health
Department:
Health
REPUBLIC OF SOUTH AFRICA

2030 NDP

SOUTH AFRICAN ADULT HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 15: MENTAL HEALTH CONDITIONS AND SUBSTANCE MISUSE
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2017 -2019)

Medicine amendment recommendations, with supporting evidence and rationale are listed below.
Kindly review the medicine amendments in the context of the chapter for mental health care conditions.

SECTION	MEDICINE/MANAGEMENT	ADDED/DELETED/AMENDED/RETAINED
MENTAL HEALTH CONDITIONS		
15.1 Aggressive disruptive behaviour in adults		
- Benzodiazepines	Benzodiazepines, oral/IM	Cautionary added; dosing amended; repeat dosing amended to minimum of 30 minute intervals
	Diazepam, IV-	Deleted
- Antipsychotics	Risperidone. oral	Not added as first line option (ipo benzodiazepines)
	Haloperidol, oral	Not added as first line option (ipo benzodiazepines)
- Inadequate response to benzodiazepines	Haloperidol, IM	Recommended for psychosis- induced aggression
	Promethazine, IM	Recommended for psychosis- induced aggression
- If haloperidol is unavailable	Chlorpromazine, IM	Deleted
	Clotiapine, IM	Added as an alternate option to haloperidol oin the therapeutic interchange database
- Under specialist care in psychiatric wards	Zuclopenthixol acetate, IM	Prescriber level amended
- If alcohol use suspected	Thiamine, oral	Added
- If patient develops acute dystonia	Anticholinergic	Deleted, but cross-referenced to PHC STGs and EML, 2018
	Biperiden, parenteral	Deleted, but cross-referenced to PHC STGS and EML, 2018
	Promethazine, parenteral	Deleted, but cross-referenced to PHC STGS and EML, 2018
15.2 Anxiety and obsessive-compulsive disorders	Fluoxetine, oral	Retained as first line SSRI treatment; directions for use amended
	Citalopram, oral	Retained as an example of second-line SSRI treatment; directions for use amended
- For short term use only in severe acute distress	Diazepam, oral	Dosing amended
- Pregnancy/breastfeeding	Antidepressants, benzodiazepines	Caution box included regarding use in pregnancy and breastfeeding
	Sertraline, oral	Not added
	Citalopram, oral	Retained as first-line option
	Treatment algorithm for depression & anxiety in pregnancy/ breastfeeding	Added
15.3.1 Depressive disorders	Fluoxetine, oral	Retained as first line SSRI treatment; directions for use amended
	Citalopram, oral	Retained as an example of second-line SSRI treatment; directions for use amended
	Amitryptiline, oral	Directions for use amended
	Combination pharmacotherapy and psychotherapy	For review in next cycle
- Pregnancy/breastfeeding	Sertraline, oral	Not added
	Citalopram, oral	Retained as first-line option
	Antidepressant/benzodiazepines	Caution box for use in pregnancy/breastfeeding added
15.3.2 Bipolar and related disorders	Management of bipolar disorder (BD)	Amended to include acute manic/depressive treatment of BD **AND** maintenance to prevent manic/depressive episodes of BD; manage in consultation with a psychiatrist
- BD: predominantly manic course of illness		
- Acute management of mania	Haloperidol, IM	Retained for aggressive and/or disruptive behaviour
- Manic symptoms	Lithium, oral	Emphasised as 1st line option for treatment and maintenance
	Valproate, oral	Retained as 2nd line option for treatment and maintenance

	Olanzapine, oral	Added as 3rd line option for treatment and maintenance (specialist prescribed)
- Depressive symptoms (new onset after manic episode)	Lithium, oral	Emphasised as 1st line option for treatment and maintenance
	Lamotrigine, oral	Added as 2nd line option for treatment and maintenance
	Quetiapine, oral	Added as 3rd line option for treatment and maintenance (specialist prescribed) and guidance provided for dose titration
	Antidepressants, oral	Not added as monotherapy or as adjunctive therapy with mood stabilizer or antipsychotic
- Treatment resistant bipolar disorder	Clozapine, oral	Added for refractory bipolar disorder (specialist prescribed)
B) BD - predominantly depressive course of illness		
- Previous algorithm	Carbamazepine, oral	Deleted
	Olanzapine + fluoxetine, oral	Deleted
- No previous history of mania (BD II or other specified BD)	Lithium, oral	Emphasised as 1st line option for treatment and maintenance
	Lamotrigine, oral	Retained as 2nd line option for treatment and maintenance
	Quetiapine, oral	Added as 3rd line option for treatment and maintenance (specialist prescribed)
- Previous manic episode (BD I)	Lithium, oral	Emphasised as 1st line option for treatment and maintenance in adequate dose to prevent mania
	Valproate, oral	Retained as 2nd line option for treatment and maintenance
	Olanzapine, oral	Added as 3rd line option for treatment and maintenance (specialist prescribed)
- Treatment resistant bipolar disorder	Clozapine, oral	Added for refractory bipolar disorder (specialist prescribed)
- Other	Combination treatment	Not added
	Lithium, oral	Caution box amended
	Guidance for bipolar disorder in pregnancy and postpartum	Added
15.4 Trauma and stress-related disorders	Non-pharmacological interventions	For review in next cycle
15.5.1 Acute and transient psychotic disorders	Management aligned with acute disruptive disorders	Cross-referenced to section 15.1: Aggressive disruptive behaviour in adults.
15.5.2 Schizophrenia spectrum disorders	Treatment protocol	Amended and manage in consultation with a psychiatrist
	Haloperidol, oral	Dose amended
	Flupenthixol decanoate, IM	Directions for use amended and dose amended
	Zuclopenthixol decanoate, IM	Directions for use amended and dose amended
	Olanzapine, oral	Added as 2nd/3rd line option
	Clozapine, oral	Added with a caution box
15.6 Insomnia	Short-acting benzodiazepines, oral	Retained as a therapeutic class
	Oxazepam, oral	Retained as example of class
	Antihistamines, oral	For review in next cycle
SUBSTANCE MISUSE		
15.8.1 Alcohol withdrawal delirium (delirium tremens)	Haloperidol, oral	Dose amended
15.9 Opiate withdrawal, e.g. heroin	Opioid withdrawal	Treatment protocol amended (using OOWS rating scale)
	Methadone, oral	Retained; directions for use not amended
	Buprenorphine, oral	Not listed in the STG, but added to therapeutic interchange database
Methadone opioid substitution treatment	Methadone, oral	Response still awaited from NDoH Mental Health Directorate regarding costed implementation strategy, with allocated budget
15.12 Cannabis withdrawal	Diazepam, oral	Not added
15.13 Benzodiazepine withdrawal	Diazepam, oral	Dose reduction protocol expanded

Updated chapter layout:

Mental Health Conditions

15.1 Aggressive disruptive behaviour in adults
15.2 Anxiety and obsessive-compulsive disorders
15.3 Mood disorders
  15.3.1 Depressive disorders
  15.3.2 Bipolar and related disorders
15.4 Trauma and stress-related disorders
15.5 Psychotic disorders

15.5.1 Acute and transient psychotic disorders
15.5.2 Schizophrenia spectrum disorders
15.6 Insomnia
15.7 Discontinuation symptoms of serotonin reuptake inhibitors

Substance misuse
15.8 Opiate withdrawal, e.g. heroin
15.9 Stimulant withdrawal, including cocaine and methamphetamines
15.10 Methaqualone withdrawal
15.11 Cannabis withdrawal
15.12 Benzodiazepine withdrawal

- Section 15.2 Confusional states/delirium moved to emergencies and injuries chapter as a medical emergency.
- Sections 15.3 Bipolar Disorder, 15.4 Depressive Disorder, Major, and 15.5 Persistent depressive disorder (dysthymic disorder) grouped together under 15.3 "Mood Disorders."
- Sections 15.4 Depressive Disorder, Major and 15.5 Persistent depressive disorder (dysthymic disorder) grouped together in Section 15.3.1 Depressive Disorders, a subsection of the Mood Disorders STG.
- Section 15.3 Bipolar Disorder amended to "Bipolar and related disorders", a subsection of the Mood Disorders STG
- Sections 15.6 Generalised Anxiety Disorder, 15.7 Obsessive-compulsive disorder, and 15.8 Panic Disorder grouped together as Section 15.2 Anxiety and Obsessive-Compulsive Disorders as they are often comorbid condition and share a common management protocol at the Adult Hospital level of care.,
- Section 15.9 Acute stress disorder and post-traumatic stress disorder amended sub-heading to "Trauma and stress-related disorders".
- Sections 15.4 Psychosis, acute and 15.11: Schizophrenia grouped under 15.6: Psychotic disorders.
- Section 15.10 Psychosis, acute amended to "Acute and transient psychotic disorders", a sub-section of Psychotic disorders.
- Section 15.11 Schizophrenia amended to "15.6.2 Schizophrenia spectrum disorders", a sub-section of Psychotic disorders.

Management was aligned with NEMLC approved PHC STG, 2018 and clinical practice, as appropriate.

General

- Guidance for maternal health conditions in pregnancy and during breastfeeding was added throughout the chapter, generally aligned with NICE[1] and British Association of Psychopharmacology (BAP) Guidelines[2].
- Sections 15.8: Alcohol and 15.8.1 Alcohol withdrawal delirium (delirium tremens) had been erroneously removed – perhaps for consideration of the poisonings chapter; but has been reinserted into the chapter.
- Determining which non-pharmacological interventions should be offered and at which service level and by which categories of allied health professionals requires a comprehensive HTA.
  Recommendation: The Adult Hospital Level Committee recommends that a comprehensive HTA be commissioned to determine which non-pharmacological treatment, at which level by which category of healthcare workers for management of mental health in the South African setting.

15.1 AGGRESSIVE DISRUPTIVE BEHAVIOUR IN ADULTS

General measures

General measures aligned with PHC STGs and EML, 2018 but adapted to include management at secondary level of care.

Rapid tranquilisation

Benzodiazepines: *cautionary added*

Cautionary guidance provided for rapid tranquilisation in the elderly, intellectually disabled, substance users and patients with comorbid conditions (with cross-referencing to the PHC STGs and EML, 2018 or other Adult Hospital Level chapters for management of acute complications associated with antipsychotic use – respiratory depression, circulatory collapse,

[1] National Institute for Health and Clinical Excellence (NICE). Antenatal and postnatal mental health: the NICE guideline on clinical management and service guidance. Updated edition. NICE clinical guidance 192. London: NICE; 2014. Available from: https://www.nice.org.uk/guidance/cg192/evidence/full-guideline-pdf-19339686

[2] British Association for Psychopharmacology consensus guidance on the use of psychotropic medication preconception, in pregnancy and postpartum 2017. McAllister-Williams RH, Baldwin DS, Cantwell R, Easter A, Gilvarry E, Glover V, Green L, Gregoire A, Howard LM, Jones I, Khalifeh H, Lingford-Hughes A, McDonald E, Micali N, Pariante CM, Peters L, Roberts A, Smith NC, Taylor D, Wieck A, Yates LM, Young AH, endorsed by the British Association for Psychopharmacology. J Psychopharmacol. 2017;31:519. Available from: https://www.bap.uk

acute dystonia and neuroleptic malignant syndrome).
The following cautionary box was added to the text, supported by detailed information yin the text of the STG; includes cautious management in pregnancy, aligned with NICE[3] and British Association of Psychopharmacology (BAP) Guidelines[4]:

CAUTION

» Rapid tranquillisation may cause cardiovascular collapse, respiratory depression, acute dystonic reactions and neuroleptic malignant syndrome.
» Pregnant women, the elderly, children, intellectually disabled and those with comorbid medical conditions and substance users are at highest risk.
» 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.**

Level of Evidence: III Guidelines

Benzodiazepines, oral/IM: *dosing amended*
Equivalent dosing of benzodiazepines for rapid tranquilisation – which varies slightly between references, was reviewed:
Equivalent dosing vary slightly from reference to reference. Summary in Table below:

	Maudsley[5]	**Bazire[6]**	**UpToDate[7]**	**SAMF[8]**
Lorazepam	0.5mg	0.5mg	1mg	1mg
Clonazepam	0.5-1mg	0.5mg (0.25 - 4mg)	0.25-0.5mg	
Diazepam	5mg	5mg	5mg	5mg
Midazolam				7.5mg

Recommendation: The Adult Hospital Level Committee recommended a lower range of doses for lorazepam, oral/IM, clonazepam, oral/IM and diazepam, oral to align with Maudsley Prescribing Guidelines[9].
Level of Evidence: III Guidelines

A further review of the evidence by the Adult Hospital Level Committee found the following:

- The active metabolites increase the half-life of some of the benzodiazepines.
- There is no risk of accumulation of lorazepam with repeated dosing. There is a risk of accumulation and enhanced adverse effects, with multiple dosing of all formulations of diazepam and of oral clonazepam[10].
- Midazolam, IM leads to a quicker time to sedation than IM lorazepam (18 minutes versus 32 minutes)[11]. Time to maximum concentration is shortest for buccal and IM midazolam (30 minutes), followed by oral and IM lorazepam (1-2 hours)[12]. Of consideration is the short half-life of IM midazolam, with its rapid clinical effect not being sustained as long as for lorazepam (81.9 minutes versus 217.2 minutes)[13].

