine And Amphetamine Type Stimulants (E.G. Methamphetamine/ TIK, Methcathinone/CAT).

15.8.4 METHAQUALONE (MANDRAX/WHITEPIPE) WITHDRAWAL

An editorial revision was made to the STG numbering; now updated to section 15.8.4 Methaqualone (Mandrax/Whitepipe) Withdrawal.

15.8.5 CANNABIS WITHDRAWAL

An editorial revision was made to the STG numbering; now updated to section 15.8.5 Cannabis Withdrawal.

15.8.6 BENZODIAZEPINE WITHDRAWAL

An editorial revision was made to the STG numbering; now updated to section 15.8.6 Benzodiazepine Withdrawal.

Clarification now provided on dose reduction of diazepam-equivalent benzodiazepines and how to adjust diazepam dosing if symptoms reappear.

[51] South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

The STG was updated as follows:

Table 15.1: Dose reduction of diazepam-equivalent benzodiazepines

Daily diazepam-equivalent doses used	**Dose reduction recommendation**
≥ 50 mg/day	Reduce daily dose every 1–2 weeks by 10 mg/day until a daily dose of 50 mg is reached.
30-50 mg/day	Reduce every 1–2 weeks by 5 mg/day until a daily dose of 30 mg is reached.
20-29 mg/day	Reduce every 1–2 weeks by 2.5 mg/day until a daily dose of 20 mg is reached.
< 20 mg/day	Reduce every 1–2 weeks by 1.25 mg/day until stopped.

Note:

- If symptoms reappear, increase the dose by 2.5 or 5mg a day and then reduce dose using 2–4 week intervals.
- Do not prescribe more than one week's duration of medication at a time.

South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Mental Health

EVIDENCE SUMMARY

Date: 27 October 2022
Reviewers: Prof L Robertson
Affiliation: Sedibeng District Health Services and Department of Psychiatry, University of the Witwatersrand

QUESTION: Use of olanzapine, oral, as a doctor initiated prescription rather than specialist initiated prescription, and eventual removal of chlorpromazine in the treatment algorithm.

Background
Olanzapine, oral is currently in the treatment algorithm for schizophrenia for poor response or tolerability to haloperidol, risperidone, and/or chlorpromazine. Its use requires specialist initiation, whereas haloperidol, risperidone, and chlorpromazine may be initiated by medical officers.

However, at tender prices, olanzapine costs less than chlorpromazine. In addition, chlorpromazine may not offer any advantage in terms of efficacy or tolerability.

Introduction
As detailed in the current treatment algorithm for schizophrenia below, olanzapine, oral requires specialist initiation. The rationale for this requirement is unclear. Olanzapine may have greater efficacy than chlorpromazine, is no less tolerable, and is cheaper at October 2022 tender prices. However, many practitioners in South Africa are more familiar with chlorpromazine than olanzapine, and supply of chlorpromazine may be more reliable in South Africa and neighbouring countries.

15.5.2 SCHIZOPHRENIA SPECTRUM DISORDERS

F20-F20.9; F22.0-22.9; F25.0-25.9 + (F10.0-F19.9/R45.0-8/Z65.0-5/Z65.8-9/Z81.0-4/ Z81.8)

Initiate treatment:

- Haloperidol, oral.
  - Initial dose: 0.75–1.5 mg daily, increasing to 5 mg daily.

If good response/ tolerability to haloperidol, or patients' preference:

- Depot antipsychotic, e.g:
- Flupenthixol decanoate, IM, 10–40 mg every 4 weeks.

OR

Zuclopenthixol decanoate, IM, 200–400 mg every 4 weeks.

If poor response/ poorly tolerated/ high risk of tardive dyskinesia/ extra-pyramidal side effects:

- Risperidone, oral
  - Initial dose: 2–4 mg at night.
  - Maximum dose: 6 mg daily.
  - Assess efficacy after 4–6 weeks:
    - If a partial response is noted, optimise the dosage.
    - If no response is noted, switch treatment.

OR

- Chlorpromazine, oral, 75–300 mg daily in divided doses.

If poor response/tolerability to haloperidol, risperidone or chlorpromazine:

- Olanzapine, oral (specialist initiated).
  - Initial dose: 5 mg at night, increase to 10 mg at night.
  - Maximum dose: 20 mg at night.

If poor response/ tolerability to olanzapine:

- Clozapine, oral (specialist initiated, preferably as inpatient):
  - Initial dose: 12.5–25 mg at night.
  - Usual dose: 200–450 mg per day in divided doses.
  - Maximum dose: 900 mg/day in divided doses.

Summary of the evidence

The medicine review: 'Olanzapine, oral for schizophrenia-Adult review_13June2019' refers.[i]

While no direct comparisons between olanzapine and chlorpromazine were found, a good quality network meta-analysis by Leucht et al., 2013,[ii] found that, vs placebo:

- olanzapine ranked higher in efficacy than chlorpromazine, measured as a reduction of the PANSS score (SMD -0.59, 95% CI -0.65 to -0.53 for olanzapine vs SMD -0.38, 95% CI -0.54 to -0.23 for chlorpromazine)
- olanzapine appears to have better or similar acceptability and tolerability than chlorpromazine"
  - discontinuation of medicine occurred less with olanzapine than with chlorpromazine
  - weight gain was similar for both medications, as was increased prolactin
  - extra-pyramidal side effects occurred with chlorpromazine but not with olanzapine
  - sedation may be more with chlorpromazine than with olanzapine

At October 2022 tender prices,[iii] olanzapine is considerably cheaper than chlorpromazine at equivalent doses:

Medicine Pack	Price	Standard dose	Cost per month
Chlorpromazine; 100mg; Tablet; 56 Tablets	R78.90	300mg per day	R118.35
Olanzapine; 10mg; Tablet; 28 Tablets	R22.43	10mg at night	R22.43

Conclusion

There is no cost, efficacy, or tolerability advantage of chlorpromazine in the treatment of schizophrenia if olanzapine is widely available.

Proposal

To alter prescribing level of olanzapine in schizophrenia to doctor initiated and to remove chlorpromazine from the treatment algorithm. However, chlorpromazine to remain on national tender to allow for supply adjustment of olanzapine.

References

[i] Olanzapine, oral for schizophrenia-Adult review_13June2019, available from https://www.knowledgehub.org.za/elibrary/hospital-level-adults-medicine-reviews-2017-2020 (accessed 23 October 2022).

[ii] Leucht S, Cipriani A, Spineli L, Mavridis D, Örey D, Richter F, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: A multiple-treatments meta-analysis. Lancet. 2013;382(9896):951–62. DOI: 10.1016/S0140-6736(13)60733-3

[iii] NDOH Tenders, available from https://www.health.gov.za/tenders/ (accessed 23 October 2022)

NEMLC MEETING OF 8 DECEMBER 2022:
NEMLC accepted the proposal as recommended by the Adult Hospital Level Committee (see above)

South African National Essential Medicine List
Primary Healthcare/ Adult Hospital Level of Care Medication Review Process
Component: Emergencies and injuries

MEDICINE REVIEW

1. Executive Summary

Date: 29 September 2022
Medicine (INN): Olanzapine
Medicine (ATC): NO5AH03
Indication (ICD10 code): Aggressive / disruptive behaviour (R45.1/R45.4-6)
Patient population: Individuals that are ≥ 18 years old with suspected severe mental illness presenting with aggressive/ disruptive behaviour to any healthcare settings.
Prevalence of condition:
South African studies

- 54-100% of healthcare workers report workplace violence (number with patients as perpetrators unclear) (Njaka, 2020)

International studies

- 8–76% of psychiatric inpatients (Weltens, 2021)
- 9-100% of healthcare workers in Africa experience workplace violence (where reported, patients were perpetrators in 46- 54% of incidents) (Njaka, 2020)

Level of Care: Primary Healthcare and Adult Hospital Level of care
Prescriber Level: Doctor prescribed
Motivator/reviewer name(s): Lesley Robertson, Shelley McGee, Tamara Kredo, Natasha Gloeck, Mashudu Mthethwa, Trudy Leong
PTC affiliation: Lesley Robertson affiliated to Sedibeng District PTC, Gauteng

Key findings

- Haloperidol IM 5mg/ml and 20mg/2ml injections were not available and currently supply is erratic in the South African market. Currently, haloperidol IM with promethazine IM is current standard of care in the management of aggressive, disruptive behaviour among people with mental illness at primary and secondary adult hospital levels of care.
- We conducted a review of available evidence to determine the efficacy and safety of olanzapine in treating acute aggression or agitation in people with mental illnesses. Three international clinical practice guidelines were identified, all poor quality with AGREE II scores less than 50%. These guidelines included olanzapine IM as an option in the pharmacological management of aggressive behaviour.
- A literature search conducted on 4 March 2022 identified six systematic reviews (four of which were not included in the evidence synthesis because of low AMSTAR II ratings) and 13 RCTs.
- **Risk of no improvement** at 24 hours was less with olanzapine (19/99) than lorazepam (18/51), Risk Ratio (RR) 0.54 (95%CI 0.31 to 0.94; NNT 7 (95% CI 4 to 116), very low certainty evidence, although there was no difference in the first hour (RR 0.80 (95%CI 0.60 to 1.05).
- **Agitated behaviour** was less with olanzapine than lorazepam at 24 hours (Mean Difference (MD) -2.91 (95% CI -5.02 to -0.80), very low certainty evidence. Compared to an equivalent dose of haloperidol + promethazine, olanzapine resulted in a greater reduction in aggression (MD= -1.20 (95% CI -2.01 to -0.39)) and agitation (MD = -13.60 (95% CI -14.56 to -12.64)) at 2 hours, very low certainty evidence.
- **Need for additional medicines** was less with olanzapine than lorazepam at 24 hours (RR 0.50 (95% CI 0.33 to 0.75)), very low certainty evidence.
- **Risk of not being tranquil or asleep** at 30 minutes was no different between olanzapine and a higher equivalent dose of haloperidol (double) + promethazine ; RR = 1.67, 95 % CI (0.62 to 4.47), high certainty evidence).

