Management of bipolar disorder in South Africa: National Department of Health essential medicine selection and treatment algorithms

L J Robertson,1 FCPsych (SA), MMed (Psyc); H Dawood,2 FCP (SA), MSc (Epi); T D Leong,3 MSc Med (Pharmacotherapy), MSc (Clin Epi)

1 Department of Psychiatry, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
2 Department of Medicine, Grey’s Hospital and Centre for the AIDS Programme of Research in South Africa (CAPRISA), University of KwaZulu-Natal, Durban, South Africa
3 Health Systems Research Unit, South African Medical Research Council, Cape Town, South Africa

Corresponding author: L J Robertson (lesley.robertson@wits.ac.za)

Background. Bipolar disorder (BD) is a severe mental illness associated with multimorbidity, psychosocial disability and significant public health issues. However, guideline heterogeneity clouds therapeutic decisions, particularly in relapse prevention. Polypharmacy and poor health outcomes are common. For low- and middle-income countries, deciding which medicines to procure and how to treat BD in an integrated manner remains elusive. Although South Africa (SA) is committed to universal health coverage, the estimated treatment gap for mental disorders in the public health sector is 91%. An Essential Medicines List (EML) enables equitable access to medicines, while Standard Treatment Guidelines (STGs) facilitate rational prescribing and quality care.

Objectives. To describe the medicine selection process for the treatment of BD in the SA public health sector, and the treatment algorithms developed to guide integrated care.

Methods. Evidence-based medicine principles, stakeholder consultation and consensus decision-making were used. The existing (2015) BD guideline and stakeholder comments were reviewed by a ministerially appointed expert review committee, following which a research question with eligibility criteria was formed, and rapid systematic evidence synthesis conducted. PubMed and Cochrane databases were searched for systematic reviews of randomised controlled trials and observational studies of acute and maintenance treatment in BD, with an additional PubMed search for primary research. Quality of the systematic reviews was appraised using the 11-item assessment of multiple systematic reviews. After costing to ensure affordability, final recommendations were made to the National EML Committee (NEMLC) using the strength of recommendation taxonomy classification. Following approval by the NEMLC, proposed medicines were incorporated into the 2019 National Department of Health Adult Hospital STGs. As the STGs are updated every 3 years, stakeholder input was sought in 2021 and 2023, with no changes to the medicine selection.

Results. Seven systematic reviews and one observational study were included in the evidence synthesis. Six medicines were selected as essential for maintenance treatment: lithium, valproate, lamotrigine, olanzapine, quetiapine and clozapine. While risperidone and benzodiazepines were retained for acute mania, carbamazepine and fluoxetine were removed from acute depression. Treatment algorithms for predominantly manic and depressive courses of illness were constructed to encourage person-centred care, aiming for euthymia, individual functioning and relapse prevention.

Conclusion. Evidence-based medicine principles enabled the NEMLC to select a range of essential medicines for the management of BD in a middle-income country. Local monitoring and evaluation are needed to inform future editions of the STGs and EML.


This article is concerned with the application of the essential medicine process in South Africa (SA) to the development of treatment algorithms for bipolar disorder (BD). Therefore, a brief introduction to the SA National Department of Health (NDoH) Standard Treatment Guidelines (STGs) and Essential Medicines List (EML) is followed by an overview of BD, its public health importance and current treatment dilemmas.

Standard Treatment Guidelines and Essential Medicine List

SA has a two-tiered health system, with a government-funded public sector serving ~80% of the population and a private sector that serves those with privately procured medical insurance and who make out-of-pocket payments. While several guidelines are available for the private sector, the NDoH STGs and EML guide
the public sector and are published on the NDoH Knowledge Hub.\(^{[5]}\)

Equitable access to essential medicines is fundamental to universal health coverage.\(^{[4]}\) An EML comprising safe, efficacious medicines, selected using evidence-based medicine principles, serves to address a country’s disease priorities within its available resources. To be sustainable, medicines must be affordable, in reliable supply and accessible. STGs facilitate good clinical practice, rational medicine use and quality assurance. An in-depth description of the SA EML process at the time the BD treatment algorithms were developed is provided by Perumal-Pillay and Suleman.\(^{[5]}\) While the methodology for medicine selection to the EML has evolved, with progress being made towards health technology assessment, little has changed in the process.\(^{[5]}\)

