health
Department:
Health
REPUBLIC OF SOUTH AFRICA

2030 NDP

**SOUTH AFRICAN PRIMARY HEALTHCARE LEVEL ESSENTIAL MEDICINES LIST**
**CHAPTER 16: MENTAL HEALTH CONDITIONS**
**NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2016-2018)**

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

## A: NEW SECTIONS(S)/ SUBSECTION(S)

| SECTION | CONDITION | MEDICINE MANAGEMENT | MEDICINE ADDED |
|---|---|---|---|
| **16.2.2** | **Neuroleptic malignant syndrome** | No | n/a |
| **16.6** | **Psychiatric patients - general monitoring and care** | Yes | Folic acid, oral |
| **16.8.1** | **Intellectual disability** | No | n/a |
| **16.8.2** | **Older patients (≥ 45 years)** | No | n/a |
| **16.8.3** | **Sexual health and sexuality** | No | n/a |
| **16.8.4** | **Maternal mental health** | No | n/a |

## 16.2.2 NEUROLEPTIC MALIGNANT SYNDROME

Following was included in the chapter, as though rare it is a life-threatening condition:

**CAUTION**
Neuroleptic malignant syndrome (NMS) rare, but a potentially fatal syndrome characterised by a tetrad of fever, muscle rigidity, altered mental state and autonomic dysfunction. If this is suspected, stop medication and urgently refer. Keep hydrated and cool.

**General measures**
Cool patient and hydrate adequately.

**Referral**
All patients.

## 16.6 PSYCHIATRIC PATIENTS - GENERAL MONITORING AND CARE

Monitoring guidance added specific to primary level of care, aligned with guidelines (SAMF, 2016 and the Adult Hospital Level STGs and EML, 2015).
**Level of Evidence: III Guidelines**

**Description**
Nursing staff are required to monitor users with serious mental illness between medical or psychiatric doctor visits. Regular monitoring with documented nursing notes in the file should occur monthly to 6-monthly depending on the severity of the illness and the risk of relapse, aggression, absconding or poor adherence, with referral as required.

Monitoring includes:
» A mental state enquiry and examination.
» A brief psychosocial assessment.
» A risk assessment for harm to self or others with referral if deemed high risk
» Adherence support.
» In women: family planning and pregnancy counselling.
» General health: screen at baseline and annually - weight and BMI, blood pressure (see Section 4.7: Hypertension), finger-prick blood glucose test for diabetes (See Section: 9.2.2: Type 2 Diabetes mellitus, adults), HIV (See chapter 11: HIV and AIDS) and tuberculosis (see Section 17.4: Pulmonary tuberculosis (TB)).

» Lifestyle advice for obesity, smoking, alcohol, other substances and high- risk sexual behaviour or victim of abuse.

**Recommendations for specific medicines include:**

» Antipsychotic medicines e.g.: haloperidol, risperidone, flupenthixol decanoate, zuclopenthixol deconate: If metabolic effects (weight gain/ hyperglycaemia) occur, refer to a dietician and encourage regular exercise. If needed, manage lipids - See Section: 4.1: Prevention of ischaemic heart disease and atherosclerosis.

» Valproic acid and carbamazepine: Avoid in women of childbearing potential.

– If alternate treatment cannot be recommended and these agents are required, give:

- Folic acid, oral, 5 mg daily; and ensure reliable contraception.

**Caution regarding valproic acid in pregnancy**

The following caution was added to the STG, following the European Medicine Agency's Pharmacovigilance Risk Assessment Committee (PRAC) assessment and recommendation to strengthen the caution to avoid valproate exposure in pregnancy.

**CAUTION**

Children born to women taking valproic acid are at significant risk of birth defects (10%) and persistent developmental disorders (40%).
Valproic acid is contra-indicated and should be avoided in pregnancy and women of child-bearing potential.

**Level of Evidence: III Registry data[1]**

Folic acid, oral: *added as a supplement for women of reproductive age groups on valproic acid or carbamazepine*

***Evidence review:***

*Guidelines:* The Royal College of Obstetricians and Gynaecologists (RCOG)[2] recommends the following:

- "All women with epilepsy should be advised to take 5 mg/day of folic acid prior to conception and to continue the intake until at least the end of the first trimester to reduce the incidence of major congenital malformation".
- "Pre-pregnancy folic acid 5 mg/day may be helpful in reducing the risk of AED-related cognitive deficits".

*Medical Research Council Vitamin Study*: This is largely based on the Medical Research Council Vitamin Study[3], that showed a 72% protective effect (RR 0.28; 95% CI 012 to 0.71) of folic acid vs non-folic acid supplements. Neural tube defects were reported in 6 of the folic acid groups and 21 in the non-folic acid group – administered until 12 weeks of pregnancy.

*Meader et al:* Meta-analysis[4] of registries and cohort studies estimated that the risk of congenital malformations was highest for women taking sodium valproate (10.7 per 100, 95% CI 8.16 to 13.29) or AED polytherapy (16.8 per 100, 95% CI 0.51 to 33.05) vs 2.3 per 100 (95% CI 1.46 to 3.1) in non-epilepsy group.