[3] National Institute for Health and Clinical Excellence (NICE). Antenatal and postnatal mental health: the NICE guideline on clinical management and service guidance. Updated edition. NICE clinical guidance 192. London: NICE; 2014. Available from: https://www.nice.org.uk/guidance/cg192/evidence/full-guideline-pdf-19339686
[4] British Association for Psychopharmacology consensus guidance on the use of psychotropic medication preconception, in pregnancy and postpartum 2017. McAllister-Williams RH, Baldwin DS, Cantwell R, Easter A, Gilvarry E, Glover V, Green L, Gregoire A, Howard LM, Jones I, Khalifeh H, Lingford-Hughes A, McDonald E, Micali N, Pariante CM, Peters L, Roberts A, Smith NC, Taylor D, Wieck A, Yates LM, Young AH, endorsed by the British Association for Psychopharmacology. J Psychopharmacol. 2017;31:519. Available from: https://www.bap.uk
[5] Taylor, David; Paton, Carol; Kapur, Shitij. The Maudsley Prescribing Guidelines, Twelfth Edition. London: CRC Press; 2015
[6] Bazire, S. (2016). Psychotropic Drug Directory 2016: The Professionals' Pocket Handbook and Aide Memoire 2016. Stratford Upon Avon: Lloyd-Reinhold Publications Ltd. p216.
[7] Park, T.W. Benzodiazepine use disorder: Epidemiology, pathogenesis, clinical manifestations, course, and diagnosis. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. https://www.uptodate.com (Accessed on August 16, 2019).
[8] SAMF, 2016
[9] Taylor, David; Paton, Carol; Kapur, Shitij. The Maudsley Prescribing Guidelines, Twelfth Edition. London: CRC Press; 2015
[10] Patel MX, Sethi FN, Barnes TR, Dix R, Dratcu L, Fox B, Garriga M, Haste JC, Kahl KG, Lingford-Hughes A, McAllister-Williams H, O'Brien A, Parker C, Paterson B, Paton C, Posporelis S, Taylor DM, Vieta E, Völlm B, Wilson-Jones C, Woods L; With co-authors (in alphabetical order):. Joint BAP NAPICU evidence-based consensus guidelines for the clinical management of acute disturbance: De-escalation and rapid tranquillisation. J Psychopharmacol. 2018 Jun;32(6):601-640. https://www.ncbi.nlm.nih.gov/pubmed/29882463
[11] Nobay F, Simon BC, Levitt MA, Dresden GM. A prospective, double-blind, randomized trial of midazolam versus haloperidol versus lorazepam in the chemical restraint of violent and severely agitated patients. Acad Emerg Med. 2004 Jul;11(7):744-9. https://www.ncbi.nlm.nih.gov/pubmed/15231461
[12] Patel MX, Sethi FN, Barnes TR, Dix R, Dratcu L, Fox B, Garriga M, Haste JC, Kahl KG, Lingford-Hughes A, McAllister-Williams H, O'Brien A, Parker C, Paterson B, Paton C, Posporelis S, Taylor DM, Vieta E, Völlm B, Wilson-Jones C, Woods L; With co-authors (in alphabetical order):. Joint BAP NAPICU evidence-based consensus guidelines for the clinical management of acute disturbance: De-escalation and rapid tranquillisation. J Psychopharmacol. 2018 Jun;32(6):601-640. https://www.ncbi.nlm.nih.gov/pubmed/29882463
[13] Nobay F, Simon BC, Levitt MA, Dresden GM. A prospective, double-blind, randomized trial of midazolam versus haloperidol versus lorazepam in the chemical restraint of violent and severely agitated patients. Acad Emerg Med. 2004 Jul;11(7):744-9. https://www.ncbi.nlm.nih.gov/pubmed/15231461

Conclusion: All benzodiazepines share the same adverse effect profile, with respiratory depression being more prominent with parenteral midazolam, compared to parenteral lorazepam[14]. The choice of benzodiazepine will depend on availability of formulations, rapidity of onset of sedation, clinical indication for sedation, duration of time that sedation is required, and risk of accumulation with repeated dosing. Onset of sedation is generally equal for both IM and oral preparations, for lorazepam and midazolam respectively[15]. Hence, the oral formulation could be considered above IM, if oral dosing is preferred by the patient. There are limited data to safely recommend the use of diazepam or clonazepam as monotherapy for sedation. Lorazepam deems to be the most preferred option. Onset of sedation is slower yet maintained for longer, and need of repeat dosing is reduced compared to midazolam. Furthermore, there is no risk of accumulation with repeated dosing in any formulation of lorazepam.

Benzodiazepine, oral/IM repeat dosing: *amended to minimum of 30 minute intervals*
Text of STG was amended to recommend repeat dosing of benzodiazepines at a minimum of *"30 minutes"* rather than *"15 minutes"*. Intramuscular midazolam leads to a quicker time to sedation than IM lorazepam (18 minutes versus 32 minutes)[16]; whilst time to maximum concentration is shortest for buccal and IM midazolam (30 minutes), followed by oral and IM lorazepam (1-2 hours)[17].
Level of Evidence: III Disease oriented RCT, Guidelines

And, the following was added to the STG, aligned with Guidelines:

» 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.

Level of Evidence: III Guidelines[18]

Treatment protocol
To minimise the possibility of double dosing benzodiazepines, before an antipsychotic is administered, text was editorially amended as follows:

Parenteral treatment:
- Benzodiazepines (if not already administered orally):

Diazepam, IV: *deleted*
No available evidence could be sourced for diazepam, IV for rapid tranquilisation and it was considered reasonable to delete diazepam, IV use in this clinical setting.
Level of Evidence: III Expert opinion

Antipsychotics
Risperidone, oral: *not added as first line option*
Haloperidol, oral: *not added as first line option*
Cochrane review suggests that oral antipsychotics (risperidone) may not beneficial as first line option for rapid tranquilisation[19]; benzodiazepines followed by IM antipsychotics are preferred (previous STG standard of care).
Level of Evidence: II Systematic review of low quality RCTs

Treatment of psychosis- induced aggression (Inadequate response to benzodiazepines)
Haloperidol, IM: *recommended for psychosis- induced aggression*

[14] Nobay F, Simon BC, Levitt MA, Dresden GM. A prospective, double-blind, randomized trial of midazolam versus haloperidol versus lorazepam in the chemical restraint of violent and severely agitated patients. Acad Emerg Med. 2004 Jul;11(7):744-9. https://www.ncbi.nlm.nih.gov/pubmed/15231461
[15] Patel MX, Sethi FN, Barnes TR, Dix R, Dratcu L, Fox B, Garriga M, Haste JC, Kahl KG, Lingford-Hughes A, McAllister-Williams H, O'Brien A, Parker C, Paterson B, Paton C, Posporelis S, Taylor DM, Vieta E, Völlm B, Wilson-Jones C, Woods L; With co-authors (in alphabetical order):. Joint BAP NAPICU evidence-based consensus guidelines for the clinical management of acute disturbance: De-escalation and rapid tranquillisation. J Psychopharmacol. 2018 Jun;32(6):601-640. https://www.ncbi.nlm.nih.gov/pubmed/29882463
[16] Nobay F, Simon BC, Levitt MA, Dresden GM. A prospective, double-blind, randomized trial of midazolam versus haloperidol versus lorazepam in the chemical restraint of violent and severely agitated patients. Acad Emerg Med. 2004 Jul;11(7):744-9. https://www.ncbi.nlm.nih.gov/pubmed/15231461
[17] Patel MX, Sethi FN, Barnes TR, Dix R, Dratcu L, Fox B, Garriga M, Haste JC, Kahl KG, Lingford-Hughes A, McAllister-Williams H, O'Brien A, Parker C, Paterson B, Paton C, Posporelis S, Taylor DM, Vieta E, Völlm B, Wilson-Jones C, Woods L; With co-authors (in alphabetical order):. Joint BAP NAPICU evidence-based consensus guidelines for the clinical management of acute disturbance: De-escalation and rapid tranquillisation. J Psychopharmacol. 2018 Jun;32(6):601-640. https://www.ncbi.nlm.nih.gov/pubmed/29882463
[18] Patel MX, Sethi FN, Barnes TR, Dix R, Dratcu L, Fox B, Garriga M, Haste JC, Kahl KG, Lingford-Hughes A, McAllister-Williams H, O'Brien A, Parker C, Paterson B, Paton C, Posporelis S, Taylor DM, Vieta E, Völlm B, Wilson-Jones C, Woods L; With co-authors (in alphabetical order):. Joint BAP NAPICU evidence-based consensus guidelines for the clinical management of acute disturbance: De-escalation and rapid tranquillisation. J Psychopharmacol. 2018 Jun;32(6):601-640. https://www.ncbi.nlm.nih.gov/pubmed/29882463
[19] Ostinelli EG, Hussein M, Ahmed U, Rehman FU, Miramontes K, Adams CE. Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation). Cochrane Database Syst Rev. 2018 Apr 10;4:CD009412. https://www.ncbi.nlm.nih.gov/pubmed/29634083

Promethazine, IM: *recommended for psychosis- induced aggression*

The following statement was added to the STG:

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

External comment was received from the South African Medical Association stating that Zaman et al "*found that the evidence for the use of benzodiazepines alone is not good and that most trials were too small to be able to highlight the differences in either positive or negative effects of the different agents and combinations included in the review*".

Small RCT reviewed in this systematic review, that compared combined benzodiazepines/ antipsychotics vs combined antihistamines/antipsychotic, showed a higher risk of no clinical improvement (n = 60, 1 RCT, RR 25.00, 95% CI 1.55 to 403.99, very low quality evidence) and sedation status (n = 60, 1 RCT, RR 12.00, 95% CI 1.66 to 86.59, very low quality evidence) in the combined benzodiazepines/antipsychotics group.

Level of Evidence: III Systematic review of single RCT of low quality evidence[20]

If haloperidol is unavailable:

Chlorpromazine, IM: *deleted*

Clotiapine, IM: *added as an alternate option to haloperidol on the therapeutic interchange database*

Historically, the erratic supply of haloperidol warranted chlorpromazine to be included in the STG as an alternative option as a rapid tranquilliser following administration of a benzodiazepine. However, supply of chlorpromazine, IM is also unreliable, and clotiapine may be considered.