- **No serious adverse events** were evident in the olanzapine, lorazepam, or haloperidol +promethazine groups.
- **Occurrence of any adverse event** was not different between olanzapine and lorazepam (similar rates of extrapyramidal side effects, dizziness, nausea, vomiting) or between olanzapine and haloperidol + promethazine (similar rates of hypotension and excessive sedation).
- Six of the 13 RCTs compared olanzapine to haloperidol or haloperidol + lorazepam. While a full synthesis of this evidence was not conducted, no difference in response between olanzapine (10mg) and haloperidol (range 5mg – 10mg) was noted.
- In summary, very low certainty evidence suggests olanzapine IM may be superior to lorazepam IM in improvement of global state, reduction of agitated behaviour, and need for additional medicines. Uncertain evidence suggests the effect of olanzapine IM may be similar to haloperidol IM + promethazine IM.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
				X	

Recommendation: Considering that haloperidol IM supply has been erratic in South Africa, we suggest using olanzapine oro-dispersible tablets or IM.

Rationale: The very low certainty evidence suggests olanzapine may be superior to lorazepam and to the combination of haloperidol and promethazine in reducing agitated or aggressive behaviour. There appears to be no difference in achieving sedation.

Level of Evidence: Very low certainty evidence

Review indicator: New evidence of benefit or harm

NEMLC RECOMMENDATION 8 DECEMBER 2022:

NEMLC accepted the proposal as recommended by the PHC/Adult Hospital Level Expert Review Committee (see above)

NEMLC RECOMMENDATION 14 MARCH 2024:

NEMLC retained the proposal as recommended by the PHC/Adult Hospital Level Expert Review Committee (see above)

Monitoring and evaluation considerations

Research priorities

Name of author(s)/motivator(s)

Lesley Robertson, Tamara Kredo, Mashudu Mthethwa, Natasha Gloeck, Shelley McGee, Trudy Leong

Author affiliation and conflict of interest details

Lesley Robertson, Department of Psychiatry, University of the Witwatersrand: no conflicts of interest related to olanzapine

Shelley McGee, Ophthalmological Society of South Africa: no conflicts of interest related to olanzapine

Tamara Kredo, Cochrane South Africa, South African Medical Research Council; Division of Clinical Pharmacology, Department of Medicine, and Division of Epidemiology and Biostatistics, department of Global Health, Stellenbosch University: no conflicts of interest related to olanzapine

Mashudu Mthethwa, Cochrane South Africa, South African Medical Research Council: no conflicts of interest related to olanzapine

Natasha Gloeck, Cochrane South Africa, South African Medical Research Council: no conflicts of interest related to olanzapine

Trudy Leong, Right-To-Care as Secretariat-support to PHC/ Adult Hospital Level Committee of the National Essential Medicines List, NDoH: no conflicts of interest related to olanzapine

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BACKGROUND

Aggressive behaviour, often common among people with mental illness, includes verbally abusive language, specific verbal threats, intimidating physical behaviour and/or actual physical violence to self, others, or property [1]. Acute aggression / agitation is therefore a safety risk to patients and staff, which requires safe, effective, and rapid treatment [2]. Over the years, management of aggressive behaviour has advanced to prioritization of rapid symptom treatment instead of patient restraint and isolation [2]. Current management and standard of care for aggressive behaviour includes de-escalation and non-pharmacological measures, use of oral benzodiazepines, benzodiazepines IM, or haloperidol IM with promethazine IM if there is poor response to non-pharmacological measures and oral benzodiazepines. In South Africa, haloperidol IM 5mg/ml and 20mg/2ml injections is erratic.

There is a need to explore other available options such as Olanzapine IM. The purpose of this review was to study the effectiveness and safety of olanzapine in treating acute aggression / agitation in people with mental illnesses.

Research question

What is the efficacy and safety of olanzapine compared to 1) benzodiazepines, 2) haloperidol or 3) placebo for management of aggressive disruptive behaviour?

ELIBILITY CRITERIA FOR REVIEW

Population	Individuals that are ≥ 18 years old with suspected severe mental illness presenting with aggressive/ disruptive behaviour to any healthcare settings.
Intervention	Olanzapine intramuscular (IM) and orodispersible tablets, any dose
Comparators	• Haloperidol IM +/- promethazine IM, any dose • Benzodiazepines any dose, given orally or IM • Placebo
Outcomes	**Efficacy** • Response: ≥ 40% reduction in symptom scale or as defined by the study within 30 minutes, 2hours, and 24 hours • Mean difference in behaviour score within 2 hours and 24 hours; • requiring further injections/number of doses in 24 hours; • requiring additional benzodiazepines in 24 hours • Sedation • Others (secondary outcomes): leaving the study early; duration of hospital stay; patient/ caregiver satisfaction with care **Safety (time frame – within 24 hours)** • Requiring anticholinergic medication • Any adverse events • Serious adverse events • Mortality

Study designs	Clinical practice guidelines, systematic reviews of randomised controlled trials (RCTs), RCTs and, if the latter is unavailable, systematic reviews of non-randomised/ observational studies or observational studies. Ongoing trials were also sought.

METHODS

A search strategy was developed for PubMed and adapted to other databases (Appendix 1). A search for systematic reviews and RCTs was conducted in PubMed, the Cochrane Library, and Epistemonikos on 4 March 2022. Clinical practice guidelines (CPGs) were sourced from the Guidelines International Network (GIN), the National Institute for Health and Care Excellence (NICE) and the British Association of Clinical Pharmacology, as well as relevant CPGs from Australia, New Zealand, and Canada on their government websites.

The search results of RCTs and systematic reviews were uploaded on to the Covidence systematic review management software (Melbourne, Victoria). As we were conducting reviews on olanzapine for aggression and delirium in parallel, the search included outputs relevant for both conditions, with screening for relevant studies done in duplicate. Duplicates were removed and screening of abstracts was conducted independently by the four reviewers (NG, MM, TK, LR). Conflicts were resolved by consensus and full text review was conducted by two reviewers (NG and MM). Conflicts were resolved by TK and LR during the full text review.

Eligible guidelines were appraised in duplicate using the AGREE II tool by two reviewers (MM and NG). Eligible systematic reviews were appraised using the AMSTAR II Checklist, and eligible randomised controlled trials were assessed for Risk of Bias using the Cochrane's RoB 2.0 Tool. Data extraction for included systematic reviews and RCTs was conducted by one reviewer and verified by a second reviewer. The main characteristics of included studies are summarized in Tables 3 and 4. Risk ratios (RR) with 95% confidence intervals (CI) for dichotomous data and mean differences with standard deviation for continuous outcomes were reported. We found that the included systematic reviews defined olanzapine as the comparator and not the main intervention (the inverse of our PICO), hence, data were therefore re-analysed in RevMan5 (The Cochrane collaboration, United Kingdom) using olanzapine as the main intervention, for our outcomes of interest. Characteristics of additional relevant RCTs that were not reported in the included systematic reviews are summarized, including appraisal, in Table 4.

Exclusion of ineligible studies was reached by consensus between two reviewers and any disputes were settled by a third reviewer.

RESULTS

a. Results of search

A systematic search was conducted in PubMed, Cochrane library and Epistemonikos. The search yielded 778 records which were subsequently imported to Covidence for screening where 147 duplicates were removed (Appendix 2). Titles and abstracts of 637 studies were screened, and 541 studies were excluded. Full texts of 95 studies were assessed for eligibility and 73 studies were excluded (see Appendix 3 for list of excluded studies). We included 13 studies of which six were systematic reviews and seven RCTs. However, only two systematic reviews were considered of sufficient quality to be eligible for inclusion because of moderate - high AMSTAR II ratings. The four systematic reviews with low AMSTAR II rating are summarized in Appendix 4.

b. Guidelines

All guidelines that were identified and appraised were of poor quality, with AGREE II scores less than 50 % (Table 1).