[1] Valproic acid – caution in pregnancy: European Medicines Agency - Pharmacovigilance Risk Assessment Committee. Assessment report EMA/198940/2018 - valproate exposure in pregnancy, 8 February 2018.
http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Valproate_2017_31/Position_provided_by_CMDh/WC500250221.pdf

Valproic acid – caution in pregnancy: Meador K, Reynolds MW, Crean S, Fahrbach K, Probst C. Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. Epilepsy Res. 2008 Sep;81(1):1-13. https://www.ncbi.nlm.nih.gov/pubmed/18565732

[2] Royal College of Obstetricians and Gynaecologists. RCOG Green-top Guideline No. 68: Epilepsy in pregnancy, June 2016. https://www.rcog.org.uk/guidelines

[3] Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. MRC Vitamin Study Research Group. Lancet. 1991 Jul 20;338(8760):131-7. https://www.ncbi.nlm.nih.gov/pubmed/1677062

[4] 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;81:1–13. https://www.ncbi.nlm.nih.gov/pubmed/18565732

*EURAP (International Registry of Antiepileptic Drugs and Pregnancy)* [5]: Risk of major congenital malformation to the fetus associated with the type, number and dose of AEDs[6]. Low dose monotherapy lamotrigine (<300 mg) and carbamazepine (<400 mg) reported to have the lowest risk. The PHC STG recommends maximum dose of lamotrigine of 200 mg daily; and 600 mg daily of carbamazepine for generalised tonic-clonic seizures in adults[7].
*Congenital defects:* The most common major congenital malformations associated with AEDs are neural tube defects, congenital heart disorders, urinary tract and skeletal abnormalities and cleft palate[8 9 10].

*Monitoring at primary level of care:* The overall NDoH strategy for Mental Health Care includes management of patients with mental health conditions as part of integrated management at primary level of care.

**Recommendation:** Folic acid be recommended for women of reproductive age groups who require to be on valproic acid or carbamazepine.
*Rationale:* Aligned with guidelines and there have been reports of congenital malformations with valproic acid and higher dose of carbamazepine (>400 mg per day).
**Level of Evidence: III Guidelines, Registry data, Cohort Studies**

**Caution regarding valproic acid in pregnancy**
The following caution was added to the STG, following the European Medicine Agency's Pharmacovigilance Risk Assessment Committee (PRAC) assessment and recommendation to strengthen the caution to avoid valproate exposure in pregnancy.

| **CAUTION** |
| --- |
| Children born to women taking valproic acid are at significant risk of birth defects (10%) and persistent developmental disorders (40%). Valproic acid is contra-indicated and should be avoided in pregnancy and women of child-bearing potential. |

**Level of Evidence: III Registry data[11]**

## 16.8.1 INTELLECTUAL DISABILITY

Following STG was included in the chapter to provide general guidance at primary level:

- » Difficulty with verbal communication in the patient may result in over diagnosis of psychiatric conditions.
- » More time is needed in the consultation and adequate history from family members.
- » High risk of being victims of sexual and physical violence, by the family, neighbours or strangers.

[5] Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Sabers A, et al.; EURAP study group. Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. Lancet Neurol 2011;10:609–17. https://www.ncbi.nlm.nih.gov/pubmed/21652013
[6] Royal College of Obstetricians and Gynaecologists. RCOG Green-top Guideline No. 68: Epilepsy in pregnancy, June 2016. https://www.rcog.org.uk/guidelines
[7] PHC STGs and EML, 2018.
[8] 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;81:1–13. https://www.ncbi.nlm.nih.gov/pubmed/18565732
[9] Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Sabers A, Perucca E, Vajda F; EURAP study group. Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. Lancet Neurol. 2011 Jul;10(7):609-17. https://www.ncbi.nlm.nih.gov/pubmed/21652013
[10] Hernández-Díaz S, Werler MM, Walker AM, Mitchell AA. Folic acid antagonists during pregnancy and the risk of birth defects. N Engl J Med 2000;343:1608–14. https://www.ncbi.nlm.nih.gov/pubmed/11096168
[11] Valproic acid – caution in pregnancy: European Medicines Agency - Pharmacovigilance Risk Assessment Committee. Assessment report EMA/198940/2018 - valproate exposure in pregnancy, 8 February 2018.
http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Valproate_2017_31/Position_provided_by_CMDh/WC500250221.pdf
Valproic acid – caution in pregnancy: Meador K, Reynolds MW, Crean S, Fahrbach K, Probst C. Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. Epilepsy Res. 2008 Sep;81(1):1-13. https://www.ncbi.nlm.nih.gov/pubmed/18565732

- » Emotional distress, fear, anxiety or depression may present as aggression or odd behaviour.
- » A supportive, caring, secure environment is essential for well-being and contained behaviour.
- » Manage together with social workers, OTs, counsellors and non-health departments e.g. social development and education.
- » Lowest doses of medication should be used; consider anxiety, depression and epilepsy before psychosis.
- » Placement in a residential facility may be necessary: Requires MHCA Form04 and two Form 05s.

