Management of physical health conditions in adults with severe mental disorders

WHO GUIDELINES

World Health Organization

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Guidelines for the management of physical health conditions in adults with severe mental disorders

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Contents

Acknowledgements 2

Acronyms & Abbreviations 3

Executive Summary 4

1. Introduction 10
1.1 Background and rationale 10
1.2 Related WHO guidelines and tools 12
1.3 Target audience 12
1.4 Goal and objective 13
1.5 Guiding principles 13

2. Guideline development process 14
2.1 Guideline development group 14
2.2 Declarations of interest and management of conflicts of interest 14
2.3 Collaboration with external partners 15
2.4 Identifying, appraising and synthesizing available evidence 15
2.5 Decision-making during the guideline development group meeting 16
2.6 Document preparation and peer review 17

3. Evidence and recommendations 18
3.1 Tobacco cessation 19
3.2 Weight management 21
3.3 Substance use disorders 24
3.4 Cardiovascular disease and cardiovascular risk 27
3.5 Diabetes mellitus 31
3.6 HIV/AIDS 34
3.7 Other infectious diseases (Tuberculosis, Hepatitis B/C) 38

4. Implementation considerations 42

5. Publication, dissemination, and evaluation 44
5.1 Publication and dissemination 44
5.2 Monitoring and evaluation 44
5.3 Implications for further research 44
5.4 Future review and update 45

References 46

Annexes 50
Annex 1: Guideline Development Group (GDG) members 50
Annex 2: Assessment of conflict of interest 52
Annex 3: Scoping questions 56
Annex 4: Background question: Association of physical health conditions with SMD 60
Annex 5: Evidence review methodology 66
Drug-drug interactions search strategy
Annex 6: Drug – drug interactions 77

Glossary 89

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Acronyms & abbreviation

AE	Adverse effect
ARV	Antiretroviral
CBT	Cognitive behaviour therapy
EMBASE	Excerpta Medica Database
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HIC	High-income country
LMIC	Low- and middle-income country
MeSH	Medical Subject Headings
MD	Mean difference
MDR-TB	Multi drug resistant tuberculosis
mhGAP	Mental Health Gap Action Programme
NCD	Non-communicable diseases
OR	Odds ratio
PEN	Package of Essential Noncommunicable Disease Interventions
PICO	Population Intervention Comparison Outcome
RCT	Randomized controlled trial
RR	Relative risk
SMD	Severe mental disorders
SMR	Standardized mortality ratio

Executive summary

INTRODUCTION

The global burden of disease due to mental disorders continues to rise, especially in low- and middle-income countries (LMIC). In addition to causing a large proportion of morbidity, mental disorders – especially severe mental disorders (SMD) – are linked with poorer health outcomes and increased mortality. SMD are defined as a group of conditions that include moderate to severe depression, bipolar disorder, and schizophrenia and other psychotic disorders. People with SMD have a two to three times higher average mortality compared to the general population, which translates to a 10-20 year reduction in life expectancy. While people with SMD do have higher rates of death due to unnatural causes (accidents, homicide, or suicide) than the general population, the majority of deaths amongst people with SMD are attributable to physical health conditions, both non-communicable and communicable. Furthermore, people with SMD are more likely to engage in lifestyle behaviours that constitute risk factors for non-communicable diseases (NCDs) such as tobacco consumption, physical inactivity and consuming unhealthy diets.

Most studies reporting the excess mortality in people with SMD are from high income countries. The situation may be much worse in LMIC where the resources are inadequate, the institutions are not well managed and access to quality mental health care and physical care is limited.

Equitable access to comprehensive health services remains out of reach for the majority of people with SMD. Unfortunately, people with SMD often lack access to health services or receive poor quality care, including promotion and prevention, screening, and treatment. It is crucial to address the disparities in health care access and provision for people with SMD. Following the principle of non-discrimination and universal health coverage as elaborated in target 3.4 of the United Nations Sustainable Development Goals ("By 2030, reduce by one third premature mortality from non-communicable diseases through prevention and treatment and promote of mental health and well-being"), people with SMD should be offered at least the same level of treatment for physical health conditions and their risk factors as the general population.

The WHO *Comprehensive Mental Health Action Plan (2013-2020)* outlines a vision where people living with mental disorders are able to exercise the full range of human rights and to access high quality, culturally-appropriate health and social care in a timely way to promote recovery. In service of this vision and as part of WHO's Mental Health Gap Action Programme (mhGAP), these *Guidelines on the management of physical health conditions in adults with severe mental disorders* will provide up-to-date, evidence-based recommendations to support the scale-up of care for physical health conditions and their risk factors affecting people living with SMD globally.

Accordingly, the objective of these guidelines is:

To improve the management of physical health conditions in adults with SMD and support the reduction of individual health behaviours constituting risk factors for these illnesses, with the aim of decreasing morbidity and premature mortality amongst people with SMD.

Existing WHO guidelines for the general population are relevant to the physical health conditions that increase the morbidity and mortality for people with SMD. For example, the *Package of Essential Noncommunicable (PEN) Disease Interventions for Primary Health Care in Low-Resource*

Settings Geneva, WHO, 2010 provides guidelines and recommendations for tobacco cessation, weight management, cardiovascular disease prevention including diabetes management and prevention of complications, treatment and prevention of chronic respiratory diseases in the general population. Other WHO guidelines for infectious disease are also relevant such as the *Consolidated guidelines on HIV prevention, diagnosis, treatment, and care for key populations. WHO, 2016 update* and *Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update. WHO, 2017.*

GUIDELINE DEVELOPMENT METHODS

The process of development of these guidelines followed the *WHO handbook for guideline development* and involved: (1) recruitment of the Guideline Development Group (GDG); (2) declaration of interest by GDG members and peer reviewers; (3) scoping review to formulate questions and select outcomes (4) identification, appraisal and synthesis of available evidence; (5) formulation of recommendations with inputs from a wide range of stakeholders; and (6) preparation of documents and plans for dissemination.

The GDG, an international group of experts, provided input into the scope of the guideline and assisted the steering group in developing the key questions. A total of one background question and seven PICO (Population, Intervention, Comparison, and Outcome) questions were developed.

To address the PICO questions, a series of searches for systematic reviews was conducted and GRADE evidence profiles prepared. During a meeting at WHO headquarters in Geneva, 9 – 10 May 2018, the GDG discussed the evidence, sought clarifications, and interpreted the findings in order to develop recommendations. The GDG considered the relevance of the recommendations for people with SMD including the balance of benefit and harm of each intervention; values and preferences of people with SMD; costs and resource use; and other relevant practical issues for providers in LMIC.

When making a strong recommendation, the GDG was confident that the desirable effects of the intervention outweigh any undesirable effects. When the GDG was uncertain about the balance between the desirable and undesirable effects, the GDG issued a conditional recommendation. Strong recommendations imply that most individuals would want the intervention and should receive it while conditional recommendations imply that different choices may be appropriate for individual people and they may require assistance at arriving at management decisions. The GDG members reached an unanimous agreement on all the recommendations and ratings.

SUMMARY OF RECOMMENDATIONS

Tobacco cessation

In the context of tobacco cessation programmes:

Recommendation 1:

In people with severe mental disorders, combined pharmacological and non-pharmacological interventions may be considered in accordance with the WHO training package (*Strengthening health systems for treating tobacco dependence in primary care. Building capacity for tobacco control: training package*). *(Strength of recommendation: Conditional; quality of evidence: Very low).*

Recommendation 2:

In people with severe mental disorders, a directive and supportive behavioural intervention programme may be considered and should be tailored to the needs of the population. *(Strength of recommendation: Conditional; quality of evidence: Very low).*

Recommendation 3:

In people with severe mental disorders, varenicline, bupropion and nicotine replacement therapy may be considered for tobacco cessation. *(Strength of recommendation: Conditional; quality of evidence: Very low).*

BEST PRACTICE STATEMENT:

Prescribers should take into account potential interactions between buproprion and varenicline with psychotropic medications as well as possible contra-indications.

Weight management

Recommendation 1:

Behavioural lifestyle (healthy diet, physical activity) interventions should be considered in all people with severe mental disorders who are overweight or obese or at risk of becoming overweight or obese in accordance with *WHO's Package of Essential Noncommunicable Disease Interventions (WHO PEN) for primary care in low-resource settings (2010).* These interventions should be appropriate and tailored to the needs of this population. *(Strength of recommendation: Strong; Quality of evidence: Very low).*

Recommendation 2:

For people with severe mental disorders who are overweight or obese, and where lifestyle interventions and/or switching psychotropic medication do not appear successful, adjunctive metformin may be considered. This should be considered under close clinical supervision and monitoring.
(Strength of recommendation: Conditional; Quality of evidence: Low).

BEST PRACTICE STATEMENTS:

- For people with severe mental disorders who are overweight or obese or at risk of becoming overweight or obese, initiating a psychotropic medication with lower propensity for weight gain should be considered, taking into account clinical benefits and potential adverse effects.
- For people with severe mental disorders who are overweight or obese, switching to a psychotropic medication with a lower propensity for weight gain may be considered, taking into account clinical benefits and potential adverse effects.

Substance use disorders

Recommendation 1:

For people with severe mental disorders and comorbid substance use disorders (drug and/or alcohol), interventions should be considered in accordance with the WHO mhGAP guidelines. *(Strength of recommendation: Conditional; Quality of the evidence: Low).*

Recommendation 2:

Non-pharmacological interventions (e.g. motivational interviewing) may be considered and tailored to the needs of people with severe mental disorders and substance use disorders *(Strength of recommendation: Conditional; Quality of the evidence: Very low).*

BEST PRACTICE STATEMENT:

Prescribers should take into account the potential for drug-drug interactions between medicines used for treatment of substance use disorders and severe mental disorders.

Cardiovascular disease and cardiovascular risk

Recommendation 1:

For people with severe mental disorders and pre-existing cardiovascular disease, or with cardiovascular risk factors (e.g. high blood pressure or high cholesterol), pharmacological and non-pharmacological interventions may be considered in accordance with the *WHO Package of Essential Noncommunicable Disease Interventions (WHO PEN) for primary care in low-resource settings (2010)* for lowering cardiovascular risk and management of cardiovascular disease.
(Strength of recommendation: Strong; Quality of evidence: High to moderate for different interventions).

Recommendation 2:

For people with severe mental disorders and pre-existing cardiovascular disease, the following is recommended:

a) Behavioural lifestyle (healthy diet, physical activity) interventions may be considered. These interventions should be appropriate and tailored to the needs of this population. *(Strength of recommendation: Conditional; Quality of evidence: Very low).*

b) Collaborative care i.e. a multi-professional approach to patient care with a structured management plan, scheduled patient follow-up, and enhanced inter-professional communication, may be considered for cardiovascular disease management. *(Strength of recommendation: Conditional; Quality of evidence: Very low).*

Recommendation 3:

For people with severe mental disorders and cardiovascular risk factors, behavioural lifestyle (healthy diet, physical activity) interventions may be considered. These interventions should be appropriate and tailored to the needs of this population. *(Strength of recommendation: Conditional; Quality of evidence: Very low).*

BEST PRACTICE STATEMENTS:

For people with severe mental disorders and pre-existing cardiovascular disease:

- Initiating a psychotropic medication with lower propensity for cardiovascular risk is a strategy that should be considered, taking into account clinical benefits and potential adverse effects.
- Switching to a psychotropic medication with lower propensity for cardiovascular risk may be considered, taking into account clinical benefits and potential adverse effects.

For people with severe mental disorders and pre-existing cardiovascular disease or cardiovascular risk factors:

- Prescribers should be aware of potential interactions between prescribed medicines for cardiovascular disease and prescribed psychotropic medications, which may affect cardiovascular risk. Cardiovascular outcomes and risk factors should be monitored and dose adjustment of cardiovascular medicines may be required.

Diabetes mellitus

Recommendation 1:

For people with severe mental disorders and diabetes mellitus, interventions in accordance with the WHO Package of Essential Non-communicable (PEN) Disease Interventions for Primary Health Care in Low-Resource Settings should be considered for diabetes management.
(Strength of recommendation: Strong; Quality of evidence: Low).

Recommendation 2:

Behavioural lifestyle interventions should be considered for all people with severe mental disorders and diabetes mellitus. These interventions should be appropriate and tailored to the needs of this population.
(Strength of recommendation: Strong; Quality of evidence: Very low).

Recommendation 3:

In people with depression and comorbid diabetes mellitus, cognitive behaviour therapy for treatment of depression may be considered. *(Strength of recommendation: Conditional; Quality of evidence: Very low).*

BEST PRACTICE STATEMENTS:

For people with severe mental disorders and diabetes mellitus:

- Initiating an anti-psychotic medication with lower propensity for producing hyperglycaemia should be considered, taking into account clinical benefits and potential adverse effects.
- Switching to an anti-psychotic medication with lower propensity for producing hyperglycaemia is a strategy that may be considered, taking into account clinical benefits and potential adverse effects.
- Prescribers should be aware of potential interactions between prescribed medicines for diabetes mellitus and prescribed psychotropic medicines, which may affect glycaemic control. Glycaemic control should be monitored and dose adjustment of medicines may be required.

HIV/AIDS

Recommendation 1:

For people with severe mental disorders and HIV/ AIDS, antiretroviral drugs should be considered in accordance with the *WHO Updated recommendations on first-line and second-line antiretroviral regimens.*
(Strength of the recommendation: Strong; Quality of the evidence: Moderate)

Recommendation 2:

Additional psychosocial support for treatment adherence should be provided to people with HIV and severe mental disorders in accordance with the *WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. (Strength of the recommendation: Strong; Quality of the evidence: Moderate)*

BEST PRACTICE STATEMENT:

For people with severe mental disorders and HIV/ AIDS, prescribers should take into account the potential for drug-drug interactions between antiretroviral drugs and psychotropic medicines.

Other infectious diseases (Tuberculosis, Hepatitis B/C)

Recommendation 1:

For people with severe mental disorders and TB, pharmacological management should be considered in accordance with the *WHO guidelines for the treatment of drug-susceptible tuberculosis and patient care* and the *WHO treatment guidelines for drug-resistant tuberculosis.*
(Strength of the recommendation: Strong; Quality of the evidence: Low).

Recommendation 2:

For people with severe mental disorders and TB, non-pharmacological (social, psychological) management should be considered in accordance with the *WHO guidelines for the treatment of drug-susceptible tuberculosis and patient care* and the *WHO treatment guidelines for drug-resistant tuberculosis.*
(Strength of the recommendation: Strong; Quality of the evidence: Low).

Recommendation 3:

For people with severe mental disorders and hepatitis B, treatment should be considered in accordance with the *WHO guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection.*
(Strength of the recommendation: Strong; Quality of the evidence: Low).

Recommendation 4:

For people with severe mental disorders and hepatitis C, treatment should be considered in accordance with the *WHO guidelines for the screening care and treatment of persons with chronic hepatitis C infection.*
(Strength of the recommendation: Strong; Quality of the evidence: Low).

BEST PRACTICE STATEMENT:

For people with severe mental disorders and TBand/or Hepatitis B/, prescribers should take into account the potential for drug-drug interactions between TB medicines, medicines for hepatitis B and C with psychotropic medicines.

1. Introduction

1.1 BACKGROUND AND RATIONALE

Worldwide, mental disorders contribute to 14% of the global burden of disease as estimated by disability adjusted life years and this is rising especially in low- and middle- income countries (LMIC) (Whiteford *et al.*, 2015). In addition to causing a large proportion of morbidity, mental disorders – especially severe mental disorders (SMD) – are linked with poorer health outcomes and increased mortality. SMD are defined as a group of conditions that include moderate to severe depression, bipolar disorder, and schizophrenia and other psychotic disorders. People with SMD have a 2-3 times higher average mortality compared to the general population, which translates to a 10-20 year reduction in life expectancy (Liu *et al.*, 2017). People with bipolar disorder and schizophrenia have been shown to have higher rates of mortality in both high and low-income settings (Tsuang, Woolson and Fleming, 1980) (Capasso *et al.*, 2008) (Laursen, 2011) (Nielsen *et al.*, 2013) (Fekadu *et al.*, 2015). One prospective cohort-study in Ethiopia found the overall standardized mortality ratio (SMR) of people with SMD to be twice that of the general population, with schizophrenia associated with the highest risk (SMR three times that of the general population) (Fekadu *et al.*, 2015). Moreover, for schizophrenia in particular, the mortality gap appears to be widening over time (Saha, Chant and McGrath, 2007).

Numerous potential causes have been proposed for the increased mortality of people with SMD, including the well-known evidence-based bidirectional relationship between mental disorders and other non-communicable diseases (NCDs) such as cardiovascular disease, diabetes, respiratory illnesses, and cancers; differential exposure to risk factors driving the aforementioned NCDs such as smoking, harmful use of alcohol, and sedentary behaviour; iatrogenic effects of medications for SMD; and inequitable access to health care services. While people with SMD do have higher rates of death due to unnatural causes (accidents, homicide, or suicide) than the general population, the majority of deaths amongst people with SMD are attributable to physical health conditions, both non-communicable and communicable (Liu *et al.*, 2017). Cardiovascular disease, for example, confers a ten-fold higher risk of death than suicide in people with SMD. Overall, people with SMD have approximately 1.5-3 times higher risk of cardiovascular morbidity and mortality when compared with the general population (Correll *et al.*, 2017). People with SMD also have higher rates of diabetes mellitus (Vancampfort *et al.*, 2016), with reports of a 2-3 fold higher prevalence compared with the general population. Infectious diseases such as HIV/AIDS also contribute to the high rates of premature death amongst people with SMD, as do other infectious diseases such as tuberculosis and hepatitis B and C (Saha, Chant and McGrath, 2007).

The figures mentioned above are chiefly drawn from studies from high income countries where health literacy is higher, better quality services are available, and there is overall better monitoring of the institutions and more regular check-ups for physical health of people with SMD. The situation may be much worse in LMICs where the resources are inadequate, the institutions are not well managed and access to quality mental health care and physical care is limited.

SMD can affect and in turn, can be affected by NCDs. People with SMD are also more likely to engage in lifestyle behaviours that constitute risk factors for NCDs. Tobacco consumption (Lasser *et al.*, 2000) is common amongst people with SMD and has been identified as a leading preventable cause of premature mortality in this population. Additionally, people with SMD are more likely to be physically inactive and consume unhealthy diets (Jakobsen *et al.*, 2018), increasing their risk of being overweight or obese. In routine clinical practice, however, such comorbidities and interactions are often overlooked.

Iatrogenic effects of psychotropic medications that are used to treat the symptoms of SMD including antipsychotic medication (and to some extent, antidepressants and mood stabilizers) are also associated with an increased risk of developing physical health conditions and associated complications (Correll *et al.*, 2015) (Correll *et al.*, 2017).

Furthermore, equitable access to comprehensive health services remains out of reach for many people with SMD. Unfortunately, people with SMD often lack access to health services or receive poor quality care, including promotion and prevention, screening, and treatment (De Hert *et al.*, 2011). The socioeconomic disadvantages not least due to the stigma and discrimination associated with SMD may further influence affected people's health and health care (Lund *et al.*, 2013). In addition, although families and other informal carers may provide vital practical help to deal with complex comorbidities and navigate health systems, they can be left to struggle under intense stress and with little support themselves (Poon *et al.*, 2017). It is therefore crucial to address the disparities in health care access and provision for people with SMD.

Following the principle of non-discrimination and universal health coverage as elaborated in target 3.4 of the United Nations Sustainable Development Goals ("By 2030, reduce by one third premature mortality from non-communicable diseases through prevention and treatment and promotion of mental health and well-being"), people with SMD should be offered at least the same level of treatment for physical health conditions and their risk factors as the general population. In some instances, as these guidelines will elaborate further, treatment recommendations for the general population need to be adapted for people with SMD. The benefits and risks of pharmacological interventions need to be balanced against the potential side effects and drug-drug interactions commonly used for SMD. People with SMD often experience impairment in functioning which makes it difficult for them to take the initiative to access health care, to keep appointments or to take medications for physical health conditions as prescribed. Non-pharmacological interventions need to be tailored according to the cognitive, motivational and socio-cultural needs of people with SMD.

Recognizing the frequent comorbidity between mental and physical health conditions, specific recommendations addressing the physical conditions causing the increased morbidity and mortality of people with SMD are needed. These new WHO guidelines constitute an important step in providing better health care for people with SMD, and offer up-to-date, evidence-based recommendations for the management of these physical health conditions and reduction of their risk factors for people with SMD. While these guidelines do not include a comprehensive list of physical health conditions, but have rather focused on those that seemed most important and for which there was evidence available, the physical health conditions (and their risk factors) addressed are those that have been shown to increase morbidity and mortality in people with SMD. It is hoped that these guidelines will benefit people with SMD whose physical health may currently be neglected and may contribute to reduced premature mortality amongst this population.

These guidelines will help achieve the United Nations Sustainable Development Goals 3.4, and facilitate the implementation of *WHO's Comprehensive Mental Health Action Plan* (World Health Organization, 2013). The guidelines build upon prior work by WHO Headquarters and Regional Offices. The WHO Regional Office for Europe published a technical report titled, *Addressing comorbidity between mental disorders and major noncommunicable diseases*, to support implementation of the *WHO European Mental Health Action Plan 2013-2020* and the *WHO European Action Plan for the Prevention and Control of Noncommunicable Diseases 2016-2025* (World Health Organization Regional Office for Europe, 2016). Additionally, the WHO Department of Mental Health and Substance Use Disorder held a consultation on excess mortality in people with SMD with key international experts in December 2015 (World Health Organization, 2015). This consultation included discussions on physical health conditions and the risk factors responsible for excess mortality in this population and the need for evidence-based guidance was recognized.