Refer to the previously NEMLC- approved PHC/Adult medicine review, clotiapine injection for acute aggressive disruptive behaviour in adults, June 2017:

Clotiapinelnj for aggressive disruptiv

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

NEMLC MEETING OF 11 JULY 2019:

Alternate option to haloperidol, IM (clotiapine) not be included in the STG; as the STGs generally do not recommend alternative options due to supply challenges. The information is disseminated to health care workers via NDoH circular and should preferably be included on the Therapeutic Interchange database.

Under specialist care in psychiatric wards

Zuclopenthixol acetate, IM: *prescriber level amended*

Refer to the previously NEMLC- approved PHC/Adult medicine review, zuclopenthixol acetate for acute psychosis in Adults (June 2017):

ZuclopenthixolAcet ate for acute psycho

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Zuclopenthixol acetate has no advantage over haloperidol except for needing fewer coercive injections over 72 hours, due to its very long half-life. Zuclopenthixol acetate has been removed with warnings from NICE rapid tranquillisation guidelines and is associated with life-threatening neuroleptic malignant syndrome[21]. However, the Adult Hospital Level Committee was of the opinion that access may be required remotely and recommendation amended to prescribing by a specialist or in consultation with a specialist.

Level of Evidence: III Guidelines[22], Case Series/Report(s)[23] [24], Expert opinion

[20] 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

[21] NICE Clinical Guideline. Violence and aggression: short-term management in mental health, health and community settings 2015. Available from: www.nice.org.uk/guidance/ng10

[22] SAMF, 2016

[23] Henderson T. Neuroleptic malignant syndrome in adolescents: four probable cases in the Western Cape. S Afr Med J. 2011 May 25;101(6):405-7. https://www.ncbi.nlm.nih.gov/pubmed/21920075

[24] Erermis S, Bildik T, Tamar M, Gockay A, Karasoy H, Ercan ES. Zuclopenthixol-induced neuroleptic malignant syndrome in an adolescent girl. Clin Toxicol (Phila). 2007;45(3):277-80. https://www.ncbi.nlm.nih.gov/pubmed/17453880

If alcohol use is suspected:
Thiamine, oral: *added*
Recommended to prevent Wernicke-Korsakoff syndrome.

If patient develops acute dystonia:
Anticholinergic: *deleted, but cross-referenced to PHC STGs and EML, 2018*
Biperiden, parenteral: *deleted, but cross-referenced to PHC STGs and EML, 2018*
Promethazine, parenteral: *deleted, but cross-referenced to PHC STGs and EML, 2018*

15.2 ANXIETY AND OBSESSIVE-COMPULSIVE DISORDERS

External comment was received by SAMA regarding operational and process issues. The Adult Hospital Level Committee recognizes the need for a clinical guideline for all levels of care and that the mapping of resource availability is essentially the responsibility of district specialist mental health teams.
Guidance aligned with PHC STGs and EML, 2018 with adaptation for secondary/regional level of care, including non-pharmacological anxiety management techniques.

Selective Serotonin Reuptake Inhibitor (SSRIs)
Refer to NEMLC approved PHC/Adult SSRI medicine review, 10 October 2017:

SSRIs for depression&anxiety

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Fluoxetine, oral: *directions for use amended*
Aligned with NEMLC approved PHC STGs and EML, 2018; but additional guidance provided to increase dose to 40 mg if partial response on lower 20 mg daily dose.

Alternate SSRI, if fluoxetine is poorly tolerated
Citalopram, oral: *directions for use amended*
Aligned with NEMLC approved PHC STGs and EML, 2018; but additional guidance provided to increase dose to 40 mg if partial response on lower 20 mg daily dose – except in patients with cardiac disease or >65 years of age due to black-box QT prolongation warning
Level of Evidence: I Systematic reviews and meta-analyses[25] [26] [27], Guidelines[28]

For short term use only in severe acute distress
Diazepam, oral: *dosing amended*
Aligned with British National Formulary, 2015[29] and SAMF, 2016[30].
Level of Evidence: III Guidelines

Pregnancy/breastfeeding
Antidepressants, benzodiazepines: *caution box included regarding use in pregnancy and breastfeeding*
The following caution box for antidepressant and benzodiazepine use for anxiety and depression in pregnancy and breastfeeding was added, aligned with NICE[31] and British Association of Psychopharmacology (BAP) Guidelines[32]:

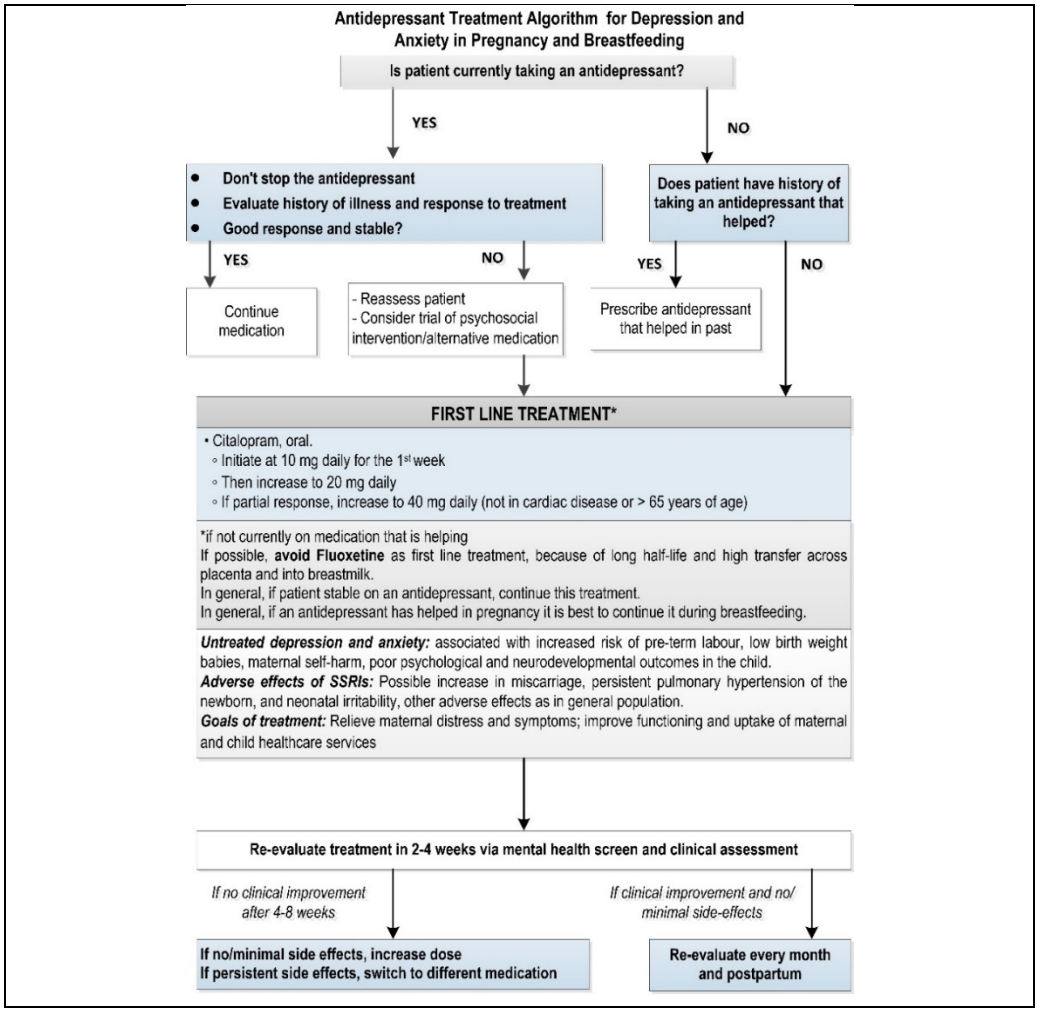
[25] Baldwin D, Woods R, Lawson R, Taylor D. Efficacy of drug treatments for generalised anxiety disorder: systematic review and meta-analysis. BMJ. 2011;342:d1199. https://www.ncbi.nlm.nih.gov/pubmed/21398351
[26] Bandelow B, Reitt M, Rover C, Michaelis S, Gorlich Y, Wedekind D. Efficacy of treatments for anxiety disorders: a meta-analysis. Int Clin Psychopharmacol. 2015;30(4):183-92. https://www.ncbi.nlm.nih.gov/pubmed/25932596
[27] Mayo-Wilson E, Dias S, Mavranezouli I, Kew K, Clark DM, Ades AE, et al. Psychological and pharmacological interventions for social anxiety disorder in adults: a systematic review and network meta-analysis. Lancet Psychiatry. 2014;1(5):368-76. https://www.ncbi.nlm.nih.gov/pubmed/26361000
[28] SAMF, 2016
[29] British National Formulary, 78th edition (September 2019-March 2020).
[30] South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town. 2016.
[31] National Institute for Health and Clinical Excellence (NICE). Antenatal and postnatal mental health: the NICE guideline on clinical management and service guidance. Updated edition. NICE clinical guidance 192. London: NICE; 2014. Available from: https://www.nice.org.uk/guidance/cg192/evidence/full-guideline-pdf-19339686
[32] British Association for Psychopharmacology consensus guidance on the use of psychotropic medication preconception, in pregnancy and postpartum 2017. McAllister-Williams RH, Baldwin DS, Cantwell R, Easter A, Gilvarry E, Glover V, Green L, Gregoire A, Howard LM, Jones I, Khalifeh H, Lingford-Hughes A, McDonald E, Micali N, Pariante CM, Peters L, Roberts A, Smith NC, Taylor D, Wieck A, Yates LM, Young AH, endorsed by the British Association for Psychopharmacology. J Psychopharmacol. 2017;31:519. Available from: https://www.bap.uk

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, psychotherapy; discuss risk/benefit of SSRIs.
» 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.

Level of Evidence: III Guidelines

The following antidepressant treatment algorithm guiding management in pregnancy and breastfeeding was added to the STG:



Sertraline, oral: *not added*
Citalopram, oral: *retained*

Background: A request was made by the Perinatal Mental Health Project, Alan J. Flisher Centre for Public Mental Health, Department of Psychiatry and Mental Health, UCT, to consider sertraline on the NEML as the preferred medication for perinatal treatment of depression and anxiety disorders.

Refer to the NEMLC report and the sertraline medicine review, below:

Sertraline for perinatal anxiety an

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation

Based on the evidence review, the Adult Hospital Level Committee does not recommend sertraline for perinatal

psychiatric conditions. Evidence from an underpowered sub-analysis of an observational study suggests that SSRIs, as a class, are associated with a non-significant risk of major congenital anomalies amongst pregnant women with psychiatric illnesses. In clinical practice, sertraline is the preferred agent. However, until there is price parity between sertraline and citalopram, the current standard of care will be retained as citalopram in this clinical setting.
The advantage of sertraline over citalopram (reduction in persistent pulmonary hypertension of the newborn and decreased transmission through breastfeeding) does not justify the additional cost.
Level of Evidence: II Meta-analyses and systematic reviews of RCTs of low to moderate quality [1]

NEMLC MEETING OF 11 JUNE 2020:
NEMLC noted that SSRIs are associated with a non-significant risk of major congenital anomalies amongst pregnant women with psychiatric illnesses. This was based on an underpowered sub-analysis of an observational study. In clinical practice, sertraline is the preferred agent. However, until there is price parity between sertraline and citalopram, the current standard of care will be retained as citalopram in this clinical setting.

15.3.1 DEPRESSIVE DISORDERS

Similar to section 15.2: Anxiety and obsessive-compulsive disorders, overall guidance aligned with PHC STGs and EML, 2018 with adaptation for secondary/regional level of care.

Selective Serotonin Reuptake Inhibitor (SSRIs)
Refer to NEMLC approved SSRI medicine review, 10 October 2017, above.

Fluoxetine, oral: *retained as first line SSRI treatment; directions for use amended*
Aligned with NEMLC approved PHC STGs and EML, 2018; but additional guidance provided to increase dose to 40 mg if partial response on lower 20 mg daily dose.