### 16.8.2 OLDER PATIENTS (≥ 45 years)

Following STG was included in the chapter to provide general guidance at primary level:

- » New psychiatric diagnoses are rare older patients.
- » Actively exclude medical causes, e.g. anaemia, pain, dementia, chronic kidney disease, COPD, malignancy.
- » Older patients are very sensitive to the side effects of psychiatric medications and these are common presentations. Use lowest possible dose.
- » Consult with family/carers: educate about the condition and provide support by explaining how to manage behaviour at home.
- » Refer family/carers to social worker/counsellor for further support.

### 16.8.3 SEXUAL HEALTH AND SEXUALITY

Sexual disorders are complex conditions that may also present at PHC. Following STG was included in the chapter to provide general information to create awareness at primary level with referral to higher levels of care for management:

Sexual problems may be more frequent amongst people with mental illness or neuropsychiatric conditions:

- » Low sex drive, anorgasmia (unable to achieve an orgasm), impotence may occur as part of the mental illness, as a result of medication side effects (e.g. fluoxetine), and/or substance use.
- » Hyper-sexuality may occur in people with intellectual disability, in manic or psychotic states, emotional dysregulation, substance use disorders
- » Specific sexual disorders, e.g. vaginismus (spasm of vagina) or other sexual dysfunction, require specialist treatment.
- » Refer for assessment and appropriate treatment.

Mental illness is more common amongst people with alternative sexual orientations or who are transgender.

- » Stigma, discrimination and victimisation increase the prevalence of mental illness amongst this group of people.
- » Response to treatment will be poor if underlying issues are not expressed and managed.
- » Disclosure to a staff depends on a non-judgemental, accepting environment.
- » Refer to counsellor/social worker.
- » Counsel family members/caregivers.
- » Refer to psychiatrist depending on clinical presentation/need.

### 16.8.4 MATERNAL MENTAL HEALTH

Cross referred to the Obstetrics and gynaecology chapter. Mental disorders in pregnancy and those occurring in postpartum are common.[12] [13]

## B: AMENDMENTS TO MEDICINE TREATMENT:

| SECTION | MEDICINE/MANAEGEMENT | ADDED/DELETED/AMENDED |
|---|---|---|
| **16.1 Aggressive disruptive behaviour** | | |
| *- If alcohol use is suspected:* | Thiamine, oral | Added |
| *- IM treatment (rapid tranquillisation):* | Midazolam, IM<br>Haloperidol, IM<br>Promethazine, IM<br>Clonazepam, IM<br>Lorazepam, IM | Retained<br>Retained<br>Retained<br>Not added<br>Not added |

[12]Mannikam L, Burns JK. Antenatal depression and its risk factors: An urban prevalence study in KwaZulu-Natal. SAMJ 2012:12(102)
[13]Peltzer K, Habil, Shikwane ME. Prevalence of postnatal depression and associated factors among HIV-positive women in primary care in Nkangala district, south Africa. SAJHIVmed. 2011:12(4).

| | | |
|---|---|---|
| **16.2.1 Extra-pyramidal side effects** | | |
| *- Acute dystonic reaction: Children* | Biperiden IM/slow IV | Dosing amended |
| *- Acute dystonic reaction: Adults* | Biperiden IM | Dosing amended |
| *- Drug induced parkinsonism: Adults* | Orphenadrine, oral | Indication and dosing amended |
| **16.3 Anxiety disorders** | | |
| | Psychotherapy | Added |
| *- For severe panic attacks* | Diazepam, oral | Retained |
| | Citalopram, oral | Deleted |
| *- First line treatment* | SSRIs, oral | Retained |
| | Benzodiazepines, oral | Deleted |
| | Fluoxetine, oral | Added as first line therapy |
| | Citalopram, oral | Deleted as first line therapy |
| *- Second line treatment* | Alternative SSRIs, oral (citalopram, escitalopram, sertraline) | Added as a therapeutic group |
| *- SSRIs – general information* | SSRIs | Caution box amended |
| | SSRIs | Duration of therapy amended |
| *- For severe panic attacks* | Diazepam, oral<br>Citalopram, oral | Retained<br>Deleted |
| *- benzodiazepines– general information* | Benzodiazepines | Caution updated |
| **16.4.1 Depressive disorders** | | |
| *- First line treatment* | Fluoxetine, oral | Retained as first line & dosing amended |
| *- Second line treatment* | Alternative SSRIs, oral (citalopram, escitalopram, sertraline) | Added as a therapeutic group |
| *- SSRIs – general information* | SSRIs | Duration of therapy amended |
| | SSRIs | Age-limit not added |
| | SSRIs | Caution box amended |
| **16.4.2 Bipolar disorders**<br>**-** *Rapid tranquilisation* | Diazepam, oral<br>Midazolam, buccal<br>Midazolam, IM<br>Haloperidol, IM<br>Promethazine, IM | Deleted<br>Deleted<br>Deleted<br>Deleted<br>Deleted |
| **16.5.1 Acute psychosis** | | |
| **-** *Rapid tranquilisation* | Diazepam, oral<br>Midazolam, buccal<br>Midazolam, IM<br>Haloperidol, IM<br>Promethazine, IM | Deleted<br>Deleted<br>Deleted<br>Deleted<br>Deleted |
| *- If known with schizophrenia, known to have used antipsychotics previously, and non-aggressive/ violent patents* | Zuclopenthixol acetate | Deleted |
| **16.5.2 Chronic psychosis (schizophrenia)** | | |
| **-** *Rapid tranquilisation* | Diazepam, oral<br>Midazolam, buccal<br>Midazolam, IM<br>Haloperidol, IM<br>Promethazine, IM | Deleted<br>Deleted<br>Deleted<br>Deleted<br>Deleted |
| *- Long-term depot therapy where adherence problem, or patient preference* | Fluphenazine, IM | Deleted |
| | Chlorpromazine, oral | Not added |
| *- Extrapyramidal side effects* | Orphenadrine, oral | Deleted |
| **16.7 Suicide risk assessment** | Suicide risk assessment tools | Deleted |