1.2
RELATED WHO GUIDELINES AND TOOLS

Several existing WHO guidelines and tools designed for the general population are relevant for addressing the physical health conditions and their risk factors causing the increased morbidity and mortality of people with SMD. These were consulted in the guideline development process (Box 1); recommendations were either added or modified for this special population, using targeted evidence reviews and expert opinions to assess the applicability of data for the general population to people with SMD.

1.3
TARGET AUDIENCE

These guidelines are primarily intended for use by health care workers providing services for people with SMD at all levels of the health care system, including outpatient and inpatient care at first-level, second-level, district and tertiary healthcare facilities. Health care providers may include primary care doctors, nurses, specialists, or other members of the health care work force.

In addition, these guidelines are of interest to the following audiences:

- Policy makers and health care planners at the national and local levels
- National and regional mental health programme managers
- National and regional primary care programme managers
- Members of national and local health departments
- People living with SMD and their families
- Groups representing people with SMD and their families

BOX 1: Related WHO guidelines and tools:

1. *Mental Health Gap Action Programme (mhGAP) Intervention Guide for mental, neurological, and substance use disorders in non-specialized health settings (Version 2.0). Geneva, WHO, 2016.* http://www.who.int/mental_health/mhgap/mhGAP_intervention_guide_02/en/
2. *Package of Essential Noncommunicable (PEN) Disease Interventions for Primary Health Care in Low-Resource Settings. Geneva, WHO, 2010.* http://www.who.int/cardiovascular_diseases/publications/pen2010/en/
3. *Strengthening health systems for treating tobacco dependence in primary care. Building capacity for tobacco control: training package.* http://www.who.int/tobacco/publications/building_capacity/training_package/treatingtobaccodependence/en/
4. *Global recommendations on physical activity for health. Geneva, WHO, 2010.* http://www.who.int/dietphysicalactivity/publications/9789241599979/en/
5. *Consolidated guidelines on HIV prevention, diagnosis, treatment, and care for key populations. Geneva, WHO, 2016 update.* http://www.who.int/hiv/pub/guidelines/keypopulations-2016/en/
6. *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection.Recommendations for a public health approach. Second edition. Geneva, WHO, 2016.* http://www.who.int/hiv/pub/arv/arv-2016/en/
7. *WHO guidelines for the treatment of drug-susceptible tuberculosis and patient care* (http://apps.who.int/iris/bitstream/handle/10665/255052/9789241550000-eng.pdf?sequence=1)
8. *WHO treatment guidelines for drug-resistant tuberculosis* (http://apps.who.int/iris/bitstream/handle/10665/250125/9789241549639-eng.pdf?sequence=1).
9. *Guidelines for the prevention, care, and treatment of persons with chronic hepatitis B infection. Geneva, WHO, 2015.* http://www.who.int/hepatitis/publications/hepatitis-b-guidelines/en/
10. *Guidelines for the screening, care, and treatment of persons with chronic hepatitis C infection. Geneva, WHO, 2016.* http://www.who.int/hepatitis/publications/hepatitis-c-guidelines-2016/en/

1.4
GOAL AND OBJECTIVE

The *WHO Comprehensive Mental Health Action Plan* (2013-2020) outlines a vision where persons living with mental disorders are able to exercise the full range of human rights and to access high quality, culturally-appropriate health and social care in a timely way to promote recovery (World Health Organization, 2013). In service of this vision and as part of *WHO's Mental Health Gap Action Programme (mhGAP)*, these guidelines provide up-to-date, evidence-based recommendations to support improved access to quality care for physical health conditions and to address the risk factors affecting people living with SMD globally. They will be consistent with services oriented towards recovery and focus on the strengths of people with SMD. Accordingly, the objective of these guidelines is:

- To improve the management of physical health conditions in adults with SMD and support the reduction of individual health behaviours constituting risk factors for these illnesses, with the aim of decreasing morbidity and premature mortality amongst people with SMD.

1.5
GUIDING PRINCIPLES

The following principles have informed the development of these guidelines and should guide the implementation of their recommendations:

- The guidelines should expedite the achievement of the goals outlined in the *Mental Health Action Plan (2013-2020)*(World Health Organization, 2013), as well as Goal 3.4 of the Sustainable Development Goals, which focuses on reducing the premature mortality from non-communicable diseases and the promotion of mental health and well-being (United Nations, 2016).

- The process of developing these guidelines and subsequent implementation of recommendations should further the realization of the right to equal levels of health for people living with SMD and promote their active involvement.

- The recommendations should be implemented with accompanying efforts to safeguard the human rights of persons living with SMD, including reduction of stigma, reducing barriers to seeking health services, and ensuring informed decision-making in treatment choices.

Implementation of the recommendations should be informed by the local context, including the availability of financial and human resources. However, the inequities addressed in these guidelines are common across all countries, and should be made a priority in health services.

2. Guideline development process

The *WHO handbook for guideline development*, 2nd edition (http://apps.who.int/medicinedocs/documents/s22083en/s22083en.pdf) describes the process used in the development of these guidelines, following the steps below.

2.1 GUIDELINE DEVELOPMENT GROUP

A WHO guideline steering group, led by the Department of Mental Health and Substance Use Disorder, was established with representatives from WHO regional offices and relevant WHO departments and programmes. The guideline steering group provided overall support to the guideline development process. Two additional groups were established: a guideline development group (GDG) and an external review group. The GDG included a panel of academics and clinicians with multidisciplinary expertise on the conditions covered by the guidelines. Consideration was given to geographic diversity and gender balance (see Annex 1).

Potential members of the GDG were selected on the basis of their contribution to the area, as well as the need for regional and area of expertise diversity. As a respected researcher in the field, the Chairperson was selected for his extensive experience of guideline development methodology, and his participation in other guideline development groups. Each potential GDG member was asked to complete the WHO declaration of interest (DOI) form. These were reviewed by the steering group.

2.2 DECLARATIONS OF INTEREST AND MANAGEMENT OF CONFLICTS OF INTEREST

All GDG members, peer reviewers and systematic review team members were requested to complete the declaration of interest (DoI) form prior to the evidence review process for guideline development. Invitations to participate in the GDG meeting were sent only after the DoI had been reviewed and approved. The GDG members were also required to complete a confidentiality undertaking. Once received, the WHO Secretariat reviewed the DoIs as well as additional information (internet and bibliographic database search) and evaluated if there are any conflicts of interest and if so, whether these require a management plan. The group composition was finalized after this process.

In order to enhance its management of conflicts of interest as well as strengthen public trust and transparency in connection with WHO meetings and activities involving the provision of technical/normative advice, the names and brief biographies of members being considered for participation in the GDG were disclosed for public notice and comment prior to the meeting.

At the beginning of the GDG meeting, the DoI of each GDG member was presented and GDG members and external partners were asked to update their DoI with relevant changes by notifying the WHO Secretariat.

DoI were reassessed for potential conflict before the face-to-face meeting in Geneva. None of the members had major conflicts of interest. All decisions were documented (see Annex 2).

2.3 COLLABORATION WITH EXTERNAL PARTNERS

The Centre for Global Mental Health, Institute of Psychiatry, Psychology & Neuroscience, King's College London, UK (WHO Collaborating Centre for Research and Training in Neurosciences) supported the development of the guidelines by conducting the evidence review and synthesis.

2.4 IDENTIFYING, APPRAISING AND SYNTHESIZING AVAILABLE EVIDENCE

A scoping review helped to identify the key questions that would establish the focus of the recommendations and consisted of the following steps:

1) Initial broad focus on identification of risk factors for excess mortality and morbidity in people with SMD and specific interventions, guided by previous work by the WHO that has highlighted a number of physical health conditions and associated risk factors as critical factors in the excess mortality and morbidity in people with SMD;

2) Review of existing WHO guidelines;

3) Findings of the WHO consultation on the above topic and other relevant WHO documents and discussions with WHO steering group.

A total of one background question and seven key questions in PICO (Population, Intervention, Comparison, and Outcome) format were developed (Annex 3).

The background question provided the context and rationale for the guidelines and addressed the association of physical health conditions with SMD. It consisted of two sub-questions: *What is the comorbidity between physical health conditions (NCDs and infectious diseases) and SMD? What is the impact of physical health conditions on the morbidity and mortality of people with SMD?* The answer to this question was found in a wide range of information sources and summarised the growing body of evidence that has demonstrated the bi-directional relationships between SMD and physical health conditions. The evidence supporting the background question is presented in Annex 4.

Outcomes were rated by GDG members according to their importance as 'critical' for a decision, 'important' or 'unimportant'. Those outcomes rated as critical and important were selected for inclusion into the PICO questions. Regular communication and discussions with the GDG were held by email and teleconferences, respectively.

The WHO steering group, in consultation with the guideline methodologist and GDG chair, proposed a framework based on the PICO questions to review the evidence. The process entailed the following steps: (i) review of evidence that exists for the interventions to manage physical health conditions in people with SMD; (ii) examination of the extent to which existing recommendations for the general population (especially from existing WHO guidelines) can be applied to people with SMD; (iii) examination of when and how these recommendations need to be adapted for people with SMD; and (iv) to provide recommendations that are specific to this population when needed.

The systematic review team developed protocols to review the evidence that existed for the interventions to manage physical health conditions and their risk factors (as outlined in the PICO questions) for people with SMD (Annex 5). Existing relevant systematic reviews were identified for each of the PICO questions. The steering group assessed the quality of existing reviews using the assessment of multiple systematic reviews (AMSTAR) checklist. Systematic reviews found to be of high quality were also assessed for timeliness to ensure that the most current evidence was used. In addition, drug-drug interaction searches were conducted between medicines relevant for each PICO question and medicines used for SMD (Annex 5).

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (Guyatt *et al.*, 2011) was used to develop the evidence profiles as well as the WHO Handbook for Guideline Development. The quality assessment of the evidence was performed according to GRADE considering study design (randomized controlled trials or observational studies), risk of bias, inconsistency, indirectness, imprecision and risk of reporting bias. Evidence was characterised as either high, moderate, low or very low. The evidence profiles are available at the WHO website (http://www.who.int/mental_health/evidence/guidelines_physical_health_and_severe_mental_disorders/en/index.html).

2.5 DECISION-MAKING DURING THE GUIDELINE DEVELOPMENT GROUP MEETING

The GDG met at the WHO headquarters in Geneva, 9 – 10 May 2018. The evidence reviews were sent out in advance and summarized in a presentation during the meeting. The GDG members discussed the evidence, clarified points, and interpreted the findings in order to develop recommendations based on the draft prepared by the WHO Secretariat. The GDG considered the relevance of the recommendations for people with SMD based on the GRADE-DECIDE framework (Alonso-Coello *et al.*, 2016):

- the balance of benefit and harm of each intervention;
- values and preferences of people with SMD and their carers;
- costs and resource use;
- acceptability of the intervention to healthcare providers in low- and middle-income countries;
- feasibility of implementation;
- impact on equity and human rights.

The discussion and assessment of values and preferences was based on the knowledge and experience of GDG members. Similarly, no surveys or formal cost-effectiveness studies to determine resource constraints were conducted but discussions of these domains were informed by the combined expertise and experience of the GDG members. Equity and human rights were considered by specifically searching databases that include studies from LMIC, examining data for disaggregation for specific subgroups of people with SMD and when direct evidence for the relevant subgroup was not available, evaluating the indirectness of evidence obtained from other populations. Potential differential effects of the interventions on different subgroups of people with SMD related to economic status, employment or occupation, education, place of residence, gender or ethnicity were considered by the GDG. Equity and human rights considerations were applied to the other criteria in the framework described above by:

- assessing both desirable and undesirable effects for different subgroups of people with SMD;
- examining if some subgroups may value the main outcomes differently than the general population;
- balancing treatment costs with effectiveness;
- varied acceptability of the intervention in different subgroups.

Taking into account these considerations, when making a strong recommendation, the GDG was confident that the desirable effects of the intervention outweighs any undesirable effects. When the GDG was uncertain about the balance between the desirable and undesirable effects, the GDG issued a conditional recommendation. Strong recommendations imply that most individuals would want the intervention and should receive it while conditional recommendations imply that different choices may be appropriate for individual patients and they may require assistance at arriving at management decisions. In some instances even when the quality of evidence was low or very low, it was agreed that if the recommendation would be of general benefit, and this was seen to outweigh the harms, it

may still be rated as strong. In the event of a disagreement, the chair and the methodologist would ascertain whether the dispute was related to the interpretation of the data or to the way that the recommendation was formulated. If a consensus agreement was not reached, the GDG members agreed to a majority vote of 70% to determine a decision The WHO staff members present at the meeting, as well as other external technical experts involved in the collection and review of the evidence, were excluded from voting. The GDG members reached a consensus agreement on all recommendations and ratings and voting was not needed.

In addition to recommendations, best practice statements were formulated which did not rely on systematic reviews of the evidence but rather on good clinical care and were consensus-based from the GDG.

2.6 DOCUMENT PREPARATION AND PEER REVIEW

In addition to the GDG members, an external review group (ERG) provided expert inputs. The draft guideline and evidence profiles prepared by WHO staff and the GDG were circulated to the external review group and the steering group. The role of the ERG was to identify any errors or missing data and to comment on clarity, setting–specific issues and implications for implementation rather than changing the recommendations. All inputs and remarks were discussed and agreed with the GDG by email.

3. Evidence and recommendations

This section provides an overview of each PICO question described under the following headings: the background; recommendations and additional considerations; supporting evidence for the recommendations and the rationale for the recommendations based on the evidence synthesized as well as criteria listed in the evidence-to-decision tables. The complete evidence profiles for each PICO question including the GRADE tables and the evidence-to-decision tables are available online on the WHO website (http://www.who.int/mental_health/evidence/guidelines_physical_health_and_severe_mental_disorders/en/index.html). Annex 6 has the drug-drug interaction evidence between medicines relevant for each PICO question and medicines used for SMD.

3.1
TOBACCO CESSATION

For people with SMD who use tobacco, are pharmacological (including nicotine replacement therapy, bupropion, varenicline) and/or non-pharmacological interventions effective to support tobacco cessation?

Population:
People with SMD who use tobacco

Intervention:

- Pharmacological interventions: including nicotine replacement therapy (NRT), bupropion, varenicline
- Non-pharmacological interventions

Comparison:
Care as usual and/or placebo

Outcomes:

- Critical
  - Tobacco cessation/abstinence rates
  - Tobacco consumption rates
  - Respiratory disease outcomes (COPD, asthma)
- Important
  - Frequency of adverse events/side-effects

BACKGROUND

People with SMD are twice as likely to use tobacco as the general population (around 61% of people with SMD smoke compared to 33% in the general population), to smoke more on average, and are less likely to quit smoking (Centers for Disease Control and Prevention, 2015). People with SMD have been reported to die 15-20 years earlier on average than people in the general population and this is often due to preventable tobacco-related health conditions for example due to heart disease, cancer, and lung disease, which can all be caused by smoking (Trainor and Leavey, 2017). Nicotine has also been shown to have mood-altering effects that can temporarily mask the negative symptoms of mental disorder, putting people with mental disorder at higher risk for cigarette use and nicotine addiction, and tobacco smoke can interact with and inhibit the effectiveness of certain medications taken for mental health conditions and substance abuse (https://www.cdc.gov/tobacco/disparities/mental-illness-substance-use/index.html).

In regard to interventions that have been recommended in the general population for tobacco cessation, bupropion, varenicline and nicotine replacement therapy (NRT) have all been recommended (e.g. mhGAP Intervention Guide, The National Institute for Health and Care Excellence (NICE)), and NICE has also recommended these pharmacological interventions for tobacco cessation for people with mental disorders (NICE guidelines CG178, CG185, CG91. PH48).

RECOMMENDATIONS AND CONSIDERATIONS

In the context of tobacco cessation programmes:

RECOMMENDATION 1:

In people with severe mental disorders, combined pharmacological and non-pharmacological interventions may be considered in accordance with the WHO training package (Strengthening health systems for treating tobacco dependence in primary care. Building capacity for tobacco control: training package) (http://www.who.int/tobacco/publications/building_capacity/training_package/treatingtobaccodependence/en/).

(Strength of recommendation: Conditional; quality of evidence: Very low)

RECOMMENDATION 2:

In people with severe mental disorders, a directive and supportive behavioural intervention programme may be considered and should be tailored to the needs of the population.

(Strength of recommendation: Conditional; quality of evidence: Very low)

RECOMMENDATION 3:

In people with severe mental disorders, varenicline, bupropion and nicotine replacement therapy may be considered for tobacco cessation.

(Strength of recommendation: Conditional; quality of evidence: Very low)

BEST PRACTICE STATEMENT:

Prescribers should take into account potential interactions between buproprion and varenicline with psychotropic medications as well as possible contra-indications.

Additional considerations

- Tobacco cessation interventions should be considered as part of broader implementation packages as described in *WHO's MPOWER* (WHO., 2008) package of effective tobacco control measures.
- The behavioral intervention programme can build on the WHO training package and should be tailored to the needs of the population. This is based on the principles of motivational interviewing and aims to increase the person's intrinsic motivation for change based on the person's own personal goals and values.
- Choice of pharmacotherapy will be understandably influenced by resource availability. In people with SMD, varenicline seems to have the highest efficacy, followed by bupropion with or without nicotine replacement therapy, followed by nicotine replacement therapy (nicotine patch) alone.
- Smoking cessation can cause an increase in serum levels of anti-psychotic medication, and smoking cessation needs to be accompanied by a reduction in dose to avoid toxicity. Smoking cessation programmes therefore need to be accompanied by monitoring of clinical state, and where appropriate monitoring of serum levels.

SUPPORTING EVIDENCE AND RATIONALE

Behavioural treatment alone for tobacco smoking cessation has a low abstinence rate in SMD of about 4% which is why combination behavioural treatment and pharmacotherapy is recommended for the population with SMD. At present there is insufficient evidence to indicate whether specialised smoking cessation interventions (vs. standard smoking cessation) and contingent reinforcement i.e. a positive reinforcement technique to increase desired behaviours, in this case tobacco cessation (vs. care as usual) are beneficial for the cessation of smoking in people with SMD. Varenicline's efficacy has been shown to be the highest of the pharmaco-therapy choices for persons with SMD including when compared to bupropion(Anthenelli *et al*., 2016). Evidence for efficacy of bupropion comes from several studies included in the Cochrane review such as the EAGLES trial (Tsoi, 2013); evidence for efficacy of nicotine patch vs. placebo can be seen in the EAGLES trial. While there are no known interactions between NRT or varenicline and medicines used for SMD, there are multiple interactions between bupropion and medicines used for SMD, specifically involving elevated seizure risk and enzymatic inhibition/induction. There is some evidence that people taking buproprion, and varenicline may have increased risk of neuropsychiatric symptoms.

Although the evidence specifically for people with SMD is limited with few studies of small size, WHO has comprehensive tools for tobacco cessation in the general population and the GDG agreed that there was no suggestion of inconsistency with the evidence for tobacco cessation interventions in the general population and in people with SMD. The GDG agreed that the benefits of the interventions outweighed the harms while recognising that prescribers should take into account potential interactions between buproprion with psychotropic medications as well as possible contra-indications of the use of bupropion and varenicline in people with SMD. In view of the low quality evidence, the GDG made conditional recommendations for tobacco cessation interventions in people with SMD.

3.2
WEIGHT MANAGEMENT

3.2.1

For people with SMD who are overweight or obese, are non-pharmacological and/or pharmacological interventions and/or pharmacological management strategies effective to support weight reduction?

Population:

People with SMD who are overweight or obese

Intervention:

- Non-pharmacological and/or pharmacological interventions and/or pharmacological management strategies:
  - Non-pharmacological interventions: e.g. cognitive-behavioural intervention strategies, lifestyle interventions (e.g. diet, exercise, physical activity / decreased sedentary behaviour, health education), family involvement in interventions
  - Pharmacological interventions: weight-loss medication (e.g. orlistat)
  - Pharmacological management strategies: e.g. switching antipsychotic medication

Comparison:

Care as usual and/or placebo

Outcomes:

- Critical
  - Change in weight
  - Mean BMI (kg/m^2) or change in BMI
- Important
  - Maintenance of weight change/attenuation/prevention of weight gain
  - Reduced sedentary behaviour
  - Frequency of adverse events/side-effects

3.2.2

For people with SMD who are at risk of becoming overweight or obese, are non-pharmacological interventions effective to support prevention of weight gain?

Population:

People with SMD who are at risk of becoming overweight or obese, e.g. people who have just started anti-psychotic medication

Intervention:

Non-pharmacological interventions, e.g. cognitive-behavioural intervention strategies, lifestyle interventions (e.g. diet, exercise, physical activity / decreased sedentary behaviour, health education), family involvement in interventions

Comparison:

Care as usual

Outcomes:

- Critical
  - Change in weight
  - Mean BMI (kg/m^2) or change in BMI
  - Maintenance of weight change
  - Attenuation/prevention of weight gain
- Important
  - Reduced sedentary behaviour
  - Frequency of adverse events/side-effects

BACKGROUND

Persons with SMD are 50% more likely to be obese than the general population; different studies have reported obesity rates of around 50% amongst women with SMD, and between around 30 to 40% for men with SMD (Dickerson *et al.*, 2006). People with SMD commonly have poor diets, and tend to consume more sugar and saturated fats than the general population. In addition, they are less likely to exercise, have a high prevalence of low physical activity, and spend over 12 hours on average in sedentary activities everyday (Janney, 2013). Also, increased appetite and metabolic effects of some psychotropic medicines can result in weight gain. Being overweight or obese may be

associated with higher rates of mortality and is related to other cardiovascular risk outcomes. Interventions in the general population have been described in the *Prevention and control of noncommunicable diseases: Guidelines for primary health care in low-resource settings (2012)* (http://www.who.int/nmh/publications/phc2012/en/).