Citalopram, oral: *retained as an example of second-line SSRI treatment; directions for use amended*
Aligned with NEMLC approved PHC STGs and EML, 2018; but additional guidance provided to increase dose to 40 mg if partial response on lower 20 mg daily dose – except in patients with cardiac disease or >65 years of age due to black-box QT prolongation warning.
Level of Evidence: I Meta-analyses[33] [34] [35], RCT[36], Guidelines[37]

Amitryptiline, oral: *directions for use amended*
Additional guidance added as follows:

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

Combination pharmacotherapy and psychotherapy: *for review*
Evidence[38] was submitted by SAMA regarding combination of pharmacotherapy and psychotherapy for depression that found combination psychotherapy and pharmacotherapy was more effective than either of these treatments alone. This chapter differs from previous editions, in that psychotherapy is now included as a 'medicine treatment' option for both anxiety and depressive disorders (previously it was not distinguished from counselling as a general measure).

[33] Bandelow B, Reitt M, Rover C, Michaelis S, Gorlich Y, Wedekind D. Efficacy of treatments for anxiety disorders: a meta-analysis. Int Clin Psychopharmacol. 2015;30(4):183-92.
[34] Mayo-Wilson E, Dias S, Mavranezouli I, Kew K, Clark DM, Ades AE, et al. Psychological and pharmacological interventions for social anxiety disorder in adults: a systematic review and network meta-analysis. Lancet Psychiatry. 2014;1(5):368-76.
[35] Thorlund K, Druyts E, Wu P, Balijepalli C, Keohane D, Mills E. Comparative efficacy and safety of selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors in older adults: a network meta-analysis. J Am Geriatr Soc. 2015;63(5):1002-9.
[36] Stahl SM, Gergel I, Li D. Escitalopram in the treatment of panic disorder: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2003 Nov;64(11):1322-7.
[37] SAMF, 2016
[38] Cuijpers P, Dekker J, Hollon SD, Andersson G. Adding psychotherapy to pharmacotherapy in the treatment of depressive disorders in adults: a meta-analysis. The Journal of clinical psychiatry. 2009;70(9):1219-29.

Recommendation: The Adults Hospital Level Committee proposes that a comprehensive HTA be done to determine the duration of psychotherapy, qualifications of personnel needed, and service levels at which it should be provided, together with what is feasible for NDoH.

Pregnancy and breastfeeding

Sertraline, oral: *not added*

Citalopram, oral: *retained*

Aligned with section 15.2 – see rationale ablove.

Antidepressant/benzodiazepines: *caution box for use in pregnancy/breastfeeding added*

The following caution box for antidepressant and benzodiazepine use for anxiety and depression in pregnancy and breastfeeding was added, aligned with NICE[39] and British Association of Psychopharmacology (BAP) Guidelines[40]:

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, psychotherapy; discuss risk/benefit of SSRIs.
- Avoid fluoxetine due to long half-life and relatively high concentration in breastmilk. Consider citalopram as alternative
- All antidepressants: possible increased risk of postpartum haemorrhage, 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.

Level of Evidence: III Guidelines

15.3.2 BIPOLAR AND RELATED DISORDERS

General

- *Description:* Overview of bipolar disorders (BDs) included informing and guiding management.
- *General measures and medicine treatment:* Management delineated to provide non-pharmacological and pharmacological guidance for i) acute manic BD; ii) maintenance to prevent manic episodes of BD; iii) acute depressive BD and iv) maintenance to prevent depressive episodes of BD.
- *Specialist consultation:* No available evidence could be sourced for management of BD by general medical officers (MOs) in district hospitals; in clinical practice BD is managed by psychiatrists/MOs with extensive psychiatric experience, with general practitioners providing maintenance treatment as prescribed by specialist level – thus, STG provides guidance for non-academic specialist level (regional hospital) and informs district-based MOs who are expected to manage BD under remote psychiatrist supervision.
  Level of Evidence: III Guidelines[41] [42]

Medicine treatment (manage in consultation with psychiatrist)

Refer to summary overview of all evidence reviews for management of bipolar disorder (March 2019).

BipolarDisorder Management in Adu

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

[39] National Institute for Health and Clinical Excellence (NICE). Antenatal and postnatal mental health: the NICE guideline on clinical management and service guidance. Updated edition. NICE clinical guidance 192. London: NICE; 2014. Available from: https://www.nice.org.uk/guidance/cg192/evidence/full-guideline-pdf-19339686

[40] British Association for Psychopharmacology consensus guidance on the use of psychotropic medication preconception, in pregnancy and postpartum 2017. McAllister-Williams RH, Baldwin DS, Cantwell R, Easter A, Gilvarry E, Glover V, Green L, Gregoire A, Howard LM, Jones I, Khalifeh H, Lingford-Hughes A, McDonald E, Micali N, Pariante CM, Peters L, Roberts A, Smith NC, Taylor D, Wieck A, Yates LM, Young AH, endorsed by the British Association for Psychopharmacology. J Psychopharmacol. 2017;31:519. Available from: https://www.bap.uk

[41] Goodwin GM, Haddad PM, Ferrier IN, Aronson JK, Barnes T, Cipriani A, Coghill DR, Fazel S, Geddes JR, Grunze H, Holmes EA, Howes O, Hudson S, Hunt N, Jones I, Macmillan IC, McAllister-Williams H, Miklowitz DR, Morriss R, Munafò M, Paton C, Saharkian BJ, Saunders K, Sinclair J, Taylor D, Vieta E, Young AH. Evidence-based guidelines for treating bipolar disorder: Revised third edition recommendations from the British Association for Psychopharmacology. J Psychopharmacol. 2016 Jun;30(6):495-553. https://www.ncbi.nlm.nih.gov/pubmed/26979387

[42] NICE. Bipolar disorder: assessment and management, Clinical Guideline 185, April 2018. https://www.nice.org.uk/guidance/cg185

A) BD - PREDOMINANTLY MANIC COURSE OF ILLNESS

Acute management of mania

Haloperidol, IM: *retained*

External comment was received to delete haloperidol. However, systematic reviews by Dundar et al, 2016[43] and Cipriani et al, 2006[44] suggest that haloperidol is safe and effective in acute management of mania. Limited data shows that there was no difference in overall efficacy of treatment between haloperidol and olanzapine or risperidone. Haloperidol, IM recommended to be retained for management of aggressive or disruptive behaviour related to acute mania and recommendation inserted in the algorithm as a cross reference to section 15.1: Aggressive disruptive behaviour in adults.

Level of Evidence: II Systematic reviews of low to moderate quality RCTs

Residual manic symptoms

Lithium, oral: *emphasised as first line option for treatment and maintenance*

Valproate, oral: *retained as second line option for treatment and maintenance*

Olanzapine, oral: *added as third line option for treatment and maintenance*

Lithium: Refer to the medicine review, lithium for bipolar disorders (October 2018):

Lithium for Bipolar Disorder_AdultsRevi

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation: Based on this evidence review, the Adult Hospital Level Committee reccomends lithium as first-line therapy for any mood episode, acute treatment and prevention of relapse of bipolar disorder; with caveats – counselling required for pregnancy, not recommended in those at risk of lithium toxicity or where lithium will be abruptly discontinuation (as this precipitates mania), previous non-response or poor tolerability). Lithium combination therapy may be beneficial in select patients.

Rationale: Evidence of efficacy of lithium for acute mania and closed-loop network analysis shows that lithium is efficacious for prevention of any mood episode, mania, and depression; though lithium is poorly tolerated. Lithium has also been shown to have a protective effect against suicide. Naturalistic data suggests lithium is superior vs other monotherapy in prevention of rehospitalisation and recurrence of BD with manic, mixed or depressive index episodes. The benefit of reducing maternal and neonatal morbidities in bipolar disorder considered to outweigh the congenital risk of lithium; though informed consent would be viable.

Level of Evidence: II Systematic reviews and meta-analyses of placebo-controlled RCTs[45] [46] [47], Observational studies [48] [49]

Valproate: Considered as second line option rather than olanzapine, although only has a LoE of III (insufficient RCT evidence, recommendation based on observational studies and standard of care). Valproate is efficacious in maintenance treatment in large-scale observational studies, is used as an internal comparator in RCTs (reflecting standard of care), and is associated with lower levels of polypharmacy in long-term treatment[50]. Notwithstanding its LoE of II, olanzapine added

[43] 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. https://www.ncbi.nlm.nih.gov/pubmed/27151529

[44] Cipriani A, Rendell JM, Geddes JR. Haloperidol alone or in combination for acute mania. Cochrane Database Syst Rev. 2006 Jul 19;(3):CD004362. https://www.ncbi.nlm.nih.gov/pubmed/16856043

[45] Butler M, Urosevic S, Desai P, Sponheim SR, Popp J, Nelson VA, et al. Treatment for Bipolar Disorder in Adults: A Systematic Review. AHRQ Comparative Effectiveness Reviews. Rockville (MD)2018. https://www.ncbi.nlm.nih.gov/books/NBK532183/

[46] Miura T, Noma H, Furukawa TA, Mitsuyasu H, Tanaka S, Stockton S, et al. Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis. Lancet Psychiatry. 2014;1(5):351-9. https://www.ncbi.nlm.nih.gov/pubmed/26360999

[47] Smith KA, Cipriani A. Lithium and suicide in mood disorders: Updated meta-review of the scientific literature. Bipolar Disord. 2017;19(7):575–86. https://www.ncbi.nlm.nih.gov/pubmed/28895269

[48] Kessing LV, Bauer M, Nolen WA, Severus E, Goodwin GM, Geddes J. Effectiveness of maintenance therapy of lithium vs other mood stabilizers in monotherapy and in combinations: a systematic review of evidence from observational studies. Bipolar Disord. 2018 Feb 14. https://www.ncbi.nlm.nih.gov/pubmed/29441712

[49] 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

[50] Fornaro M, De Berardis D, Koshy AS, Perna G, Valchera A, Vancampfort D, Stubbs B. Prevalence and clinical features associated with bipolar disorder polypharmacy: a systematic review. Neuropsychiatr Dis Treat. 2016 Mar 31;12:719-35. https://www.ncbi.nlm.nih.gov/pubmed/27099503

as a 3rd line option as it is associated with extrapyramidal side-effects and the risk of metabolic syndrome. However, olanzapine is generally preferred in women of child-bearing potential.

Olanzapine: Refer to the medicine review, olanzapine for manic bipolar episodes (March 2019):

Olanzapine for Manic Bipolar Episo

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation: Based on the evidence review, the Adult Hospital Level Committee recommends that olanzapine be used in the following scenario(s):
- Third line option, following non-response or poor tolerability of lithium as 1st line, valproate as 2nd line.

Rationale: Evidence of efficacy for acute treatment of depressive episodes of bipolar disorder and prevention of relapse of mania or hypomania. Alternative option to lithium and valproate where there are teratogenic concerns.
Level of Evidence: II Systematic reviews of RCTs of low to moderate quality[15 16 17 51]

Depressive residual symptoms
Lithium, oral: *emphasised as first line option for treatment and maintenance*
Lamotrigine, oral: *added as maintenance treatment for residual depression*
Quetiapine, oral: *added as second line option for maintenance treatment for residual depression*

Lamotrigine: Considered as second line option rather than quetiapine although only has a LoE of III (inconsistent RCT evidence, recommendation based on observational studies and expert opinion), because of its more favourable adverse effect profile.

Quetiapine: Refer to the medicine review, quetiapine for depressive bipolar episodes (March 2019):

Quetiapine for Depressive Bipolar E

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation: Based on this evidence review, the Adult Hospital Level Committee recommends that for illness of a predominantly depressive polarity, non-responsive or poor tolerance to lithium and lamotrigine, quetiapine may be considered as a third line option.
Rationale: Quetiapine has RCT (Lindstrom 2017) and network meta-analysis evidence of efficacy for prevention of bipolar depression, noting that quetiapine may cause more weight gain and somnolence than lamotrigine.
Level of Evidence: II Meta-analyses and systematic reviews of RCTs of low to moderate quality[52 53 54 55]

Quetiapine, oral: *guidance provided for dose titration*
The following narrative was included in the STG to provide for titration to clinical effect for the treatment of depression in bipolar disorder. Aligned with the British National Formulary.