## 16.1.2 AGGRESSIVE DISRUPTIVE BEHAVIOUR IN ADULTS

General guidance was aligned with NICE guidelines on short-term management of violence and aggression in mental health and community settings[14]. Delirium is now included under the general heading of 'aggressive disruptive behaviour', as a distinction between the two conditions is not always clear or practical.

**If alcohol use is suspected:**
Thiamine, oral: *added*
Aligned with Adult Hospital Level STGs and EML, 2015.
**Level of Evidence: III Guidelines**

**IM treatment (rapid tranquillisation):**
Midazolam, IM: *retained*
Haloperidol, IM: *retained*
Promethazine, IM: *retained*
Clonazepam, IM: *not added*
Lorazepam, IM: *not added*

*C*lonazepam, IM[15] considered too expensive for PHC level of care and to be available at all primary healthcare facilities. The other option for short acting benzodiazepine, IM is lorazepam, IM. However, the latter requires refrigeration which is not practical at every PHC facility.

The rapid tranquillisation sequence is followed by remedial measures for complications, and the following caution box was added to the text of the STG:

**CAUTION**

- Rapid tranquillisation may cause cardiovascular collapse, respiratory depression, neuroleptic malignant syndrome and acute dystonic reactions.
- The elderly, children, those with comorbid medical conditions, and substance users are at highest risk.
- A**n emergency trolley, airway, bag, oxygen and intravenous line must be available.**

Clotiapine injection: *not added*
Refer to the medicine review: Clotiapine injection for acute aggressive disruptive behaviour in adults, 6 June 2017.

ClotiapineInj_Aggre
ssiveDisruptiveBeha

Based on the above appraisal of the evidence, the Expert Review Committees recommend that chlorpromazine injection is replaced by clotiapine injection for use in rapid tranquillisation of aggressive/ disruptive patients when the haloperidol + promethazine is not available
*Rationale*: Available evidence overall is very low quality and insufficient evidence to recommend one injectable antipsychotic over another as an alternative to haloperidol + promethazine. The decision to use clotiapine IM as an alternative to chlorpromazine IM is related to reliability of supply, possible safety considerations in comparison to zuclopenthixol acetate and cost.
**Level of Evidence: II Low quality systematic review [16]**

[14]https://www.nice.org.uk/guidance/ng10/resources/violence-and-aggression-shortterm-management-in-mental-health-health-and-community-settings-1837264712389
[15] Contract circular HP09-2017SVP:
- Clonazepam 1mg/ml, 1 mL injection: R19.42
- Midazolam 1mg/ml, 5 mL injection: R3.53
[16]Carpenter S, Berk M, Rathbone J. Clotiapine for acute psychotic illnesses. Cochrane Database Syst Rev. 2004 Oct 18;(4):CD002304.

**NEMLC recommended the following on 14 December 2017[17]:**
*Clotiapine, IM:* There are pragmatic implications for long-acting psychotic use in the emergency setting in PHC, prior to referral to the secondary level. The PHC STG does provide an alternative option to haloperidol, benzodiazepine and orthostatic hypotension associated with clotiapine is a concern.
**NEMLC Recommendation:** Clotiapine, IM not be recommended for primary level EML.

### 16.2.1 EXTRA-PYRAMIDAL SIDE EFFECTS

**Acute dystonic reaction**
**Children**
Biperiden IM/slow IV: *dosing amended*
Dosing of biperiden retained as follows, aligned with SAMF, 2016; Paediatric Hospital Level STGs and EML, 2017 and the package insert for MCC registered medicine, Akineton® injection:

- Biperiden, IM/slow IV, 0.05–0.1 mg/kg, to a maximum of:
  - 1–6 years: 1–2 mg
  - 7–10 years:3 mg
  - > 10 years: 5 mg

**Level of Evidence: III Guidelines**

**Adults**
Biperiden, IM: *dosing amended*
Dosing aligned with SAMF, 2016. However, as biperiden is only available as a 5 mg ampoule, text amended from "2 mg" to "2.5 mg".
**Level of Evidence: III Guidelines, Expert opinion**

**Drug-induced parkinsonism**
**Adults**
Orphenadrine, oral: *indication and dosing amended*
Recommended for parkinsonism, whilst awaiting review; and not for tremor (which is preferably managed at secondary level). Dosing aligned with SAMF, 2016.
**Level of Evidence: III Guidelines**

### 16.3 ANXIETY DISORDERS

**Psychotherapy has been included.**
There is evidence that psychotherapy is effective in the short and long term treatment of anxiety disorders and may be as effective as medication. The Mental Health Policy requires the provision of psychological services in at least some CHCs and PHCs. Also note cost-effective review by Ophuis 2016[18]. Recommendation differs from NICE Guideline[19] only in that psychotherapy is not recommended as superior to pharmacotherapy but rather as an option (consistent with Cuijpers et al, 2016[20] and Bandelow et al, 2015[21]).