Resource constraints and competing health priorities impact national choices regarding healthcare provision. Although mental disorders are a leading cause of disease burden, access to treatment remains poor in low- to middle-income countries (LMICs). For mental disorders, medicine selection is also compromised by blurred diagnostic boundaries of illness, shared characteristics among many medicines and weak scientific evidence.\(^{[4]}\)

**Bipolar disorder**

BD represents a group of episodic mood disorders that usually have their onset in youth.\(^{[7]}\) The course of illness is variable, with depressive, hypomanic and/or manic episodes that often recur over the person’s lifetime. Mood episodes are characterised by marked behavioural disturbance and, except for hypomania, significant impairment in social and/or occupational functioning. While BD subtypes are diagnosed according to a history of mania or hypomania, depressive episodes frequently predominate, particularly in women.

Neurocognitive impairment is common, may be persistent and is aggravated by recurrent episodes.\(^{[8]}\) Executive functions (including sustained attention, verbal learning, working memory, visuo-spatial functioning) and social cognition are most affected. A multisite magnetic resonance imaging study\(^{[9]}\) found that compared with healthy controls, people with BD had bilateral reduced cortical thickness of the frontal, temporal and parietal regions of the brain (irrespective of mood state or BD subtype) and, among those with a history of psychosis, reduced cortical surface area.

**Public health impact of bipolar disorder**

The true impact of BD in SA is unknown. Most of the disease burden is indirect (Table 1), associated with complex multimorbidity, mood episode and psychosocial disability.\(^{[11,12]}\)

Comorbid non-communicable diseases are more common among people with BD than those without, possibly related to a common genetic predisposition\(^{[29]}\) as well as complex neuro-immunological and neuro-endocrinological pathways.\(^{[10]}\) Notably, BD is associated with increased inflammatory cytokines (including tumour necrosis factor, interleukin-6 and interleukin-8), thyroid disease, insulin resistance and disturbance of the hypothalamic-pituitary-adrenal axis.\(^{[30]}\)

Mood episodes impact the incidence or outcome of medical conditions through behaviour, including high-risk sexual intercourse when hypomanic or manic, interpersonal conflict when irritable and physical inactivity when depressed. Poor executive functioning and/or comorbid substance use exacerbate medical morbidity through poor treatment adherence or lifestyle choices.\(^{[11]}\)

Psychosocial disability refers to the interaction between the environment and the individual’s impairment in psychosocial function.\(^{[13]}\) For people with BD, stigma, discrimination and social exclusion are common, even within the health system.\(^{[14]}\) While an impoverished social environment contributes to poor general health, unapproachable healthcare services worsen healthcare utilisation, increasing delays in help-seeking and poor treatment adherence.

**Treatment dilemmas**

Therapeutic goals include the prevention of disability and optimisation of wellbeing.\(^{[15]}\) However, these goals remain elusive, related to weak scientific evidence as well as fragmented health and social care systems.

In practice, treatment is typically initiated during acute mood episodes to reduce symptoms, with continuation of acute medication as maintenance care.\(^{[12]}\) Polypharmacy is common globally, with 36% of people with BD prescribed four or more psychotropic medicines at one time,\(^{[13]}\) and has been noted in SA.\(^{[24,25]}\) Polypharmacy is more commonly associated with a depressive course of illness (with increased use of antidepressants and benzodiazepines) than a predominantly manic course.\(^{[15]}\) Guideline heterogeneity may perpetuate polypharmacy. In their Lancet seminar for primary care treatment of BD, McIntyre et al.\(^{[26]}\) list 16 medicines, with overlapping choices for acute depression, acute mania and maintenance treatment. Noting disparities in medication access between countries, and increasing polypharmacy, they stress the need for empirically based guidelines and implementation research with respect to BD.

The World Health Organization (WHO) mental health gap action programme (mhGAP)\(^{[20]}\) provides guidance for LMICs that may be adapted to local conditions. For BD, treatment algorithms aimed at primary healthcare (PHC) practitioners guide the management of acute episodes. However, a range of antipsychotics is included in their evidence review for maintenance treatment, which should be provided under specialist supervision. In SA, a consensus-based guideline for private sector psychiatrists\(^{[27]}\) does not provide a clear hierarchy of choice in recommended medicines. Consequently, there is little clarity as to which medicines should be procured for national use in the public sector.