Table 1: Guidelines and recommendations for management of acute aggression

Citation	Recommendation	AGREE II score
Patel MX, Faisil NS, Barned TR, Dix R, Dratcu L, Fox B, et al. Joint BAP NAPICU evidence-based consensus guidelines for the clinical management	Pre- (rapid tranquilisation) RT: Oral, oral-inhaled and bucca olanzapine and risperidone are effective (Ib; A). Oral	42 %

of acute disturbance: De-escalation and rapid tranquillisation. J Psychopharmacol. 2018; 32(6):601-40. Doi: doi.org/10.1177/0269881118776738. [3]	haloperidol is effective and a baseline ECG is advised before use due to the risk of QTc prolongation (III; C). "RT: IM monotherapy – IM olanzapine is effective, but it should only be administered by itself and not concurrently with IM benzodiazepines due to risk of hypotension; thus, there should be an interval of at least 1 hour between the two (Ia; A).	
Galletly C, Castle D, Dark F, Humberstone V, Jablensky A, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders. Aus N Z J Psychiatry. 2016; 50(5):410-72. Doi: 10.1177/0004867416641195 [4].	Oral agents (including wafers) are preferable to medications given by injection. If parenteral antipsychotic agents are required, second-generation antipsychotic agents are preferred. Flowchart for pharmacological mx of acute behavioral disturbance in psychosis. Arousal level 2 to 3: lorazepam or olanzapine orally. Arousal level 3 to 4: Lorazepam AND olanzapine orally. Arousal level 4 to 5: olanzapine (1st line) IMI	33%
Queensland Health. Management of patients with Acute Severe Behavioural Disturbance in Emergency Departments. [Internet] Queensland: Queensland Health; 2016 [updated October 2021]. Available from: https://www.health.qld.gov.au/__data/assets/pdf_file/0031/629491/qh-gdl-438.pdf	Use sedation assessment tool Flow chart: sedation for acute behavioural disturbance in emergency department. +1: diazepam or olanzapine wafer or diazepam plus olanzapine Flow chart: sedation for acute behavioural disturbance in medically frail patients in emergency department. +1: diazepam or olanzapine wafer Flow chart: Sedation for acute behavioural disturbance in child/adolescent in ED Not know ASD or intellectual disability: +1: Diazepam or olanzepine wafer or risperidone +2 or +3: droperidol or consider olanzapine or ketamine if droperidol C/I	17 %

Included systematic reviews

Two systematic reviews were included in evidence synthesis. Zaman *et al* (2017) [5] compared benzodiazepines with antipsychotics, and placebo for the treatment of psychosis-induced aggression. The aim of the review was to compare the tranquilising or sedative effects of benzodiazepines versus antipsychotics / placebo in psychosis-induced aggression. The review was rated as high quality according to the Amstar II rating. Of the twenty trials included in the systematic review only one used olanzapine as the comparator. The quality of evidence was very low due to serious risk of bias, imprecision, and small size. The trial took place in hospitals in Romania and the US and included 201 adults with bipolar disorder who had psychosis induced agitation deemed clinically severe enough to require injections. A summary of the trial and effect sizes according to reported outcomes is presented in Table 2.

Huf *et al* (2016)[6] reviewed the effectiveness of haloperidol + promethazine on psychosis-induced aggression. This review was of moderate quality according to the AMSTAR II rating. Three studies compared haloperidol plus promethazine with olanzapine, with sample sizes ranging from 56 to 300. Study settings were psychiatric emergency rooms. Participants were adults with psychosis-induced aggressive behaviour. Other diagnoses such as drug or alcohol intoxication, dementia, non-psychotic mental illnesses, or learning disabilities were included if they did not exceed the proportion of participants with psychosis. Quality of evidence for included studies ranged from low to high. A summary of haloperidol plus promethazine versus olanzapine reported outcomes are presented in Table 2. Of note, dosing was only equivalent (haloperidol 5mg vs olanzapine 10mg) in one study (n=60); the largest study (n=300) used a higher equivalent dose of haloperidol vs olanzapine (10mg vs 10mg), and the smallest study (n=56) used a lower equivalent dose of haloperidol versus olanzapine (2.5mg vs 10mg, respectively).

Our outcomes of interest, summarized and re-analysed to match our PICO format from the two reviews, are presented below:

Effectiveness of the intervention

Comparison 1: Olanzapine vs benzodiazepines

The results below are from the included review (Zaman et al 2017) reporting of the trial, Battaglia *et al* 2003, n = 151 [7].

1. **Response: reported as 'Global state: No improvement (> 40% reduction Positive and Negative Syndrome Scale-Excited Component (PANSS-EC)'.**
   At 1 hour: Risk Ratio (RR) 0.80 (95%CI 0.60 to 1.05), very low certainty evidence
   At 24 hours: RR 0.54 (95%CI 0.31 to 0.94), very low certainty evidence.
   There may be a slight difference favouring olanzapine compared to lorazepam at 24 hours. However, with very low certainty evidence the overall result is uncertain.

2. **Behaviour: reported as 'Behavior: mean change/endpoint score (Agitated Behavior Scale, high = worse)'**
   At 24 hours: Mean difference -2.91 (95% CI -5.02 to -0.80). GRADE certainty of evidence was not reported.
   There may be a reduction in Agitated Behaviour Scale with olanzapine compared to lorazepam at 24 hours, but the evidence is uncertain.

3. **Requiring further injections/number of doses in 24 hours:** not reported.

4. **Requiring additional medicine in 24 hours**
   RR 0.50 (95% CI 0.33 to 0.75), very low certainty evidence.
   Olanzapine compared to lorazepam at 24 hours may result in less additional medication, however, the certainty of the evidence is very low and we are therefore uncertain of the true effect.

5. **Sedation: Tranquillization or asleep**
   At 24 hours: RR 1.34 (95%CI 0.51 to 3.55), very low certainty evidence. There may be no difference in tranquilization between olanzapine and benzodiazepines, however, the true effect is uncertain.

6. **Leaving the study early**
   RR = 0.17 (95%CI 0.02 to 1.61), very low certainty evidence.
   In the olanzapine group, 1/99 versus 3/51 participants in the benzodiazepine group left the study early for any reason.

7. **Duration of hospital stays:** not reported

8. **Patient/ caregiver satisfaction with care:** not reported

9. **Safety (time frame – within 24 hours):** not reported

10. **Requiring anticholinergic medication:** not reported

11. **Any adverse events**
    Extrapyramidal symptoms (EPS)
    - At 24 hours: RR 4.12 (95%CI 0.53 to 32.1). GRADE certainty of evidence was not reported, 8/99 in the olanzapine group vs 1/51 in the benzodiazepine group experienced extrapyramidal symptoms.
    - Use of medication for EPS: At 24 hours: RR 4.12 (95%CI 0.53 to 32.1). GRADE certainty of evidence was not reported. 8/99 in the olanzapine group vs 1/51 in the benzodiazepine group experienced extrapyramidal symptoms.

- Specific adverse effects:

Dizziness: RR 0.66 (95%CI 0.26 to 1.61). GRADE certainty of evidence was not reported. 9/99 participants in olanzapine group experienced dizziness, compared to 7/51 people in the benzodiazepine group.

Nausea: RR 0.13 (95%CI 0.01 to 1.12). GRADE certainty of evidence was not reported. 1/99 participants in olanzapine group experienced nausea, compared to 4/51 people in the benzodiazepine group.

Vomiting: RR 0.07 (95%CI 0.0 to 1.41). GRADE certainty of evidence was not reported. 0/99 participants in olanzapine group experienced vomiting, compared to 3/51 people in the benzodiazepine group.

12. **Serious adverse:** not reported

Comparison 2: Olanzapine vs haloperidol + promethazine

The results below are from the included review, Huf *et al* 2016 [6].

1. **Response: reported as 'Global state: No overall improvement'**
   Single trial, n = 300 (TREC-Vellore-II, dosing of haloperidol > dosing of olanzapine)
   By 30 minutes: RR = 1.74 (95% CI 1.10 to 2.76)
   by 2 hours: RR = 2.73 (95% CI 1.43 to 4.98)
   By 24 hours: not reported
   GRADE certainty of evidence was not reported.
   The risk of no improvement appears to be greater with olanzapine compared to haloperidol + promethazine.

2. **Behaviour: Mean difference in behaviour score within 2 hours and 24 hours**

   2a. Average aggression score (OAS, high score = bad)
   Single trial, n = 60 (equivalent dosing of haloperidol and olanzapine)
   by 2 hours: MD= -1.20 (95% CI -2.01 to -0.39)
   by 24 hours*:* not reported
   GRADE certainty of evidence was not reported. There is evidence that olanzapine may result in a greater reduction in the average aggression score compared to haloperidol + promethazine after 2 hours.

   2b. Average agitation score (OASS, high score=bad)
   Single trial, n = 60 (equivalent dosing of haloperidol and olanzapine)
   by 2 hours: MD = -13.60 (95% CI -14.56 to -12.64)
   by 24 hours**:** not reported
   GRADE certainty of evidence was not reported. There is evidence that olanzapine may result in a reduction in average agitation score compared to haloperidol + promethazine after 2 hours.

2c. Severe agitation

By 24 hours: RR 0.14 (95% CI 0.01 to 2.64), n = 56, 1 trial (dosing of haloperidol < dosing of olanzapine). GRADE certainty of evidence was not reported. 0/28 participants in the olanzapine group experienced severe agitation, compared to 3/28 people in the haloperidol + promethazine group.

3. **Requiring further injections/number of doses in 24 hours:** not reported
4. **Requiring additional benzodiazepines in 24 hours:** not reported

5. **Sedation:**

Single trial, n=300 (TREC-Vellore-II, dosing of haloperidol > dosing of olanzapine)

Not tranquil or asleep by 30 minutes: RR = 1.67, 95 % CI (0.62 – 4.47), high quality evidence. 10/150 and 6/150 in the olanzapine and the haloperidol + promethazine groups, respectively, were not tranquil or asleep by 30 minutes.

6. Leaving the study early:
by 30 minutes: RR= 0.33 (95%CI 0.01 to 8.12); n = 300, 1 trial.
by 2 hours: RR = 0.14 (95%CI 0.01 to 2.74); n = 300, 1 trial.
by 4 hours: RR = 0.09 (95% CI 0.01 to 1.63); n = 300; 1 trial.
by 24 hours: RR 0.33 (95% CI 0.04 to 3.01); n = 116, 2 trials.

There were no differences in leaving the study between olanzapine and haloperidol + promethazine groups.

7. Duration of hospital stay: not reported

8. Patient/ caregiver satisfaction with care: not reported

9. Safety (time frame – within 24 hours): not reported

10. Requiring anticholinergic medication: not reported

11. Any adverse events

a. Hypotension

RR 0.33 (95% CI 0.05 to 2.03), 2 trials, n = 116. GRADE certainty of evidence was not reported. 1/58 participants in olanzapine group experienced hypotension, compared to 4/58 people in the haloperidol + promethazine group.

b. Central nervous system - sedation – excessive

RR 1.50 (95% CI 0.26 to 8.64), 2 trials, n = 116, low quality of evidence.
3/58 participants in olanzapine group experienced severe agitation, compared to 2/58 people in the haloperidol + promethazine group.