*If response only partial – may combine medication with brief psychotherapy:*

[17] NEMLC minutes of the meeting of 14 December 2017.
[18] Ophuis RH, Lokkerbol J, Heemskerk SC, van Balkom AJ, Hiligsmann M, Evers SM. Cost-effectiveness of interventions for treating anxiety disorders: A systematic review. J Affect Disord. 2017;210:1-13.
[19] NICE. Generalised anxiety disorder and panicdisorder in adults: management, 26 January 2011. http://nice.org.uk/guidance/cg113
[20] Cuijpers P, Cristea IA, Karyotaki E, Reijnders M, Huibers MJ. How effective are cognitive behavior therapies for major depression and anxiety disorders? A meta-analytic update of the evidence. World Psychiatry. 2016;15(3):245-58.
[21] Bandelow B, Reitt M, Rover C, Michaelis S, Gorlich Y, Wedekind D. Efficacy of treatments for anxiety disorders: a meta-analysis. IntClinPsychopharmacol. 2015;30(4):183-92

*Cuijpers et al. 2014*[22]*:*52 studies, 3623 patients – 32 on depression and 21 on anxiety (one on both). For panic disorder and obsessive compulsive disorder combined therapy superior (antidepressant medication and psychotherapy) to antidepressant medication treatment alone – moderate effect size, NNT 3.36 and 2.63 respectively. No difference for social anxiety disorder and insufficient evidence for generalized anxiety disorder.
*Furukawa et al. 2007*[23]**:** Cochrane review – 21 trials, 1709 participants. Only included RCTs for combined vs antidepressants alone or vs psychotherapy alone or with placebo. Only for panic disorder. In the acute phase, combined therapy was superior to medication alone or placebo and for continued therapy: combined remained superior for response rate, global severity of anxiety, depression and social functioning. After treatment discontinuation, the effect was not sustained.

**For severe panic attacks**
Diazepam, oral: *retained*
Citalopram, oral: *deleted*
Consensus opinion (NICE[24] and SAMF, 2016) is that benzodiazepines should be reserved for acute crises only.
**Level of Evidence: III Guidelines**

**First line treatment**
SSRIs, oral: *retained*
Benzodiazepines, oral: *deleted*
Fluoxetine, oral: *added as first line therapy*
Citalopram, oral: *deleted as first line therapy*
Alternative SSRIs, oral (citalopram, escitalopram, sertraline): *added as a therapeutic group for second line treatment*
*SSRIs vs benzodiazepines* Evidence[25] of acute response to benzodiazepines but no good evidence of superiority to SSRIs in acute phase treatment. (Refer to medicine review: SSRIs for depression and anxiety, 10 October 2017). Consensus opinion (NICE[26]and SAMF, 2016) is that benzodiazepines should be reserved for acute crises only
**Level of Evidence: I Systematic reviews and meta-analyses, Guidelines**

Refer to the updated SSRI medicine review (for anxiety disorders and depression) with accompanying appendices:

SSRIs_Depression&
anxiety_PHC-Adult_F

**Recommendation:** Based on this evidence review, the Primary Health Care Committee recommends that fluoxetine be used as first line for depression and anxiety in all patients. Sertraline, citalopram, and escitalopram are suitable alternatives if fluoxetine is poorly tolerated. The decision regarding which SSRI to use as second line for depression and anxiety should be based on cost.
*Rationale:* To simplify treatment of mental health conditions at primary health care, it would be preferable to have one first-line SSRI to treat both depression and anxiety. This SSRI should ideally work well across all populations, including children, adolescents, adults, the elderly, and those with co-

[22]Cuijpers P, Cristea IA, Karyotaki E, Reijnders M, Huibers MJ. How effective are cognitive behavior therapies for major depression and anxiety disorders? A meta-analytic update of the evidence. World Psychiatry. 2016;15(3):245-58.
[23] Furukawa TA, Watanabe N, Churchill R. Combined psychotherapy plus antidepressants for panic disorder with or without agoraphobia. Cochrane Database Syst Rev. 2007(1):CD004364.
[24]NICE. Generalised anxiety disorder and panicdisorder in adults: management, 26 January 2011. http://nice.org.uk/guidance/cg113
[25]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.
[26] NICE. Generalised anxiety disorder and panicdisorder in adults: management, 26 January 2011. http://nice.org.uk/guidance/cg113

morbidities, especially HIV. As SSRIs might be poorly tolerated, there should be an alternative SSRI for those who are unable to tolerate the first line SSRI.
Fluoxetine is relatively well-studied and is effective for depression in adults, adolescents, and HIV-infected patients. It is effective for GAD, and for anxiety in HIV-infected patients. It is also reasonably well-tolerated.
In terms of a second line SSRI, escitalopram, citalopram, and sertraline are all effective in depression. Sertraline is the most effective for depression in elderly patients. Sertraline and escitalopram are also effective in anxiety. The included studies did not assess citalopram in GAD, but there is evidence of its benefit in Panic Disorder. Assuming that citalopram is comparable to escitalopram in equivalent doses, citalopram, escitalopram, or sertraline may be used as second line treatment in anxiety, as for depression.
**Level of Evidence: I Meta-analyses[27] [28] [29], RCT[30]**

Text of the STG was updated as follows:

- Fluoxetine, oral.
  - Initiate at 20 mg alternate days for 2 weeks.
  - Increase to 20 mg daily after 2–4 weeks.
  - Delay dosage increase if increased agitation/panicky feelings occur.