The treatment gap for mental disorders among the SA population reliant on the public health sector is estimated at 91%, even though 5% of government health expenditure is spent on mental healthcare.\(^{[28]}\) Hospital readmissions within 3 months of discharge (an indication of inadequate relapse prevention) cost the state 18% of total mental health expenditure. Expansion of quality mental health coverage in a cost-contained manner is necessary. This article aims to describe the process by which medicines for the treatment of adults with BD were selected for inclusion in the NDoH
According to the WHO:

Associations with bipolar disorder

Medicine choices for acute mania comprised lithium, valproate, lamotrigine and carbamazepine as second-line options. For maintenance treatment, lithium, valproate and continuation of acute treatment were recommended.

Methods

Evidence-based medicine principles were used, in accordance with standard practice of the adult hospital expert review committee (AHERC) for the EML. The AHERC started by reviewing the 2015 BD guideline and stakeholder comments. Consistent with the 12th edition of the UK-based Maudsley Prescribing Guidelines in Psychiatry,[3] the 2015 treatment algorithms focused on acute treatment of mania and depression. Medicine choices for acute mania comprised lithium, valproate, risperidone and benzodiazepines. For acute depression, olanzapine and fluoxetine in combination were first-line treatment, with lithium, valproate, lamotrigine and carbamazepine as second-line options. For maintenance treatment, lithium, valproate and continuation of acute treatment were recommended.

One stakeholder comment drew attention to the depression algorithm being too cumbersome for medical officers and secondary level services. Furthermore, the AHERC stated that greater clarity regarding relapse prevention was required. Therefore, a systematic rapid evidence synthesis was conducted to establish best practice in the management of BD, with a focus on maintenance treatment.

Review question

The review question was constructed using the PICO model, as follows:

- **Population:** adults with BD
- **Interventions:** oral formulations of lithium, anti-epileptic medicines, second-generation antipsychotics and antidepressants
- **Comparators:** placebo or active control
- **Outcomes:** prevention of relapse into depression or mania during maintenance treatment, reduction of manic or depressive symptomatology in acute treatment and adverse effects.

Study types included systematic reviews of randomised controlled trials (RCTs) and/or observational studies, and primary research if not included in the systematic reviews.

### Table 1. Public health issues associated with bipolar disorder

<table>
<thead>
<tr>
<th>Public health item</th>
<th>Associations with bipolar disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burden of Disease</td>
<td>According to the 2019 Global Burden of Disease study,[7] the prevalence of BD in SA is 0.6%, causing 0.26% of disability adjusted life years, 1.06% of years lived with disability, and no years lost to life.</td>
</tr>
</tbody>
</table>
| Mortality                        | According to the WHO:[7]  
  - the mortality rate among people with BD is approximately double that of the general population, with 10 - 20 years' reduced life expectancy.  
  - natural causes account for ~75% of deaths; cardiovascular and respiratory diseases in HICs and infectious diseases in an Ethiopian cohort.  
  - unnatural causes of death are greater than in the general population with standardised mortality rates of 7.42 overall (14.4 for suicide and 3.68 for assault or trauma) among people with BD. Compared with the general population, accidental deaths are noted to be 2.3 and 3.5 times more frequent in men and women with BD, respectively. |
| Maternal and child health        | BD is associated with:  
  - increased risk of gestational hypertension, antepartum haemorrhage, preterm birth, small for gestational age babies and neonatal morbidity:[8]  
  - problematic mother-infant interactions,[8] poor family functioning,[8] and out-of-home placement of children,[9] |
| HIV/AIDS                         | Among people with HIV/AIDS, the prevalence of BD is:  
  - 2.5 and 3 times higher among women and men, respectively, than the general population in Sweden.[10]  
  - 8.1% in a small study in Brazil.[11]  
  - In Taiwan, HIV infection is 3.6 times more prevalent among people with BD than the general population.[12]  
  - Localised studies found BD among people with HIV/AIDS is associated with poor adherence to ART,[13,14] worsened neurocognitive functioning,[15] increased HIV transmission[16] and increased risk of other non-communicable diseases.[17] |
| Non-communicable diseases        | High levels of medical comorbidity, with:  
  - current prevalence of cardiovascular disease (23%), type 2 diabetes mellitus (10%), dyslipidaemias (29%), hypertension (26%), metabolic syndrome (30%), obesity (31%) and thyroid disorders (12%).[18]  
  - lifetime prevalence of musculoskeletal conditions (63%), neurological disorders (35%) and migraine headaches (29%).[19]  
  - A localised study among people with BD found non-adherence to medications for comorbid medical conditions is associated with number of BD medications prescribed, anxiety and somatic symptoms of depression. |
| Substance use                    | In the general population:[20]  
  - those with an alcohol use disorder are four times more likely to have BD than those without an alcohol use disorder.  
  - those who use drugs are five times more likely to have BD than those who do not use drugs.  
  - Among people with BD:  
    - 42% have an alcohol use disorder, 20% use cannabis and 17% use illicit drugs.[21]  
    - 44 - 71% use tobacco with indications of nicotine addiction and a need for smoking cessation interventions.[22] |