RECOMMENDATIONS AND CONSIDERATIONS

RECOMMENDATION 1:

Behavioural lifestyle (healthy diet, physical activity) interventions should be considered in all people with severe mental disorders who are overweight or obese or at risk of becoming overweight or obese in accordance with *WHO's Package of Essential Noncommunicable Disease Interventions (WHO PEN) for primary care in low-resource settings (2010).* These interventions should be appropriate and tailored to the needs of this population.

(Strength of recommendation: Strong; Quality of evidence: Very low).

Package of Essential Noncommunicable Disease Interventions (WHO PEN) for primary care in low-resource settings (2010).

Prevention and control of noncommunicable diseases: Guidelines for primary health care in low-resource settings (2012) (http://www.who.int/nmh/publications/phc2012/en/)

- Advise overweight patients to reduce weight by following a balanced diet.
- Advise patients to give preference to low glycaemic-index foods (beans, lentils, oats and unsweetened fruit) as the source of carbohydrates in their diet.
- Advise patients to reduce sedentary behaviour and practice regular daily physical activity appropriate for their physical capabilities (e.g. walking).

RECOMMENDATION 2:

For people with severe mental disorders who are overweight or obese, and where lifestyle interventions and/or switching psychotropic medication do not appear successful, adjunctive metformin may be considered. This should be considered under close clinical supervision and monitoring.

(Strength of recommendation: Conditional; Quality of evidence: Low)

BEST PRACTICE STATEMENTS:

- For people with severe mental disorders who are overweight or obese or at risk of becoming overweight or obese, initiating a psychotropic medication with lower propensity for weight gain should be considered, taking into account clinical benefits and potential adverse effects.
- For people with severe mental disorders who are overweight or obese, switching to a psychotropic medication with a lower propensity for weight gain may be considered, taking into account clinical benefits and potential adverse effects.

Additional considerations

- Metformin is a commonly used anti-diabetic medication but it can be used for weight loss in people who are not diabetic. Metformin for people with SMD who are overweight or obese:
  - Should preferably be initiated in specialist settings, and should be closely monitored.
  - Should be tried in the short-term before being used in the long-term.
  - Availability may be an issue, i.e. metformin is not reliably available in all settings.
- Fluoxetine may increase the potency of metformin based on the drug-drug interaction searches (Annex 6). Monitor blood glucose control and adjust doses of metformin accordingly, especially when starting or stopping fluoxetine. Risperidone and clozapine are associated with hyperglycaemia and as such may decrease the efficacy of anti-diabetic medication including metformin. Monitor glycaemic control and adjust doses of anti-diabetic medications accordingly.

SUPPORTING EVIDENCE AND RATIONALE

Evidence was extracted from one systematic review with regards to lifestyle interventions for the prevention of weight gain amongst people with SMD who are at risk of becoming overweight/obese, though most of the studies in the review included participants who were already overweight (i.e. BMI over 25) on average. For this reason, the recommendations for the two PICO questions (3.2.1 and 3.2.2) were combined into one when formulating the recommendations.

For non-pharmacological interventions for weight management amongst people with SMD who were already overweight or obese, evidence was extracted from two systematic reviews for short-term lifestyle interventions (Gierisch *et al*., 2013; Naslund et al., 2017), and from one systematic review for long-term lifestyle interventions (Naslund *et al.*, 2017). With regards to anti-psychotic switching from olanzapine, evidence was extracted from one systematic review. Several systematic reviews have reported on the use of metformin for weight management amongst people with SMD who were already overweight or obese; evidence was considered from two systematic reviews when formulating the recommendations (Mizuno *et al*., 2014; de Silva *et al*., 2016).

The systematic reviews revealed very low to low quality evidence from randomized controlled trials for all of these interventions. With regards to all of the included lifestyle interventions, statistically significant effects were reported in favour of all of these. The most consistent evidence was for metformin, as – even though the quality of evidence was very low to low – the six systematic reviews from which evidence was extracted showed positive effects in terms of weight change when compared to placebo. The drug interaction review showed moderate interaction between metformin and some psychotropic medicines (fluoxetine, risperidone and clozapine) for which monitoring of blood glucose and dose adjustment may be needed. Other pharmacological interventions for which statistically significant weight change effects were found in the systematic reviews (Gierisch *et al*., 2013; Mizuno *et al*., 2014) were aripiprazole, reboxetine, sibutramine and topiramate, though the evidence base for these are only emerging and results need to be treated with caution. Sibutramine in particular has been withdrawn from use in several countries due to cardiac risks and so cannot be recommended. There is also some evidence in favour of switching from olanzapine to aripiprazole for the management of weight.

The GDG concluded that the behavioural lifestyle interventions recommended in the WHO guidelines for the general population should be followed in people with SMD since there is some evidence from the general population that advising people to give preference to low glycaemic index foods, follow a balanced diet and advice on exercise may have a beneficial effect on glycaemic control. Although the evidence in the general population is of low quality, these simple interventions are deemed as low-cost, feasible and with a negligible risk of adverse events. The GDG made a strong recommendation for non-pharmacological behavioural/lifestyle interventions, as they concluded that the benefits outweighed the harms including benefits of the intervention on other non-communicable disease outcomes. WHO general population guidelines (WHO PEN) also make a strong recommendation for these interventions in the general population. With regards to pharmacological interventions, the GDG made a strong recommendation for initiating a psychotropic medication with lower propensity for weight gain. The recommendation for switching antipsychotic medication was rated by the GDG as conditional since the quality of the evidence was low and switching antipsychotics because of weight gain should be offset against the risk of relapse of the mental disorder, as well as any potential side effects associated with the newly introduced medication.

3.3
SUBSTANCE USE DISORDERS

For people with SMD and substance (drug and/or alcohol) use disorder, are pharmacological and/or non-pharmacological interventions for substance use disorder effective to support reduction in substance use-related outcomes?

Population:
People with SMD and substance (drug and/or alcohol) use disorder

Intervention:
Pharmacological and/or non-pharmacological interventions for substance use disorders:

- Pharmacological interventions
- Non-pharmacological interventions:
  e.g. motivational interviewing and/or cognitive behaviour therapy (CBT), psychoeducation, brief assessment interview, dual-focus interventions

Comparison:
Care as usual / placebo or one treatment vs another

Outcomes:
- Critical
  - Level of consumption
  - Frequency of use
  - Abstinence
  - Relapse rates
- Important
  - Frequency of adverse events / side-effects

BACKGROUND

Comorbid substance use disorders are the most prevalent psychiatric conditions associated with SMD. The pooled prevalence for comorbid substance use disorders in SMD has been noted to range up to 42% (for alcohol use disorders), 69% (for cannabis use in schizophrenia), and just over 50% (for affective disorder amongst those on a methadone maintenance programme) (McLoughlin *et al*., 2014) (Di Florio, Craddock and van den Bree, 2014). The relationship between substance use disorders and SMD is likely bidirectional and their co-occurrence has been associated with a number of adverse outcomes, including: relapse of the mental disorder and longer hospital admissions, more positive symptoms in people with schizophrenia, and an increased risk of fatal and non-fatal overdoses and suicide.

There have been several Cochrane systematic reviews conducted on interventions for people with substance use disorder (in the general population), which have provided evidence on the effectiveness of the following interventions: Psychosocial interventions, such as combined motivational enhancement therapy (MET) and cognitive behaviour therapy (CBT) with abstinence-based incentives in cannabis use disorder (Gates *et al*., 2016); methadone in people with opioid dependence (Mattick *et al*., 2014). *WHO mhGAP Intervention Guide* provides recommendations for the management of substance use disorders. We have considered these pharmacological and/or non-pharmacological interventions for people with co-morbid SMD and substance use disorder.

RECOMMENDATIONS AND CONSIDERATIONS

RECOMMENDATION 1:

For people with severe mental disorders and comorbid substance use disorders (drug and/or alcohol) interventions should be considered in accordance with the WHO mhGAP guidelines.

(Strength of recommendation: Conditional; Quality of the evidence: Low).

RECOMMENDATION 2:

Non-pharmacological interventions (e.g. motivational interviewing) may be considered and tailored to the needs of people with severe mental disorders and substance use disorders.

(Strength of recommendation: Conditional; Quality of the evidence: Very low).

WHO mhGAP guidelines

(http://www.who.int/mental_health/mhgap/mhGAP_intervention_guide_02/en/)

The *mhGAP Intervention Guide* recommends the following:

- **Alcohol use disorders:**
  - Thiamine during alcohol use
  - Diazepam during alcohol detoxification to treat withdrawal symptoms
  - Naltrexone, acamprosate or disulfiram to prevent relapse after detoxification
  - Psychosocial interventions if available, e.g. cognitive behaviour therapy, motivational enhancement therapy, contingency management therapy, family counselling or therapy, problem-solving counselling or therapy; self-help groups
- **Drug use disorders:**
  - For opioid misuse: buprenorphine, methadone, clonidine, lofexidine, opioid agonist maintenance treatment (OAMT) for relapse prevention.
  - Psychosocial interventions, e.g. CBT, motivational enhancement therapy, contingency management therapy, family counselling or therapy, problem-solving counselling or therapy; self-help groups.

BEST PRACTICE STATEMENT:

- Prescribers should take into account the potential for drug-drug interactions between medicines used for treatment of substance use disorders and severe mental disorders.

Additional considerations

- Certain side effects (somnolence, hypersalivation, and constipation) may be more prevalent in people treated with clozapine, which should be a consideration when determining choice of pharmacotherapy.

- People with SMD who are injecting drug users may be at an increased risk of Hepatitis B and C through the sharing of contaminated instruments and/ or needles. The Centers for Disease Control and Prevention (CDC) in the USA has reported outbreaks of Hepatitis A in people who inject drugs, which may also be through the sharing of contaminated instruments and needles or through faeco-oral transmission. Therefore members of the GDG recommended that in people with SMD who also inject drugs, Hepatitis A and Hepatitis B vaccination, and Hepatitis B and Hepatitis C testing should be undertaken. This has also been recommended by the CDC, USA. (https://www.cdc.gov/hepatitis/populations/idu.htm).

SUPPORTING EVIDENCE AND RATIONALE

Evidence of pharmacological interventions for mental disorders comorbid with substance use disorders was extracted from two systematic reviews which focused on antipsychotic prescribing (Wilson and Bhattacharyya, 2016; Temmingh *et al.*, 2018) and one systematic review which focused on antidepressant prescribing in depression comorbid with alcohol use (Agabio *et al.*, 2018). Evidence on psychological interventions for these populations were extracted from two systematic reviews (Hunt *et al.*, 2014; Boniface, 2018).

Detailed reviews revealed very low to low quality evidence from randomized controlled trials, which did not support the superiority of any of the pharmacological interventions against each other. Potential side effects from pharmacological therapies were noted as moderate and will need to be considered when determining the choice of pharmacotherapy. Methadone and buprenorphine, medicines used for treatment of substance use disorders, have major interactions with commonly prescribed psychotropic medications including increased risk of for CNS depression (sedation, confusion, decreased respiratory drive), QT prolongation on ECG, and serotonergic effects (confusion, neuromuscular excitability, and dysautonomia) (Annex 6).

There was no evidence to support superiority of any of the psychosocial interventions against each other in populations with comorbid SMD and substance use disorder. None of the reviewed trials for psychosocial therapies have been conducted in LMIC settings. The absence of high quality evidence does not mean that these treatments do not work but that at present the evidence is of insufficient quality to support the use of one form of non-pharmacological or psychosocial intervention over another in these special populations. One reason for the lack of evidence may be that people with comorbidities are commonly excluded from research (Dennis *et al.*, 2015).

The resource requirements for offering interventions (both pharmacological and psychological) are currently unclear with only one study identified which estimated the cost of providing CBT plus motivational interviewing compared to care-as-usual in a well-resourced setting (USA).

There is good indirect evidence that certain interventions work for alcohol and substance use disorders in the general population, which have been detailed in the current mhGAP 2.0 guidelines, as well as in other guidelines such as those for Opioid Agonist Maintenance Treatment (OAMT) for relapse prevention. The GDG agreed that although the quality of evidence was very low for most psychological interventions in populations with co-morbid SMD and substance use disorders, the psychological interventions which are currently recommended in the MHGAP 2.0 guidelines for the general population (in particular- CBT plus motivational interviewing, motivational interviewing and contingency management) may also be effective in people with SMD . Furthermore, undesirable side effects from non-pharmacological treatments were noted to be trivial. Noting the risk of drug interactions between medicines used for treatment of opioid use disorders and SMD, the GDG agreed that the interactions are outweighed by the risk of other harms of untreated opioid use disorders in people with SMD and rather than withholding opioid replacement therapy, cautious medication management is advised.

Given the low quality of evidence and that all the evidence identified for the treatment of substance use disorders comorbid with SMD came from well-resourced/ high- income settings, the GDG made conditional recommendations.

3.4
CARDIOVASCULAR DISEASE AND CARDIOVASCULAR RISK

3.4.1

For people with SMD and pre-existing cardiovascular disease, what pharmacological and/or non-pharmacological interventions are effective to support reduction of cardiovascular disease outcomes?

Population:

People with SMD and pre-existing cardiovascular disease: e.g. coronary heart disease, prior heart failure or stroke, cardiomyopathy, congenital heart disease, peripheral vascular disease

Intervention:

Pharmacological and/or non-pharmacological interventions

Comparison:

One treatment versus another or care as usual / placebo

Outcomes:

- Critical
  - Major adverse cardiovascular event (MACE) - includes cardiovascular death, myocardial infarction, stroke, heart failure, hospitalization, amputation
- Important
  - Frequency of adverse events/side-effects

3.4.2

For people with SMD and cardiovascular risk factors (a. high blood pressure; b. high lipid levels), what pharmacological and/or non-pharmacological interventions are effective to support reduction of cardiovascular risk factors?

Population:

People with SMD and cardiovascular risk factors (a. high blood pressure; b. high lipid levels)

Intervention:

Pharmacological and/or non-pharmacological interventions:

- pharmacological interventions: a) medication to control high blood pressure; b) medications for high lipid levels
- non-pharmacological interventions

Comparison:

One treatment versus another or care as usual / placebo

Outcomes:

- Critical
  - Adequacy of control of CVD risk factors (a. blood pressure <130/80mmHg; b. cholesterol <200mg/dl)
  - Cardiovascular disease incidence
- Important
  - Frequency of adverse events/side-effects

BACKGROUND

Cardiovascular disease is considered as one of the main potentially avoidable contributors to excess mortality amongst people with SMD. Overall, people with SMD have an approximately 1.5 to 3 times higher risk of cardiovascular morbidity and mortality compared to the general population (Laursen, 2011). There is a complex interplay between several non-communicable diseases, such as diabetes, hypertension and cardiovascular disease, and the presence of SMD. People with SMD are more likely to engage in lifestyle behaviours that contribute to increased cardiovascular risk including tobacco use, harmful use of alcohol, unhealthy diets, and physical inactivity. The iatrogenic effects of medicines used to treat SMDs are linked with increased risk of cardiometabolic diseases. The use of antipsychotic medications has been associated with obesity, insulin resistance, diabetes, myocardial infarctions, atrial fibrillation, stroke, and death.

Pharmacological and non-pharmacological interventions for the general population have been described in the *Package of Essential Noncommunicable (PEN) Disease Interventions for Primary Health Care in Low-Resource Settings* (WHO, 2010).

RECOMMENDATIONS AND CONSIDERATIONS

RECOMMENDATION 1:

For people with severe mental disorders and pre-existing cardiovascular disease, or with cardiovascular risk factors (e.g. high blood pressure or high cholesterol), pharmacological and non-pharmacological interventions may be considered in accordance with the *WHO Package of Essential Noncommunicable Disease Interventions* (WHO PEN) for primary care in low-resource settings (2010) for lowering cardiovascular risk and management of cardiovascular disease.

(Strength of recommendation: Strong; Quality of evidence: High to moderate for different interventions).

Package of Essential Noncommunicable Disease Interventions (WHO PEN) for primary care in low-resource settings (2010).

http://www.who.int/cardiovascular_diseases/publications/pen2010/en/

- **Primary prevention of heart attacks and strokes:**
  - Tobacco cessation; regular physical activity 30 minutes a day; reduced intake of salt <5 g per day; fruits and vegetables at least 400g per day
  - Statins and antihypertensives for people with 10-year cardiovascular risk >30%
  - Antihypertensives for people with blood pressure ≥160/100
  - Anthypertensives for people with persistent blood pressure ≥140/90 and 10 year cardiovascular risk >20% unable to lower blood pressure through life style measures
- **Acute myocardial infarction: Aspirin and referral to next level of care**
- **Secondary prevention (post myocardial infarction):**
  - Tobacco cessation, healthy diet and regular physical activity.
  - Aspirin, antihypertensive (low dose thiazide, angiotensin-converting enzyme inhibitor), and statin
- **Secondary prevention (Rheumatic heart disease):**
  - Regular administration of antibiotics to prevent streptococcal pharyngitis and recurrent acute rheumatic fever

RECOMMENDATION 2:

For people with severe mental disorders and pre-existing cardiovascular disease, the following is recommended:

a) **Behavioural lifestyle (healthy diet, physical activity) interventions may be considered. These interventions should be appropriate and tailored to the needs of this population.**

(Strength of recommendation: Conditional; Quality of evidence: Very low).

b) **Collaborative care, i.e. a multi-professional approach to patient care with a structured management plan, scheduled patient follow-up, and enhanced inter-professional communication, may be considered for cardiovascular management.**

(Strength of recommendation: Conditional; Quality of evidence: Very low).

RECOMMENDATION 3:

For people with severe mental disorders and cardiovascular risk factors, behavioural lifestyle (healthy diet, physical activity) interventions may be considered. These interventions should be appropriate and tailored to the needs of this population.

(Strength of recommendation: Conditional; Quality of evidence: Very low).

BEST PRACTICE STATEMENTS:

For people with severe mental disorders and pre-existing cardiovascular disease:

- Initiating a psychotropic medication with lower propensity for cardiovascular risk is a strategy that should be considered, taking into account clinical benefits and potential adverse effects.
- Switching to a psychotropic medication with lower propensity for cardiovascular risk may be considered, taking into account clinical benefits and potential adverse effects.

For people with severe mental disorders and pre-existing cardiovascular disease or cardiovascular risk factors:

- Prescribers should be aware of potential interactions between prescribed medicines for cardiovascular disease and prescribed psychotropic medications, which may affect cardiovascular risk. Cardiovascular outcomes and risk factors should be monitored and dose adjustment of cardiovascular medicines may be required.

SUPPORTING EVIDENCE AND RATIONALE

For people with SMD and pre-existing cardiovascular disease, two systematic reviews were included that reported on anti-depressants as compared to care as usual (Maslej *et al.*, 2017; Nieuwsma *et al.*, 2017); one systematic review was included that reported on psychosocial interventions (Ski *et al.*, 2016); and one systematic review each for exercise therapy (Verschueren *et al.*, 2018) and collaborative care (Tully and Baumeister, 2015).

For people with SMD and cardiovascular risk (e.g. high blood pressure or cholesterol), regarding the use of pharmacological interventions, two systematic reviews were used to extract evidence on the use of metformin versus placebo (Mizuno *et al.*, 2014; de Silva *et al.*, 2016), and two on the use of aripiprazole versus placebo (Gierisch *et al*, 2013; Mizuno *et al*, 2014), in the management of either blood pressure or cholesterol, or the frequency of adverse effects. Two systematic reviews were included that reported on non-pharmacological interventions as compared to care as usual (Gierisch *et al*, 2013; Teasdale *et al*, 2017). None of these systematic reviews included cardiovascular disease incidence as an outcome which is one of the critical outcomes for this PICO question. All of the systematic reviews and meta-analyses for comorbid cardiovascular disease focused on interventions for people with depression. No reviews assessed interventions in populations with other SMD (e.g. schizophrenia, bipolar disorder) with comorbid cardiovascular disease. The evidence and recommendations are therefore indirect for populations with SMD and comorbid cardiovascular disease.

No sufficiently high-quality systematic reviews could be identified that reported on either pharmacological or non-pharmacological interventions compared to another treatment, either for SMD and pre-existing cardiovascular disease or cardiovascular risk.

The systematic reviews revealed either very low or low quality evidence from randomized controlled trials for all of these interventions; the only exception to this was for psychosocial interventions for people with SMD and pre-existing cardiovascular disease, for which some of the evidence was graded as moderate quality. The only included intervention for which statistically significant effects were reported for people with SMD and pre-existing cardiovascular disease was collaborative care, which may show a relative and absolute reduction in major adverse cardiac events in the short to medium-term (less than 12 months), though it is less clear whether this is the case in the longer-term (over 12 months).

Major drug-drug interactions were found between several psychotropic medications and commonly prescribed medications for cardiac conditions, hypertension and cholesterol control. Some examples of these are: the risk of hypotension or beta-blocker toxicity (including hypotension, bradycardia, and heart block/prolonged PR interval) with beta blockers and the risk of hypotension with diuretics (Annex 6).

Given the evidence was limited for people with SMD, the GDG used evidence from general populations and thought it to be applicable because they would benefit people with SMD too. However, the GDG agreed that it is important to exercise caution in the initiation of psychotropic medication due to the heightened risk of cardiovascular disease and potential drug interactions. There is currently insufficient evidence for behvioural lifestyle interventions for people with SMD and cardiovascular disease and risk, conditional recommendations have been made for these interventions as the GDG agreed that there the benefits outweighed the risks including benefits of the intervention on other non-communicable disease outcomes.