**OR**

If fluoxetine is poorly tolerated:

- Alternative SSRI e.g.:
- Citalopram, oral.
  - Initiate at 10 mg daily for the 1st week.
  - Then increase to 20 mg daily.

SSRIs: *caution amended*
Caution box for SSRI treatment in anxiety disorders was amended as follows, aligned with SAMF 2016:

**CAUTION**
SSRIs (e.g. fluoxetine, citalopram) may cause agitation initially.
This typically resolves within 2-4 weeks.
Ask about suicidal ideation in all patients, particularly adolescents and young adults. (See Section 16.6: Suicide risk assessment).
If suicidal ideation present, refer before initiating SSRI.
Once started, monitor closely for clinical worsening, suicidality, or unusual changes in behaviour. Advise families and caregivers of the need for close observation and refer as required.

**Level of Evidence: III Guidelines**

SSRIs: *duration of therapy amended*
Duration of therapy of SSRIs for anxiety disorders was amended to align with evidence extrapolated from a RCT and guidelines.

*Extrapolation from RCT:* RCT of 136 patients with GAD who had experienced reduced anxiety during six months of treatment with venlafaxine extended-release were assigned to continue medicine or placebo for an additional six months. Cohort of patients continuing venlafaxine XR had a much lower rate of relapse vs patients receiving placebo (9.8% vs 53.7%). Incidence rates of side effects during the second six months vs the first six months were lower, but did not differ statistically between treatment arms, and included no new side effects.

[27] 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.
[28] 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.
[29] 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.
[30] 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.

*Guidelines:* WHO Mental Health Gap Action Programme (mhGAP) intervention guide for mental, neurological and substance use disorders in non-specialized health settings provides general guidance on duration of SSRI therapy.[31]

**Level of Evidence: III Guidelines, Extrapolation from RCT**

**Benzodiazepines**

Benzodiazepines: *caution updated*

The caution box was amended, as association between benzodiazepine therapy and cognitive decline in elderly patients is evident, though causality not proven[32] [33]. Caution with long-term use of benzodiazepines in the elderly is advised.

| **CAUTION - BENZODIAZEPINES** |
|---|
| » Short-term use is associated with reversible cognitive impairment. |
| » Elderly are at risk of over-sedation, falls and hip fractures. |
| » Dependence may occur after only a few weeks of treatment. |
| » Prescribe for as short a period of time as possible. |
| » Warn patient not to drive or operate machinery when used short-term. |
| » Long-term use is associated with irreversible cognitive decline. |
| » Avoid use in people at high risk of addiction: e.g. personality disorders |
| » and those with previous or other substance misuse. |

*Evidence:* Most studies reviewed by Picton et al[34] suggested an association between benzodiazepine use and cognitive impairment in the elderly. However, there is conflicting evidence regarding the degree of cognitive decline (accelerated rate versus transient decline). It is noted that the systematic review mostly reviewed observational studies.

**Level of Evidence: III Systematic review of observational studies**

## 16.4.1 DEPRESSIVE DISORDERS

Fluoxetine, oral: *retained as first line treatment and dosing amended*

Alternative SSRIs, oral (citalopram, escitalopram, sertraline): *added as a therapeutic group for second line treatment*

Refer to the SSRI medicine review with accompanying appendices, for anxiety and depressive disorders discussed under 16.3 Anxiety disorders of this report.

Dose titration of fluoxetine was aligned with the SAMF, 2016[35].

**Level of Evidence: I Meta-analyses[36] [37] [38], Guidelines**

Text of the STG was updated as follows:

- ~~SSRI, e.g.:~~
- ~~Fluoxetine, oral.~~
  - ~~Initial dose: 20 mg.~~
  - ~~Increase to 40 mg if there is only a partial response after 4 weeks.~~

[31] World Health Organisation. mhGAP intervention guide for mental, neurological and substance use disorders in non-specialized health settings: mental health Gap Action Programme (mhGAP), version 2.0. Geneva, 2016 http://www.who.int/mental_health/mhgap/mhGAP_intervention_guide_02/en/

[32] Picton JD, Marino AB, Nealy KL. Benzodiazepine use and cognitive decline in the elderly. Am J Health Syst Pharm. 2018 Jan 1;75(1):e6-e12.

[33] Brandt J, Leong C. Benzodiazepines and Z-Drugs: An Updated Review of Major Adverse Outcomes Reported on in Epidemiologic Research. Drugs R D. 2017 Dec;17(4):493-507.