Included RCTs

We summarized seven RCTs that were not reported in the included systematic reviews. Characteristics of the RCTs including outcomes, findings, and risk of bias assessment are summarized in Table 3.

Of the seven RCTs, three were conducted in Taiwan, one in Japan, one in the United States (US), and two were multi-country studies including Australia, Austria, Belgium, Czech Republic, Canada, France, Greece, Hungary, Israel, United Kingdom (UK), Spain and South Africa (SA). Participants were aged from 18 to 65 years and were mostly diagnosed with schizophrenia and /or schizophreniform or schizoaffective disorders. Studies were conducted in hospital or emergency room settings and participants were considered clinically agitated (minimum score ≥ 14 on the PANSS-EC scale). Sample sizes ranged from 42 to 311. Studies compared IM olanzapine (5 to 10 mg) with IM haloperidol (5 to 7.5 mg -/+ 2 mg lorazepam) or placebo. Measured outcomes were efficacy and safety across all studies. Efficacy outcomes included PANSS-EC scores, agitation-calmness evaluation scales (ACES), brief psychiatry rating scale total score (BRS), clinical global impression-severity index scale (CGI), Barnes akathisia rating scale (BARS) and Simpson-Angus scale (SAS). Risk of bias was unclear for all studies due to some concerns in one or more domains.

Future research directions:

- This review highlighted an important gap in the literature, larger and high methodological quality trials are required to sufficiently address this research question. Furthermore, most studies were conducted in high income countries, there is limited evidence from low-income settings and SA context.
- Updated high quality systematic reviews are also required.

Table 2. Characteristics of included systematic reviews

CITATION	STUDY DESIGN	POPULATION (N)	INTERVENTION VS COMPARATOR	OUTCOMES AND EFFECT SIZE	APPRAISAL
Zaman H, Sampson SJ, Beck ALS, Sharma T, Clay FJ, Spyridi S, Zhao S, Gillies D. Benzodiazepines for psychosis-induced aggression or agitation. Cochrane Database of Systematic Reviews 2017, Issue 12. Art. No.: CD003079. DOI: 10.1002/14651858.CD003079.pub4. [5]	Systematic review of 20 RCTs examining effectiveness of benzodiazepines among people with psychosis-induced aggression or agitation. One RCT used olanzapine as a comparator	N=201 Adults with bipolar disorder (manic or mixed), deemed by a physician to have agitation severe enough to receive injections, minimum total PANSS-EC score of 14, and ≥ 1 individual item score of ≥ 4.	Lorazepam (2 to 5mg IM, n=51) versus olanzapine (10 to 25 mg IM, n=99), and versus placebo (n=51)	**1. Global state: Risk of no improvement in reduction of symptom scale (≥ 40% reduction Positive and Negative Syndrome Scale-Excited Component (PANSS-EC))** *Short term (<1 hour):* RR1.26, 95%CI 0.95 to 1.66, n=150 *Medium term (24 hours):* RR 1.84, 95%CI 1.06 to 3.18, n=150, 1 RCT **2. Behaviour: mean change/endpoint score (Agitated Behaviour Scale, high =worse)** *Medium term (24 hours):* MD 2.91, 95%CI 0.80 to 5.02, n = 149 **3. Requiring additional medicine** *Medium term (24 hours):* RR 2.02, 95% CI 1.33,3.07, n=150 **4. Tranquillization or asleep: sedation.** *Medium term (24 hours):* RR 0.75, 95% CI 0.28 to 1.98, n=150, 1 RCT **5. Adverse effects/events: Extrapyramidal symptoms (EPS).** *Medium term (24 hours):*RR 0.24, 95%CI 0.03 to 1.89, n=150, 1 RCT 6. **Adverse effects/events: use of medication for EPS** *Medium term (24 hours):* RR= 0.24, 95%CI 0.03 to 1.89 **7. Adverse effects/events: 3. Specific** Dizziness: RR= 1.51, 95%CI 0.60 to 3.82 Nausea: RR= 7.76, 95%CI 0.89 to 67.67 Vomiting: 13.46, 95%CI 0.71 to 255.70 **8. Leaving study early** RR=5.82, 95%CI 0.62 to 54.58, N = 150, 1 RCT	AMSTAR II rating HIGH ROB of the RCT: Low risk for attrition bias and selective reporting. High risk for other bias (industry funded) Unclear risk for selection bias and performance bias.

Huf G, Alexander J, Gandhi P, Allen MH. Haloperidol plus promethazine for psychosis-induced aggression. Cochrane Database of Systematic Reviews 2016, Issue 11. Art. No.: CD005146. DOI: 10.1002/14651858.CD005146.pub3.[6]	Systematic Review of six studies, examining the effectiveness of haloperidol and promethazine. Data relevant to six comparisons are presented. Three RCTs (Baldacara, 2011; Mantovani,2013; TREC-Vellore-II) used olanzapine as a comparator.	N=416 Adults with psychosis-induced aggression behaviour presenting to emergency rooms.	Haloperidol (2.5 – 10mg) + promethazine (25 – 50mg) versus olanzapine (5 – 10mg) Baldacara, 2011 (n=60) 5mg haloperidol vs 10 mg olanzapine (i.e., equivalent dosing) TREC-Vellore-II (n=300)– haloperidol 10mg vs olanzapine 10 mg (n=296) and 5mg vs 5mg (n=4) (note, dosing not equivalent) Mantovani, 2013 (n=56), haloperidol 2.5mg vs olanzapine 10mg (note, dosing not equivalent)	**Primary Outcomes** **1. Not tranquil or asleep at 30 mins** Single trial, n=300 RR = 0.60 (0.22 to 1.61), high quality evidence **2. Global state: Needing restraints or seclusion by 12 hours** Single trial, n=60 RR 5.00 (0.62 to 40.28), low quality evidence **3. Adverse effects: Specific and serious adverse effects by 24 hours** Two trials, n=116 RR 0.67 (0.12 to 3.84), low quality evidence **Secondary Outcomes,** **4. Tranquil or asleep: Average sedation score (Ramsay sedation scale)** Single trial, n=60 ***by 1 hour:*** MD= 0.20, 95% CI -0.26 to 0.66 ***by 2 hours:*** MD= 0.10, 95% CI -0.26 to 0.46 ***by 4 hours:*** MD=0.10, 95% CI -0.34 to 0.54 ***by 6 hours:*** MD= 0.10, 95% CI -0.15 to 0.35 ***by 12 hours:*** MD= 0.00, 95% CI -0.23 to 0.23 **5. Global state: No overall improvement** Single trial, N = 300 ***by 30 minutes:*** RR = 0.57, 95% CI 0.36 to 0.91 ***by 1 hour:*** RR = 0.40, 95% CI 0.21 to 0.75 ***by 2 hours:*** RR = 0.44, 95% CI 0.24 to 0.79 ***by 4 hours:*** RR = 0.47, 95%CI 0.22 to 1.01 **6. Global state: Needing restraints or seclusion** Single trial, N =300 ***by 30 minutes:*** RR = 1.02, 95% CI 0.71 to 1.47 ***by 1 hour:*** RR = 0.97, 95%CI 0.66 to 1.44 ***by 2 hours:*** RR = 0.79, 95% CI 0.51 to 1.25 ***by 4 hours:*** RR 0.63, 95% CI 0.34 to 1.14 ***by 12 hours:*** RR 5.00, 95% CI 0.62 to 40.28, N = 60, single trial 7. **Requiring additional drugs during initial phase - by 4 hours** Two trials, N = 356 RR = 0.52, 95% CI 0.37 to 0.74.	AMSTAR II rating Moderate quality ROB of the three relevant RCTs largely unclear. All three had low risk of attrition bias. Mantovani and TREC-Vellore-II had low risk of selection bias, but Mantovani had high risk of reporting bias.

				Moderate heterogeneity (Chi^2 =2.25; df=1.0; P=0.13; I^2=55%. **8. General - serious adverse effect** Single trial, N = 300 ***by 4 hours:*** RR = 0.33, 95% CI 0.04 to 3.17 ***at 2 weeks:*** RR = 0.33, 95%CI 0.01 to 8.12 **9. Specific adverse effects** **a. Cardiovascular - hypotension** Two trials, N = 116 RR 3.00, 95% CI 0.49 to 18.31 **b. Central nervous system - sedation – excessive** Two trials, N = 116 RR 0.67, 95% CI 0.12 to 3.84 **c. Extrapyramidal problems - 0 to 4 hours** Three trials, N = 416 RR 1.76, 95% CI 1.12 to 2.77. This subgroup had important levels of heterogeneity (Chi^2 =2.45; df=1.0; P=0.12; I^2=59%). **10. Specific behaviours: 1. Severe agitation** RR 7.00, 95% CI 0.38 to 129.55, N = 56, single study **11. Specific behaviours: 2. Average aggression score (OAS, high score=bad)** **Single trial, N = 60** ***by 1 hour:*** MD = 5.40, 95% CI 3.72 to 7.08 ***by 2 hours*:** MD= 1.20, 95% CI 0.39 to 2.01 ***by 4 hours*:** MD = -0.50,95% CI -0.68 to -0.32 **by 6 hours**: MD = -1.20, 95% CI -1.90 to -0.50 ***by 12 hours***: MD= -2.00, 95% CI -2.21 to -1.79 **12. Specific behaviors: 3. Average agitation score (OASS, high score=bad)** **Single trial, N = 60** ***by 1 hour*:** MD = 26.50, 95% CI 23.76 to 29.24 ***by 2 hours***: MD = 13.60, 95% CI 12.64 to 14.56 ***by 4 hours:*** MD = 4.00, 95% CI 3.47 to 4.53 **by 6 hours**: MD = 2.80, 95% CI 2.31 to 3.29 ***by 12 hours*:** MD = 1.7, 95% CI 1.44 to 1.96 **13. Hospital outcomes** Single trial, N = 300 ***admitted - by 4 hours*** RR = 0.81, 95% CI 0.56 to 1.16	

				not discharged - by 4 hours RR = 0.94, 95%CI 0.77 to1.16 **14. Leaving the study early** ***by 30 minutes*:** RR= 0.33, 95%CI 0.01 to 8.12; N = 300, 1 trial. ***by 2 hours:*** RR = 0.14, 95%CI 0.01 to2.74; N = 300, 1 trial. ***by 4 hours:*** RR = 0.09, 95% CI 0.01 to 1.63; N = 300; 1 trial. **by 24 hours:** RR 0.33, 95% CI 0.04 to 3.01; N = 116, 2 trials. ***by 2 weeks***: RR 0.71, 95% CI 0.33 to 1.56; N = 300, 1 trial. Service outcomes: Not discharged - by 4 hours	