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

Level of Evidence: III Guidelines[56]

[51] Lindstrom L, Lindstrom E, Nilsson M, Hoistad M. Maintenance therapy with second generation antipsychotics for bipolar disorder - A systematic review and meta-analysis. Journal of affective disorders. 2017;213:138-50. https://www.ncbi.nlm.nih.gov/pubmed/28222360
[52] Butler M, Urosevic S, Desai P, Sponheim SR, Popp J, Nelson VA, et al. Treatment for Bipolar Disorder in Adults: A Systematic Review. AHRQ Comparative Effectiveness Reviews. Rockville (MD)2018. https://www.ncbi.nlm.nih.gov/books/NBK532183/
[53] Miura T, Noma H, Furukawa TA, Mitsuyasu H, Tanaka S, Stockton S, et al. Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis. Lancet Psychiatry. 2014;1(5):351-9. https://www.ncbi.nlm.nih.gov/pubmed/26360999
[54]Lindstrom L, Lindstrom E, Nilsson M, Hoistad M. Maintenance therapy with second generation antipsychotics for bipolar disorder - A systematic review and meta-analysis. Journal of affective disorders. 2017;213:138-50. https://www.ncbi.nlm.nih.gov/pubmed/28222360
[55] Kessing LV, Bauer M, Nolen WA, Severus E, Goodwin GM, Geddes J. Effectiveness of maintenance therapy of lithium vs other mood stabilizers in monotherapy and in combinations: a systematic review of evidence from observational studies. Bipolar Disord. 2018 Feb 14. https://www.ncbi.nlm.nih.gov/pubmed/29441712
[56] British National Formulary, 78th edition (September 2019-March 2020).

Antidepressants, oral: *not added as monotherapy or as adjunctive therapy with mood stabilizer or antipsychotic*
Refer to the medicine review, antidepressants for depressive bipolar episodes (May 2019):

Antidepressants for depressive bipolar e

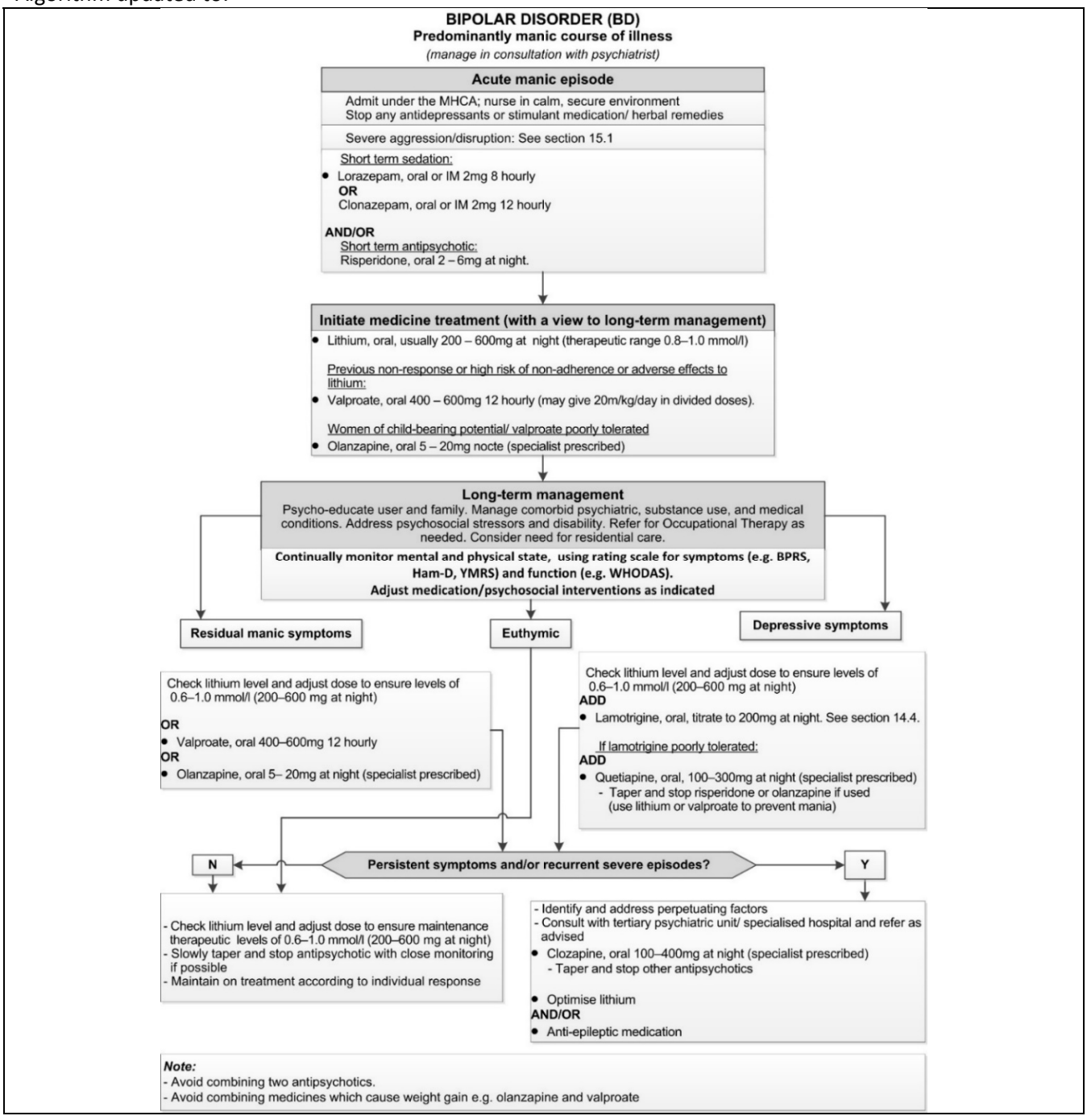
http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation: Based on the evidence review, the Adult Hospital Level Committee recommends that SSRI antidepressants not be recommended as monotherapy in BD-II or adjunctive therapy or as adjunctive treatment in BD-I, in the Adult Hospital Level EML.

Rationale: Evidence is insufficient for routine use of SSRIs in BD. However, may be efficacious in select patients with olanzapine for short-term treatment of a depressive episode – specialist psychiatrist management at tertiary/quaternary level of care may be required. Long-term treatment with adjunctive antidepressants is not recommended due to increased risk of switching and no evidence of efficacy in prevention of relapse.

Level of Evidence: II Systematic review of RCTs of low to moderate quality

Algorithm updated to:



Treatment resistant bipolar disorder

Clozapine, oral: *added for refractory BD (specialist prescribed)*

Refer to the medicine review, clozapine for bipolar disorders (March 2019):

Clozapine for Bipolar Disorder_Ad

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation: Based on this evidence review, the Adult Hospital Level Committee recommends that clozapine be recommended for treatment refractory bipolar disorder.

Rationale: Limited evidence of efficacy suggest that clozapine is safe and efficacious for treatment resistant bipolar disorder.

Level of Evidence: II Systematic review of low quality RCTs and observational studies[57]

B) BD - PREDOMINANTLY DEPRESSIVE COURSE OF ILLNESS

Carbamazepine, oral*: deleted*

Olanzapine + fluoxetine, oral: *deleted*

Carbamazepine: Refer to the medicine review, carbamazepine for depressive bipolar episodes (May 2019):

Carbamazepinefor Depressive Bipolar E

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation: Based on the evidence review the Adult Hospital Level Committee recommends that carbamazepine not be recommended for management of bipolar depression.

Rationale: Insufficient evidence of efficacy in the management of bipolar depression with the possibility of severe adverse effects (RCT showed that carbamazepine had a significant response rate, but no significant reduction in symptoms compared to placebo). Lithium also shown to be more efficacious than carbamazepine for reducing time to recurrence of any mood episode in BD-I study participants.

Level of Evidence: II Systematic review of RCTs of low to moderate quality[58]

Olanzapine + fluoxetine, oral: Refer to the medicine review, combination treatment for bipolar disorders (May 2019):

CombinationTreatment for Bipolar Disor

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation: Based on the evidence review, the Adult Hospital Level Committee recommends that SSRI antidepressants not be recommended as monotherapy in BD-II or adjunctive therapy or as adjunctive treatment in BD-I, in the Adult Hospital Level EML.

Rationale: Evidence is insufficient for routine use of SSRIs in BD. However, may be efficacious in select patients with olanzapine for short-term treatment of a depressive episode – specialist psychiatrist management at tertiary/quaternary level of care may be required. Long-term treatment with adjunctive antidepressants is not recommended due to increased risk of switching and no evidence of efficacy in prevention of relapse.

Level of Evidence: II Systematic review of RCTs of low to moderate quality[59] [60] [61] [62]

[57] Li XB, Tang YL, Wang CY, de Leon J. Clozapine for treatment-resistant bipolar disorder: a systematic review. Bipolar Disord. 2015 May;17(3):235-47. https://www.ncbi.nlm.nih.gov/pubmed/25346322

[58] Selle V, Schalkwijk S, Vazquez GH, Baldessarini RJ. Treatments for acute bipolar depression: meta-analyses of placebo-controlled, monotherapy trials of anticonvulsants, lithium and antipsychotics. Pharmacopsychiatry. 2014;47(2):43-52. https://www.ncbi.nlm.nih.gov/pubmed/24549862

[59] McGirr A, Vohringer PA, Ghaemi SN, Lam RW, Yatham LN. Safety and efficacy of adjunctive second-generation antidepressant therapy with a mood stabiliser or an atypical antipsychotic in acute bipolar depression: a systematic review and meta-analysis of randomised placebo-controlled trials. Lancet Psychiatry. 2016;3(12):1138-46. https://www.ncbi.nlm.nih.gov/pubmed/28100425

[60] Butler M, Urosevic S, Desai P, Sponheim SR, Popp J, Nelson VA, et al. Treatment for Bipolar Disorder in Adults: A Systematic Review. AHRQ Comparative Effectiveness Reviews. Rockville (MD)2018. https://www.ncbi.nlm.nih.gov/books/NBK532183/

[61] Selle V, Schalkwijk S, Vazquez GH, Baldessarini RJ. Treatments for acute bipolar depression: meta-analyses of placebo-controlled, monotherapy trials of anticonvulsants, lithium and antipsychotics. Pharmacopsychiatry. 2014;47(2):43-52. https://www.ncbi.nlm.nih.gov/pubmed/24549862

Previous Adult Hospital Level STG and EML, 2015 recommendation of olanzapine + fluoxetine[63] recommended for deletion as evidence was insufficient for adjunctive antidepressant therapy for depressive bipolar disorders (single placebo-controlled RCT (n=86) [64] of low to moderate quality). Adjunctive antidepressants in BD-I may improve acute depression symptoms but not response rates.[65] [66] Meta-analysis by McGirr et al[13] showed adjunctive antidepressants with lithium was not efficacious in maintenance of depression treatment, with a risk of manic/hypomanic switch. Olanzapine has insufficient RCT evidence of efficacy for prevention of depression, in monotherapy[67] or in combination with fluoxetine.[13] However, observational studies[68] suggest that olanzapine may have efficacy in prevention of depression in BD-I with an index manic episode.