3.5
DIABETES MELLITUS

For people with SMD and diabetes mellitus, what pharmacological and/or non-pharmacological interventions are effective to improve glycaemic control?

Population:
People with SMD and diabetes mellitus

Intervention:
- Pharmacological interventions: e.g. medication to treat diabetes
- Non-pharmacological interventions: e.g. behavioural lifestyle interventions, cognitive behaviour therapy

Comparison:
One treatment versus another or care as usual

Outcomes:
- Critical
  - Fasting blood glucose <120mg/dl; post-prandial blood glucose<160mg/dl
  - Glycosylated haemoglobin A1c (HbA1c<7 for people below 60 years and 7-8 for people above 60 years with other risk factors)
  - Diabetes complications – Major Atherosclerotic Cardiovascular Events (MACE), chronic kidney disease, diabetic retinopathy, diabetic neuropathy, hospitalization for infection
- Important
  - Frequency of adverse events/side-effects

BACKGROUND

There is high co-morbidity between SMD and diabetes mellitus. People with SMD are at an increased risk of diabetes (around double for schizophrenia and bipolar disorder, and 1.5 times the risk for depression), and people with diabetes are at a heightened risk of SMD (around double for depression), with a higher risk in low- and middle-income countries(Vancampfort et al., 2016). However, this often goes undetected, and people with comorbid SMD and diabetes have an increased risk of mortality. There is an association with diabetes with some anti-psychotics, anti-depressants and lithium, as well as with health-related behaviours (such as physical activity and diet), other environmental factors, and gender (elevated risk in women).

This section covers evidence regarding pharmacological and/or non-pharmacological interventions for people with SMD and diabetes mellitus. The inclusion of interventions was guided by the research evidence available for people with diabetes and SMD.

RECOMMENDATIONS AND CONSIDERATIONS

RECOMMENDATION 1:

For people with severe mental disorders and diabetes mellitus, interventions in accordance with the *WHO Package of Essential Non-communicable (PEN) Disease Interventions for primary care in low-resource settings* should be considered for diabetes management

(Strength of recommendation: Strong; Quality of evidence: Low).

Package of Essential Noncommunicable Disease Interventions (WHO PEN) for primary care in low-resource settings (2010)

http://apps.who.int/iris/bitstream/handle/10665/133525/9789241506557_eng.pdf;jsessionid=C8B92D24C7F27E9E3BEBC2957FB8CCE8?sequence=1

- **For Type 1 diabetes:**
  - Daily insulin injections
- **For Type 2 diabetes:**
  - Anti-diabetic agents for type 2 diabetes, if glycaemic targets are not achieved with modification of diet, maintenance of a healthy body weight and regular physical activity
  - Metformin as initial drug in overweight patients and non-overweight
  - Other classes of anti-diabetic agents, added to metformin if glycaemic targets are not met
  - Reduction of cardiovascular risk for those with diabetes and 10-year cardiovascular risk >20% with aspirin, angiotensin converting enzyme inhibitor and statins

WHO NCD 2012: Prevention and control of noncommunicable diseases: Guidelines for primary health care in low-resource settings

(http://www.who.int/nmh/publications/phc2012/en/):

- **Diagnosing diabetes:** Laboratory services. If not available, point of care devices may be used
- **Glycaemic control:** Diet and physical activity as first-line treatment, Metformin as first-line oral hypoglycaemic agent where diet is not sufficient, sulfonylureas for those patients where metformin is not effective/patient has contraindications
- **Reducing the risk of cardiovascular disease and diabetic nephropathy:** Statins for all people with Type-2 diabetes over 40 years of age, antihypertensive agents to reduce blood pressure, choice of antihypertensive agent
- **Prevention of lower limb amputations:** Educate patients and health care workers
- **Prevention of blindness:** Screening for diabetic retinopathy
- **Severe hypoglycaemia, hypoglycaemic emergencies**: Intravenous hypertonic glucose treatment or glucose (dextrose) for unconscious patients, referral to hospital and drip in emergencies

RECOMMENDATION 2:

Behavioural lifestyle interventions should be considered for all people with severe mental disorders and diabetes mellitus. These interventions should be appropriate and tailored to the needs of this population.

(Strength of recommendation: Strong; Quality of evidence: Very low).

RECOMMENDATION 3:

In people with depression and comorbid diabetes mellitus, cognitive behaviour therapy for treatment of depression may be considered.

(Strength of recommendation: Conditional; Quality of evidence: Very low).

BEST PRACTICE STATEMENTS:

For people with severe mental disorders and diabetes mellitus:

- Initiating an anti-psychotic medication with lower propensity for producing hyperglycaemia should be considered, taking into account clinical benefits and potential adverse effects.
- Switching to an anti-psychotic medication with lower propensity for producing hyperglycaemia is a strategy that may be considered, taking into account clinical benefits and potential adverse effects.
- Prescribers should be aware of potential interactions between prescribed medicines for diabetes and prescribed psychotropic medicines, which may affect glycaemic control. Glycaemic control should be monitored and dose adjustment of medicines may be required.

SUPPORTING EVIDENCE AND RATIONALE

With regards to pharmacological interventions for people with SMD and diabetes, one (the same) systematic review was used to extract evidence for diabetes medication, weight loss medications, anti-psychotic switching, and weight loss and diabetes medications combined.

The systematic reviews revealed very low quality evidence from randomized controlled trials for all of these interventions. There was some evidence to suggest anti-psychotic switching had beneficial effects. The drug-drug interaction review showed moderate interactions between some psychotropic medicines and anti-diabetic medicines (increased or decreased potency of the anti-diabetic medicine) that requires blood glucose monitoring and dose adjustment of anti-diabetic medicines.

With regards to non-pharmacological interventions, evidence from one systematic review each was considered for behavioural interventions (Taylor *et al.*, 2017) and cognitive behaviour therapy (Li *et al.*, 2017), and one systematic review for self-management interventions (McBain *et al.*, 2016). There was some evidence that cognitive behaviour therapy for treatment of depression shows positive effects on blood glucose amongst people with diabetes and comorbid depression (probably by eliminating the negative effects of depression on diabetes). There is insufficient evidence available for the management of diabetes amongst people with SMD for all other reviewed interventions.

Since all of the evidence was rated as very low in quality, and there was insufficient evidence available for most of the reviewed interventions, the GDG concluded that the WHO guidelines for the general population in low-resource settings should be followed as a first step as the underlying pathophysiological mechanisms would be similar in people with SMD. Nevertheless, the GDG made additional best practice statements for the initiation of psychotropic medication and potential drug-drug interactions, to counter the risks of taking these medications. A strong recommendation has also been made for behavioural lifestyle interventions despite very low quality evidence as the GDG agreed that the benefits outweighed the harms and as there is a strong recommendation for this by WHO for the general population (WHO PEN). The GDG also concluded that there are benefits of the intervention on other noncommunicable disease outcomes. The GDG made a conditional recommendation for cognitive behaviour therapy because of very low quality evidence and the possible lack of generalizability to all people with SMD.

3.6
HIV/AIDS

For people with SMD and HIV/AIDS, what pharmacological (i.e. antiretroviral drugs, psychopharmacology) and nonpharmacological interventions are effective to support reduction in HIV-related outcomes?

Population:
People with SMD and HIV/AIDS

Intervention:

- Pharmacological interventions (e.g. antiretroviral drugs, psychopharmacology)
- Nonpharmacological interventions

Comparison:
One treatment versus another or care as usual

Outcomes:

- Critical
  – HIV-related outcomes
- Important
  – Frequency of adverse events/side-effects

BACKGROUND

The association between mental health disorders and HIV/AIDS is complex and bi-directional - they frequently co-occur: mental disorders can be precursors to HIV/AIDS, consequences of HIV infection, or the result of interactive effects. They also have similar consequences in terms of their public health, social, and economic impacts.

International evidence has found that populations with SMD have higher rates of HIV infection. Among persons with SMD, the median prevalence of HIV in the US is 1.8 % (range: 0.1%-5.0%) with a high rate among inpatient populations (3.8%), whereas the overall US adult population estimated prevalence of HIV is 0.5% (Janssen *et al.*, 2015). HIV rates may be even higher in certain vulnerable populations, such as those who have SMD and are also homeless(Susser, Valencia and Conover, 1993). People with SMD and HIV experience a complex set of medical, psychological and social complications that need to be tackled through integrated care. The interventions included pharmacological interventions for SMD and HIV as well as non-pharmacological interventions such as psychosocial support.

RECOMMENDATIONS AND CONSIDERATIONS

RECOMMENDATION 1:

For people with severe mental disorders and HIV/ AIDS, antiretroviral drugs should be considered in accordance with the WHO Updated recommendations on first-line and second-line antiretroviral regimens.

(Strength of the recommendation: Strong; Quality of the evidence: Moderate)

Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: interim guidelines. Supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization; 2018 (WHO/ CDS/HIV/18.45). Licence: CC BY-NC-SA 3.0 IGO.

http://www.who.int/hiv/pub/guidelines/ARV2018update/en/

RECOMMENDATIONS: FIRST-LINE ARV DRUG REGIMENS

A DTG based regimen is recommended as a preferred first-line regimen for people living with HIV initiating ART (conditional recommendation)

- Adults and adolescents (moderate-certainty evidence)
- Women and adolescent girls of childbearing potential (very-low-certainty evidence)
  Note of caution on using DTG during the periconception period and for women and adolescent girls of childbearing potential*
- Exposure to DTG at the time of conception may be associated with neural tube defects among infants.
- DTG appears to be safe when started later in pregnancy: after the period of risk of neural tube defects, up to eight weeks after conception.
- Adolescent girls and women of childbearing potential who do not currently want to become pregnant can receive DTG together with consistent and reliable contraception; based on limited data, hormonal contraception and DTG have no reported or expected drug–drug interactions.
- An EFV-based regimen is a safe and effective first-line regimen recommended for use by the WHO 2016 ARV drug guidelines and can be used among women of childbearing potential during the period of potential risk for developing neural tube defects (at conception and up to eight weeks after conception).

Further guidance on the treatment and care of people living with HIV can be found in *"Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – 2nd edition 2016."* http://www.who.int/hiv/pub/arv/arv-2016/en

[List of abbreviations: DTG: dolutegravir; EFV efavirenz]

* an ongoing observational study in Botswana recently identified a signal of potential safety risk for developing neural tube defects among infants born to women who were taking DTG at conception. WHO is taking this potential safety issue seriously and is working closely with all relevant stakeholders to further investigate these preliminary findings. WHO will update these guidelines and provide additional information as it becomes available

RECOMMENDATION 2:

Additional psychosocial support for treatment adherence should be provided to people with HIV and severe mental disorders in accordance with the WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection.

(Strength of the recommendation: Strong; Quality of the evidence: Moderate)

Adherence support interventions extracted from WHO Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – 2nd ed. 2016

http://apps.who.int/iris/bitstream/handle/10665/208825/9789241549684_eng.pdf?sequence=1

RECOMMENDATION: Adherence support interventions should be provided to people on ART (strong recommendation, moderate-quality evidence).

The following interventions have demonstrated benefit in improving adherence and viral suppression:

- peer counsellors (moderate-quality evidence)
- mobile phone text messages (moderate-quality evidence)
- reminder devices (moderate-quality evidence)
- cognitive-behavioural therapy (moderate-quality evidence)
- behavioural skills training and medication adherence training (moderate-quality evidence)
- fixed-dose combinations and once-daily regimens (moderate-quality evidence).

Considerations in specific populations: People with HIV with uncontrolled depressive symptoms are more likely to have poor adherence to ART. Adherence is complicated by mental health comorbidity that results in forgetfulness, poor organization and poor comprehension of treatment plans. Counselling for HIV and depression and appropriate medical therapies for people with mental disorders can help to improve adherence. WHO recommends that assessment and management of depression should be included in care services for all people living with HIV.

BEST PRACTICE STATEMENT:

For people with severe mental disorders and HIV/ AIDS prescribers should take into account the potential for drug-drug interactions between antiretroviral drugs and psychotropic medicines.

SUPPORTING EVIDENCE AND RATIONALE

There is limited RCT evidence for pharmacological treatment in people with SMD and HIV/AIDS. One systematic review that was included in the evidence profile assessed the efficacy of antidepressant therapy for treatment of depression in people with HIV/AIDS (Eshun-Wilson, 2018). The evidence was of very low quality and the results inconclusive. The drug interaction review reveals multiple interactions between efavirenz and psychotropic medicines, specifically involving the risk of QT interval prolongation, CNS depression and /or enzyme induction (Annex 6). No reviews were identified for non-pharmacological treatments including adherence management specifically in people with SMD and comorbid HIV/ AIDS.

These recommendations are based on indirect evidence of HIV treatment in the general population that are provided in existing WHO guidelines that strongly recommend ARV and adherence management to support ARV adherence in people with HIV/AIDS with or without SMD. The GDG concluded that the balance between desirable and undesirable effects favor the intervention leading to strong recommendations while noting the need to consider drug interactions. They also concluded that there was no important uncertainty about or variability in how much people value the main outcomes and that the interventions would increase health equity. The GDG agreed that people with SMD would need additional support for adherence as the presence of SMD and its associated symptoms can have a detrimental impact on adherence to ARV and progression of AIDS.

3.7
OTHER INFECTIOUS DISEASES (TUBERCULOSIS, HEPATITIS B/C)

For people with SMD and infectious diseases (Tuberculosis, Hepatitis B/C), what pharmacological and nonpharmacological (social, psychological) interventions are effective for treatment of infectious diseases (i.e. tuberculosis, hepatitis B, hepatitis C)?

Population:
People with SMD and infectious diseases (Tuberculosis, Hepatitis B/C)

Intervention:
- Pharmacological interventions for infectious diseases
- Nonpharmacological (social, psychological) interventions for infectious diseases

Comparison:
One treatment versus another or care as usual

Outcomes:
- Critical
  – Infectious disease-related outcomes
- Important
  – Frequency of adverse events/side-effects

BACKGROUND

People with SMD are at greater risk than the general population for exposure to infectious diseases, including tuberculosis (TB) and chronic hepatitis(Rosenberg *et al.*, 2010). Infectious diseases appear to contribute to an increased risk of death in persons with SMD, with a 4- to 8-fold risk of death due to infection compared to the general population.

Tuberculosis and SMD share common risk factors including homelessness, HIV positive serology, alcohol/substance abuse and migrant status leading to frequent co-morbidity. There are widespread discriminatory attitudes and behaviours towards patients with TB and SMD in the community which affects health-related quality of life. In people with SMD and TB, there may be a negative impact on health behaviours such as medication adherence leading to greater morbidity, mortality, amplification of drug-resistance, transmission and all the associated social costs of these outcomes (Alene *et al.*, 2018).

The WHO End TB strategy calls to provide TB care through an integrated approach in collaboration with other public health programmes including mental health services such as tailoring TB care delivery models to the specific needs of populations with mental health problems.

There is also a high prevalence of hepatitis B and C in people with SMD. There is evidence that hepatitis C infection itself may be directly associated with psychiatric symptoms, independent of pre-existing psychiatric disorders. Stigmatization and the fact that people have to cope with a chronic infectious disorder increase the risk of depression. As is seen with TB, mental health problems during antiviral treatment have a strong impact on quality of life, may reduce treatment compliance and are risk factors for treatment failure.

For people with SMD and TB or hepatitis B/C, pharmacological and non-pharmacological interventions need to be considered as in the general population.

RECOMMENDATIONS AND CONSIDERATIONS

RECOMMENDATION 1:

For people with severe mental disorders and TB, pharmacological management should be considered in accordance with the *WHO guidelines for the treatment of drug-susceptible tuberculosis and patient care*, and the *WHO treatment guidelines for drug-resistant tuberculosis*.

(Strength of the recommendation: strong; Quality of the evidence: Low).

WHO guidelines for the treatment of drug-susceptible tuberculosis and patient care

(http://apps.who.int/iris/bitstream/handle/10665/255052/9789241550000-eng.pdf?sequence=1)

In patients with drug-susceptible pulmonary TB, the 6-month rifampicin-based regimen 2HRZE/4HR and daily dosing is the recommended regimen and dosing frequency.

WHO treatment guidelines for drug-resistant tuberculosis

(http://apps.who.int/iris/bitstream/handle/10665/250125/9789241549639-eng.pdf?sequence=1).

Note: The guidelines are currently being updated and the recommendations will be replaced with the revised ones as soon as they are available.

1) Shorter MDR-TB regimen

In patients with RR-TB or MDR-TB who were not previously treated with second-line drugs and in whom resistance to fluoroquinolones and second-line injectable agents was excluded or is considered highly unlikely, a shorter MDR-TB regimen of 9–12 months may be used instead of the longer regimens (conditional recommendation, very low certainty in the evidence).

2) Longer MDR-TB regimens

2a) In patients with RR-TB or MDR-TB, a regimen with at least five effective TB medicines during the intensive phase is recommended, including pyrazinamide and four core second-line TB medicines – one chosen from Group A, one from Group B, and at least two from Group C2 (conditional recommendation, very low certainty in the evidence). If the minimum number of effective TB medicines cannot be composed as given above, an agent from Group D2 and other agents from Group D3 may be added to bring the total to five.

2b) In patients with RR-TB or MDR-TB, it is recommended that the regimen be further strengthened with high-dose isoniazid and/or ethambutol (conditional recommendation, very low certainty in the evidence).

(Group A=levofloxacin, moxifloxacin, gatifloxacin; Group B=amikacin, capreomycin, kanamycin, (streptomycin); Group C= ethionamide (or prothionamide), cycloserine (or terizidone), linezolid, clofazimine).(Group D2=bedaquiline, delamanid; Group D3=p-aminosalicylic acid, imipenem–cilastatin, meropenem, amoxicillin clavulanate, (thioacetazone)).

RECOMMENDATION 2:

For people with severe mental disorders and TB, non-pharmacological (social, psychological) management should be considered in accordance with the WHO guidelines for the treatment of drug-susceptible tuberculosis and patient care, and the WHO treatment guidelines for drug-resistant tuberculosis.

(Strength of the recommendation: strong; Quality of the evidence: Low).

Cross-cutting interventions for drug-susceptible TB and drug-resistant TB: effectiveness of patient care and support interventions

(http://apps.who.int/iris/bitstream/handle/10665/255052/9789241550000-eng.pdf?sequence=1)

RECOMMENDATIONS:

Health education and counselling on the disease and treatment adherence should be provided to patients on TB treatment. (Strong recommendation, moderate certainty in the evidence)

A package of treatment adherence interventions may be offered to patients on TB treatment in conjunction with the selection of a suitable treatment administration option. (Conditional recommendation, low certainty in the evidence)

One or more of the following treatment adherence interventions (complementary and not mutually exclusive) may be offered to patients on TB treatment or to health-care providers: a) tracers and/or digital medication monitor (Conditional recommendation, very low certainty in the evidence) b) material support to patient (Conditional recommendation, moderate certainty in the evidence) c) psychological support to patient (Conditional recommendation, low certainty in the evidence) d) staff education (Conditional recommendation, low certainty in the evidence).

[The GDG suggests that psychological support* should be provided to patients with TB (conditional recommendation, low certainty of evidence). *Psychological support includes counselling sessions and peer-group support.]

Psychological support was varied and could include self-help groups, alcohol cessation counselling and TB clubs. Patients who had access to psychological support had higher rates of treatment completion and cure, as well as lower rates of treatment failure and loss to follow-up. When considering this data, it should also be noted that psychological support types are very broad and may not be adequately represented in this review. To maximize health equity, psychological support should be targeted at the most marginalized populations.

RECOMMENDATION 3:

For people with severe mental disorders and hepatitis B, treatment should be considered in accordance with the WHO guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection.

(Strength of the recommendation: strong; Quality of the evidence: Low)

Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. March 2015

http://apps.who.int/iris/bitstream/handle/10665/154590/9789241549059_eng.pdf?sequence=1

In all adults, adolescents and children aged 12 years or older in whom antiviral therapy is indicated, the nucleos(t)ide analogues (NAs) which have a high barrier to drug resistance (tenofovir or entecavir) are recommended. Entecavir is recommended in children aged 2–11 years. *(Strong recommendation, moderate quality of evidence)*

RECOMMENDATION 4:

For people with severe mental disorders and hepatitis C, treatment should be considered in accordance with the WHO guidelines for the screening care and treatment of persons with chronic hepatitis C infection.

(Strength of the recommendation: strong; Quality of the evidence: Low)

Guidelines for the screening care and treatment of persons with chronic hepatitis C infection. Updated version, April 2016

http://www.who.int/hepatitis/publications/hepatitis-c-guidelines-2016/en/

Treatment with direct-acting antiviral agents: it is recommended that direct-acting antivirals (DAA) regimens be used for the treatment of persons with hepatitis C infection rather than regimens with pegylated interferon and ribavirin. *(Strong recommendation, moderate quality of evidence)*

BEST PRACTICE STATEMENT:

For people with severe mental disorders and TB, Hepatitis B/C prescribers should take into account the potential for drug-drug interactions between TB medicines, medicines for hepatitis B and C with psychotropic medicines.

Additional considerations

People with SMD may be at an increased risk of Hepatitis B and C for example due to injection drug use. The CDC in the USA has reported outbreaks of Hepatitis A in people who inject drugs, which may also be through the sharing of contaminated instruments and needles or through faeco-oral transmission. Therefore members of the GDG recommended that in people with SMD who also inject drugs, Hepatitis A and Hepatitis B vaccination, and Hepatitis B and Hepatitis C testing should be undertaken. This has also been recommended by the CDC, USA (https://www.cdc.gov/hepatitis/populations/idu.htm).