Table 3: Characteristics of included RCTs

CITATION	STUDY DESIGN	POPULATION	INTERVENTION	OUTCOMES AND MAIN FINDINGS	RISK OF BIAS
a. OLANZAPINE VS HALOPERIDOL					
Chan HY; Ree SC; Su LW; Chen JJ; Chou SY; Chen CK; Chen YS A double-blind, randomized comparison study of efficacy and safety of intramuscular olanzapine and intramuscular haloperidol in patients with schizophrenia and acute agitated behavior. J Clin Psychopharmacol Jun 2014;34(3):355-8 [8].	Multicenter, randomized, double blind, controlled parallel group study Trial conducted at four trial centers between June 2004 and January 2005 in Taiwan. The study protocol was approved by the independent ethics committee at each center.	Patients aged 18 to 65 years with primary diagnosis of schizophrenia: Clinically agitated hospitalized due to an acute relapse, A minimum total score of ≥ 14 on the 5 items of PANSS-EC and at least 1 individual item score of ≥ 4 using the 1 to 7 scoring system before the first IM injection of the study drug. **N = 49** - 2 patients – olanzapine group and 1 patient – haloperidol group not included in the efficacy analysis (did not receive the study drug administration). 1 patient – olanzapine group was withdrawn because of the investigator's decision and not subjected to postbaseline assessment**. Overall, 45 patients** (92%) completed the 2-hour study period. Exclusion criteria: serious or unstable medical conditions, Treatment with BZDs within 4 hours before the first IM study drug administration, and Treatment with an injection depot neuroleptic within 1 injection interval before the study drug administration. Illness caused by substance abuse	Olanzapine IM 10 mg/d, N = 25 Haloperidol IM 7.5 mg/d, N = 24 over 24 hours.	Efficacy Olanzapine group and haloperidol group showed significant improvement at 2 hours in the primary efficacy analysis vs baseline (olanzapine, -9.0 ± 5.7, P < 0.001; haloperidol, - 7.9 ± 4.0, P < 0.001). Both treatments showed rapid onset of efficacy from 15 minutes. No difference in improvement between 2 groups except at the 1-hour visit where the olanzapine group showed significantly greater improvement (olanzapine, -8.5 ± 5.0; haloperidol, -6.3 ± 4.3, P = 0.013). Compared with baseline, both groups presented significant change at 2 hours in all secondary efficacy parameters including ACES (olanzapine, 2.6 ± 1.8, P < 0.001; haloperidol, 2.3 ± 1.8, P G 0.001), PANSS-derived BPRS total score (olanzapine, -17.9 ± 17.0, P< 0.001; haloperidol, -19.1 ± 15.9, p < 0.001), and PANSS-derived BPRS positive score (olanzapine, -4.7 ± 5.5, P < 0.001; haloperidol, -5.7 ± 5.3, P < 0.001). On the other hand, there were no significant differences between these 2 groups. Safety: 9 patients (36%) from the olanzapine group and 7 patients (29%) from the haloperidol group experienced at least 1 adverse event. The most frequently reported adverse event was insomnia in both groups with the incidence of 24% in olanzapine group and 25% in haloperidol group. The other adverse events were less than 5%, except for the haloperidol group that had 8% vomiting.	Some concerns D5 – selection of reported results.
Huang CL; Hwang TJ; Chen YH; Huang GH; Hsieh MH; Chen HH; Hwu HG	Prospective, randomized, parallel trial in three acute	**N = 67** Inclusion criteria: Recently hospitalized patients	10 mg IM olanzapine (n = 37)	Efficacy: PANSS-EC scores decreased significantly at 2 hours following the first injection in both	Low

Intramuscular olanzapine versus intramuscular haloperidol plus lorazepam for the treatment of acute schizophrenia with agitation: An open-label, randomized controlled trial. J Formos Med Assoc May 2015;114(5):438-45 [9].	psychiatric inpatient units [National Taiwan University Hospital (NTUH) and its Yun-Lin branch hospital, Yu-Li Psychiatric Hospital] in a 24-hour treatment period. Conducted between September 2006 to February 2009	18–65 years old with: Schizophrenia or schizoaffective disorder. Total score of ≥ 14 (of a maximum of 35) on the PANSS-EC scale and having a score of ≥ 4 (of a maximum of 7) on at least one of these five items of PANSS-EC being acutely agitated to the extent that parenteral antipsychotic therapy was indicated. <u>Exclusion criteria:</u> pregnant or lactating severe medical illnesses having received injectable depot antipsychotics within 1 month use of psychostimulants or reserpine within 1 week having received newly added oral or IM benzodiazepines within 4 hours having received newly added oral or rapid-acting IM antipsychotics within 2 hours; and history of allergic reaction or intolerance to the study medication(s).	5 mg IM haloperidol plus 2 mg IM lorazepam (n = 30). 24 hours	groups (olanzapine: –10.2 ± 6.5, t = 9.750, p < 0.001; haloperidol + lorazepam: –9.9 ± 5.6, t = 9.900, p < 0.001). The difference between haloperidol plus lorazepam and olanzapine was 0.3 units favoring olanzapine (with one-sided lower 97.5% confidence limit = −3); therefore noninferiority (−3 vs. −10.2 × 0.4 = −4.1) could be concluded. ACES scores increased significantly at 2 hours in both groups (olanzapine: 2.1 ± 1.7, t = 7.225, p < 0.001; haloperidol + lorazepam: 2.2 ± 1.7, p < 0.001). The percentage of responder (defined as at least 40% reduction from baseline on the PANSS-EC at 2 hours) was not significantly different between the two groups [19 (51%) in the olanzapine group vs. 11 (37%) in the haloperidol + lorazepam group; Fisher's exact test, p = 0.323]. <u>Safety:</u> The changes in SAS and Barnes Akathisia Rating Scale scores from baseline to 24 hours after the first injection showed no significant differences between the two groups. The incidences of adverse reactions were also not significantly different between the two groups. However, acute dystonia only occurred in the haloperidol plus lorazepam group.	
Hsu WY, Huang SS, Lee BS, Chiu NY. Comparison of intramuscular olanzapine, orally disintegrating olanzapine tablets, oral risperidone solution, and intramuscular haloperidol in the management of acute agitation in an acute care psychiatric ward in Taiwan. J Clin Psychopharmacol. 2010 Jun;30(3):230-4 [10].	Prospective, randomized, rater-blinded study comparing olanzapine IM, olanzapine ODT, risperidone OS, and intramuscular haloperidol (haloperidol IM) in an acute care psychiatric unit for the first 24 hours after admission.	**N=42** Patients in acute care psychiatric ward 18 to 65 years old; DSM-IV diagnosis: schizophrenia, bipolar I disorder, schizoaffective disorder, delusional disorder, or other psychotic disorders; and Excited component score of 14 or higher PANSS-EC, with a score of 4 or higher on at least 1 item (1- to 7-point scale). <u>Exclusion criteria</u>	Patients were randomly assigned to receive 1 of 4 interventions over a 24-hour period: 10-mg olanzapine IM (n = 11), 10-mg olanzapine ODT (n = 10), 3-mg risperidone oral solution (n = 10), or 7.5-mg haloperidol IM (n = 11).	<u>Efficacy</u> PANSS-EC score: Baseline PANSS-EC score, Olanzapine IM 25.55 ± 3.8, haloperidol 28.18 ± 2.82 Olanzapine IM vs Haloperidol IM 30 minutes: -5.00 ± 1.62, p = 0.0042 2 hours: -3.60 ± 1.47, p = 0.089 24 hours: -2.97 ± 1.31, p = 0.157 <u>Safety</u> The most reported and observed adverse effects related to medications were found	Some concerns D2-deviation from intended use and D5 selection of reported result.