BD II (depressive episode) or other specified BD
Lithium, oral: *emphasised as first line option for treatment and maintenance*
Lamotrigine, oral: *retained as second line option for treatment and maintenance*
Quietapine, oral: *added as third line option for treatment and maintenance (specialist prescribed)*

Lithium: Refer to medicine review, above.
Quetiapine: Refer to medicine review, above.
BD I (manic episode)
Lithium, oral: *emphasised as first line option for treatment and maintenance*
Valproate, oral: *retained as second line option for treatment and maintenance*
Olanzapine, oral: *added as third line option for treatment and maintenance (specialist prescribed)*

Treatment resistant bipolar disorder
Clozapine, oral: *added for refractory BD (specialist prescribed)*
Refer to medicine review, above.

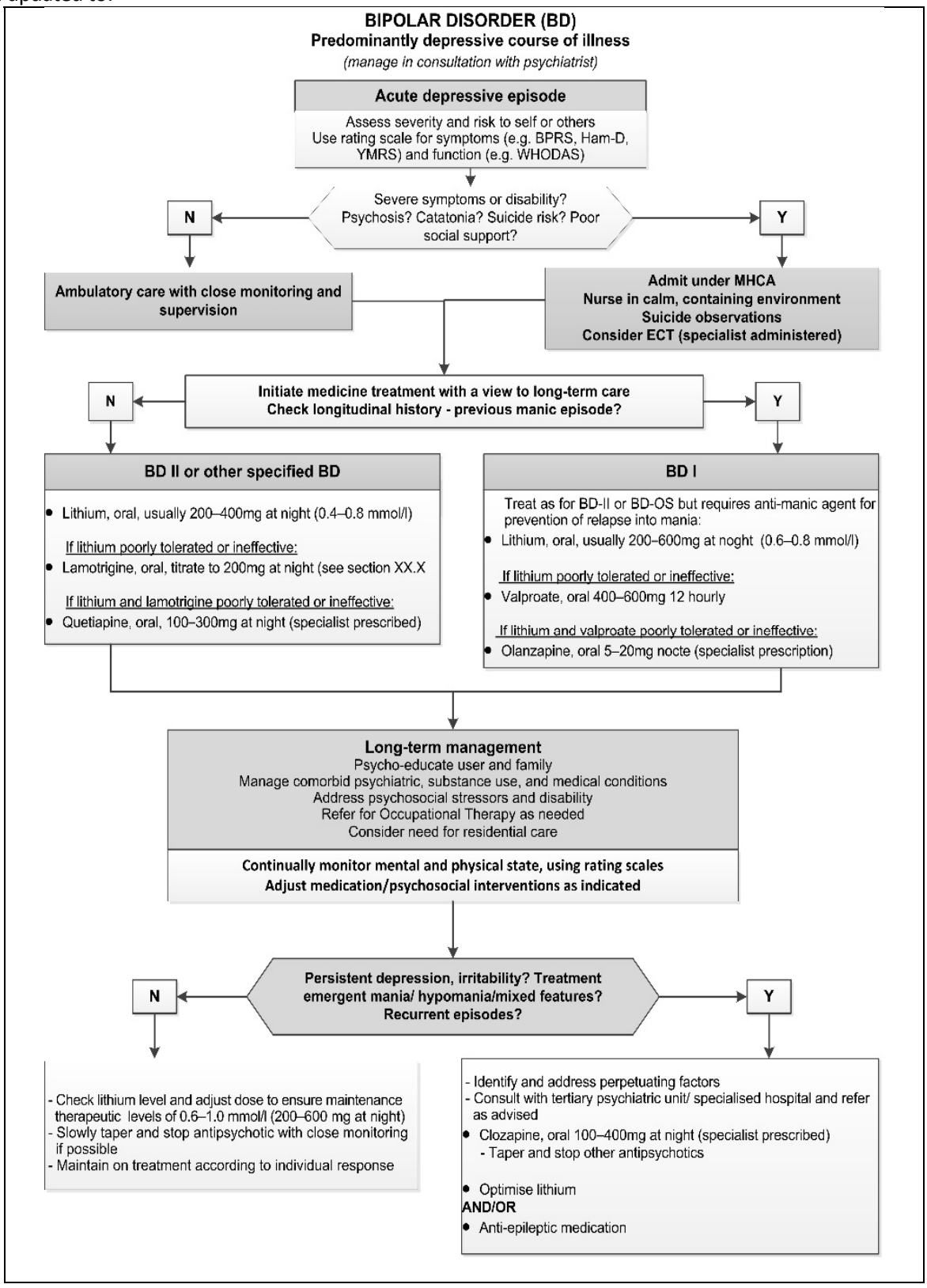
Combination therapy
Algorithms for BD preferably recommends monotherapy; noting that not all patients will respond and thus, repeated evaluation of treatment is recommended and augmentation may be required in certain patients under psychiatrist management. Refer to medicine review.
Recommendation: Based on this evidence review, the Adult Hospital Level Committee recommends that for patients non-responding to monotherapy, combination therapy of olanzapine/quetiapine plus lithium/valproate or lamotrigine with lithium/antipsychotic be considered for bipolar disorders. This excludes combination therapy, lithium and valproate or risperidone with lithium/valproate; or maintenance treatment with three or more agents. Combination treatment must be weighed up against increased harm with use of rating scales and a level of function measure to enable objective evaluation of clinical response. Where medication is added or changed, ineffective medicine must be withdrawn.
Rationale: Limited RCT evidence suggesting that selected patients may benefit from the combination of olanzapine or quetiapine plus lithium or valproate; whilst lithium with valproate was shown not to be superior to lithium monotherapy. RCT evidence could not be sourced to support maintenance treatment with risperidone in combination with lithium or valproate. There is a paucity of RCT evidence for lamotrigine used with lithium,

[62] Miura T, Noma H, Furukawa TA, Mitsuyasu H, Tanaka S, Stockton S, et al. Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis. Lancet Psychiatry. 2014;1(5):351-9. https://www.ncbi.nlm.nih.gov/pubmed/26360999
[63] National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Olanzapine-fluoxetine for depressive episodes in bipolar disorder, March 2015. http://www.health.gov.za/
[64] Tohen M, Vieta E, Calabrese J, Ketter TA, Sachs G, Bowden C, Mitchell PB, Centorrino F, Risser R, Baker RW, Evans AR, Beymer K, Dube S, Tollefson GD, Breier A. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. Arch Gen Psychiatry. 2003 Nov;60(11):1079-88. Erratum in: Arch Gen Psychiatry. 2004 Feb;61(2):176. https://www.ncbi.nlm.nih.gov/pubmed/14609883
[65] Selle V, Schalkwijk S, Vazquez GH, Baldessarini RJ. Treatments for acute bipolar depression: meta-analyses of placebo-controlled, monotherapy trials of anticonvulsants, lithium and antipsychotics. Pharmacopsychiatry. 2014;47(2):43-52. https://www.ncbi.nlm.nih.gov/pubmed/24549862
[66] McGirr A, Vohringer PA, Ghaemi SN, Lam RW, Yatham LN. Safety and efficacy of adjunctive second-generation antidepressant therapy with a mood stabiliser or an atypical antipsychotic in acute bipolar depression: a systematic review and meta-analysis of randomised placebo-controlled trials. Lancet Psychiatry. 2016;3(12):1138-46. https://www.ncbi.nlm.nih.gov/pubmed/28100425
[67] Lindstrom L, Lindstrom E, Nilsson M, Hoistad M. Maintenance therapy with second generation antipsychotics for bipolar disorder - A systematic review and meta-analysis. Journal of affective disorders. 2017;213:138-50. https://www.ncbi.nlm.nih.gov/pubmed/28222360
[68] Kessing LV, Bauer M, Nolen WA, Severus E, Goodwin GM, Geddes J. Effectiveness of maintenance therapy of lithium vs other mood stabilizers in monotherapy and in combinations: a systematic review of evidence from observational studies. Bipolar Disord. 2018 Feb 14. https://www.ncbi.nlm.nih.gov/pubmed/29441712

valproate, or an antipsychotic, but this combination treatment is commonly used in clinical practice for prevention of depression in bipolar disorders. There is also no evidence to support the use of three or more medicines in maintenance treatment.

Level of Evidence: II Systematic reviews of RCTs of low to moderate quality[69] [70], Standard of care

Algorithm updated to:



[69] Butler M, Urosevic S, Desai P, Sponheim SR, Popp J, Nelson VA, et al. Treatment for Bipolar Disorder in Adults: A Systematic Review. AHRQ Comparative Effectiveness Reviews. Rockville (MD)2018. https://www.ncbi.nlm.nih.gov/books/NBK532183/

[70] Lindstrom L, Lindstrom E, Nilsson M, Hoistad M. Maintenance therapy with second generation antipsychotics for bipolar disorder - A systematic review and meta-analysis. Journal of affective disorders. 2017;213:138-50. https://www.ncbi.nlm.nih.gov/pubmed/28222360

CAUTION BOX:

Lithium, oral: *caution box amended*

Amended and aligned with the evidence reviewed in the lithium medicine review and the SAMF, 2016:

CAUTION

» 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 – causes anorexia, nausea, diarrheoa, muscle weakness, drowsiness, ataxia, disorientation, seizures, coma & death. Manage as for lithium poisoning: section 19.9.2
» ~~Concomitant use of many medicines e.g. ACE-inhibitors, NSAIDs and diuretics may increase the risk of lithium toxicity.~~ Risk of toxicity increased with e.g. change to a low salt diet, dehydration, drug-drug interactions (~~thiazide~~ diuretics, ACE-inhibitors, NSAIDs).
» Therapeutic drug monitoring is essential when using lithium.
» Clinical toxicity may occur even within the therapeutic range.

GUIDANCE FOR BIPOLAR DISORDER IN PREGNANCY AND POSTPARTUM:

External comments received, suggesting guidance for management of BD in pregnancy and the following was added to the STG, aligned with SAMF 2016:

PREGNANCY AND BREASTFEEDING

Valproate: [71] [72]
» Contraindicated due to high teratogenic risk and adverse neurodevelopmental outcomes with any pregnancy exposure.
» If no alternative, the acknowledgment of risk form must be signed.
» If already on valproate: cross-titrate if possible (consult specialist if required).
» Not recommended in breastfeeding as associated with adverse
» neurodevelopmental outcomes.

Lithium: [73]
» 1st trimester exposure associated with increased risk of congenital anomalies.
» Foetal anomaly ultrasound at 18–22 weeks gestation.
» Adjust dose with physiological changes of pregnancy: monitor levels monthly, then weekly after 36 weeks.
» 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:[74] [75] [76] Increased hepatic clearance in pregnancy, returns to normal post-partum; adjust dose according to clinical response. May cause a rash in breastfed infant.

Antipsychotics[77] [78]**:** Considered safest, particularly quetiapine. Increase risk of gestational diabetes and obesity (highest risk with olanzapine, clozapine).
Clozapine is not recommended due to risk of agranulocytosis.

Benzodiazepines[79]: Avoid in pregnancy. Use only very short-term for severe distress.

Level of Evidence: III Observational and Pharmacokinetic studies, Guidelines

[71] Valproate, oral (caution in pregnancy/breastfeeding): European Medicines Agency - Pharmacovigilance Risk Assessment Committee. Assessmentreport 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

[72] Valproate (caution in pregnancy/breastfeeding): 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

[73] Lithium, oral (risk in pregnancy/breastfeeding): 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

[74] Lamotrogine, oral (risk in pregnancy/breastfeeding): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town. 2016.