SUPPORTING EVIDENCE AND RATIONALE

No reviews were identified for interventions in people with SMD and comorbid TB, Hepatitis B/C. A recent systematic review reported that programmes that included educational, psychological, and/or material support were associated with better TB outcomes, and can now be considered best practice(Alipanah *et al*., 2018). Some trial evidence shows effectiveness of treatment of pulmonary TB in people with SMD (Mishin *et al* 2008) and of a brief intervention to deliver best practice services for infectious diseases to people with mental disorders in increasing participation and acceptance of core services, including testing for hepatitis B/C; immunization for hepatitis A and B; increased hepatitis knowledge reduction of substance use (Rosenberg *et al*., 2010).

The drug-drug interaction review showed that major interactions exist between medicines used for TB, hepatitis B/C and psychotropic medicines (Annex 6). These require close clinical monitoring and dose adjustments and in some cases use of alternate psychotropic medicines with less potential for interaction.

These recommendations are based on indirect evidence of TB/Hepatitis treatment in the general population that are provided in existing WHO guidelines as the GDG concluded that the same pathophysiological mechanisms for these conditions would apply to people with SMD. The GDG provided strong recommendations as they agreed that the benefits of the interventions outweighed the harms while noting the need to consider drug interactions. The GDG also agreed that there was no important uncertainty about or variability in how much people value the main outcomes and that the interventions would increase health equity. The GDG agreed that people with SMD would need additional support for adherence to TB treatments and provided a strong recommendation for this intervention drawing from existing general population guidelines.

4. Implementation considerations

The recommendations in these guidelines must be implemented using a person-centred and integrated approach to address factors associated with excess mortality in persons with SMD. This integration is needed at four levels – screening and early detection of physical health conditions, counselling for behavioural risk factors, assessment and management of cardiovascular disease risk and management of established physical and mental health conditions.

We propose a multilevel intervention framework that will be useful for designing, implementing and evaluating interventions and programmes to reduce excess mortality in persons with SMD (Liu et al., 2017). The first level is individual-focused interventions. The second and third levels of the framework consist of strategies focussed on the health systems and socio-environmental context, respectively, which provide the enabling environment for implementation of the recommendations.

The ***individual-focused interventions*** i.e. strategies delivered to individuals with SMD to target their mental health condition, physical health and lifestyle behaviours should be guided by the recommendations proposed in these guidelines.

Health screening facilitates early detection and treatment for many of these conditions, though rates of screening in people with SMD appear to be reduced compared with the general population. A UK survey(Patel *et al.*, 2014) found that only 33% of people with schizophrenia had received adequate cardiovascular disease screening in the previous 12 months. Effective interventions for increasing access to, or uptake of, screening for a range of conditions in the general population (Camilloni *et al.,* 2013) exist. A recent review identified interventions to increase both access to and uptake of physical health screening in people with SMD amongst which are staff and stakeholder involvement in screening, staff flexibility when taking physical measurements (e.g. using adapted equipment) and strong links with primary care (Lamontagne-Godwin *et al.*, 2018).

Psychosocial interventions that promote adherence in people with SMD are particularly important when addressing physical health conditions. This can also take the form of generic advice and psychoeducation at the time of diagnosis of the SMD.

Adherence to medication guidelines − such as the American Schizophrenia Patient Outcomes Research Team (PORT) Treatment Recommendations (Kreyenbuhl *et al.*, 2010) − appear to have an effect on reducing mortality in schizophrenia. These, along with other specific recommendations for psychosocial treatments as described in these guidelines, are important considerations when developing intervention plans for people with SMD. The full participation of persons with SMD in their treatment and recovery plans is a very important factor in improving health outcomes (Vahdat *et al.*, 2014).

The next level in the framework encompasses strategies within ***health systems*** targeting health care providers and service delivery components. These will vary across different settings depending upon many parameters, such as the number of specialists versus primary care providers, the different distribution of health risk factors, the presence or absence of universal health care, and the availability of health technologies and medications. Strengthening of the six building blocks of the health systems – service delivery; health workforce; information; medical products, vaccines and technologies; financing; and leadership and governance (stewardship) – would improve outcomes for persons with SMD.

Care coordination, collaborative care or integrated care programmes that include support to better equip health systems, usually through the provision of additional supportive members who can serve as a liaison between mental health and physical health care systems or through linking of delivery of physical and mental health services are particularly important. Mental health practitioners need to be better at physical health skills, as well as physical health clinicians/ systems being better at addressing needs of people with SMD.

In countries with limited resources, evidence suggests that mental health care can be delivered effectively in primary health-care settings, through community-based programmes and task-shifting approaches. Non-specialist health professionals, lay workers, affected individuals, and caregivers with brief training and appropriate supervision by mental health specialists are able to detect, diagnose, treat, and monitor individuals with mental disorders and reduce caregiver burden. Physical health in people with SMD should also be considered in community-based programmes and task-shifting approaches (Kakuma *et al.*, 2011).

The broadest level of the framework incorporates ***socio-environmental factors*** and the social determinants of health. This part of the model acknowledges the range of potential strategies originating from the community to address contributors to premature mortality such as peer and family support programmes and stigma reduction programmes. At a wider level, public health policies providing mental health parity are essential to improve lives of those with SMD. A twin-track approach is likely to work best with improved public health for all, recognising that the broader social determinants like poverty affect certain groups more, and, targeted interventions for at-risk groups. Strategies at the policy level that affect screening or management of HIV, TB or tobacco consumption are especially relevant to those with SMD and may have even greater effects on the health and well-being of this high-risk population.

The recommendations contained in these guidelines should be adapted into a locally appropriate document that can meet the needs of each country and its health services. WHO headquarters will work closely with the regional and country offices, as well as implementing partners, to ensure communication and country-specific adaptations of the guidelines, through regional and national meetings.

As countries consider how to implement these guidelines, the budgetary and human resource requirements, and other health systems implications should be analysed to identify which inputs and systems are currently available, and which areas require additional investment, including training of health workers; supply of medicines; and adaptations of health information systems to collect data on service utilization.

To support country implementation, WHO will produce a series of subsidiary tools that will address clinical and service delivery aspects of the implementation of the recommendations included in these guidelines.

5. Publication, dissemination, and evaluation

5.1 PUBLICATION AND DISSEMINATION

The guidelines are disseminated as a print publication and electronically on a dedicated internet space on the WHO website (http://www.who.int/mental_health/evidence/guidelines_physical_health_and_severe_mental_disorders/en/index.html).

WHO publications, training and clinical management manuals will be revised to reflect the updated recommendations. A range of subsidiary products will be developed to support the implementation including job aids and policy briefs.

The guidelines and products are developed in English, and will be translated into other WHO official languages for wider dissemination and in collaboration with WHO Regional Offices.

Dissemination will be supported by publication of selected systematic reviews and evidence in peer review journals, and presentations and workshops at key conferences and events.

5.2 MONITORING AND EVALUATION

Implementation of the recommendations will be monitored at the health facility level. Facility data will be collected through surveys or routine health information systems. Special studies can be considered where routine monitoring is not feasible or appropriate.

WHO will continue to solicit and collect regular feedback through process indicators by Ministries of Health regarding implementation activities in order to evaluate the impact and usefulness of this guideline. This feedback will also identify areas where improvement is warranted.

5.3 IMPLICATIONS FOR FURTHER RESEARCH

While evidence for mental health treatments is strong, the evidence for effectiveness of interventions to prevent and treat physical conditions in those with SMD is limited. Interventions developed for the general population geared at non-communicable diseases, infectious diseases or other health problems are likely as effective for persons with SMD but given the special needs of this population, interventions for SMD require tailoring. However, more research is needed on the degree of tailoring required. For this, it is essential to include people with SMD in research studies to a much greater extent than is being currently done.

For current evidence-based interventions, research is needed on optimal length and dose needed to positively affect health, which will also be important for resource allocation. Multimodal approaches, which can include behavioural plus pharmacological interventions and include components such as peer support or technology are promising, but have yet to be studied systematically to clarify whether or which multicomponent programs are effective, and which components of the intervention are most beneficial. Many people with SMD have multiple cardiovascular and other risk behaviours which may be modifiable, and future research should test interventions addressing multiple risk factors, as well as those which are directly linked to mortality.

Cost-effectiveness models of different approaches in people with SMD are important, especially in low resource settings, as we aim to achieve universal health coverage and to address the physical health needs of this vulnerable population.

Research is needed to identify and manage barriers to and facilitators of implementing evidence-based guidance and policy recommendations. We need to understand how to deliver evidence-based interventions successfully in the real world, taking into account training and workforce issues and often-limited resources in local community settings. We need to understand to what extent interventions and programmes could or should be disseminated across countries.

Another important area of research will be to assess the effects of health system and policy interventions on excess mortality in SMD. We need to understand why those with SMD have not benefitted from trends in the general population towards reduced mortality in some diseases and smoking cessation. Researchers should take advantage of natural experiments and also design studies in health systems and at the population level to evaluate the impact of these programmes.

Finally, to gain a better understanding of the different perspectives involved, qualitative research is needed to understand the experiences of users, providers, family members, as well as professionals' receptivity to education and training.

5.4 FUTURE REVIEW AND UPDATE

These guidelines will be reviewed in three to five years, unless an earlier review and update is warranted by breakthrough research. New evidence in these areas is regularly monitored by the WHO Secretariat, in consultation with GDG members and technical experts identified for the evidence review process, WHO collaborating centres, and academic institutions.

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Annex 1. Guideline Development Group (GDG) members

	Name	Gender	WHO Region	Affiliation	Area of expertise
1.	**Abdullah Al Khathami**	M	**EMR**	Ministry of Health, Saudi Arabia	Family and community medicine, medical education, program management
2.	**Corrado Barbui**	M	**EUR**	University of Verona, Italy	Mental health research and training, public health, health systems strengthening
3.	**Jackie Curtis**	F	**WPR**	University of New South Wales, Australia	Psychiatry, early psychosis, comorbidity
4.	**Gail L. Daumit**	F	**AMR**	Johns Hopkins Medical Institutions, Division of General Internal Medicine, Welch Center for Prevention, Epidemiology and Clinical Research Baltimore, USA	Psychiatry, Epidemiology, Health Policy and Management and Mental Health
5.	**Chris Dowrick**	M	**EUR**	University of Liverpool, Institute of Psychology, Health and Society	Medically unexplained somatic complaints, mental health in primary care, guideline development (NICE) for depression
6.	**Benjamin Druss**	M	**AMR**	Center for Behavioural Health Policy Studies, Rollins School of Public Health, 1518 Clifton Rd, Atlanta, USA	Health policy, health outcomes and mental health
7.	**Rabih El Chammay**	M	**EMR**	Ministry of Health, Beirut, Lebanon	Public mental health, mental health policy, health equity
8.	**Suhaila Ghuloum**	F	**EMR**	Weill Cornell Medicine, Qatar Hamad Medical Corporation, Qatar	Mental health service planning, schizophrenia, psychiatric epidemiology
9.	**Oye Gureje**	M	**AFR**	Department of Psychiatry, University College Hospital, Ibadan, Nigeria	Global mental health; epidemiology; aging; health system strengthening; classification of mental disorders
10.	**Yueqin Huang**	F	**WPR**	National Clinical Research Center for Mental Disorders, Peking University Sixth Hospital, Peking University Institute of Mental Health, China	Psychiatry, child behavioural and developmental disorders, self-harm, suicide, depression
11.	**Asma Humayun**	F	**EMR**	Meditrina Health Care, Pakistan	Depression, psychosocial support and interventions for mental disorders

	Name	Gender	WHO Region	Affiliation	Area of expertise
12.	**Thomas Munk Laursen**	M	**EUR**	National Centre for Register-Based Research, Aarhus University, School of Business and Social Sciences, Institute of Economics and Business, Aarhus, Denmark	Research in schizophrenia and bipolar disorder
13.	**Mario Maj**	M	**EUR**	Department of Psychiatry, University of Naples, Italy	Research in bipolar disorder, psychiatric comorbidity, classification of mental disorders
14.	**Soontareeporn Meepring**	F	**WPR**	Department of Nursing, Faculty of Nursing, Naresuan University, Phitsanulok, Thailand	Physical health in people with SMD, technology in mental health
15.	**Shanthi Mendis**	F	**SEAR**	Independent consultant in Global Health, Sri Lanka	Noncommunicable diseases and cardiology, health policy development, capacity strengthening, implementation research particularly in low- and middle-income countries.
16.	**Dorairaj Prabhakaran**	M	**SEAR**	Centre for Chronic Conditions and Injuries and Vice President, Public Health Foundation of India, Haryana, India	Cardiovascular disease prevention, epidemiology, developmental origin, and biomarkers of cardiovascular diseases and diabetes
17.	**Martin Prince**	M	**EUR**	King's College London, Institute of Psychiatry, Psychology & Neuroscience, London, UK	Dementia, global mental health, guidelines development, dementia in LMIC
18.	**Thara Rangaswamy**	F	**SEAR**	Schizophrenia Research Foundation, Chennai, India	Mental health research, policy and advocacy
19.	**David Shiers**	M	**EUR**	Psychosis Research Unit, Greater Manchester Mental Health Trust, UK; Division of Psychology and Mental Health, University of Manchester, UK	Early intervention, physical health in people with SMD, health inequality
20.	**Ezra Susser**	M	**AMR**	Columbia University, 722 West 168th Street, New York, USA	Psychiatric epidemiology, research on course and outcome of schizophrenia, homelessness
21.	**Graham Thornicroft**	M	**EUR**	Health Service and Population Research Department, King's College London, Institute of Psychiatry, Psychology & Neuroscience, London, UK	Global mental health, guidelines development, mental health services research, mental health stigma, health equity.
22.	**Abe Fekadu Wassie**	M	**AFR**	Department of Psychiatry, College of Health Sciences, Addis Ababa University, Ethiopia	Psychopharmacological studies, service development, cultural aspects of depression, programme management

Annex 2. Assessment of conflict of interest

INDIVIDUALS INVOLVED IN ASSESSMENT OF CONFLICT OF INTEREST:

Shekhar Saxena, Director
Department of mental health and substance abuse
WHO headquarters

Tarun Dua, Programme manager
Department of mental health and substance abuse
WHO headquarters

Neerja Chowdhary, Technical officer
Department of mental health and substance abuse
WHO headquarters

To comply with WHO's Conflict of Interest Policy, the Secretariat followed the revised Guidelines for Declaration of Interests (WHO Experts)[1]. Declarations of interest (DoI) were requested from a) all GDG members b) all external partners involved in the evidence review process; c) all experts invited to review the evidence profiles.

A letter requesting completion of a DoI form and submission of a curriculum vitae was sent to all GDG members, the external review group and external partners. They were asked to agree to the publication of a summary of declarations in the guideline. The GDG members were also required to complete a confidentiality undertaking. Once received, the WHO Secretariat reviewed the DoIs as well as additional information (internet and bibliographic database search) and evaluated if there are any conflicts of interest and if so, whether these require a management plan.

In order to enhance its management of conflicts of interest as well as strengthen public trust and transparency in connection with WHO meetings and activities involving the provision of technical/normative advice, the names and brief biographies of members being considered for participation in the GDG were disclosed for public notice and comment prior to the meeting.

At the beginning of the GDG meeting, the DoI of each GDG member were presented and GDG members and external partners were asked to update their DoI with relevant changes by notifying the responsible technical officer.

[1] WHO Office of Compliance, Risk Management and Ethics (CRE) http://intranet.who.int/homes/cre/ethics/doiexperts/

The follow up and suggested actions agreed upon to manage the conflicts of interest declared are summarized below:

- If members declare interests that are relevant to the meeting, the WHO Secretariat will note any potential conflict of interest and summarize these and then decide whether and to what extent they can participate in the guideline development.
- If the conflict is deemed to be significant, the WHO Secretariat will decide if the conflict necessitates exclusion of that person from participating in the guideline process or if their participation should be limited.
- These decisions are made on a case-by-case basis.

Below is a summary of the declared conflicts of interest and how these were managed.

A. GDG MEMBERS

GDG Members with no relevant interests declared on the DOI form and no relevant interests found in the CV

1. **Abdullah Al-Khathami**
   Ministry of Health, Riyadh, Saudia Arabia.
2. **Corrado Barbui**
   University of Verona, Verona, Italy.
3. **Christopher Dowrick**
   University of Liverpool, Liverpool, United Kingdom.
4. **Benjamin Druss**
   Emory University, Atlanta, USA.
5. **Rahib El Chammay**
   National Mental Health Programme, Beirut, Lebanon.
6. **Suhaila Ghuloum**
   Weill Cornell Medicine, Doha, Qatar.
7. **Yueqin Huang**
   Peking University Institute of Mental Health, Beijing, China.
8. **Asma Humayun**
   Meditrina Healthcare, Islamabad, Pakistan.
9. **Mario Maj**
   University of Naples, Italy
10. **Soontareeporn Meepring**
    Naresuan University, Bangkok, Thailand.
11. **Shanthi Mendis**
    Colombo, Sri Lanka.
12. **Thomas Munk Laursen**
    Aarhus University, Aarhus, Denmark.
13. **Dorairaj Prabhakaran**
    Public Health Foundation of India, New Delhi, India.
14. **Thara Rangaswamy**
    Schizophrenia Research Foundation, Chennai, India
15. **Ezra Susser**
    Columbia University, New York, USA.

16. **Graham Thornicroft**
    King's College London, London, United Kingdom.
17. **Abe Fekadu Wassie**
    College of Health Sciences, Addis Ababa University, Ethiopia

GDG members who have declared an interest on the DOI form or where a potentially relevant interest has been noted from the CV

Jacqueline Curtis
University of New South Wales (UNSW), Sydney, Australia.

Dr Curtis received grants for research activities (three current grants amounting to a total of USD310,400 and three previous grants amounting to a total of USD16,600) from UNSW, New South Wales (NSW) government, commonwealth Bank of Australia and Prince of Wales Hospital, Sydney Foundation Patient Care Grant. She has been an expert advisor to the Orygen Youth Health (OYH) Research Centre, Melbourne for which she received USD440 remuneration in 2014. The OYH is part of the public mental health system in Melbourne, Australia, and sees young people aged 15 to 24, with a focus on early intervention and youth specific approaches. She also received honoraria for speaking at various scientific fora amounting to a total of USD5900 between 2014 and 2016 from the Adelaide Clinic, Tokyo Metropolitan Institute if Medical Science, Lundbeck, Townsville and Cairns Mental Health Services and OYH.

Action: *It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect Dr Curtis's judgement in the development of the present guidelines. No further action was necessary.*

Gail L. Daumit
Johns Hopkins University School of Medicine, Baltimore, USA.

Dr Gail Lois Daumit is a Professor at Johns Hopkins Medical Institutions, Maryland, USA. In her DOI, she noted that the Johns Hopkins University School of Medicine received four Federal grants for research projects in which she is the principal investigator, with total annual direct costs of USD 1.7 million.

Action: *It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect, Dr Daumit's judgement in the development of the present guidelines. No further action was necessary.*

Christopher Dowrick
University of Liverpool, Institute of Psychology, Health and Society

Dr Dowrick declared in his DOI form that as Chair of the Working Party for Mental Health of the World Organization of Family Doctors (WONCA) he has overseen the production and publication of a set of guidance documents and training materials for family doctors on the topic related to these guidelines.

Action: *It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect, Dr Dowrick's judgement in the development of the present guidelines. He is deemed to be participating in the guideline development process in an individual capacity and not representing any organization. No further action was necessary.*

Oye Gureje
Department of Psychiatry University College Hospital, Ibadan, Nigeria.

Professor Oye Gureje is Professor of Psychiatry and Director, WHO Collaborating Centre for Research and Training in Mental Health, Neuroscience, Drug and Alcohol Abuse, University of Ibadan, Nigeria. In his DOI, he noted that he received research support amounting to $2.5million from the National Institute of Mental Health for a current project to study collaborative shared care for people with SMD.

Action: *It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect, Professor Gureje's judgement in the development of the present guidelines. No further action was necessary.*

Martin Prince
King's College London, London, United Kingdom.

Professor Prince declared in his DOI form that he currently receives research support through a grant from the National Institute of Health Research (NIHR, UK) amounting to GBP 7 million over four years. Prof Prince is the PI and 20% of his salary costs are charged to the grant. The work focuses on health systems strengthening in sub Saharan Africa and one theme relates to the topic of these guidelines i.e. integrated primary healthcare for multimorbid conditions.

Action: *It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect, Professor Prince's judgement in the development of the present guidelines. No further action was necessary.*

David Shiers
Healthy Active Lives (HeAL), Manchester, United Kingdom.

Dr David Shiers has honorary appointment with the Greater Manchester Mental Health NHS Foundation Trust and University of Manchester. In his DOI, he noted that he received remuneration as consultant the National Health Service, Royal College of Psychiatrists, NICE and Health Services Executive, Ireland for activities related to the subject of the meeting or the work. He also noted that he has received, along with other partners, a total of GBP 3.2 million funding for 6 research projects from the National Institute of Health Research, UK.