		Pregnant or lactating women; patients with serious medical illnesses; closed-angle glaucoma; allergic reaction to olanzapine, risperidone, or haloperidol; received a long-acting antipsychotic agent injection.		in all the 4 groups. Drowsiness was most common. Olanzapine IM and olanzapine ODT produced more drowsiness than oral risperidone and haloperidol IM, but the difference was not significant.	
Kinon BJ; Ahl J; Rotelli MD; McMullen E. Efficacy of accelerated dose titration of olanzapine with adjunctive lorazepam to treat acute agitation in schizophrenia**.** Am J Emerg Med May 2004;22(3):181-6 [11].	Prospective, randomized, double-blind, multicenter, parallel 3-week study of acutely agitated inpatients diagnosed with schizophrenia, schizophreniform, or schizoaffective disorder.	**N = 100** Inclusion criteria: 18 to 50 years old PANSS Agitation subscale scores > 20 (0-60 scale) and Clinical Global Impressions-Severity (CGI) scale scores > 4 (1-7 scale). <u>Exclusion criteria:</u> Pregnant or lactating women or patients with serious unstable illnesses, including hepatic, renal, gastroenterologic, respiratory, cardiovascular, endocrinologic, neurologic, immunologic, or hematologic disease, in which pharmacotherapy posed a substantial clinical risk or confounded diagnosis.	Oral olanzapine (10 mg per day), N = 52 or oral haloperidol (10 mg per day), N = 48 Plus lorazepam as needed (up to 12 mg per day)	Of the 57 patients who completed the study, significantly more were from the olanzapine treatment group than from the haloperidol treatment group (67.3% vs. 45.8%, P = .043, Fisher's exact test). The mean time to discontinuation was significantly greater for the olanzapine-treated patients than the haloperidol-treated patients (17.69 ± 6.51 days vs. 14.21 ± 7.65 days, respectively, P = .016, t test, 98 df). <u>Efficacy:</u> Significant within-group improvement was demonstrated in PANSS Agitation scores for both groups as early as 1 hour after initiating therapy (-5.79 ± 6.30 for olanzapine and -4.89 ± 6.05 for haloperidol, P <.001). Within-group mean changes from baseline continued to be significant at each assessment during the first 24 hours for both treatment groups. Olanzapine group experienced significantly greater improvement than the haloperidol group (P = .044, F test, 1.76 df) in mean PANSS Agitation scores (LOCF) (-14.00 ± 10.71 and -11.21 ± 11.67, respectively). <u>Safety:</u> Olanzapine vs haloperidol Dystonia, hypertonia, and increased salivation (0 % vs 8.3 %, p =0.05). Headache (11.5 vs. 25.0 %, p = .117) Nervousness (7.7 vs. 16.7 %, p= .223) Anxiety (11.5 vs. 4.2%, p= .272) Insomnia (5.7 vs. 13%, p= .305) Somnolence (17.3 vs. 25.0 %, p =.462)	Some concerns, D1- randomization sequence not described, D4 – measurement of outcome – not information on whether outcome assessors were aware of the intervention.

				Pain (9.6 vs. 10 %, p = 1.00) Agitation (9.6 vs. 10 %, p = 1.00)	
Wright P, Birkett M, David SR, Meehan K, Ferchland I, Alaka KJ, Saunders JC, Krueger J, Bradley P, San L, Bernardo M, Reinstein M, Breier A. Double-blind, placebo-controlled comparison of intramuscular olanzapine and intramuscular haloperidol in the treatment of acute agitation in schizophrenia. Am J Psychiatry. 2001 Jul;158(7):1149-51. doi: 10.1176/appi.ajp.158.7.1149. PMID: 11431240 [12].	Double-blind, randomized, controlled trial conducted in hospitals in Australia, Austria, Belgium, Canada, the Czech Republic, France, Greece, Hungary, Israel, the Republic of South Africa, Spain, the United Kingdom, and the United States	**N = 311** Inpatients diagnosed with schizophrenia (according to the DSM-IV) who scored ≥ 14 on the PANSS-EC (≥4 on at least 1 item) clinically agitated. <u>Exclusion criteria:</u> Pregnant or lactating, Patients with serious medical conditions for whom treatment with medication posed a substantial clinical risk or confounded diagnosis.	Olanzapine 10 mg, N = 131 Haloperidol 7.5 mg, N = 126 or Placebo (saline), N = 54 over 24 hours	<u>Efficacy:</u> 91.6 % participants completed the study. Mean changes in excited component scores on the PANSS from baseline to 2 hours (adjusted for country differences): olanzapine: –7.7 ± 6.1, haloperidol: –7.6 ± 5.0 and placebo: –3.6 ± 5.2). The difference between olanzapine and haloperidol was 0.1 units favoring olanzapine (one-sided lower 97.5% confidence limit=–1.2); noninferiority (–1.2 versus –7.6 × 0.4=–3.0) was concluded. Mean changes in scores from baseline to 2 hours after the first injection on the Agitated Behavior Scale and Agitation Calmness Evaluation Scale (adjusted for country differences): Olanzapine: –8.3 ± 0.6 and 1.6 ± 0.1, respectively, Haloperidol: –8.2 ± 0.6 and 1.5 ± 0.1 respectively, Placebo: –4.8 ± 0.9 and 0.6 ± 0.2 Mean change from baseline in the PANSS-EC scale at 24 hours: olanzapine, haloperidol, and placebo (O: –6.5 ± 5.3, H: –6.7± 4.6, and P: –3.1 ± 5.1, respectively) (F=10.7, df=2, 298, p<0.001), Agitated Behavior Scale score (O: –6.4 ± 5.9, H: –6.6 ± 5.3, and P: –3.7 ± 6.7, (F=5.5, df=2, 298, p=0.004), Agitation Calmness Evaluation Scale score O: 0.8 ± 1.0, H: 1.1 ± 1.0, and P: 0.6 ± 1.2 (F=5.5, df=2, 298, p= 0.004). Pairwise comparisons (adjusted for country differences) of haloperidol and olanzapine, olanzapine, and placebo, respectively: **PANSS**: (t=–0.3, df=298, p=0.76; t=–4.2, df=	Some concerns D2- deviations from intended interventions – no information analysis used to estimate effect of intervention

Wright P; Meehan K; Birkett M; Lindborg SR; Taylor CC; Morris P; Breier A A comparison of the efficacy and safety of olanzapine versus haloperidol during transition from intramuscular to oral therapy. Clin Ther. 2003;25(5):1420-8 [13].				298, p<0.001; t=–4.4, df=298, p<0.001), the **Agitated Behavior Scale** (t=–0.1, df=298, p=0.91; t=–3.0, df=298, p=0.003; t=–3.1, df=298, p=0.002), and the **Agitation Calmness Evaluation Scale** (t=2.3, df=298, p=0.02; t=1.3, df=298, p=0.20; t=3.1, df=298, p=0.002 <u>Safety:</u> Acute dystonia: Olanzapine = 0 Haloperidol = 9 (7.1%), Fisher's exact p=0.001. Extrapyramidal syndrome: Olanzapine = 1 (0.8%), Haloperidol =seven (5.6%), p=0.03, Fisher's exact test. Received anticholinergics: Haloperidol-treated =26 (20.6%), Olanzapine-treated patients 6 (4.6%) (p<0.001, Fisher's exact test, or placebo patients 2 (3.7%) (p=0.003, Fisher's exact test). <u>2003 study</u> 85.5% (112/131) of olanzapine-treated patients and 84.1% (106/126) of haloperidol-treated patients completed the PO period. <u>Efficacy:</u> For the IM-treated patients continuing to the PO period, mean (SD) PANSS-EC scores were significantly reduced from the IM period baseline to the 24-hour IM end point with both olanzapine (-7.1 14.81; tZZZ = -14.59; P < 0.001) and haloperidol (-6.7 14.31; tZZZ = -13.06; P < 0.001, with no significant between-group differences. <u>Safety:</u> Haloperidol-treated patients spontaneously reported more acute dystonia and akathisia than olanzapine-treated patients during PO treatment (dystonia, 4.3%	Some concerns D2- deviations from intended interventions – no information analysis used to estimate effect of intervention.

				5 /116] vs 0% [0/122], respectively [P = 0.0261; akathisia, 5.2% [6/116] vs 0% [O/122], respectively [P = 0.0131). At PO period baseline, significant between group differences were found in scores on the BAS (Ft 221 = 9.26; P = 0.003) and the SAS (Fr 222 = 10.10; P = 0.002) due to a general worsening of mean EPS scores in the haloperidol group, however, no significant between-group differences were found in the changes in these scores from baseline to end point during the PO period.	
b. OLANZAPINE VERSUS PLACEBO					
Katagiri H; Fujikoshi S; Suzuki T; Fujita K; Sugiyama N; Takahashi M; Gomez JC. A randomized, double-blind, placebo-controlled study of rapid-acting intramuscular olanzapine in Japanese patients for schizophrenia with acute agitation. BMC Psychiatry Jan 2013; 13:20 [14].	Placebo-controlled, randomized, double-blind, parallel-group study in Japanese patients diagnosed with schizophrenia according to the diagnostic criteria specified in the DSM-IV-TR.	Outpatients with an exacerbation of schizophrenia with acute psychotic agitation who required hospitalization at a regular doctor visit or in an emergency room. In patients with acute psychotic agitation were eligible for this study. Patients with acute psychotic agitation were defined as those who met any of following 3 criteria: patients whose agitation occurred or worsened within the prior 2 weeks, patients who were considered to require rapid tranquilization, or patients who needed careful consideration for examination or treatment (for example, more than 1 medical staff, special room). Age 20 years – 65 years **N = 91** - 1 patient in the randomized group was excluded from full analysis due to discontinuation by physician's decision before the first IM injection. 1 patient was excluded from the efficacy analysis because	Olanzapine IM 10 mg, N = 45 Placebo, N = 45 over 24 hours	<u>Efficacy</u> Mean change of PANSS-EC total score: 2 hours: −9.2 ± 4.5 in IM olanzapine group, -2.8 ± 5.6 in IM placebo group, p < 0.001 The change from baseline to each evaluation timepoint (15, 30, 60 and 90 minutes, and 2 and 24 hours after the first IM injection) in PANSS-EC total scores was a secondary efficacy endpoint. At every timepoint, statistically significant differences were observed between IM olanzapine and IM placebo groups (p<.001 The maximum change in PANSS-EC total score in the IM olanzapine group was observed at the 2-hour time point. At the 24-hour timepoint the mean change in PANSS-EC total score in the IM olanzapine group decreased to −5.6 (from −9.2 at 2 hours), while IM placebo group remained at -2.8 (from −2.8 at 2 hours) (p=.008). At 2 hours after the first IM injection, the proportion of responders (≥40% decrease in the PANSS-EC total score) was 40% (18/45 patients) in the IM olanzapine group and	Some concerns D1 – randomization sequence not described. D2 – no further information on blinding and type of analysis used to estimate effect of intervention.