[34] Picton JD, Marino AB, Nealy KL. Benzodiazepine use and cognitive decline in the elderly. Am J Health Syst Pharm. 2018 Jan 1;75(1):e6-e12. https://www.ncbi.nlm.nih.gov/pubmed/29273607

[35] SAMF, 2016

[36] ipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, Leucht S, Ruhe HG, Turner EH, Higgins JPT, Egger M, Takeshima N, Hayasaka Y, Imai H, Shinohara K, Tajika A, Ioannidis JPA, Geddes JR. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet. 2018 Apr 7;391(10128):1357-1366.

[37] Magni LR, Purgato M, Gastaldon C, Papola D, Furukawa TA, Cipriani A, Barbui C. Fluoxetine versus other types of pharmacotherapy for depression. Cochrane Database Syst Rev. 2013 Jul 17;(7):CD004185.

[38] 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.

- ~~If no response after 4 weeks, refer.~~

- Fluoxetine, oral.
  - Initiate at 20 mg alternate days for 2 weeks.
  - Increase to 20 mg daily after 2–4 weeks.
  - Delay dosage increase if increased agitation/panicky feelings occur.
  - Reassess response after 4 weeks on daily fluoxetine. Symptoms may take up to 2-4 weeks to resolve. If only a partial or no response after 8 weeks of treatment refer to doctor.
  - See note below for treatment duration.

**OR**

If fluoxetine is poorly tolerated:

- Alternative SSRI e.g.:
- Citalopram, oral.
  - Initiate at 10 mg daily for the 1st week.
  - Then increase to 20 mg daily.

SSRIs: *duration of therapy amended*

*Evidence:*

- *Geddes et al*[39]*:* Systematic review of 31 RCTs showed that prolonged treatment with antidepressants reduced the odds of relapse by 70% (95% CI 62 to 78%); 2p<0·00001):

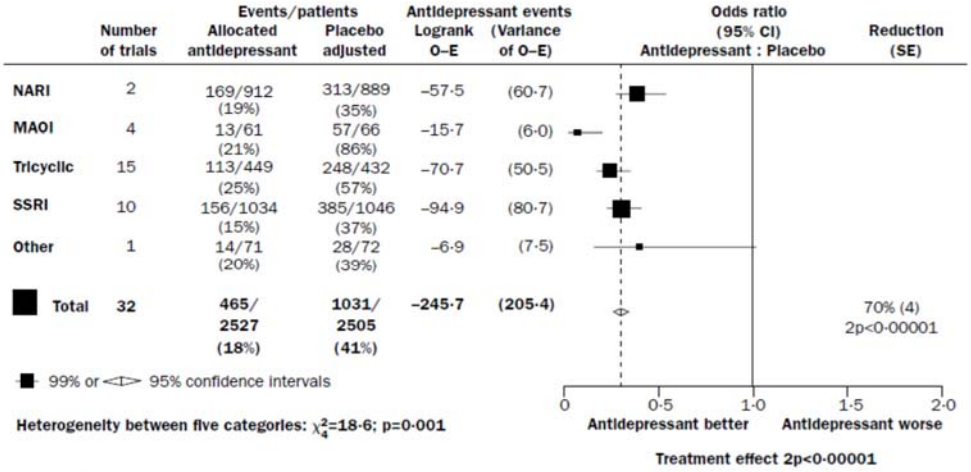


Figure 1: **Risk of relapse: odds ratios by drug type**
NARI=noradrenaline (norepinephrine) reuptake inhibitor. MAOI=monoamine oxidase inhibitor. SSRI=selective serotonin reuptake inhibitor.

- *Bauer et al*[40]: Guidelines recommends *"Continuation of successful treatment for 6 – 9 months after remission of the acute depressive episode".*
- *El-Mallakh et al*[41]*:* Systematic review of RCTs showed that continuation of antidepressant therapy is superior to placebo in preventing relapses. Most relapses occurred within the first 6 months after randomisation.
- *Guidelines:* WHO Mental Health Gap Action Programme (mhGAP) intervention guide for mental, neurological and substance use disorders in non-specialized health settings recommends that Antidepressant medications usually need to be continued for at least 9-12 months after the resolution of symptoms.[42]

[39] Geddes JR, Carney SM, Davies C, Furukawa TA, Kupfer DJ, Frank E, et al. Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. Lancet. 2003;361(9358):653-61

[40] Bauer M, Severus E, Kohler S, Whybrow PC, Angst J, Moller HJ. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders. part 2: maintenance treatment of major depressive disorder-update 2015. The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry. 2015;16(2):76-95.

[41] El-Mallakh RS, Briscoe B. Studies of long-term use of antidepressants: how should the data from them be interpreted? CNS Drugs. 2012 Feb 1;26(2):97-109. https://www.ncbi.nlm.nih.gov/pubmed/22296314

[42] World Health Organisation. mhGAP intervention guide for mental, neurological and substance use disorders in non-specialized health settings: mental health Gap Action Programme (mhGAP), version 2.0. Geneva, 2016 http://www.who.int/mental_health/mhgap/mhGAP_intervention_guide_02/en/

**Recommendation:** Recommend continuation of SSRIs for a minimum of 9 months, as maintenance treatment.
*Rationale:* Aligned with Guidelines
**Level of Evidence: IIII Guidelines.**

SSRIs: *age-limit not added*
The PHC Committee was of the opinion that an age limit for the prescribing of SSRIs was not required as the SSRI caution box in the anxiety and depression sections does provide a warning regarding suicidal ideation in adolescents and young adults, requiring referral as required and close monitoring and continuous observation.