Action: *It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect, Dr Shiers's judgement in the development of the present guidelines. No further action was necessary.*

B. EXTERNAL REVIEW GROUP

Members of the external review group with no relevant interests declared on the DOI form and no relevant interests found in the CV

1. **Atalay Alem**
   Department of Psychiatry, Faculty of Medicine, Addis Ababa University, Ethiopia
2. **Zipporah Ali**
   Kenya Hospices and Palliative Care Association, Kenya
3. **Lydia Chwastiak**
   University of Washington Medical Centre, USA
4. **Pim Cuijers**
   Vrije Universiteit Amsterdam, The Netherlands
5. **Alan Cohen**
   West London Mental Health Trust, UK
6. **Julian Eaton**
   CBM and the London School of Hygiene and Tropical Medicine, UK
7. **Alberto Minoletti**
   School of Public Health, Faculty of Medicine, University of Chile, Chile
8. **Rajat Ray**
   National Drug Dependence Treatment Centre, All India Institute of Medical Sciences, New Delhi, India
9. **Sarrafzadegan Nizal**
   Isfahan University of Medical Sciences in Iran and School of Population and Public Health in the University of British Columbia in Canada
10. **John Saunders**
    The University of Sydney, Australia;
11. **Najma Siddiqi**
    University of York, UK
12. **Isolde Sommers**
    Danube University Krems, Austria
13. **Héðinn Unnsteinsson**
    Prime Minister's Office, Iceland
14. **Pieter Ventevogel**
    UNHCR, Switzerland
15. **Lakshmi Vijaykumar**
    Voluntary Health Services, Chennai, India.

Members of the external review group who have declared an interest on the DOI form or where a potentially relevant interest has been noted from the CV

Ayesha Motala
University of KwaZulu-Natal, South Africa

Dr Motala declared that as a public servant working in a government institute, she seeks sponsorships to meetings from various organizations, especially when her scientific abstracts are accepted for presentations. The sponsorships are merely for attending the meetings, with no obligation to the sponsoring companies.

Details of such sponsorship for which she received a total amount of $26,000:

4-8 December 2017: International Diabetes Federation(IDF) Congress, Abu Dhabi: Sanofi Aventis sponsorship for travel and Accommodation; 11-15 September 2017: European Association for the Study of Diabetes(EASD) Congress, Lisbon: Pfizer sponsorship for Travel and accommodation; 8-13 June 2018: American Diabetes Association (ADA), San Diego: Boehringer Ingelheim sponsorship for Travel and accommodation: a member of her collaborating scientific team presented a paper.

Action: *It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect, Dr Motala's contribution as an external reviewer for these guidelines. No further action was necessary.*

Charlene Sunkel
Central Gauteng Mental Health Society, South Africa

Ms Sunkel is a service user group representative and declared that she has published in the World Psychiatry journal on premature mortality of people with SMD titled: "A service users perspective" https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5269497/

Action: *It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect, Ms Sunkel's contribution as an external reviewer for these guidelines. No further action was necessary.*

Inka Weissbecker
International Medical Corps, Washington DC, USA.

Dr Weissbecker works for International Medical Corps (IMC) which is a humanitarian non-profit organization and has an interest in the subject of mental health and distress related to humanitarian crises (as IMC has various global projects integrating mental health and psychosocial support). She has also worked as a consultant in the field of mental health in the past (more than 10 years ago) including for WHO.

Action: *It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect, Dr Weissbecker's contribution as an external reviewer for these guidelines. No further action was necessary.*

C. EXTERNAL PARTNERS

External partners with no relevant interests declared on the DOI form and no relevant interests found in the CV

Maya Semrau
King's College London, London and Global Health and Infection Department, Brighton and Sussex Medical School, Brighton, United Kingdom.

External partners who have declared an interest on the DOI form or where a potentially relevant interest has been noted from the CV

Kavitha Kolappa
Harvard Medical School, Boston, USA

Dr Kolappa is part of the systematic review team for the development of these guidelines. Dr Kolappa declared that she received research support amounting to approximately USD 56,000 (USD 51,000 as stipend and USD 5000 for travel costs and purchase of computer) from the National Institutes of Health, USA. The period of this grant was for one year and ended in October 2017. Her area of study was the proposed relationship between social relationships, metabolic disease, and post-traumatic stress disorder.

Action: *It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect, Dr Kolappa's contribution to the evidence review and synthesis process for the development of the present guidelines. As a member of the systematic review group she will be a technical resource and, therefore, will not participate in any of the closed sessions (voting or drafting final recommendations). No further action was necessary.*

Jayati Das-Munshi
King's College London, London, United Kingdom

Dr Das-Munshi is part of the systematic review team. In her DOI she noted that she is funded (amount GBP578198) by a Clinical Scientist Fellowship by a UK health charity, Health Foundation, in partnership with the Academy of Medical Sciences. She stated that the funder does not have any business or commercial interest in the work related to these guidelines and her research is independent of the funder's views.

Action: *It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect, Dr Das-Munshi's contribution to the evidence review and synthesis process for the development of the present guidelines. As a member of the systematic review group she will be a technical resource and, therefore, will not participate in any of the closed sessions (voting or drafting final recommendations). No further action was necessary.*

Annex 3. Scoping questions

BACKGROUND QUESTIONS

1. Association of physical health conditions with SMD

What is the comorbidity between physical health conditions (NCDs and infectious diseases) and SMD?

What is the impact of physical health conditions on the morbidity and mortality of people with SMD?

PICO (POPULATION, INTERVENTION, COMPARISON, OUTCOME) QUESTIONS

2. Tobacco cessation

For people with SMD who use tobacco, are pharmacological (including nicotine replacement therapy, bupropion, varenicline) and/or non-pharmacological interventions effective to support tobacco cessation?

P: people with SMD who use tobacco

I: pharmacological interventions and/or non-pharmacological interventions:

- pharmacological interventions: including nicotine replacement therapy, bupropion, varenicline
- non-pharmacological interventions

C: care as usual and/or placebo

O:

- Critical
  - Tobacco cessation/abstinence rates
  - Tobacco consumption rates
  - Respiratory disease outcomes (COPD, asthma)
- Important
  - Frequency of adverse events/side-effects (including drug interactions)

3. Weight management

3.1 For people with SMD who are overweight or obese, are non-pharmacological and/or pharmacological interventions and/or pharmacological management strategies effective to support weight reduction?

P: people with SMD who are overweight or obese

I: non-pharmacological and/or pharmacological interventions and/or pharmacological management strategies:

- Non-pharmacological interventions: e.g. cognitive-behavioural intervention strategies, lifestyle interventions (e.g. diet, exercise, physical activity / decreased sedentary behaviour, health education), family involvement in interventions
- Pharmacological interventions: weight-loss medication (e.g. orlistat)
- Pharmacological management strategies: e.g. switching antipsychotic medication

C: care as usual and/or placebo

O:

- Critical
  - Change in weight
  - Mean BMI (kg/m2) or change in BMI
- Important
  - Reduced sedentary behaviour
  - Maintenance of weight change/ Attenuation/prevention of weight gain
  - Frequency of adverse events/side-effects

3.2 For people with SMD who are at risk of becoming overweight or obese, are non-pharmacological interventions effective to support prevention of weight gain?

P: people with SMD who are at risk of becoming overweight or obese, e.g. people who have just started anti-psychotic medication

I: non-pharmacological interventions, e.g. cognitive-behavioural intervention strategies, lifestyle interventions (e.g. diet, exercise, physical activity / decreased sedentary behaviour, health education), family involvement in interventions

C: care as usual

O:

- Critical
  - Change in weight
  - Mean BMI (kg/m2) or change in BMI
  - Maintenance of weight change
  - Attenuation/prevention of weight gain
- Important
  - Reduced sedentary behaviour
  - Frequency of adverse events/side-effects

4. Substance use disorders; drugs and/or alcohol

For people with SMD and substance (drug and/or alcohol) use disorder, are pharmacological and/or non-pharmacological interventions for substance use disorder effective to support reduction in substance use-related outcomes?

P: people with SMD and substance (drug and/or alcohol) use disorder

I: pharmacological and/or non-pharmacological interventions for substance use disorders:

- Pharmacological interventions
- Non-pharmacological interventions: e.g. motivational interviewing and/or CBT, psychoeducation, brief assessment interview, dual-focus interventions

C: care as usual / placebo or one treatment vs another

O:

- Critical
  - Level of consumption
  - Frequency of use
  - Abstinence
  - Relapse rates
- Important
  - Frequency of adverse events / side-effects

5. Cardiovascular disease / risk factors

5.1 For people with SMD and pre-existing cardiovascular disease, what pharmacological and/or non-pharmacological interventions are effective to support reduction of cardiovascular disease outcomes

P: people with SMD and pre-existing cardiovascular disease: e.g. coronary heart disease, prior heart failure or stroke, cardiomyopathy, congenital heart disease, peripheral vascular disease

I: pharmacological and/or non-pharmacological interventions:

- pharmacological interventions
- non-pharmacological interventions

C: one treatment versus another or care as usual/placebo

O:

- Critical
  - Major adverse cardiovascular event (MACE) - includes cardiovascular death, myocardial infarction, stroke, heart failure, hospitalization, amputation
- Important
  - Frequency of adverse events/side-effects

5.2 For people with SMD and cardiovascular risk factors (a. high blood pressure; b. high lipid levels), what pharmacological and/or non-pharmacological interventions are effective to support reduction of cardiovascular risk factors?

P: people with SMD and cardiovascular risk factors: a) high blood pressure (BP>140/90 mmHg; b) high lipid levels (e.g. cholesterol>200mg/dl or 5.2 mmol/l)

I: pharmacological and/or non-pharmacological interventions:

- pharmacological interventions: a) medication to control high blood pressure; b) medications for high lipid levels
- non-pharmacological interventions

C: one treatment versus another or care as usual/placebo

O:

- Critical
  - Adequacy of control of CVD risk factors (a. blood pressure <130/80mmHg; b. cholesterol <200mg/dl)
  - Cardiovascular disease incidence - MI, stroke, chronic cardiovascular disease
- Important
  - Frequency of adverse events/side-effects

6. Diabetes mellitus

For people with SMD and diabetes mellitus, what pharmacological and/or non-pharmacological interventions are effective to improve glycaemic control?

P: people with SMD and diabetes mellitus

I: pharmacological interventions and/or non-pharmacological interventions:

- pharmacological interventions: e.g. medication to treat diabetes
- non-pharmacological interventions: e.g. e.g. behavioural lifestyle interventions, cognitive behaviour therapy

C: one treatment versus another or care as usual

O:

- Critical
  - Fasting blood glucose <120mg/dl; post-prandial blood glucose<160mg/dl,
  - Glycosylated haemoglobin A1c (HbA1c<7 for people below 60 years and 7-8 for people above 60 years with other risk factors)
  - Diabetes complications – MACE, chronic kidney disease, diabetic retinopathy, diabetic neuropathy, hospitalization for infection
- Important
  - Frequency of adverse events / side-effects

7. HIV/AIDS

For people with SMD and HIV/AIDS, what pharmacological (i.e. ARV drugs, psychopharmacology) and nonpharmacological interventions are effective to support reduction in HIV-related outcomes?

P: people with SMD and HIV/AIDS

I:

- pharmacological interventions (ARV drugs, psychopharmacology)
- Nonpharmacological interventions

C: one treatment versus another or care as usual

O:

- Critical
  - HIV-related outcomes
- Important
  - Frequency of adverse events / side-effects

8. Other infectious diseases (Tuberculosis, Hepatitis B/C)

For people with SMD and infectious diseases (Tuberculosis, Hepatitis B/C), what pharmacological and nonpharmacological (social, psychological) interventions are effective for treatment of infectious diseases (i.e. tuberculosis, hepatitis B, hepatitis C)?

P: people with SMD and infectious diseases (Tuberculosis, Hepatitis B/C)

I:

- pharmacological interventions for infectious diseases
- Nonpharmacological (social, psychological) interventions for infectious diseases

C: one treatment versus another or care as usual

O:

- Critical
  - Infectious disease-related outcomes
- Important
  - Frequency of adverse events / side-effects

Annex 4. Background question: Association of physical health conditions with severe mental disorders

A. WHAT IS THE COMORBIDITY BETWEEN PHYSICAL HEALTH CONDITIONS (NCDS AND INFECTIOUS DISEASES) AND SMD?

A growing body of evidence has demonstrated the bi-directional relationships between SMD, including moderate to severe depression, bipolar disorder, as well as schizophrenia and other psychotic disorders, and physical health conditions including both non-communicable and infectious diseases.

SMD and non-communicable diseases (NCDs):

SMD and the major NCDs, including cardiovascular diseases, diabetes, respiratory illnesses, and cancers, are related in complex ways. From an epidemiological standpoint, mental disorder itself is a well-known risk factor for NCDs; its presence increases the chance that an individual will also suffer from one or more chronic illnesses. Overall, people with SMD have 1.53 times greater risk of cardiovascular disease and 1.85 times greater risk of death due to cardiovascular disease (Correll *et al.*, 2017). People with SMD, particularly those who have had multiple episodes of illness, also have higher rates of diabetes mellitus, with 1.85 times greater risk than the general population (Vancampfort *et al.*, 2016).

The reasons for the high co-morbidity between SMDs and NCDs have been extensively studied. People with SMD are more likely to engage in lifestyle behaviours that contribute to or exacerbate NCDs; that is, poor mental health is associated with the major modifiable risk factors for NCDs including tobacco use, harmful use of alcohol, unhealthy diets, and physical inactivity, which is elaborated further below. Additionally, pathophysiologically, persistent and SMD can affect and in turn, can be affected by stress-related NCDs (Watson *et al.*, 2017),(Kapczinski *et al.*, 2008; Nugent *et al.*, 2015). Furthermore, the iatrogenic effects of medicines used to treat SMDs are linked with increased risk of cardiometabolic diseases. Lastly, individuals with mental disorders are less likely to seek and receive screening and adequate treatment for NCDs, and symptoms may affect adherence to treatment as well as prognosis.

Tobacco consumption (Lasser *et al.*, 2000) is common amongst people with SMD and has been identified as a leading preventable cause of premature mortality in this population. Persons with schizophrenia and bipolar disorder are 5 times and 3 ½ times more likely to smoke currently than the general population, respectively (de Leon and Diaz, 2005),(Jackson *et al.*, 2015). ***Alcohol use disorders*** are also common amongst people with SMD, with one study using the national Danish registry finding the comorbidity of alcohol use disorder with schizo-phrenia, bipolar disorder, and depression to be approxi-mately 35%, 33%, and 23%, respectively. The comorbidity rates of ***all substance use disorders*** combined were even higher, with 48%, 40%, and 29% for schizophrenia, bipolar disorder, and de-pression, respectively (Jørgensen, Nordentoft and Hjorthøj, 2018).

Additionally, people with SMD are more likely to consume ***unhealthy diets*** and be ***physically inactive*** (Dipasquale *et al.*, 2013) (Jakobsen *et al.*, 2018) (Vancampfort *et al.*, 2017), which can lead to overweight, obesity, diabetes, and cardiovascular diseases. Overall, the risk of being ***overweight or obese*** as defined by a body mass index (BMI) of 25 or greater has been shown to be increased 3.4 fold for people with schizophrenia and 3.9 fold for people with bipolar disorder when compared with people without diagnoses of SMD (Gurpegui *et al.*, 2012). When considering obesity alone, as defined by a BMI of 30 or greater, the risk associated with schizophrenia and bipolar disorder jumps to 4.3 fold 4.6 fold, respectively (Gurpegui *et al.*, 2012).

Compounding the risks outlined above, the iatrogenic effects of psychotropic medications frequently used to treat the symptoms of SMD including antipsychotic medication (and to some extent, antidepressants and mood stabilizers) are linked with an increased risk of developing physical health conditions and associated complications (Correll *et al.*, 2015) (De Hert *et al.*, 2011) (Correll *et al.*, 2017). The use of antipsychotic medications has been associated with obesity, insulin resistance, diabetes, myocardial infarctions, atrial fibrillation, stroke, and death (Lieberman *et al.*, 2005) (Henderson *et al.*, 2005) (Chou *et al.*, 2017) (Sacchetti, Turrina and Valsecchi, 2010) (Yang *et al.*, 2018).

SMD and infectious diseases:

People with SMD are at greater risk than the general population for exposure to infectious diseases, including HIV, tuberculosis (TB) and chronic hepatitis. In the US, for example, persons with SMD were found to have a 10-fold higher prevalence of HIV (Hughes *et al.*, 2016). In a population-wide study in Sweden, persons with SMD when compared with the general population were found to have approximately 2.6 times greater risk of HIV infection, as well as 2.3 and 6.1 times greater risk of hepatitis B and C infections, respectively (Bauer-Staeb *et al.*, 2017). Further, one country-wide study in Taiwan revealed that persons with schizophrenia have a 1.5 times greater risk for tuberculosis infections than that of the rest of the population (Kuo *et al.*, 2013).

As is seen with NCDs, there is a bi-directionality of the association between SMD and infectious diseases. HIV virus and opportunistic infections associated with AIDS can cause neurological damage, while mental disorders can also arise as a side effect of antiretroviral treatment or from the stigma, stress and socio-economic predicaments associated with the infection and treatment process. There are widespread discriminatory attitudes and behaviours towards people with HIV, TB and Hepatitis B/C in the community where they reside, particularly in developing countries. The psychological distress associated with stigma and discrimination may also trigger or aggravate the symptoms of SMD in affected individuals.

B. WHAT IS THE IMPACT OF PHYSICAL HEALTH CONDITIONS ON THE MORBIDITY AND MORTALITY OF PEOPLE WITH SMD?

The mortality gap for people with SMD:

People with SMD, including moderate to severe depression, bipolar disorder, as well as schizophrenia and other psychotic disorders, have a 2-3 times higher average mortality compared to the general population, which translates to a 10-20 year reduction in life expectancy (Liu *et al.*, 2017). Patients with bipolar disorder and schizophrenia have been shown to have higher rates of mortality in both high and low-income settings (Tsuang, Woolson and Fleming, 1980) (Capasso *et al.*, 2008) (Laursen, 2011) (Nielsen *et al.*, 2013) (Fekadu *et al.*, 2015) (Krupchanka *et al.*, 2018). One prospective cohort-study in Ethiopia, for example, found the overall standardized mortality ratio (SMR) of patients with SMD (schizophrenia, bipolar disorder, or severe depression) to be twice that of the general population, with schizophrenia associated with the highest risk (SMR three times that of the general population) (Fekadu *et al.*, 2015). Moreover, for schizophrenia in particular, the mortality gap appears to be widening over time (Saha, Chant and McGrath, 2007). While people with SMD do have higher rates of death due to unnatural causes (accidents, homicide, or suicide) than the general population, the majority of deaths amongst people with SMD are attributable to comorbid physical health conditions, both non-communicable and communicable (Liu *et al.*, 2017). Mortality in people with SMD is far higher in individuals with substance use disorders than in those without. It has been shown that alcohol use disorders as a comorbid condition to SMD doubled risk of all-cause mortality (Hjorthøj *et al.*, 2015).

The reasons for the mortality gap in people with SMD:

Numerous potential causes have been proposed for the increased mortality of patients with SMD including the well-known bidirectional relationship between mental disorders and other NCDs as elaborated above; differential exposure to risk factors driving the development of NCDs; iatrogenic effects of medications for SMD; increased risk for infectious diseases; comorbid substance use disorders; and inequitable access to health care services.

Equitable access to comprehensive health services remains out of reach for the majority of people with SMD. Unfortunately, people with SMD often lack access to health services or receive poor quality care, spanning from promotion and prevention, screening, and treatment (De Hert *et al.*, 2011). Despite the elevated risks facing persons with SMD, screening for infectious illnesses such as HIV is poor (Mangurian *et al.*, 2017) (Senn and Carey, 2009). Screening for metabolic risk factors for persons with SMD, as well as those receiving antipsychotic medications also remains abysmal in low and high-income settings (Saloojee, Burns and Motala, 2014) (Morrato *et al.*, 2009) (Barnes *et al.*, 2007). Further, persons with SMD may not receive the life-saving care that they need. A large retrospective cohort analysis in the US found that when compared with people without mental disorder, people with schizophrenia were not even half as likely to receive cardiac catheterization after a heart attack (Druss *et al.*, 2000). It is crucial to address the disparities in health care access and provision for people with SMD. Recognizing the frequent comorbidity between mental and physical health conditions, specific recommendations addressing the physical conditions causing the increased morbidity and mortality of people with SMD are needed. In some instances, treatment recommendations for the general population may need to be adapted for people with SMD. Non-pharmacological interventions might warrant tailoring to account for cognitive, motivational, and social needs of people with SMD, and the benefits and risks of pharmacological interventions will need to be balanced against the potential side effects and drug-drug interactions between proposed interventions and psychotropic medications commonly used for SMD.

Annex 4. References

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Annex 5. Evidence review methodology

Comprehensive searches of major bibliographic databases were conducted in order to identify one or more systematic reviews that matched each of the outcomes for each of the PICO questions. The aim was to identify systematic reviews that were timely, of high quality and relevant to each of the PICO questions.

THE FOLLOWING PROCESS WAS EMPLOYED FOR THE SEARCHES:

1. Searched for systematic reviews (including meta-analyses) that were published in the last five years for each of the PICO questions. Guidelines from the last five years were also included, if these closely matched the population to whom the PICO question applies; any guidelines used needed to adhere to the WHO rules for guidelines. The searches were run in February 2018.

2. If no relevant high-quality systematic reviews were identified from the last five years for any of the PICO questions, the search was expanded to include systematic reviews from the last ten years for that PICO question. This was the case for the two PICO questions on HIV/AIDS and other infectious diseases; these searches were re-run in March 2018.

3. Where relevant, any guidelines that did not closely match the population to whom the PICO question applied (e.g. guidelines that apply to the general population) were used as indirect evidence.

4. For the PICO question on substance use disorder, based on the GDG's feedback during the GDG meeting in May 2018, the searches were expanded to include further search terms and were re-run in June 2018 (searching for systematic reviews from the last five years).