BD = bipolar disorder; SA = South Africa; WHO = World Health Organization; HIC = high-income countries.
Search strategy
To update evidence used for the 2015 STGs and EML, the PubMed and Cochrane databases were searched by LJR in March 2019 for systematic reviews of comparative effectiveness or tolerability published in English during the preceding 5 years (Appendix 1: https://www.samedical.org/file/2112). Quality appraisal of the systematic reviews was conducted by LJR using the 11-item assessment of multiple systematic reviews (AMSTAR). An overview of the evidence was drafted (Appendix 2 https://www.samedical.org/file/2113), following which changes to the 2015 STG and EML were proposed and evidence syntheses conducted.

To update the most comprehensive systematic review retrieved, an additional PubMed search was conducted by LJR in December 2019, for primary studies on maintenance treatment of BD published after 1 January 2017 (Appendix 1). Studies were excluded from the evidence syntheses of individual medicines if they did not meet PICO criteria, add further information to the most recent and best quality systematic reviews, or state their funding source. These criteria were applied conjunctively. Because of a lack of capacity and time constraints, the quality of primary studies was not appraised.

Evidence to decision and drafting of the guideline
Final recommendations for the EML were made by the AHERC to the national EML committee (NEMLC) using the strength of recommendation taxonomy (SORT) classification, which focuses on patient-oriented outcomes measuring changes in morbidity or mortality. A level 1 recommendation is based on good-quality patient-oriented evidence; a level 2 recommendation is based on limited-quality patient-oriented evidence; and a level 3 recommendation is based on other evidence such as consensus, usual practice, opinion, disease-oriented outcomes, or case series.

Once consensus regarding efficacy, safety, affordability, supply reliability and acceptability was reached by the NEMLC, the revised BD guideline was circulated by the NDoH for stakeholder comment. Comments received were resolved iteratively, and the guideline published in chapter 15 of the 2019 Adult Hospital STGs. In 2021, at the start of the current review cycle, the STGs were circulated again by the NDoH to stakeholders. While no new comments on the BD algorithms were received, minor edits were made for clarity. The mental health chapter was recirculated by the NDoH in 2023; received comments were addressed by the AHERC and final approval for publication made by the NEMLC in July 2023.

Results
The PRISMA flow diagram and list of excluded systematic reviews are available in Appendix 3 (https://www.samedical.org/file/2114), while more detail is provided in Appendix 2 (bipolar disorder overview) regarding all studies that informed the guideline. The search for systematic reviews yielded 347 titles, of which 7 (42-47) were included in the evidence syntheses for individual medicines (Table 2). The search for primary studies yielded 168 titles, with one meeting all criteria for inclusion in the evidence syntheses.

The evidence syntheses, evidence-to-decision frameworks and costing are described for each medicine in Appendices 4 – 8 (4: https://www.samedical.org/file/2115; 5: https://www.samedical.org/file/2116; 6: https://www.samedical.org/file/2117; 7: https://www.samedical.org/file/2119) (lithium as first-line treatment; adjunctive antidepressants, carbamazepine, clozapine, olanzapine and quetiapine, respectively). Overall, the available evidence was of poor quality with a high risk of bias, particularly in RCTs on maintenance treatment. For relapse prevention, lithium was the only medicine with evidence of efficacy from direct and network meta-analyses. For prevention of hospitalisation, observational studies suggested superiority of lithium compared with other medications. Additionally, lithium is associated with a reduced suicide risk in BD.