SSRIs: *caution box amended*
The caution box was amended for correctness, aligned with SAMF 2016:

| **CAUTION** |
| --- |
| SSRIs may cause agitation ~~initially~~ during the first 2 to 4 weeks. |
| Ask about suicidal ideation in all patients, particularly adolescents and young adults. (See Section 16.6: Suicide risk assessment). |
| If suicidal ideation present, refer before initiating SSRI. |
| Once started, monitor closely for clinical worsening, suicidality, or unusual changes in behaviour. Advise families and caregivers of the need for close observation and refer as required. |

**Level of Evidence: III Guidelines[43]**

### 16.5.2 CHRONIC PSYCHOSIS (SCHIZOPHRENIA)

Chlorpromazine, oral: *not added*
Chlorpromazine oral not included in PHC EML for the continuous treatment of patients already stabilised on chlorpromazine and where a sedating agent is required. The PHC Committee was of the opinion that initiation of treatment would generally occur at higher level of care with continuation of chronic treatment through down-referral mechanisms or the CCMD programme. Furthermore, Provincial Pharmaceutics and Therapeutics Committees could make allowance for PHC doctors to access chlorpromazine as required in specific districts/facilities.

### 16.4.2 BIPOLAR DISORDERS

**Rapid tranquilisation**
Diazepam, oral: *deleted*
Midazolam, buccal: *deleted*
Midazolam, IM: *deleted*
Haloperidol, IM: *deleted*
Promethazine, IM: *deleted*
Rather than repeat the protocol for rapid tranquilisation in the manic bipolar disorder STG, a cross reference was made to section 16.1.2: Aggressive disruptive behaviour in adults (general measures and medicine treatment).

### 16.5.1 ACUTE PSYCHOSIS

**Rapid tranquilisation**
Diazepam, oral: *deleted*
Midazolam, buccal: *deleted*
Midazolam, IM: *deleted*
Haloperidol, IM: *deleted*

[43] SAMF, 2016

Promethazine, IM: *deleted*
Rather than repeat the protocol for rapid tranquilisation, a cross reference was made to section 16.1.2: Aggressive disruptive behaviour in adults (general measures and medicine treatment).

Zuclopenthixol acetate: *deleted*
Refer to the medicine review: Zuclopenthixol acetate for acute psychosis in adults, 6 June 2017.

ZuclopenthixolAcet
ate_AcutePsychosis_

Based on the evidence reveiw, the Adult Hospital Level and Primary Health Care Committees reccommend that zuclopenthixol acetate be deleted from the PHC EML, but retained in the Adult Hospital Level EML for use at regional hospitals, as specialist prescribed.
*Rationale:* Zuclopenthixol acetate has been removed from guidelines for rapid tranquillisation. The reason is that it has no advantage over haloperidol except for needing fewer coercive injections over 72 hours, due to its very long half-life. There have been reports of associated neuroleptic malignant syndrome and the long half-life provides additional challenges at PHC level.
**Level of Evidence: III Guidelines, Case series, Expert opinion**

## 16.5.2 CHRONIC PSYCHOSIS (SCHIZOPHRENIA)

**Rapid tranquilisation**
Diazepam, oral: *deleted*
Midazolam, buccal: *deleted*
Midazolam, IM: *deleted*
Haloperidol, IM: *deleted*
Promethazine, IM: *deleted*
Rather than repeat the protocol for rapid tranquilisation, a cross reference was made to section 16.1.2: Aggressive disruptive behaviour in adults (general measures and medicine treatment).

**Long-term depot therapy where adherence problem, or patient preference**
Fluphenazine, IM*: deleted*
Product has been discontinued. Alternative agents, flupenthixol decanoate, IM and zuclopenthixol decanoate, IM are recommended in the STG.

**For breakthrough episodes**
The following text was updated for completeness:

» For breakthrough episodes, consider short-term therapy of:
- Risperidone, oral 2 mg daily (Doctor prescribed).

» Long-acting antipsychotics are particularly useful in patients unable to adhere to their oral medication regimens but need to be accompanied by a track and trace programme to be effective for adherence

**Extrapyramidal side effects**
Orphenadrine, oral: *deleted*
Rather than repeat management for extra-pyramidal side-effects, a cross reference was made to section 16.2.1: Extra-pyramidal side effects.

## 16.7 SUICIDE RISK ASSESSMENT

Suicide risk assessment tools: *deleted*
There is insufficient evidence to predict the risk of suicide using various tick-box tools -.the best predictive risk factor for assessing suicide attempts is a previous suicide attempt. Suicide risk tools

were removed and replaced with text creating awareness of the risk of suicide with referral as required.
Furthermore, the suicide risk assessment tool, the MINI, is used for diagnostic screening mainly in research / surveys rather than as a clinical tool to determine who does and does not get referred.
The following warning was added to the text of the STG:

| **WARNING** |
| --- |
| Suicide risk assessment tools and guidelines do not replace clinical judgment. |