		of a problem in the maintenance of the blind. <u>Exclusion criteria:</u> Patients whose agitation continued more than 2 weeks before providing informed consent, Patients whose agitation was caused by substance abuse, neurologic conditions or the comorbidity of mental retardation or personality disorders, and Patients who had inadequately controlled diabetes, or patients whose treatments for diabetes had been changed within 4 weeks before the first IM injection of the investigational product.		13.6% (6/44 patients) in the IM placebo group At 2 hours after the first IM injection the mean agitation-calmness evaluation scale (ACES) score for IM olanzapine group was 3.5 ± 1.7 (n=45) and in the IM placebo group the mean was 2.2 ± 1.3 (n=44) <u>Safety:</u> Treatment-emergent adverse events were reported in 19 of the 90 patients during the study: 28.9% were in the IM olanzapine group, and 13.3% were in the IM placebo group. *somnolence* (IM olanzapine, n=7 [15.6%]; IM placebo, n=2 [4.4%]; p=.157) *blood urine present* (IM olanzapine, n=0; IM placebo, n=2 [4.4%]; p=.494). *Parkinsonism:* IM olanzapine group (2/43 patients, 4.7%), and in the IM placebo group (3/44 patients, 6.8%) (p=1.000)	

Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High [ ] Moderate [ ] Low [ ] Very low [X] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	<u>Olanzapine vs Benzos</u> Single trial with small sample size. <u>Olanzapine vs haloperidol + promethazine</u> Evidence uncertain – best quality RCT (n=300) used a higher equivalent dose of haloperidol. Other RCTs small and of very low certainty evidence.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large [ ] Moderate [ ] Small [X] None [ ]	<u>Vs lorazepam</u> Greater improvement (NNT 7, 95% CI 4 to 116) and slightly reduced agitation and need for additional medicines. <u>Vs haloperidol + promethazine</u> Possibly less improvement in global state but reduced aggression and agitation and no difference in sedation.
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High [ ] Moderate [ ] Low [ ] Very low [X] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	<u>Olanzapine vs Benzos</u> Single trial with small sample size. <u>Olanzapine vs haloperidol + promethazine</u> Evidence uncertain – best quality RCT (n=300) used a higher equivalent dose of haloperidol. Other RCTs small and of very low certainty evidence
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** **L**arge [ ] Moderate [ ] Small [ ] None [X]	There were no significant differences in safety outcomes
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention [ ] Favours control [ ] Intervention = Control *or* Uncertain [X]	No evidence that undesirable effects with olanzapine are worse than those of lorazepam or haloperidol + promethazine.
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes [ ] No [X]	N/a
FEASABILITY	**Is implementation of this recommendation feasible?** Yes [X] No [ ] Uncertain [ ]	Generic formulations of olanzapine IM and olanzapine ODT are available in SA.
RESOURCE USE	**How large are the resource requirements?** More intensive [ ] Less intensive [ ] Uncertain [ ]	**Price of medicines** **Medicine** | **Tender price (ZAR)** | **SEP (ZAR)** | **60% SEP ZAR** Haloperidol 5 mg tablet | 0.24* | - | - Haloperidol 5mg/ml injection | - | 45.68** | -

JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS

Lorazepam 4mg/ml injection	-	89.17***	53.50
Clonazepam 2mg/ml injection	-	55.49***	66.59
Midazolam 15mg/3ml injection	7.50****	-	-
Promethazine 50mg/2ml injection	8.22****	-	-
Olanzapine 10mg ODT	-	11.43***	6.86
Olanzapine 10 mg injection	-	72.84***	43.71

* Contract circular HP09-2021SD (weighted average price)
** SEP database, (S21 State access price)
***SEP database, July 2022 (cheapest generic price, if available)
**** Contract circular HP06-2021SVP

Comparative costing analysis

Notes:
1) Comparing maximum recommended adult doses of the various interventions.
2) Lorazepam 4mg/ml ampoule costed, noting wastage as the maximum single dose is 2mg.
3) If the medicine not available on tender, the price of the cheapest available generic was considered at 60% of SEP.
4) Olanzapine co-administered with parenteral benzodiazepines not recommended due to the possible safety concerns of respiratory depression (expert opinion).
5) Only direct medicine prices considered (excluding administration costs)

Recommended treatment protocols and price per treatment course

a. Current standard of care (PHC STG, 2020/ Adult Hospital Level STG, 2019)
If initial oral benzodiazepine dose not sufficient:
- Lorazepam, IM, 0.5–2 mg, immediately

OR
- Midazolam, IM, 7.5–15 mg immediately

OR
- Clonazepam, IM, 0.5–2 mg, immediately

(may repeat dose if required)

Inadequate response to benzodiazepines (after 30-60 minutes):
- Haloperidol, IM, 2.5–5 mg, immediately.

AND
- Promethazine, deep IM, 25–50 mg.

(may repeat dose if required)

COST FOR TREATMENT COURSE A (maximum dosing):

Treatment protocol	60%SEP + contract price (ZAR)
• Lorazepam protocol	214.81
• Midazolam protocol	122.80
• Clonazepam protocol	240.98

b. Proposed olanzapine recommendation
If initial oral benzodiazepine dose not sufficient:
- Olanzapine 5-10 mg, ODT, immediately

OR
- Olanzapine 5-10 mg, IM, immediately

(may repeat dose 30-60 minutes later, if required)

COST FOR TREATMENT COURSE B (maximum dosing):

Treatment protocol	60%SEP (ZAR)
• Olanzapine ODT	13.72
• Olanzapine, IM	87.41

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
		Other resources: n/a
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [ ] Major [ ] Uncertain [X] **Is the option acceptable to key stakeholders?** Yes [X] No [ ] Uncertain [ ]	There is no local survey data available, and judgements were based on Committee expert opinion through consensus.
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [X] Uncertain [ ]	

Version	Date	Reviewer(s)	Recommendation and rationale
Initial	29 September 2022	LR, TK, MM, NG, SM, TL	Haloperidol IM is no longer available in South Africa, and olanzapine oro-dispersible tablets or IM may be considered as an alternative. Olanzapine may be superior to lorazepam and to the combination of haloperidol and promethazine in reducing agitated or aggressive behaviour (very low certainty evidence).
Version 2	14 March 2024	LR, TK, MM, NG, SM, TL	NEMLC, deliberated the erratic supply of Haloperidol IM, but retained the proposal as recommended by the PHC/Adult Hospital Level Expert Review Committee. Wording revisions regarding erratic Haloperidol IM supply was added to the review.

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12. Wright P, Birkett MA, Meehan K, David SR, Brook S, Breier. A double-blind dose response study comparing intramuscular olanzapine, haloperidol and placebo in acutely agitated schizophrenic patients. Schizophrenia research (abstracts of the VIII international congress on schizophrenia research; 2001 april 28-may 2; british columbia, canada). 2001;49(1‐2 Suppl):250‐1,
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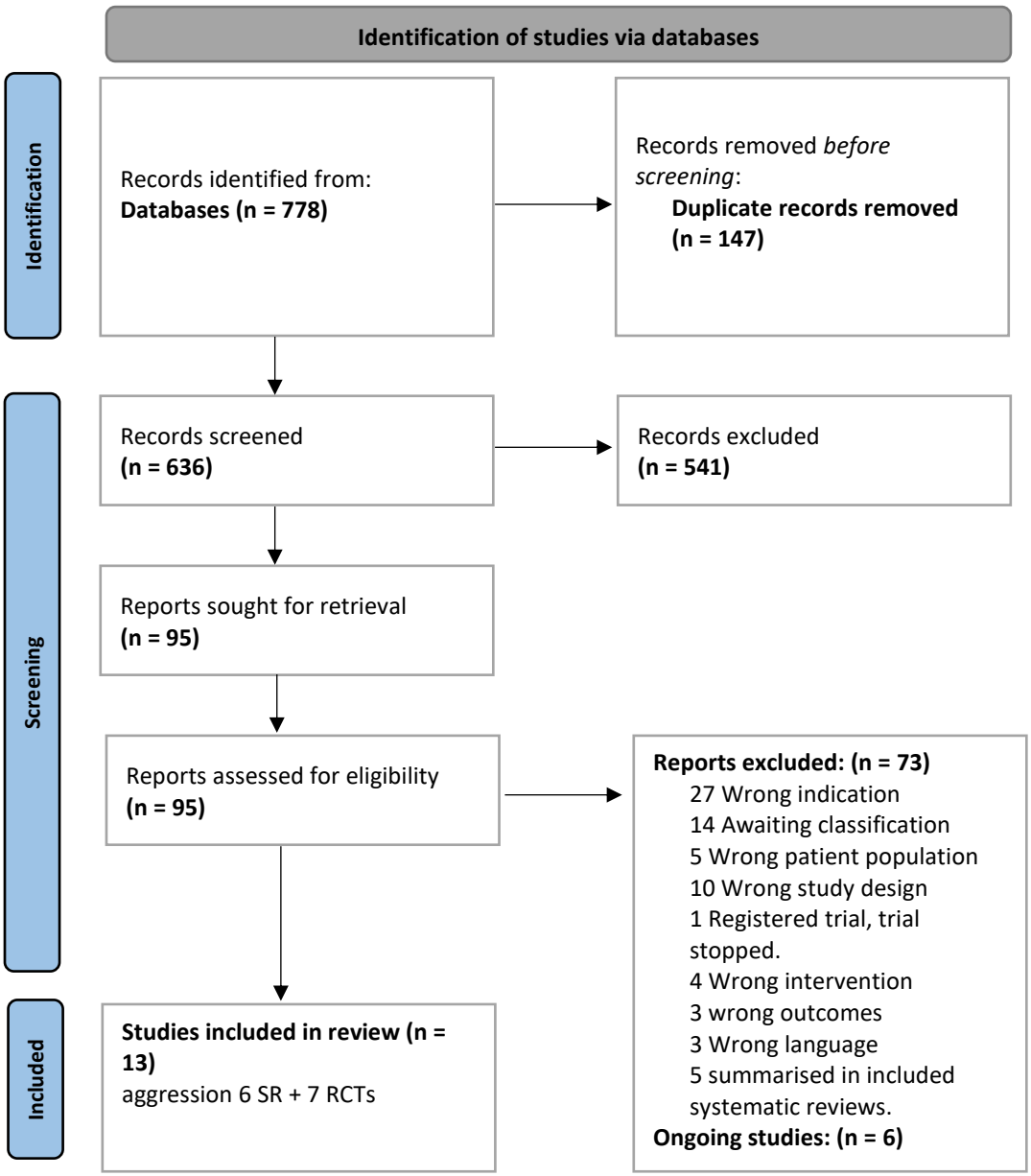
Appendix 1: Search strategy