Insufficient evidence was found for adjunctive antidepressants in acute or maintenance treatment to justify their recommendation. For carbamazepine, the AHERC found only very weak evidence of efficacy, and evidence of harm. Considering this and potential drug-drug interactions with medicines for comorbid medical conditions, the AHERC recommended removal of carbamazepine from the STG. Although effective in acute mania, no evidence was found to support the use of oral risperidone in maintenance treatment (see Appendix 7 on olanzapine). Finally, six medicines were selected as essential for relapse prevention in maintenance treatment: lithium (SORT level 1), valproate (SORT level 3), lamotrigine (SORT level 3), olanzapine (SORT level 2), quetiapine (SORT level 2) and clozapine (SORT level 3). Oral risperidone and benzodiazepines were retained for acute mania but not recommended for maintenance treatment.

Treatment algorithms
The 2023 treatment algorithms are presented in Figs 1 and 2. Importantly, the algorithms emphasise that management of acute episodes is done with consideration of the longitudinal course of illness, medical comorbidity, pregnancy risk and medicine tolerability. Variability in clinical presentation is also accommodated by including three BD subtypes (bipolar I disorder, bipolar II disorder and bipolar otherwise specified). A medicine hierarchy is provided, with lithium as first line, anticonvulsants second and antipsychotics third and fourth. Anticonvulsants are placed before antipsychotics despite their lower strength of recommendation in terms of efficacy, because of potential long-term metabolic and neurological adverse effects of antipsychotics. Further recommendations regarding general medical work-up, medication monitoring and management during pregnancy are available in the mental health chapter of the Adult Hospital STGs.

Overall, an individualised, recovery-oriented treatment approach is used, with goals of achieving euthymia, optimal functioning and prevention of relapse. It is hoped that such an approach will simultaneously improve individual wellbeing and associated public health issues, with improved lifestyle choices and self-contained behaviour. Thus, repeated re-evaluation during maintenance care is encouraged, with use of social support, social services and occupational therapy, if accessible. Rating scales are suggested to assist objective measurement of symptomatology and function. Throughout the process, management in consultation with a psychiatrist is recommended.
**Discussion**

BD is a severe mental illness associated with multimorbidity and premature mortality. Although various medicines are available for its treatment, the range of medicines procured by LMICS must be sustainable. This article describes the medicine selection process for the SA EML. To encourage rational medicine use, person-centred, recovery-oriented treatment algorithms were developed for the NDoH Adult Hospital STGs.

Universal access to quality care depends on multiple factors. Issues to consider include prescriber and service level restrictions, alignment with mental health legislation, and policy and systemic barriers to implementation.

**Prescriber level and treatment setting**

Except for lamotrigine and valproate, all medicines in the BD treatment algorithms are schedule 5 medicines, as scheduled by the SA Health Products Regulatory Authority. Schedule 5 medicines may only be prescribed by medical practitioners. They may not be initiated or re-prescribed by PHC nurses who have authorisation to prescribe medicines for selected conditions under section 56(6) of the Nursing Act No. 33 of 2005. While medical officers and family physicians working in PHC clinics may prescribe schedule 5 medicines, these doctors are not available in all PHC settings, especially in rural areas. Therefore the algorithms in the Adult Hospital STGs and EML are aimed at medical officers.