[75] Lamotrogine, oral (risk in pregnancy/breastfeeding): Wesseloo R, Liu X, Clark CT, Kushner SA, Munk-Olsen T, Bergink V. Risk of postpartum episodes in women with bipolar disorder after lamotrigine or lithium use during pregnancy: A population-based cohort study. J Affect Disord. 2017 Aug 15;218:394-397. https://www.ncbi.nlm.nih.gov/pubmed/28501739

[76] Lamotrogine, oral (risk in pregnancy/breastfeeding): Ding Y, Tan X, Zhang S, Guo Y. Pharmacokinetic changes and therapeutic drug monitoring of lamotrigine during pregnancy. Brain Behav. 2019 Jul;9(7):e01315. https://www.ncbi.nlm.nih.gov/pubmed/31104352

[77] Antipsychotics, oral (risk in pregnancy/breastfeeding): Uguz F. Antipsychotic Use During Pregnancy and the Risk of Gestational Diabetes Mellitus: A Systematic Review. J Clin Psychopharmacol. 2019 Mar/Apr;39(2):162-167. https://www.ncbi.nlm.nih.gov/pubmed/30624301

[78] Antipsychotics, oral (risk in pregnancy/breastfeeding): Damkier P, Videbech P. The Safety of Second-Generation Antipsychotics During Pregnancy: A Clinically Focused Review. CNS Drugs. 2018 Apr;32(4):351-366. https://www.ncbi.nlm.nih.gov/pubmed/29637530

[79] Benzodiazepines, oral (risk in pregnancy/breastfeeding): National Institute for Health and Clinical Excellence (NICE). Antenatal and postnatal mental health: the NICE guideline on clinical management and service guidance. Updated edition. NICE clinical guidance 192. London: NICE; 2014. Available from: https://www.nice.org.uk/guidance/cg192/evidence/full-guideline-pdf-19339686

Risk of postpartum relapse in women with bipolar disorder was decreased with continuation of prophylactic medication during pregnancy, shown to be protective for maintaining mood stability postpartum.[80]

Note: Refer to the lithium medicine review, above that cites a systematic review of five observational studies[81] that suggests that the benefit of reducing relapse of bipolar disorder during pregnancy and post-partum possibly outweighs the risk of lithium. However, counselling and informed consent particularly regarding congenital anomaly risk associated with 1st trimester exposure is advised.

Level of Evidence: III Observational studies, Guidelines

15.4 TRAUMA AND STRESS-RELATED DISORDERS

Non-pharmacological interventions: *for review in next cycle*

SAMA commented that first-line of treatment for Trauma and stress related disorders is non-pharmacological and that the evidence for pharmacological interventions in acute stress disorder and post-traumatic stress disorder is generally poor.

However, SAMA feels that the guidelines should put more emphasis on the importance of psychotherapy in these instances. A single counselling session is unlikely to be effective. Psychotherapies found to be effective for PTSD in multiple clinical trials include exposure therapy (e.g. prolonged exposure), a combination of exposure and a cognitive therapy (also referred to as trauma-focused cognitive-behavioural therapy; e.g. cognitive processing therapy), or eye movement desensitization and reprocessing[82].

Recommendation: The Adult Hospital Level Committee recommends that HTA for non-pharmacological treatment of trauma and stress orders be deferred to the next review cycle, as the current review cycle is ending.

15.5.1 ACUTE AND TRANSIENT PSYCHOTIC DISORDERS

Management aligned with acute aggressive disruptive disorders, and cross-referenced to section 15.1: Aggressive disruptive behaviour in adults.

15.5.2 SCHIZOPHRENIA SPECTRUM DISORDERS

Acute psychotic episode

The following text was included, based on a meta-analysis of observational studies[83], describing indications for haloperidol and newer generation antipsychotics in the management of acute psychosis:

High risk of tardive dyskinesia (age > 50 years, female sex, prominent mood symptoms, cognitive or neurological disturbance e.g. intellectual disability, autistic spectrum, HIV-positive): avoid haloperidol and antiparkinsonian medicines; use chlorpromazine, risperidone or olanzapine at lowest doses possible.

Level of Evidence: III Meta-analysis of observational studies

Treatment protocol

Treatment algorithm was amended slightly with recommendation to "**manage all patients in consultation with a psychiatrist":**

- Acute psychotic episode treated with haloperidol and if responds well continue treatment with flupenthixol depot.
- Poor response or tolerability to haloperidol, consider risperidone or chlorpromazine.
- Treatment failure, then consider olanzapine.
- Clozapine recommended for refractory cases (specialist prescribed, preferably as inpatient).

Haloperidol, oral: *dose amended*

External comments were received recommending dose ranges for antipsychotics for the management of psychosis, as

[80] Wesseloo R, Kamperman AM, Munk-Olsen T, Pop VJ, Kushner SA, Bergink V. Risk of Postpartum Relapse in Bipolar Disorder and Postpartum Psychosis: A Systematic Review and Meta-Analysis. Am J Psychiatry. 2016 Feb 1;173(2):117-27. https://www.ncbi.nlm.nih.gov/pubmed/26514657

[81] 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

[82] Bisson J, Andrew M. Psychological treatment of post-traumatic stress disorder (PTSD). The Cochrane database of systematic reviews. 2007(3):Cd003388.

[83] Correll CU, Kane JM, Citrome LL. Epidemiology, Prevention, and Assessment of Tardive Dyskinesia and Advances in Treatment. J Clin Psychiatry. 2017 Sep/Oct;78(8):1136-1147. https://www.ncbi.nlm.nih.gov/pubmed/29022654

standard doses are not used in clinical practice. However, the sole pharmaceutical supplier has discontinued haloperidol 0.5 mg from the South African market; however the 1.5 mg and 2.5 mg formulations are still currently available. Therefore, the dose for haloperidol was amended to,
"Initial dose: 0.75–2.5 mg daily, increasing to 5 mg daily".
Level of Evidence: III Guidelines[84]

Flupenthixol decanoate, IM: *directions for use amended and dose amended*
Zuclopenthixol decanoate, IM: *directions for use amended and dose amended*
Directions for use: No need for test dose in patients who have responded well to haloperidol as long-acting psychotic injections reduce emergency hospitalisations/ recurrence rates[85] and thus, recommended early in treatment algorithm if responsive to initial oral haloperidol therapy[86]. However, a test dose (half the recommended dose) may be required in recurrent psychotic episodes due to poor adherence as per standard clinical practice; and is thus, included under general measures in the STG.
Level of Evidence: III Observational studies

Flupenthixol decanoate dose: Amended from "*20-40 mg"* to "*10–40 mg"* every 4 weeks.
Zuclopenthixol decanoate dose: Amended from "*200-600 mg"* to "*200–400 mg"* every 4 weeks.
Level of Evidence: III Guidelines[87]

Olanzapine, oral: *added as 2nd/3rd line option*
Refer to medicine review: Olanzapine, oral for schizophrenia and related disorders, 13 June 2019.

Olanzapine for schizophrenia-Adult

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

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 those with weight gain or metabolic syndrome, and possibly 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; 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[88] [89]

Clozapine, oral: *added with a caution box*
STG recommends that all patients should be managed in consultation with a psychiatrist, and the Adult Hospital Level Committee was of the opinion that continuum of care with clozapine was warranted in poor responders to initial treatment, though under specialist management. In addition, guidance on management of seizure ADRs was added to the text of the STG, aligned with SAMF, 2016 and expert opinion:

If seizures occur on clozapine (increased risk at doses > 450 mg/day)
» Manage as for epilepsy, section 14.4: Epilepsy.
» Lamotrigine may be preferable as it is weight neutral and does not interfere with clozapine metabolism
» Avoid carbamazepine because of possible myelosuppression and enzyme induction.

Level of Evidence: III Guidelines[90]**, Expert opinion**

[84] SAMF, 2016
[85] Bobrovitz N, Heneghan C, Onakpoya I, Fletcher B, Collins D, Tompson A, Lee J, Nunan D, Fisher R, Scott B, O'Sullivan J, Van Hecke O, Nicholson BD, Stevens S, Roberts N, Mahtani KR. Medications that reduce emergency hospital admissions: an overview of systematic reviews and prioritisation of treatments. BMC Med. 2018 Jul 26;16(1):115. https://www.ncbi.nlm.nih.gov/pubmed/30045724
[86] Kirson NY, Weiden PJ, Yermakov S, Huang W, Samuelson T, Offord SJ, Greenberg PE, Wong BJ. Efficacy and effectiveness of depot versus oral antipsychotics in schizophrenia: synthesizing results across different research designs. J Clin Psychiatry. 2013 Jun;74(6):568-75. https://www.ncbi.nlm.nih.gov/pubmed/23842008
[87] SAMF, 2016
[88] 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. https://www.ncbi.nlm.nih.gov/pubmed/23810019
[89] Krause M, Zhu Y, Huhn M, Schneider-Thoma J, Bighelli I, Nikolakopoulou A, et al. Antipsychotic drugs for patients with schizophrenia and predominant or prominent negative symptoms: a systematic review and meta-analysis. Eur Arch Psychiatry Clin Neurosci [Internet]. 2018;268(7):625–39. DOI: 10.1007/s00406-018-0869-3. https://www.ncbi.nlm.nih.gov/pubmed/29368205

Caution box:

The following caution box related to clozapine use was added to the STG, following NEMLC's recommendation [91]and external comment received from SAMA, adapted from FDA guidance, SAMF and Maudsley Prescribing Guidelines:

CAUTION - CLOZAPINE

» May cause neutropenia (3% of cases) and agranulocytosis (0.8% of cases):
- Pre-treatment: Normal white cell count and absolute neutrophil count
- Monitor absolute neutrophil count regularly.
- Withdraw clozapine and review medication if:
  - Neutrophils < 1.0 x10^9/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 > 450mg/ day.

» Manage as for epilepsy, section 14.4: Epilepsy.Lamotrigine preferable 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 for PHC Chapter X. Psychiatric patients general monitoring and care, Prevention of ischaemic heart disease and atherosclerosis, and Type 2 diabetes.

FDA drug safety communication:

- Recommends that only absolute neutrophil count required for monitoring of neutropenia associated with clozapine and not white cell count.
- Recommends 2 monitoring algorithms to allow for people with benign ethnic neutropenia (BEN).
- Recommends absolute neutrophil count for interruption of clozapine reduced to < 1.0 x10^9/L for general population and to < 0.5 x10^9/L for (BEN) patients.
- Recommends 'regular' monitoring with no apparent change to frequency of monitoring.

Infectious disease concern: Due to the high infectious disease exposure in South Africa, there is insufficient evidence to state that patients with BEN are not more vulnerable to infectious diseases in our local context and thus a specific algorithm for BEN was not included in the STG.

Level of Evidence: III Safety alert[92], Guidelines[93] [94]

15.6 INSOMNIA

Short-acting benzodiazepines, oral: *retained as a therapeutic class*

Oxazepam, oral: *retained as example of class*

Antihistamines, oral: *for review in next cycle*

Due to time constraints the Adult Hospital Level Committee recommends that this STG be reviewed more comprehensively in the next review cycle. There is uncertainty regarding the efficacy of antihistamines for insomnia, which requires further review.

15.9 OPIATE WITHDRAWAL, E.G. HEROIN

Sub-heading amended to, "*Opiate (e.g. heroin, unga, whoonga, nyaope) withdrawal",* relevant to local setting.

"*Substitution treatment*" amended to "*Opioid assisted withdrawal*" for correctness.

External comment received to add the OOWS for rational management of opioid assisted withdrawal using an objective rating scale and to minimise the risk of over-medication.

[90] SAMF, 2016

[91] Minutes of the NEMLC meeting of 11 July 2019

[92] South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town. 2016.

[93] 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

[94]Taylor, David; Paton, Carol; Kapur, Shitij. The Maudsley Prescribing Guidelines, Twelfth Edition. London: CRC Press; 2015

Opioid withdrawal: *treatment protocol amended*

Objective opioid withdrawal scale (OOWS) rating scale[95] (with a hyperlink) recommended for use for opioid withdrawal to guide management: https://medicine.yale.edu/sbirt/OOWS_251773_284_5_v1.pdf

Level of Evidence: III Observational study

STG was updated to:

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

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

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

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

For headaches:
- Paracetamol, oral, 1 g 4–6 hourly when required to a maximum of 4 doses per 24 hours.
  - Maximum dose: 15mg/kg/dose.
  - Maximum dose: 4g in 24 hours.

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

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 need.