The following bibliographic databases were searched:

- Cochrane Library (including DARE) (title, abstract, keywords + mesh terms)
- PubMed/Medline (all fields)
- EMBASE (Ovid)
- PSYCINFO (anywhere)
- Epistemonikos (title/abstract)
- Global Health Library (title/abstract/subject)
- For those PICO questions where the search was expanded (see step 2 above), the National Guideline Clearing House was also searched.

After the searches were run using the search strategies listed on the pages below, titles and abstracts of all results were screened in Endnote; subsequently the full texts of those papers were reviewed that could not be excluded based on the title/abstract review.

GRADE EVIDENCE TABLES

All systematic reviews / meta-analyses that were identified as matching one of the PICO questions based on the search strategy described above were then assessed using the AMSTAR methodology[2], which evaluates the quality of systematic reviews using eleven criteria.

For each outcome of each PICOquestion, one or more systematic reviews were then selected to be used within the GRADE evidence tables for the PICO questions' evidence profiles. The following criteria were used when selecting which systematic review to use within the GRADE evidence tables:

- Published in the last five years, ideally three years (timeliness)
- High quality (i.e. at least six, but ideally more, of the eleven criteria of the AMSTAR scored positively)
- Closely relevant to the PICO
- Systematic reviews that dealt with SMD generally (rather than specific mental disorders) given preference
- Comprehensive systematic reviews given preference, where possible
- Cochrane reviews or other meta-analyses given preference, where possible/appropriate

The GRADE methodology involves rating the quality of the studies included in the systematic review according to study design, risk of bias, inconsistency, indirectness, imprecision, and publication bias. Together with the effect sizes of studies, an overall 'certainty of evidence' is provided of either very low, low, moderate or high.

GRADE evidence tables were completed using the GRADEpro online tool[3]; the same criteria were used as for the mhGAP Intervention Guide when completing the GRADE evidence tables in terms of the assessment of the quality of studies (for risk of bias, inconsistency, indirectness, imprecision, and publication bias)[4].

[2] Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Medical Research Methodology.* 2007; 7:10

[3] https://gradepro.org/

[4] See http://www.who.int/mental_health/mhgap/evidence/mhgap_guideline_process_2009.pdf

SEARCH STRATEGIES

Separate searches were performed for each of the seven PICO questions. Where PICO questions included both pharmacological and non-pharmacological interventions, searches were run separately for these.

The three search sets outlined below for each of the PICO questions were separated by an 'AND' when running the searches.

Filters were used in the bibliographic databases where possible to restrict the searches to systematic reviews and meta-analyses, as well as to humans. No further restrictions were employed, for example in terms of language (apart from the publication date, as mentioned above).

The 'Advanced Search' option was selected in bibliographic databases, where possible.

PICO QUESTION 2

For people with SMD who are use tobacco, are pharmacological (including nicotine replacement therapy, bupropion, varenicline) interventions effective to support tobacco cessation?

Search #1: SMD

(exp Mental Disorders/ OR exp Psychotic Disorders/ OR exp Bipolar and Related Disorders/ OR exp Depressive Disorder) OR

((Mental AND (disorder* OR disabilit* OR illness OR "health condition" OR "health problem" OR distress)) OR "psychological distress" OR "psychiatric disorder") OR

((schizophrenia OR schizophrenic) OR Schizotyp* OR ((Delusional OR paranoid) AND disorder*) OR hallucination* OR Psychotic OR Schizoaffective OR psychosis) OR

(((manic OR bipolar OR mood) AND disorder*) OR (depressive AND (disorder* OR episode*)) OR "depressive symptom*" OR hypomania OR mania* OR ((major OR psychotic OR disorder*) AND depression))

Search #2: smoking

(exp Smoking/ OR exp Smokers/ OR exp Tobacco Smoking/ OR exp Tobacco Use/ OR exp Tobacco/ OR exp Nicotine/) OR

(smok* OR tobacco OR nicotin* OR cigarette*)

Search #2: smoking

(exp Smoking/ OR exp Smokers/ OR exp Tobacco Smoking/ OR exp Tobacco Use/ OR exp Tobacco/ OR exp Nicotine/) OR

(smok* OR tobacco OR nicotin* OR cigarette*)

Search #3: pharmacological tobacco cessation interventions

(exp Smoking Cessation/ OR exp Smoking Reduction/ OR exp Tobacco Use Cessation/ OR exp Tobacco Use Cessation Products/ OR exp Bupropion/ OR exp Varenicline/ OR exp Nicotine Chewing Gum) OR

(exp Drug Therapy/ OR exp Pharmacology/ OR exp Psychopharmacology/ OR exp Metabolic Side Effects of Drugs and Substances/ OR exp Pharmacologic Actions/ OR exp Drug Effects/ OR exp Psychotropic Drugs/) OR

((drug* OR pharmac* OR medic* OR psychotrop*) AND (intervent* OR therap* OR treat* OR care OR servic*)) OR (drug* OR medic*) OR

((smok* OR tobacco OR nicotin* OR cigarette*) AND (cessation OR reduc* OR abst*)) OR

(bupropion OR varenicline OR "nicotine replacement therapy" OR "nicotine gum" OR "nicotine patch")

For people with SMD who are use tobacco, are non-pharmacological interventions effective to support tobacco cessation?

Search #1: SMD

(exp Mental Disorders/ OR exp Psychotic Disorders/ OR exp Bipolar and Related Disorders/ OR exp Depressive Disorder) OR

((Mental AND (disorder* OR disabilit* OR illness OR “health condition” OR “health problem” OR distress)) OR "psychological distress" OR "psychiatric disorder") OR

((schizophrenia OR schizophrenic) OR Schizotyp* OR ((Delusional OR paranoid) AND disorder*) OR hallucination* OR Psychotic OR Schizoaffective OR psychosis) OR

(((manic OR bipolar OR mood) AND disorder*) OR (depressive AND (disorder* OR episode*)) OR "depressive symptom*" OR hypomania OR mania* OR ((major OR psychotic OR disorder*) AND depression))

Search #2: smoking

(exp Smoking/ OR exp Smokers/ OR exp Tobacco Smoking/ OR exp Tobacco Use/ OR exp Tobacco/ OR exp Nicotine) OR

(smok* OR tobacco OR nicotin* OR cigarette*)

Search #3: non-pharmacological tobacco cessation interventions

(exp Smoking Cessation/ OR exp Smoking Reduction/ OR exp Tobacco Use Cessation/OR exp Tobacco Use Cessation Products/) OR

(exp Exercise Therapy/ OR exp Therapy/ OR exp Therapeutics/ OR exp Family Therapy/ OR exp Psychotherapy/ OR exp Cognitive Therapy/ OR exp Behaviour Therapy/ OR exp Counseling/ OR exp Mental Health Services/ OR exp Problem Based Learning/ OR exp Problem Solving/) OR

((psychosocial OR psycho* OR lifestyle* OR cognit* OR behaviour* OR behaviour* OR non-pharmac*) AND (intervent* OR therap* OR treat* OR care OR servic*)) OR

(“problem solving” OR psychoeducation OR couns*) OR

((smok* OR tobacco OR nicotin* OR cigarette*) AND (cessation OR reduc* OR abst*))

PICO QUESTIONS 3.1 & 3.2

For people with SMD who are overweight or obese, are pharmacological interventions effective to support weight reduction?

Search #1: SMD

(exp Mental Disorders/ OR exp Psychotic Disorders/ OR exp Bipolar and Related Disorders/ OR exp Depressive Disorder) OR

((Mental AND (disorder* OR disabilit* OR illness OR “health condition” OR “health problem” OR distress)) OR "psychological distress" OR "psychiatric disorder") OR

((schizophrenia OR schizophrenic) OR Schizotyp* OR ((Delusional OR paranoid) AND disorder*) OR hallucination* OR Psychotic OR Schizoaffective OR psychosis) OR

(((manic OR bipolar OR mood) AND disorder*) OR (depressive AND (disorder* OR episode*)) OR "depressive symptom*" OR hypomania OR mania* OR ((major OR psychotic OR disorder*) AND depression))

Search #2: overweight

(exp Overweight/ OR exp Obesity/) OR

(“overweight” OR obes* OR “weight-related side-effects” OR “weight gain”)

Search #3: pharmacological interventions for weight reduction

(exp Obesity Management/ OR exp Anti-Obesity Agents/ OR exp Body Weight Changes/ OR exp Body Weight Maintenance/ OR exp Weight Reduction Programs/) OR

(exp Drug Therapy/ OR exp Pharmacology/ OR exp Psychopharmacology/ OR exp Metabolic Side Effects of Drugs and Substances/ OR exp Pharmacologic Actions/ OR exp Drug Effects/ OR exp Psychotropic Drugs/) OR

((drug* OR pharmac* OR medic* OR psychotrop*) AND (intervent* OR therap* OR treat* OR care OR servic)) OR (drug* OR medic*) OR

((weight OR BMI OR “body mass*” OR fat* OR waist*) AND (loss OR reduc* OR maint*)) OR (“weight gain” AND (prevent* OR manag*)) OR

(orlistat OR “appetite suppressant*”)

For people with SMD who are overweight or obese, are pharmacological management strategies effective to support weight reduction?

Search #1: SMD

(exp Mental Disorders/ OR exp Psychotic Disorders/ OR exp Bipolar and Related Disorders/ OR exp Depressive Disorder) OR

((Mental AND (disorder* OR disabilit* OR illness OR "health condition" OR "health problem" OR distress)) OR "psychological distress" OR "psychiatric disorder") OR

((schizophrenia OR schizophrenic) OR Schizotyp* OR ((Delusional OR paranoid) AND disorder*) OR hallucination* OR Psychotic OR Schizoaffective OR psychosis) OR

(((manic OR bipolar OR mood) AND disorder*) OR (depressive AND (disorder* OR episode*)) OR "depressive symptom*" OR hypomania OR mania* OR ((major OR psychotic OR disorder*) AND depression))

Search #2: overweight

(exp Overweight/ OR exp Obesity/) OR

("overweight" OR obes* OR "weight-related side-effects" OR "weight gain")

Search #3: pharmacological interventions for weight reduction

(exp Obesity Management/ OR exp Anti-Obesity Agents/ OR exp Body Weight Changes/ OR exp Body Weight Maintenance/ OR exp Weight Reduction Programs/) OR

(exp Drug Therapy/ OR exp Pharmacology/ OR exp Psychopharmacology/ OR exp Metabolic Side Effects of Drugs and Substances/ OR exp Pharmacologic Actions/ OR exp Drug Effects/ OR exp Psychotropic Drugs/) OR

((drug* OR pharmac* OR medic* OR psychotrop*) AND (intervent* OR therap* OR treat* OR care OR servic)) OR (drug* OR medic*) OR

((weight OR BMI OR "body mass*" OR fat* OR waist*) AND (loss OR reduc* OR maint*)) OR ("weight gain" AND (prevent* OR manag*)) OR

(switch* AND (medic* OR drug*))

For people with SMD who are overweight or obese, are non-pharmacological interventions effective to support weight reduction?

For people with SMD who are at risk of becoming overweight or obese, are non-pharmacological interventions effective to support prevention of weight gain?

Search #1: SMD

(exp Mental Disorders/ OR exp Psychotic Disorders/ OR exp Bipolar and Related Disorders/ OR exp Depressive Disorder) OR

((Mental AND (disorder* OR disabilit* OR illness OR "health condition" OR "health problem" OR distress)) OR "psychological distress" OR "psychiatric disorder") OR

((schizophrenia OR schizophrenic) OR Schizotyp* OR ((Delusional OR paranoid) AND disorder*) OR hallucination* OR Psychotic OR Schizoaffective OR psychosis) OR

(((manic OR bipolar OR mood) AND disorder*) OR (depressive AND (disorder* OR episode*)) OR "depressive symptom*" OR hypomania OR mania* OR ((major OR psychotic OR disorder*) AND depression))

Search #2: overweight

(exp Overweight/ OR exp Obesity/) OR

("overweight" OR obes* OR "weight-related side-effects" OR "weight gain")

Search #3: non-pharmacological intervention for weight reduction and prevention

(exp Obesity Management/ OR exp Nutrition Therapy/ OR exp Body Weight Changes/ OR exp Body Weight Maintenance/ OR exp Weight Reduction Programs/ OR exp Health Promotion/ OR exp Diet/ OR exp Risk Reduction Behaviour/ OR Risk Management/ OR exp Health Risk Behaviours/ OR exp Risk Factors/ OR exp Risk-Taking/) OR

(exp Exercise Therapy/OR exp Therapy/ OR exp Therapeutics/ OR exp Family Therapy/ OR exp Psychotherapy/ OR exp Cognitive Therapy/ OR exp Behaviour Therapy/ OR exp Counseling/ OR exp Mental Health Services/ OR exp Problem Based Learning/ OR exp Problem Solving/) OR

(exp Preventive Health Services/) OR

((psychosocial OR psycho* OR lifestyle* OR cognit* OR behaviour* OR behaviour* OR non-pharmac*) AND (intervent* OR therap* OR treat* OR care OR servic*)) OR

(problem solving OR psychoeducation OR couns*) OR

((weight OR BMI OR body mass* OR fat* OR waist*) AND (loss OR reduc* OR maint*)) OR (weight gain AND (prevent* OR manag*)) OR

(diet* OR nutrition* OR exercis* OR sport* OR physical activit* OR health promot* OR self-monit* OR calor* OR healthy eating OR food intake)

PICO QUESTIONS 4

For people with SMD and substance (drug and/or alcohol) use disorder, are pharmacological interventions for substance use disorder effective to support reduction in substance use-related outcomes?

Search #1: SMD

(exp Mental Disorders/ OR exp Psychotic Disorders/ OR exp Bipolar and Related Disorders/ OR exp Depressive Disorder) OR

((Mental AND (disorder* OR disabilit* OR illness OR "health condition" OR "health problem" OR distress)) OR "psychological distress" OR "psychiatric disorder") OR

((schizophrenia OR schizophrenic) OR Schizotyp* OR ((Delusional OR paranoid) AND disorder*) OR hallucination* OR Psychotic OR Schizoaffective OR psychosis) OR

(((manic OR bipolar OR mood) AND disorder*) OR (depressive AND (disorder* OR episode*)) OR "depressive symptom*" OR hypomania OR mania* OR ((major OR psychotic OR disorder*) AND depression))

Search #2: Substance use disorder

(exp Narcotics/ OR exp Substance-Related Disorders/ OR exp Alcoholism/ OR exp Alcoholics/ OR exp Alcohol Related-Disorders/ OR exp Drug Users/ OR exp Drug Misuse/ OR exp Street Drugs/ OR exp Nonprescription Drugs/ OR exp Drug-Seeking Behaviour/ OR exp substance abuse, intravenous/) OR

("drug abuse" OR "drug addict*" OR "drug depend*" OR "drug withdrawal" OR "drug misuse") OR

("addictive disease*" OR "addictive disorder*" OR addiction OR addictive OR "substance abuse" OR "substance misuse" OR "withdrawal syndrome" OR psychoactive*) OR

("alcoholic patient*" OR "alcoholic subject*" OR alcoholism OR "alcohol depend*" OR "fetal alcohol*" OR "prenatal alcohol*" OR "chronic ethanol*" OR "chronic* alcohol*" OR "alcohol withdrawal" OR "ethanol withdrawal" OR "excessive alcohol consumption" OR "alcohol use disorder" OR "alcohol misuse" OR "alcohol abuse") OR

((cocaine OR heroin OR cannabis OR marijuana OR mdma OR methylenedioxymethamphetamin* OR ecstasy OR morphine* OR amphetamin* OR methamphetamin* OR opioid* OR opiat* OR "prescription drug*" OR "illegal drug*" OR "illicit drug*" OR "street drug" OR benzodiazepin* OR tranquiliz* OR narcot* OR methadone OR fentanyl) AND (abuse OR misuse OR depend* OR addict* OR withdrawal OR overdose OR intoxication OR "harmful use")) OR

("injecting drug use" OR IDU$1 OR IVDU$1 OR PWID$1 OR "injecting drug" OR "intravenous drug" OR "injecting substance" OR "intravenous substance")

Search #3: pharmacological interventions for substance use disorders

(exp Substance Abuse Treatment Centers/ OR exp Alcohol Abstinence/) OR

(exp Drug Therapy/ OR exp Pharmacology/ OR exp Psychopharmacology/ OR exp Metabolic Side Effects of Drugs and Substances/ OR exp Pharmacologic Actions/ OR exp Drug Effects/ OR exp Psychotropic Drugs/) OR

(exp buprenorphine/ OR exp methadone/ OR exp opiate substitution treatment/ OR exp buprenorphine, naloxone drug combination/) OR

((drug* OR pharmac* OR medic* OR psychotrop*) AND (intervent* OR therap* OR treat* OR care OR servic*)) OR (drug* OR medic*) OR

(methadone OR buprenorphine OR naloxone OR naltrexone OR disulfiram OR nalmefene OR thiamine OR clonidine OR lofexidine OR acamprosate OR baclofen) OR

("opioid agonist maintenance treatment" OR OST OR MMT OR BMT OR "opioid substitution treatment" OR "methadone" OR "methadone maintenance" OR "buprenorphine" OR "buprenorphine maintenance" OR "opioid replacement")

For people with SMD and substance (drug and/or alcohol) use disorder, are non-pharmacological interventions for substance use disorder effective to support reduction in substance use-related outcomes?

Search #1: SMD

(exp Mental Disorders/ OR exp Psychotic Disorders/ OR exp Bipolar and Related Disorders/ OR exp Depressive Disorder) OR

((Mental AND (disorder* OR disabilit* OR illness OR "health condition" OR "health problem" OR distress)) OR "psychological distress" OR "psychiatric disorder") OR

((schizophrenia OR schizophrenic) OR Schizotyp* OR ((Delusional OR paranoid) AND disorder*) OR hallucination* OR Psychotic OR Schizoaffective OR psychosis) OR

(((manic OR bipolar OR mood) AND disorder*) OR (depressive AND (disorder* OR episode*)) OR "depressive symptom*" OR hypomania OR mania* OR ((major OR psychotic OR disorder*) AND depression))

Search #2: Substance use disorder

(exp Narcotics/ OR exp Substance-Related Disorders/ OR exp Alcoholism/ OR exp Alcoholics/ OR exp Alcohol Related-Disorders/ OR exp Drug Users/ OR exp Drug Misuse/ OR exp Street Drugs/ OR exp Nonprescription Drugs/ OR exp Drug-Seeking Behaviour/ OR exp substance abuse, intravenous/) OR

("drug abuse" OR "drug addict*" OR "drug depend*" OR "drug withdrawal" OR "drug misuse") OR

("addictive disease*" OR "addictive disorder*" OR addiction OR addictive OR "substance abuse" OR "substance misuse" OR "withdrawal syndrome" OR psychoactive*) OR

("alcoholic patient*" OR "alcoholic subject*" OR alcoholism OR "alcohol depend*" OR "fetal alcohol*" OR "prenatal alcohol*" OR "chronic ethanol*" OR "chronic* alcohol*" OR "alcohol withdrawal" OR "ethanol withdrawal" OR "excessive alcohol consumption" OR "alcohol use disorder" OR "alcohol misuse" OR "alcohol abuse") OR

((cocaine OR heroin OR cannabis OR marijuana OR mdma OR methylenedioxymethamphetamin* OR ecstasy OR morphine* OR amphetamin* OR methamphetamin* OR opioid* OR opiat* OR "prescription drug*" OR "illegal drug*" OR "illicit drug*" OR "street drug" OR benzodiazepin* OR tranquiliz* OR narcot* OR methadone OR fentanyl) AND (abuse OR misuse OR depend* OR addict* OR withdrawal OR overdose OR intoxication OR "harmful use")) OR

("injecting drug use" OR IDU$1 OR IVDU$1 OR PWID$1 OR "injecting drug" OR "intravenous drug" OR "injecting substance" OR "intravenous substance")

Search #3: non-pharmacological interventions for substance use disorders

(exp Substance Abuse Treatment Centers/ OR exp Alcohol Abstinence/ OR exp Needle-Exchange Programs/) OR

(exp Exercise Therapy/ OR exp Occupational Therapy/ OR exp Therapy/ OR exp Therapeutics/ OR exp Family Therapy/ OR exp Psychotherapy/ OR exp Cognitive Therapy/ OR exp Behaviour Therapy/ OR exp Counseling/ OR exp Mental Health Services/ OR exp Problem Based Learning/ OR exp Problem Solving/ OR exp harm reduction/) OR

((psychosocial OR psycho* OR lifestyle* OR cognit* OR behaviour* OR behaviour* OR non-pharmac*) AND (intervent* OR therap* OR treat* OR care OR servic*)) OR

("problem solving" OR psychoeducation OR couns*) OR

("motivational interviewing" OR "motivational enhancement therapy" OR MET OR CBT OR "cognitive behavioural therapy" OR "cognitive behavioural therapy" OR "brief assessment interview" OR "contingency management" OR "social skills training" OR "relapse prevention" OR "case management" OR "assertive community treatment" OR "family interventions") OR

(SBIRT OR "screening and brief interventions" OR outreach OR "residential programmes" OR "recovery management" OR "mutual self-help group" OR "Alcoholic Anonymous" OR "Narcotic Anonymous") OR

("harm reduction" OR NSP$1 OR NSEP$1 OR "needle syringe program$" OR "needle syringe exchange program$" OR "needle exchange$1" OR "syringe exchange $1")

PICO QUESTIONS 5.1 AND 5.2

For people with SMD and pre-existing cardiovascular disease, what pharmacological interventions are effective to support reduction of cardiovascular disease outcomes?

For people with SMD and cardiovascular risk factors (a. high blood pressure; b. high lipid levels), what pharmacological interventions are effective to support reduction of cardiovascular risk factors?