**Table 2. Articles included in the evidence syntheses of individual medicines**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Source</th>
<th>Study details</th>
<th>Quality appraisal</th>
<th>Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comparative effectiveness reviews of multiple medicines</strong></td>
<td>Butler et al.</td>
<td>Systematic review and meta-analysis of RCTs: • acute mania (follow-up 3 weeks) n=67 RCTs • acute depression (follow-up minimum of 12 weeks), n=7 RCTs • maintenance (follow-up 6 months) n=36 RCTs</td>
<td>AMSTAR 11/11</td>
<td>Agency for Healthcare Research and Quality</td>
</tr>
<tr>
<td><strong>Miura et al.</strong></td>
<td>Systematic review and network meta-analysis of RCTs, n=33 evaluating comparative efficacy and tolerability of maintenance treatments; (follow up ranged from 17.3 - 171.4 weeks)</td>
<td>AMSTAR 9/11</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td><strong>Selle et al.</strong></td>
<td>Meta-analysis of RCTs (N=24) for acute bipolar depression (follow-up 6 – 10 weeks)</td>
<td>AMSTAR 4/11</td>
<td>Non-profit donors</td>
<td></td>
</tr>
<tr>
<td><strong>Effectiveness reviews of individual medicines or medicines from a single category</strong></td>
<td>McGirr</td>
<td>Systematic review and meta-analysis of RCTs (n=6) evaluating adjunctive second-generation antidepressant therapy: • acute bipolar depression (follow-up 6 - 26 weeks), n=6 RCTs • maintenance treatment (follow-up 52 weeks), n=2 RCTs</td>
<td>AMSTAR 11/11 (Note: score provided in Appendix 1 is in error)</td>
<td>None</td>
</tr>
<tr>
<td><strong>Lindstrom et al.</strong></td>
<td>Systematic review and meta-analysis of RCTs (n=15) evaluating maintenance treatment with second-generation antipsychotics (follow-up 6 months - 2 years)</td>
<td>AMSTAR 8/11</td>
<td>Swedish Agency for Health Technology Assessment and Assessment of Social Services</td>
<td></td>
</tr>
<tr>
<td><strong>Li et al.</strong></td>
<td>Systematic review of studies (n=15) evaluating clozapine in treatment resistant BD: • n=2 RCTs, duration 6 weeks and 1 year • n=3 retrospective studies, duration 6 weeks - 2 years • n=10 prospective open-label studies, duration 2 - 60 months</td>
<td>AMSTAR 8/10 (statistics not applicable)</td>
<td>Beijing Science and Technology Commission</td>
<td></td>
</tr>
<tr>
<td><strong>Kessing et al.</strong></td>
<td>Systematic review of observational studies (n=9) evaluating maintenance treatment with lithium compared with other medications (follow-up 12 months - 19 years)</td>
<td>AMSTAR 3/10 (statistics not applicable)</td>
<td>Wellcome Trust</td>
<td></td>
</tr>
<tr>
<td><strong>Primary study</strong></td>
<td>Joas et al.</td>
<td>Observational, registry-linked study (n=35 022 individuals) evaluating maintenance treatment. A within-individual analysis was conducted, comparing the effect of receiving treatment with not receiving treatment on hospital admissions for relapse into any episode, mania or depression.</td>
<td>Not appraised</td>
<td>Swedish Medical Research Council, the Swedish Foundation for Strategic Research, Swedish federal government under the LUA/ALF agreement and the Sigurd and Elsa Golje Foundation</td>
</tr>
</tbody>
</table>

**RCT** = randomised controlled trial; **AMSTAR** = assessment of multiple systematic reviews; **BD** = bipolar disorder.
ARTICLE

BIPOLAR DISORDER
Predominantly manic course of illness
(manage in consultation with psychiatrist)

Acute manic episode
Admit under MHCA; nurse in calm, secure environment.
Stop any antidepressants or stimulant medication/herbal remedies.

Severe aggression/disruption: see section 15.1: ‘Aggressive disruptive behaviour in adults’ in the Hospital Level (Adults) STGs and EML.

Short-term sedation:
• Lorazepam, oral or IM, 2 mg 8-hourly.
• Clonazepam, oral or IM, 2 mg 12-hourly.
AND/OR
• Short-term antipsychotic: Risperidone, oral, 2 - 6 mg at night.

Initiate medicine treatment (with view to long-term management):
• Lithium, oral, usually 200 - 600 mg at night (therapeutic range 0.8 - 1.0 mmol/L).
• Previous non-response or high risk of non-adherence or adverse effects with lithium:
  • Valproate, oral, 400 - 600 mg 12-hourly (may give 20 mg/kg/day in divided doses).
  • Women of child-bearing potential/valproate poorly tolerated:
    • Olanzapine, oral 5 - 20 mg at night.

Short-term antipsychotic:
• Risperidone, oral, 2 - 6 mg at night.

Long-term management
Psycho-educate user and family. Manage comorbid psychiatric, substance use and medical conditions.
Address psychosocial stressors and disability. Refer for occupational therapy as needed.
Consider need for residential care.
Continually monitor mental and physical state, using rating scale for symptoms (e.g. BPRS, Ham-D, YMRS) and function (e.g. WHODAS).
Adjust medication/psychosocial interventions as indicated.