#9	#1 AND #2 AND #8
#8	#3 OR #4 OR #5 OR #6 OR #7
#7	schizophrenia[mh] OR schizophreni*[tiab]
#6	dementia[mh] OR dementia*[tiab]
#5	confusion[mh] OR confus*[tiab] OR disorientat*[tiab] OR bewilderment[tiab] OR delirium*[tiab]
#4	paranoid disorders[mh] OR paranoi*[tiab]
#3	psychotic disorders[mh] OR psychosis[tiab] OR psychotic[tiab] OR psychoses[tiab] OR psychiatric disorder*[tiab] OR mental disorders[mh] OR mental illness*[tiab] OR mental disorder*[tiab] OR mood disorders [mh] OR mood disorder*[tiab] OR affective disorder*[tiab] OR bipolar disorder[mh] OR bipolar[tiab] OR mania*[tiab] OR manic[tiab]
#2	Search: aggression[mh] OR aggress*[tiab] OR disruptive behavior*[tiab] OR disruptive behaviour*[tiab] OR agitat*[tiab] OR violent behavior*[tiab] OR violent behaviour*[tiab]
#1	Search: olanzapine[mh] OR olanzapine*[tiab] OR zyprexa*[tiab] OR zolafren*[tiab] OR LY 170053[tiab] OR LY170053[tiab] OR LY 170052[tiab]

Appendix 2: PRISMA flow chat identified studies



Modified From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. http://www.prisma-statement.org/

Appendix 3: Excluded studies

Author, date	Type of study	Reason for exclusion
1. Finucane 2020	SR	Wrong indication
2. Fernández Sánchez, 2009	SR	Wrong indication
3. Belgamwar 2005	SR	Wrong indication
4. Burry, 2018	SR	Wrong indication
5. Burry, 2019	SR	Wrong indication
6. Nikooie, 2019	SR	Wrong indication
7. NICE review	SR	Wrong indication
8. Huf, 2009	SR	Wrong language
9. Lacasse, 2016	SR	Wrong intervention
10. Maglione, 2011	SR	Wrong indication
11. Mühlbauer, 2021	SR	Wrong patient population
12. Pelland, 2009	SR	Wrong language
13. Seida, 2012	SR	Wrong patient population
14. Shoptaw, 2009	SR	Wrong indication
15. Williamson, 2019	SR	Wrong indication
16. Yildiz, 2003	SR	Wrong language
17. Yildiz, Sachs 2003	SR	Wrong study design
18. Yunusa, 2019	SR	Wrong indication
19. Skrobik 2004	RCT	Wrong indication
20. Van der Vorst	RCT	Wrong indication
21. Jain 2017	RCT	Wrong indication
22. Beasley, 1996	RCT	Wrong indication
23. Bozzatello, 2017	RCT	Wrong patient population
24. Breier, 2000	RCT	Awaiting classification
25. Breier, 2001	RCT	Awaiting classification
26. Battaglia 2005	RCT	Wrong outcome
27. Clark, 2001	RCT	Wrong indication
28. David, 2001	RCT	Awaiting classification
29. Eli, 2005	RCT	Awaiting classification
30. Faay, 2020	RCT	Wrong indication
31. Fontaine, 2003	RCT	Wrong patient population
32. Gareri, 2004	RCT	Wrong indication
33. Huf, 2009	RCT	Wrong intervention
34. Hwang, 2012	RCT	Awaiting classification
35. Jin, 2009	RCT	Awaiting classification
36. Kinon, 2000	RCT	Wrong indication
37. Kinon, 2001	RCT	Wrong outcomes
38. Kittipeerachon, 2016	RCT	Wrong intervention
39. Kong, 2009	RCT	Awaiting classification
40. Krakowski, 2014	RCT	Wrong indication
41. Lindbord, 2003	RCT	Wrong outcomes
42. Meehan, 2001	RCT	Awaiting classification
43. Meehan, 2001 (1)	RCT	Awaiting classification
44. Meehan, 2001 (2)	RCT	Awaiting classification
45. Mintzer, 2002	RCT	Awaiting classification
46. Ono, 2008	RCT	Awaiting classification
47. Schneider, 2006	RCT	Wrong indication
48. Smith, 2003	RCT	Awaiting classification
49. Street, 2000	RCT	Wrong patient population
50. Svestka, 2002	RCT	Awaiting classification
51. Verhey, 2006	RCT	Wrong indication
52. Villari, 2009	RCT	Wrong intervention

53. Hirsch, 2019	Narrative review	Wrong study design
54. Houston, 2019	Narrative review	Wrong study design
55. Wagstaff, 2005	Narrative review	Wrong study design
56. Pascual, 2007	Observational study	Wrong study design
57. Walther, 2014	Observational study	Wrong study design
58. NCT00833300, 2009	Registered trial	Registered trial, trial stopped for recruitment issues
59. Elsayem, 2010	Pilot study	Wrong study design
60. Citrome, 2007	Quantitative review	Wrong study design
61. Srivastava, 2010	Summary of review	Wrong study design
62. deAlmeida, 2017	Review of reviews	Wrong study design
63. IRCT20200927048852N1 2020	Ongoing trial	Wrong indication
64. NCT00485901	Ongoing trial	Wrong indication
65. NCT04750395 2021	Ongoing trial	Wrong indication
66. IRCT20141209020258N114 2019	Ongoing trial	Wrong indication
67. NCT04833023 2021	Ongoing trial	Wrong indication
68. Jones, 2001	Summary of RCTs	Wrong study design
69. Battaglia 2003	RCT	Summarized in included systematic review
70. Baldacara 2011	RCT	Summarized in included systematic review
71. Raveendran 2007	RCT	Summarized in included systematic review
72. Mehaan 2002	RCT	Summarized in included systematic review
73. Breier 2002	RCT	Summarized in included systematic review

Appendix 4: Systematic reviews excluded from evidence synthesis

Citation	INTERVENTION	Appraisal
Paris G, Bighelli I, Deste G, Siafis S, Schneider-Thoma J, Zhu Y, Davis JM, Vita A, Leucht S. Short-acting intramuscular second-generation antipsychotic drugs for acutely agitated patients with schizophrenia spectrum disorders. A systematic review and network meta-analysis. Schizophr Res. 2021 Mar;229:3-11. doi: 10.1016/j.schres.2021.01.021. Epub 2021 Feb 17. PMID: 33607608.	Network meta-analysis of antipsychotics: Ziprasidone, olanzapine, aripiprazole, haloperidol and placebo	Low
Bak M, Weltens I, Bervoets C, De Fruyt J, Samochowiec J, Fiorillo A, Sampogna G, Bienkowski P, Preuss WU, Misiak B, Frydecka D, Samochowiec A, Bak E, Drukker M, Dom G. The pharmacological management of agitated and aggressive behaviour: A systematic review and meta-analysis. Eur Psychiatry. 2019 Apr;57:78-100. doi: 10.1016/j.eurpsy.2019.01.014. Epub 2019 Feb 2. PMID: 30721802.	Comparison of various antipsychotics including haloperidol plus promethazine, risperidone, olanzapine, droperidol and aripiprazole.	Low
Tulloch KJ, Zed PJ. Intramuscular olanzapine in the management of acute agitation. Ann Pharmacother. 2004 Dec;38(12):2128-35. doi: 10.1345/aph.1E258. Epub 2004 Nov 2. PMID: 15522977.	Olanzapine versus haloperidol / lorazepam monotherapy	Low
Dundar Y, Greenhalgh J, Richardson M, Dwan K. Pharmacological treatment of acute agitation associated with psychotic and bipolar disorder: a systematic review and meta-analysis. Hum Psychopharmacol. 2016 Jul;31(4):268-85. doi: 10.1002/hup.2535. Epub 2016 May 5. PMID: 27151529.	Comparison of antipsychotics of various including olanzapine, aripiprazole, risperidone, lorazepam or placebo	Low