Day 1:
Wait for early evidence of withdrawal (OOWS ≥ 4)
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 or 2 divided doses.
- Monitor for on-going sign and symptoms of withdrawal.
- If the signs and symptoms of withdrawal are still present on day 2, top-up doses of 5mg may be given at 2–4 hourly intervals with a total daily dose of 30 mg. Consult a person experienced in opioid withdrawal if symptoms not controlled on 30 mg/day.

Day 3 onwards:
Methadone, oral.
- Repeat total dose of day 2 if top-ups were needed and begin reductions on day 4.
- If no top-ups were required on day 2 and withdrawal symptoms are adequately controlled, begin dose reduction.
- Decrease dose by 10 – 20% over a period of 3 – 10 days
- The withdrawal regimen may be shortened, if the patient's withdrawal symptoms allow it.

Methadone, oral: *retained and directions for use not amended*

External comment received to align opioid withdrawal management to WHO mhGAP dosing schedule[96] [97]. However, it is noted that the doses of methadone are considerably higher and not based on South African experience. The Adult Hospital Level Committee opted to stay with local clinical experience, given the variable profile of the South

[95] Handelsman L, Cochrane KJ, Aronson MJ, Ness R, Rubinstein KJ, Kanof PD. Two new rating scales for opiate withdrawal. Am J Drug Alcohol Abuse. 1987;13(3):293-308. https://www.ncbi.nlm.nih.gov/pubmed/3687892
[96] WHO. Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence. Geneva: WHO; 2009.
[97] WHO, MHGAP. mhGAP Intervention Guide for mental, neurological and substance use disorders in non-specialized health settings. Version 2.0. Geneva: WHO; 2016.

African patients.
Level of Evidence: III Guidelines[98] [99]

Buprenorphine, oral: *not listed in the STG, but added to therapeutic interchange database*
Refer to medicine review, buprenorphine for opiate withdrawal, September 2018:

Buprenorphine for opiate withdrawal_A

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation: Based on this evidence review, the Adult Hospital Level Committee recommended that buprenorphine (in monotherapy or in combination with naloxone) be regarded a therapeutic equivalent of methadone and thus procured if methadone is unavailable.
Rationale: There is no evidence of any significant difference between methadone and buprenorphine in efficacy or adverse effects in medication assisted opioid withdrawal. Because of current cost differences, methadone is still considered the preferred option.
Level of Evidence: II Meta-analysis of low-moderate quality studies[100]

The Adult Hospital Level Committee further recommends that a comprehensive HTA be done for opioid withdrawal and opioid substitution considering the various treatment options (methadone, buprenorphine, buprenorphine-naloxone) factoring in all relevant costs required for counselling, human resources, infrastructure and management of adverse events.

METHADONE OPIOD SUBSTITUTION TREATMENT

Motivation was received from the NDoH Mental Health Directorate through the Deputy Director General of Programmes office on the 20 December 2018, for consideration of methadone as opioid substitution therapy (OST) at primary level of care (refer to motivation, dated 21 November 2018). This was reviewed by the Adult Hospital Level Committee and collaborative meeting ensued between the Committee, NDoH Mental Health Directorate and one of the motivators who co-authored the review document.

Discussion
Guidelines for opioid substitution therapy: There are currently no official NDoH Programme Guidelines for the opioid substitution therapy. Furthermore, neither the Adult Hospital Level or Primary Health Care STGs and EML provides guidance on OST.

Evidence of efficacy: It was agreed that methadone has been shown to be efficacious for OST[101] and there is a need for OST as well as other substance use treatment for both the individual and public health in South Africa.

Community-based OST projects: Currently there are important community-based OST projects in operation, funded by NGOs, based in Cape Town, Tshwane, Johannesburg and Durban. However, funding for these projects expires early 2019. Although urbanisation determines the geography where the need for OST is required, the Adult Hospital Level Committee recommended that establishing OST project sites in all Provinces should be considered for equity purposes (currently a site under development in Port Elizabeth).

The Health Sector Drug Master Plan: This was not shared with the NEMLC or the Technical Sub-Committees for review prior to adoption by the National Health Council. The policy indicates the STGs and EML would increase accessibility of methadone and prevent its diversion. The Adult Hospital Level Committee was of the opinion that policy alone will not ensure successful treatment nor prevent diversion. An implementation strategy with a viable service delivery platform is required.

[98] National Department of Health. National Policy guidelines on detoxification of psychoactive substances.http://www.health.gov.za/
[99] Weich L, Nowbath H, Flegar S, Mahomedy Z, Ramjee H, Hitzeroth V, et al. South African guidelines for the management of opioid dependence. Updated 2013. Pretoria: South African Addiction Medicine Society; 2013.
https://www.saams.co.za/Content/Documents/South_African_Guidelines_for_the_Management_of_Opioid_use_disorders_2015.pdf
[100] Gowing L, Ali R, White JM, Mbewe D. Buprenorphine for managing opioid withdrawal. Cochrane Database Syst Rev. 2017 Feb 21;2:CD002025. https://www.ncbi.nlm.nih.gov/pubmed/28220474
[101] Nielsen S, Larance B, Degenhardt L, Gowing L, Kehler C, Lintzeris N. Opioid agonist treatment for pharmaceutical opioid dependent people. Cochrane Database Syst Rev. 2016 May 9;(5):CD011117. https://www.ncbi.nlm.nih.gov/pubmed/27157143

Misuse and diversion: It is difficult to estimate the potential impact of misuse and diversion in South Africa but as an addictive medication with a street market value, possibilities include a) misuse and sharing or selling of methadone amongst substance users b) accidental or intentional overdose by dependents or contacts of users c) selling of methadone to children, adolescents and youth in the community d) usage/selling of methadone in neighbouring countries. A trusting therapeutic relationship with healthcare workers is the cornerstone for preventing adverse effects and misuse. Prevention of diversion also requires that all those who need OST can access it. There are concerns of whether medication access should be in place, before the staffing, infrastructure and referral support are in place. If there is inadequate staffing to provide appropriate care to these service users, stigma will increase, and so then will diversion.

Human resources: Adequate consultation time, shared decision-making, and regular supervision for OST is required. Inadequate staffing requirements may negatively impact implementation resulting in stigma and worsen diversion. The Adult Hospital Level Committee recommended that implementation strategy as well as a cost of care analysis be developed; and that the cost of care in terms of consultation time and clinician contact time be included (utilising data from the Tshwane project site).

Inter-sectoral engagement: The Health Sector Drug Master Policy recommends the "*Referral of patients according to the established referral and admission routes*"; however, these routes encompass care delivery pathways beyond the health sector alone – i.e.: Social Development, Education, Housing, Correctional Services, and South African Polices Services. The Adult Hospital Level Committee recommended that inter-sectoral service delivery agreements be implemented to ensure integration and linking of services according to respective budgeting.

Primary level of care: For universal access, treatment should be at district clinics. However, human resources and infrastructure does not allow for the therapeutic process involved, which requires shared decision-making as well as monitoring. Continuity of care with a regular counsellor/ clinical person is fundamental. District clinics are being staffed according to WISN (workload indicators of staffing needs) – and the consultation time and regular supervision for OST has not been incorporated into this assessment of staffing needs. Restricting methadone to district hospitals would have similar constraints with regards to personnel for consultation time, continuity of care, and monitoring of usage, and limits accessibility. Furthermore, legislation does not allow for nurse prescribers to prescribe schedule 5 medicines and mental health care and psychiatry component of substance abuse have been removed from the new Basic Nursing Curriculum – these matters should be addressed with the South African Nursing Council.

A letter raising the Adult Hospital Level Committee's concerns were forwarded to the DDG-Programmes' office and to the NDoH Mental Health Directorate requesting the following information (20 March 2019):

- Cost of care in terms of consultation time and clinician contact time be included in the costing analysis (utilising data from the Tshwane project site)
- Business plan and budget for funding the optimal implementation of OST and confirmed budgetary allocation should be verified.
- Indication that inter-sectoral collaboration would be formalised with negotiated service delivery agreements.
- Indication that the South African Nursing Council had been engaged with regards to nurse prescribing of psychiatric medicines and mental health care training in the Nursing curriculum.
- Indication of considering the establishment of OST project sites in all Provinces for equity purposes.

Programme is revising the NDoH OST implementation plan and a costing analysis is reported to be underway.

SUMMARY: In summary, the Adult Hospital Level Committee recognises that OST has an important role to play in rehabilitation for opioid addiction. However, the current local service delivery platform does not allow for the implementation of effective OST. A response is awaited from the NDoH Mental Health Directorate regarding a costed implementation strategy, with allocated budget (currently in progress).

NEMLC MEETING OF 11 JULY 2019:

NEMLC Recommendation: The NEMLC accepted the Adult Hospital Level Committee's recommendations (as indicated in the NEMLC report and letter addressed to the Programme) and acknowledged that a health technology assessment would be required.

15.10 STIMULANT WITHDRAWAL, INCLUDING COCAINE AND AMPHETAMINE TYPE STIMULANTS

Sub-heading amended to "*Stimulant withdrawal, including cocaine and amphetamine type stimulants (e.g. methamphetamine/ tik, methcathinone/cat)",* as relevant to local setting.

15.11 METHAQUALONE WITHDRAWAL

Sub-heading amended to *"Methaqualone (mandrax/whitepipe) withdrawal)",* as relevant to local setting.

15.12 CANNABIS WITHDRAWAL

Diazepam, oral: *not added*

Recommendation: The Adult Hospital Level Committee acknowledges that more comprehensive guidance for cannabis withdrawal would be required. As this review cycle has come to an end, it is recommended that this be undertaken in the next review cycle.

15.13 BENZODIAZEPINE WITHDRAWAL

Diazepam, oral: *dose reduction protocol expanded*

Comprehensive dose reduction protocol included in the STG aligned with the Maudsley[102] Prescribing Guidelines; noting that authors of a Cochrane review[103] of low to very low quality RCTs concluded that "it is not possible to draw firm conclusions regarding pharmacological interventions to facilitate benzodiazepine discontinuation in chronic benzodiazepine users".

Level of Evidence: III Guidelines

Approximate equivalent doses of benzodiazepines and non-benzodiazepines with similar effects, to diazepam, oral 5 mg were aligned to Guidelines[104] [105] [106].

Guidance for non-pharmacological management of benzodiazepine toxicity has been included. This is aligned with evidence from a Cochrane review[107] that suggests that cognitive behavioural therapy *together with* tapering of benzodiazepines is effective short-term in reducing benzodiazepine overuse harmful use, abuse or dependence.

15.8.1 ALCOHOL WITHDRAWAL DELIRIUM (DELIRIUM TREMENS)

Haloperidol, oral: *dose amended*

The sole pharmaceutical supplier has discontinued haloperidol 0.5 mg from the South African market; however the 1.5 mg and 2.5 mg formulations are still currently available. Therefore, the dose for haloperidol was amended as follows:

15.8.1: Alcohol withdrawal delirium (delirium tremens)

Neuroleptic medicines, e.g. haloperidol, are associated with a reduced seizure threshold. **Consider only for severe agitation and restlessness persisting after adequate doses of benzodiazepines.**

- 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, ~~0.5~~ 0.75–5 mg 4–8 hourly.

Level of Evidence: III Guidelines[108]

Report prepared by TD Leong: Secretariat to the Adult Hospital Level Committee (2017-2020)

- ***Note:*** *Information was sourced from NEMLC ratified minutes and NEMLC-approved documents.*

[102] Taylor, David; Paton, Carol; Kapur, Shitij. The Maudsley Prescribing Guidelines, Twelfth Edition. London: CRC Press; 2015

[103] 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

[104] British National Formulary, 78th edition (September 2019-March 2020).

[105] South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town. 2016.

[106] Taylor, David; Paton, Carol; Kapur, Shitij. The Maudsley Prescribing Guidelines, Twelfth Edition. London: CRC Press; 2015

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[108] SAMF, 2016