Check lithium level and adjust dose to ensure levels of 0.6 - 1.0 mmol/L (200 - 600 mg at night).
OR
• Valproate, oral, 400 - 600 mg 12-hourly.
• Olanzapine, oral, 5 - 20 mg at night.

Check lithium level and adjust dose to ensure levels of 0.6 - 1.0 mmol/L (200 - 400 mg at night).
ADD
• Lamotrigine, oral, titrate to 200 mg at night.
See section 14.4: ‘Epilepsy in the Hospital Level (Adults) STGs and EML.
If lamotrigine poorly tolerated:
ADD
• Quetiapine, oral, 100 - 300 mg at night.
  • Taper and stop risperidone or olanzapine if used (use lithium or valproate to prevent mania).

If lamotrigine poorly tolerated:
ADD
• Olanzapine, oral, 5 - 20 mg at night.
  • Taper and stop risperidone if used (use lithium or valproate to prevent mania).

Persistent symptoms and/or recurrent severe episodes

N
• Check lithium level and adjust dose to ensure maintenance therapeutic levels of 0.6 - 1.0 mmol/L (200 - 400 mg at night).
• Slowly taper and stop antipsychotic with close monitoring if possible.
• Maintain on treatment according to individual response.

Y
• Identify and address perpetuating factors.
  • Consult with tertiary psychiatric unit/specialised hospital and refer as advised.
  • Clozapine, oral, 100 - 400 mg at night.
  • Taper and stop other antibiotics.
  • Optimise lithium.
AND/OR
• Anti-epileptic medication.

Note:
• Avoid combining two antipsychotics.
• Avoid combining medicines that cause weight gain, e.g. olanzapine and valproate.

Fig. 1. Treatment algorithm for predominantly manic course of illness. (MHCA = Mental Health Care Act No. 17 of 2002; STGs = Standard Treatment Guidelines; EML = Essential Medicines List; IM = intramuscular; BPRS = Brief Psychiatric Rating Scale; Ham-D = Hamilton Depression Scale; YMRS = Young Mania Rating Scale; WHODAS = World Health Organization Disability Assessment Schedule.)
Source: NDoH Hospital Level (Adults) Standard Treatment Guidelines (STGs) And Essential Medicines List (EML) (2024 edition).15
and family physicians in public sector hospitals, and provide a progression in care from non-pharmacological mental healthcare interventions in the PHC STGs.[3]

Public sector hospitals exist in a hierarchical relationship, with specified packages of care at each service level.[1,4] District hospitals (the first level of care) take referrals from PHC and refer up to regional (secondary), tertiary, central (quaternary), or specialised hospitals, depending on clinical need. Psychiatric services are not included in the district hospital package of care, and are optional at regional hospitals. People with severe mental illness requiring

---

**Fig. 2. Treatment algorithm for predominantly depressive course of illness.** (IM = intramuscular; BPRS = Brief Psychiatric Rating Scale; Ham-D = Hamilton Depression Scale; YMRS = Young Mania Rating Scale; WHODAS = World Health Organization Disability Assessment Schedule; MHCA = Mental Health Care Act No. 17 of 2002; ECT = electroconvulsive therapy; STGs = Standard Treatment Guidelines; EML = Essential Medicines List; BD = bipolar disorder; BD-OS = other specified bipolar disorder.)

Source: NDoH Hospital Level (Adults) Standard Treatment Guidelines And Essential Medicines List (2024 edition).[10]
specialist assessment and treatment are referred from district and regional hospitals to tertiary, central or specialised psychiatric hospitals. Upon hospital discharge, they are referred back to PHC, with referral up to district and regional hospitals for chronic care prescriptions and readmission.

While the BD treatment algorithms are intended for district and regional hospitals, they impact psychiatric care provided at higher level hospitals. Firstly, the choice of maintenance treatment is dependent on what is available to the individual after discharge from a tertiary, quaternary, or specialised hospital. Secondly, there are no additional medicines for BD on the EML specifically for tertiary and quaternary services.6

Alignment with SA mental health legislation and policy

The STGs and EML are aligned to the Mental Health Care Act No. 17 of 200224 in that they enable equitable mental healthcare in the best interests of the mental healthcare user within available resources (section 3(a)(i)), which is integrated into the ‘general health services environment’ (section 3(a)(iii)), at primary, secondary and tertiary service levels (section 4(a)).

The BD treatment algorithms fall short of the requirement to ‘promote the provision of community-based care, treatment and rehabilitation services’ (section 4(b)), owing to prescriber-level restrictions and the scarcity of medical practitioners in PHC settings. Nevertheless, they do provide guidance for district and regional hospitals, the levels of hospital care closest to the community. To address limitations regarding scope of practice of medical officers (section 6(1)), the guideline recommends that people with BD are managed in consultation with a psychiatrist.

Together with the NDoH STGs and EML in general, the BD treatment algorithms facilitate implementation of the National Mental Health Policy Framework and Strategic Plan 2023 – 203025 in that they provide guidance for:

- which medicines must be available at each service level
- secondary and tertiary preventative treatment of BD
- a task-sharing, collaborative approach to care
- integration of physical and mental healthcare
- referral for rehabilitative and community-based care.

Implementation barriers and facilitators

Barriers to implementation of the treatment algorithms include medicine supply issues and poor access to clinical expertise. Facilitators include innovative ways to achieve collaborative care across and within service levels.

All the medicines for BD on the EML are on national tender for the current procurement cycle.24 However, supply of any medicines for BD at facility level is driven by service user demand for and access to mental healthcare, including access to accurate clinical assessment and appropriate prescribing.24 While stigma and poor help-seeking behaviour affect the demand for care, the distribution of human resources affects access to clinical expertise.

The BD algorithms recommend that patients are managed in consultation with a psychiatrist. However, public sector psychiatrists are scarce, ranging from 0.08 - 0.89 per 100 000 population dependent on public health services, in Mpumalanga and Western Cape provinces, respectively.26 Most psychiatrists, and mental health resources, are at specialised, central or tertiary hospitals, remote from district level healthcare practitioners and service users. At district level, general healthcare staff shortages are severe and unable to meet population needs.22 Furthermore, the training of healthcare providers in SA is not conducive to the provision of collaborative care.22

It may not be possible for district hospital medical officers to liaise with psychiatrists, PHC and allied healthcare providers to provide optimal care to people with BD. Nevertheless, various efforts to decentralise and integrate mental healthcare services are being made in SA.31 Thus the STGs and EML serve to facilitate integrated mental healthcare wherever systems enable collaboration between healthcare providers.

Limitations

Two substantial limitations of our BD STG are present: the weak evidence base for treatment of BD, and appraisal of the evidence by one primary reviewer. Although mitigated by secondary review within the AHERC and the NEMLC, limited human resource capacity in these committees may lead to some factors being overlooked. External stakeholder comment is therefore vital. However, engagement with people with lived experience is insufficient.

Conclusions

Evidence-based medicine principles enabled selection of a range of medicines and development of treatment algorithms suitable for the public sector in a middle-income country. A STG for the mental healthcare of people with BD within local resource constraints should facilitate access to treatment, and serves as a comparator for health technology assessment. Quality assurance, further research and stakeholder input are necessary to inform future guideline development.

Declaration. None.

Acknowledgements. Gratitude is expressed to all members and secretariat of the 2017 - 2020 AHERC and 2017 - 2021 NEMLC for their input and support in the medicine selection and drafting of the 2019 BD STG. Particular thanks are extended to Dr Andrew Black (AHERC chair until 2019), Dr Ebrahim Bera (AHERC Vice Chair, acknowledged posthumously), Prof. Andrew Parrish (NEMLC Chair), Dr Gary Reubenson (NEMLC vice chair), AHERC members Prof. Patrick Commerford, Dr Alicia Sherriff, Dr R Kaswa, Dr Simba Takuva, Dr Stacy Rossouw, Dr G A Timothy, Prof. Gerhard Gebhardt, Prof. Renier Coetzee and Mr Johnson Nabyma, and secretariat Dr Janine Jugathpal, Dr Jane Riddin, Dr Ruth Lancaster and Ms Sheeren Govender.

Author contributions. LJR conceptualised the article, drafted the manuscript and was primary reviewer for the STG. HD and TDL reviewed and edited the article and provided extensive guidance in the selection of medicines and development of the STG (HD as chair of the AHERC (2019 - 2020) and NEMLC member; TL as secretariat for the AHERC and NEMLC).

Funding. None.


Accepted 5 September 2023.