Search #1: SMD

(exp Mental Disorders/ OR exp Psychotic Disorders/ OR exp Bipolar and Related Disorders/ OR exp Depressive Disorder) OR

((Mental AND (disorder* OR disabilit* OR illness OR "health condition" OR "health problem" OR distress)) OR "psychological distress" OR "psychiatric disorder") OR

((schizophrenia OR schizophrenic) OR Schizotyp* OR ((Delusional OR paranoid) AND disorder*) OR hallucination* OR Psychotic OR Schizoaffective OR psychosis) OR

(((manic OR bipolar OR mood) AND disorder*) OR (depressive AND (disorder* OR episode*)) OR "depressive symptom*" OR hypomania OR mania* OR ((major OR psychotic OR disorder*) AND depression))

Search #2: cardiovascular disease / risk factors

(exp Cardiovascular Diseases/) OR

("heart disease" OR "heart attack*" OR stroke* OR "myocardial infarction" OR "transient ischemic attack" OR "cerebrovascular disease" OR "congestive heart failure" OR "vascular disease") OR

("cardiovascular risk*" OR ((high OR abnormal OR elevat*) AND ("blood pressure" OR cholesterol OR "blood glucose")))

Search #3: pharmacological interventions for cardiovascular disease/risk

(exp Cardiac Rehabilitation/ OR exp Risk Reduction Behaviour/ OR exp Risk Management/ OR exp Health Risk Behaviours/ OR exp Risk Factors/ OR exp Risk-Taking/) OR

(exp Drug Therapy/ OR exp Pharmacology/ OR exp Psychopharmacology/ OR exp Metabolic Side Effects of Drugs and Substances/ OR exp Pharmacologic Actions/ OR exp Drug Effects/ OR exp Psychotropic Drugs/) OR

((drug* OR pharmac* OR medic* OR psychotrop*) AND (intervent* OR therap* OR treat* OR care OR servic)) OR (drug* OR medic*) OR

(exp Preventive Health Services/) OR

(switch* AND (medic* OR drug*))

For people with SMD and pre-existing cardiovascular disease, what non-pharmacological interventions are effective to support reduction of cardiovascular disease outcomes?

For people with SMD and cardiovascular risk factors (a. high blood pressure; b. high lipid levels), what non-pharmacological interventions are effective to support reduction of cardiovascular risk factors?

Search #1: SMD

(exp Mental Disorders/ OR exp Psychotic Disorders/ OR exp Bipolar and Related Disorders/ OR exp Depressive Disorder) OR

((Mental AND (disorder* OR disabilit* OR illness OR "health condition" OR "health problem" OR distress)) OR "psychological distress" OR "psychiatric disorder") OR

((schizophrenia OR schizophrenic) OR Schizotyp* OR ((Delusional OR paranoid) AND disorder*) OR hallucination* OR Psychotic OR Schizoaffective OR psychosis) OR

(((manic OR bipolar OR mood) AND disorder*) OR (depressive AND (disorder* OR episode*)) OR "depressive symptom*" OR hypomania OR mania* OR ((major OR psychotic OR disorder*) AND depression))

Search #2: cardiovascular disease / risk factors

(exp Cardiovascular Diseases/) OR

("heart disease" OR "heart attack* OR stroke* OR "myocardial infarction" OR "transient ischemic attack" OR "cerebrovascular disease" OR "congestive heart failure" OR "vascular disease") OR

("cardiovascular risk*" OR (("high OR abnormal OR elevat*) AND ("blood pressure" OR cholesterol OR "blood glucose")))

Search #3: non-pharmacological interventions for cardiovascular disease/risk

(exp Cardiac Rehabilitation/ OR exp Risk Reduction Behaviour/ OR exp Risk Management/ OR exp Health Risk Behaviours/ OR exp Risk Factors/ OR exp Risk-Taking/OR exp Health Promotion/) OR

(exp Exercise Therapy/OR exp Therapy/ OR exp Therapeutics/ OR exp Family Therapy/ OR exp Psychotherapy/ OR exp Cognitive Therapy/ OR exp Behaviour Therapy/ OR exp Counseling/ OR exp Mental Health Services/ OR exp Problem Based Learning/ OR exp Problem Solving/) OR

((psychosocial OR psycho* OR lifestyle* OR cognit* OR behaviour* OR behaviour* OR non-pharmac*) AND (intervent* OR therap* OR treat* OR care OR servic*)) OR

("problem solving" OR psychoeducation OR couns*) OR

(exp Preventive Health Services/)

PICO QUESTION 6

For people with SMD and diabetes mellitus, what pharmacological interventions are effective to improve glycaemic control?

Search #1: SMD

(exp Mental Disorders/ OR exp Psychotic Disorders/ OR exp Bipolar and Related Disorders/ OR exp Depressive Disorder) OR

((Mental AND (disorder* OR disabilit* OR illness OR "health condition" OR "health problem" OR distress)) OR "psychological distress" OR "psychiatric disorder") OR

((schizophrenia OR schizophrenic) OR Schizotyp* OR ((Delusional OR paranoid) AND disorder*) OR hallucination* OR Psychotic OR Schizoaffective OR psychosis) OR

(((manic OR bipolar OR mood) AND disorder*) OR (depressive AND (disorder* OR episode*)) OR "depressive symptom*" OR hypomania OR mania* OR ((major OR psychotic OR disorder*) AND depression))

Search #2: Diabetes mellitus

(exp Diabetes Mellitus/) OR

(diabet* OR NIDDM OR IDDM OR T2D* OR T1D*) OR

("non-insulin* depend*" OR "noninsulin* depend*" OR "insulin* depend*")

Search #3: pharmacological interventions for diabetes

(exp Drug Therapy/ OR exp Pharmacology/ OR exp Psychopharmacology/ OR exp Metabolic Side Effects of Drugs and Substances/ OR exp Pharmacologic Actions/ OR exp Drug Effects/ OR exp Psychotropic Drugs/) OR

((drug* OR pharmac* OR medic* OR psychotrop*) AND (intervent* OR therap* OR treat* OR care OR service)) OR (drug* OR medic*) OR

((glucose* OR glycaem*) AND (treat* OR control* OR care OR servic* OR therap* OR interven* OR manag* OR monit*)) OR

(metformin OR sulphonylureas OR insulin OR thiazolidinediones) OR

((switch* AND (medic* OR drug*)) OR "appetite suppressant*" OR antiparkinsonian OR anticonvulsant* OR antidepressant* OR "health check*") OR

(weight AND (loss OR reduc* OR maint*)) OR ("weight gain" AND (prevent* OR manag*)) OR

((smok* OR tobacco OR nicotin* OR cigarette*) AND (cessation OR reduc* OR abst*))

For people with SMD and diabetes mellitus, what non-pharmacological interventions are effective to improve glycaemic control?

Search #1: SMD

(exp Mental Disorders/ OR exp Psychotic Disorders/ OR exp Bipolar and Related Disorders/ OR exp Depressive Disorder) OR

((Mental AND (disorder* OR disabilit* OR illness OR "health condition" OR "health problem" OR distress)) OR "psychological distress" OR "psychiatric disorder") OR

((schizophrenia OR schizophrenic) OR Schizotyp* OR ((Delusional OR paranoid) AND disorder*) OR hallucination* OR Psychotic OR Schizoaffective OR psychosis) OR

(((manic OR bipolar OR mood) AND disorder*) OR (depressive AND (disorder* OR episode*)) OR "depressive symptom*" OR hypomania OR mania* OR ((major OR psychotic OR disorder*) AND depression))

Search #2: Diabetes mellitus

(exp Diabetes Mellitus/) OR

(diabet* OR NIDDM OR IDDM OR T2D* OR T1D*) OR

("non-insulin* depend*" OR "noninsulin* depend*" OR "insulin* depend*")

Search #3: non-pharmacological interventions for diabetes

(exp Diet, Diabetic/) OR

(exp Exercise Therapy/ OR exp Occupational Therapy/ OR exp Therapy/ OR exp Therapeutics/ OR exp Family Therapy/ OR exp Psychotherapy/ OR exp Cognitive Therapy/ OR exp Behaviour Therapy/ OR exp Counseling/ OR exp Mental Health Services/ OR exp Problem Based Learning/ OR exp Problem Solving/) OR

((psychosocial OR psycho* OR lifestyle* OR cognit* OR behaviour* OR behaviour* OR non-pharmac* OR organisat* OR organizat*) AND (intervent* OR therap* OR treat* OR care OR servic*)) OR

("problem solving" OR psychoeducation OR couns* OR education) OR

((glucose* OR glycaem*) AND (treat* OR control* OR care OR servic* OR therap* OR interven* OR manag* OR monit*)) OR

(diet* OR nutrition* OR exercis* OR "physical activity" OR "health promot*" OR self-monit* OR self-manag* OR self-care OR calor* OR "healthy eating" OR "healthy body weight" OR "food intake" OR "health check*") OR

(weight AND (loss OR reduc* OR maint*)) OR ("weight gain" AND (prevent* OR manag*)) OR

((smok* OR tobacco OR nicotin* OR cigarette*) AND (cessation OR reduc* OR abst*))

PICO QUESTION 7

For people with SMD and HIV/AIDS, what pharmacological interventions (i.e. ART drugs) and non-pharmacological interventions are effective to support reduction in HIV-related outcomes?

Search #1: SMD

(exp Mental Disorders/ OR exp Psychotic Disorders/ OR exp Bipolar and Related Disorders/ OR exp Depressive Disorder) OR

((Mental AND (disorder* OR disabilit* OR illness OR "health condition" OR "health problem" OR distress)) OR "psychological distress" OR "psychiatric disorder") OR

((schizophrenia OR schizophrenic) OR Schizotyp* OR ((Delusional OR paranoid) AND disorder*) OR hallucination* OR Psychotic OR Schizoaffective OR psychosis) OR

(((manic OR bipolar OR mood) AND disorder*) OR (depressive AND (disorder* OR episode*)) OR "depressive symptom*" OR hypomania OR mania* OR ((major OR psychotic OR disorder*) AND depression))

Search #2: HIV/AIDS

(exp HIV/ OR exp Sexually Transmitted Diseases/ OR exp Lymphoma, AIDS-Related/ OR exp HIV Long-Term Survivors/ OR exp HIV Infections OR exp Acquired Immunodeficiency Syndrome/) OR

(HIV OR "human immunodeficiency syndrome" OR "human immunodeficiency virus" OR AIDS OR "acquired immunodeficiency syndrome")

Search #3: interventions for HIV/AIDS

(exp HIV Antigens/ OR exp Anti-HIV Agents/ OR exp Anti-Retroviral Agents/ OR exp Antiretroviral Therapy, Highly Active/ OR exp AIDS Vaccines/) OR

(exp Drug Therapy/ OR exp Pharmacology/ OR exp Psychopharmacology/ OR exp Metabolic Side Effects of Drugs and Substances/ OR exp Pharmacologic Actions/ OR exp Drug Effects/ OR exp Psychotropic Drugs/) OR

((drug* OR pharmac* OR medic* OR psychotrop*) AND (intervent* OR therap* OR treat* OR care OR servic)) OR (drug* OR medic*) OR

((“anti-retroviral” OR ART) AND (drug* OR medic* OR intervent* OR therap* OR treat* OR care)) OR

(tenofovir OR TDF OR lamivudine OR 3TC OR emtricitabine OR FTC OR efavirenz OR EFV OR Abacavir

OR Zidovudine OR Nevirapine OR Atazanavir OR ritonavir OR Darunavir OR Lopinavir OR Dolutegravir OR Raltegravir)

PICO QUESTION 8

For people with SMD and infectious diseases (Tuberculosis, Hepatitis B/C), what pharmacological and non-pharmacological interventions are effective for treatment of infectious diseases (e.g. tuberculosis, hepatitis B, hepatitis C)?

Search #1: SMD

(exp Mental Disorders/ OR exp Psychotic Disorders/ OR exp Bipolar and Related Disorders/ OR exp Depressive Disorder) OR

((Mental AND (disorder* OR disabilit* OR illness OR “health condition” OR “health problem” OR distress)) OR "psychological distress" OR "psychiatric disorder") OR

((schizophrenia OR schizophrenic) OR Schizotyp* OR ((Delusional OR paranoid) AND disorder*) OR hallucination* OR Psychotic OR Schizoaffective OR psychosis) OR

(((manic OR bipolar OR mood) AND disorder*) OR (depressive AND (disorder* OR episode*)) OR "depressive symptom*" OR hypomania OR mania* OR ((major OR psychotic OR disorder*) AND depression))

Search #2: infectious diseases (tuberculosis, hepatitis B/C)

(exp Hepatitis/ OR exp Hepatitis, Viral, Human/ OR exp Tuberculosis/ OR exp Hepatitis B/ OR exp Hepatitis B Virus/ OR exp Hepatitis C/) OR

(“hepatitis B” OR “hepatitis C” OR tuberculosis)

Search #3: interventions for infectious diseases

(exp Hepatitis B Vaccines/ OR exp Hepatitis B Antigens/ OR exp Hepatitis C Antigens/ OR exp Tuberculosis Vaccines/) OR

(exp Drug Therapy/ OR exp Pharmacology/ OR exp Psychopharmacology/ OR exp Metabolic Side Effects of Drugs and Substances/ OR exp Pharmacologic Actions/ OR exp Drug Effects/ OR exp Psychotropic Drugs/) OR

((drug* OR pharmac* OR medic* OR psychotrop*) AND (intervent* OR therap* OR treat* OR care OR servic)) OR (drug* OR medic*) OR

(vaccin* OR BCG OR treatment adherence OR treatment completion) OR

(Ethambutol OR Rifampicin OR Insoniazid OR Pyrazinamide OR Rifabutin OR Rifampicin OR Rifapentine OR Entecavir OR Tenofovir OR Sofosbuvir OR Simeprevir OR Daclatasvir OR Dasabuvir OR Ribavarin OR Pegylated interferon)

Drug-drug interactions search strategy

Drug-drug interaction searches were conducted between medicines relevant for each PICO question and medicines used for SMD. The following process was employed for the searches:

Medicines of interest were identified for each PICO question by referring to relevant sections of the 2017 WHO Model List of Essential Medicines (EML), as well as prior WHO Guidelines and WHO Mental Health Gap Action Programme Intervention Guide (mhGAP-IG) where applicable. Physical health medicines were limited in scope to those used on a routine basis, rather than emergently. Technical consultation was also sought with relevant departments of WHO. Pharmacological interventions recommended in the forthcoming guidelines were also included.

Medicines used for SMD were limited to those included in the WHO mhGAP-IG and/or the 2017 WHO EML. These will be expanded to include a wider range of medicines which may be used in different settings based on availability and costs. Since its inception in 1977, the WHO Model List of Essential Medicines has played an important role in identifying priority medications for major health conditions in countries of all income groups. Updated every two years, this list in many cases has been used as a gold standard for national health systems and non-governmental organization. Priority medications are selected based on efficacy, safety, and cost-effectiveness.

Searches between both lists (medicines relevant for each PICO question and medicines used for SMD) were run using the drug-drug interaction software Lexi-Interact. Lexi-Interact was chosen as it is commonly used in clinical practice and scored well on accuracy and comprehensiveness in a recent review comparing 5 drug-drug interaction engines[5]. Severity of drug-drug interactions (minor, moderate, major)) were reported in the Lexi-Interact database and have reported here.

Search results for each PICO question were summarized into a narrative synthesis within each Evidence Profile, as well as a table coded by drug-drug interaction severity with accompanying information in the annex.

[2] Sh Kheshti R, Aalipour M, Namazi S. "A comparison of five common drug-drug interaction software programs regarding accuracy and comprehensiveness." Journal of Research in Pharmacy Practice. 2016; 5: 257-263.

Annex 6. Drug – drug interactions

PICO 2: TOBACCO CESSATION

[The following table and information is summarized from drug-drug interaction searches using Lexi-Interact.]

- No interaction known or minor interaction
- Moderate interaction
- Major interaction

	Amitriptyline	Fluoxetine	Haloperidol	Risperidone	Chlorpromazine	Fluphenazine	Clozapine	Biperiden	Trihexyphenidyl	Lithium	Valproic acid	Carbamazepine	Diazepam
Bupropion	🟡	🟡	🟡	🟡	🟡	🟡	🟡	🟢	🟢	🟢	🟢	🟡	🟢
Varenicline	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢
NRT	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢

There are no known interactions between **NRT** or **varenicline** and medicines used for SMD.

BUPROPION:
There are multiple interactions between bupropion and medicines used for SMD, specifically involving elevated seizure risk and enzymatic inhibition/induction.

- **Amitriptyline:** Moderate interaction [elevated amitriptyline levels via CYP2D6 inhibition]. ADVICE: Consider other medications. If using, monitor clinically for signs of amitriptyline toxicity.
- **Fluoxetine:** Moderate interaction [elevated fluoxetine levels via CYP2D6 inhibition]. ADVICE: Monitor clinically for signs of fluoxetine toxicity and/or serotonin syndrome.
- **Haloperidol, risperidone, chlorpromazine, fluphenazine:** Moderate interaction [decreased seizure threshold]. Advise caution.
- **Clozapine:** Moderate interaction [decreased seizure threshold, elevated clozapine levels via CYP2D6 inhibition]. ADVICE: Monitor for signs of clozapine toxicity clinically and via testing of levels. Adjust clozapine dose accordingly.
- **Carbamazepine (CBZ):** Moderate interaction [lower levels of bupropion via CYP2B6 induction]. ADVICE: Monitor for clinical efficacy of bupropion.

PICO 3: WEIGHT MANAGEMENT

[The following table and information is summarized from drug-drug interaction searches using Lexi-Interact.]

- No interaction known or minor interaction
- Moderate interaction
- Major interaction

	Amitriptyline	Fluoxetine	Haloperidol	Risperidone	Chlorpromazine	Fluphenazine	Clozapine	Biperiden	Trihexyphenidyl	Lithium	Valproic acid	Carbamazepine	Diazepam
Metformin	●	●	●	●	●	●	●	●	●	●	●	●	●

METFORMIN:

- **Fluoxetine:** Moderate interaction [increased potency of anti-diabetic medicine]. ADVICE: Monitor blood glucose control and adjust dosing of anti-diabetic medicine.

- **Risperidone, Clozapine:** Moderate interaction [decreased efficacy of anti-diabetic medicine]. ADVICE: Monitor glycemic control and adjust dosing of anti-diabetic medicine.

PICO 4: SUBSTANCE USE DISORDERS

[The following table and information is summarized from drug-drug interaction searches using Lexi-Interact.]

- No interaction known or minor interaction
- Moderate interaction
- Major interaction

	Amitriptyline	Fluoxetine	Haloperidol	Risperidone	Chlorpromazine	Fluphenazine	Clozapine	Biperiden	Trihexyphenidyl	Lithium	Valproic acid	Carbamazepine	Diazepam
Methadone	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🟡	🟡	🔴	🟢	🟡	🔴
Buprenorphine	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🟡	🟡	🔴	🟢	🔴	🔴

METHADONE:
There are multiple interactions between methadone and medicines for SMD, including increased risk for CNS depression* (sedation, confusion, decreased respiratory drive), QT-prolongation (methadone carries moderate risk), and serotonergic effects. Signs of serotonin syndrome include confusion, neuromuscular excitability, and dysautonomia.

- **Biperiden, trihexyphenidyl:** Moderate interaction. Elevated risk of side effects and toxicity of methadone including urinary retention and constipation [via anticholinergic activity]. ADVICE: Monitor for side effects.
- **Carbamazepine (CBZ):** Moderate interaction [reduced methadone levels and efficacy via CYP3A4 induction]. ADVICE: If using, monitor for reduced efficacy of methadone or opioid withdrawal symptoms.
- **Amitriptyline:** Major interaction [risk of CNS depression, serotonergic effects]. ADVICE: Avoid concurrent use if possible. If using, use lowest doses possible; monitor for clinical signs of CNS depression and signs of serotonin syndrome. Stop both medicines if serotonin syndrome suspected.
- **Fluoxetine:** Major interaction [high risk of QT prolongation, serotonergic effects]. ADVICE: Avoid using.
- **Haloperidol, risperidone, chlorpromazine, clozapine:** Major interaction [risk of CNS depression, risk of QT prolongation]. ADVICE: Avoid using if possible. If using, use lowest doses possible; monitor for clinical signs of CNS depression; monitor for QT-prolongation and arrhythmias on ECG.
- **Fluphenazine:** Major interaction [risk of CNS depression]. ADVICE: Avoid using if possible. If using, use lowest doses possible and monitor for clinical signs of CNS depression.
- **Lithium:** Major interaction [serotonergic effects], Moderate interaction [risk of QT prolongation]. ADVICE: If using, monitor clinically for signs of serotonin syndrome. Stop both medicines if serotonin syndrome is suspected. Additionally, monitor for QT prolongation and arrhythmias on ECG if possible.
- **Diazepam:** Major interaction [risk of CNS depression]. ADVICE: Avoid using if possible. If using, monitor for clinical signs of CNS depression.

BUPRENORPHINE:
There are multiple interactions between buprenorphine and medicines for SMD, including increased risk for CNS depression* (sedation, confusion, decreased respiratory drive), QT prolongation, and serotonergic effects (bupropion can increase the risk of serotonin toxicity or serotonin syndrome if used with medicines that have serotonergic effects). Signs of serotonin syndrome include confusion, neuromuscular excitability, and dysautonomia.

- **Biperiden, trihexyphenidyl:** Moderate interaction. Elevated risk of side effects and toxicity of buprenorphine including urinary retention and constipation [via anticholinergic activity]. ADVICE: Monitor for side effects.

- **Amitriptyline:** Major interaction [risk of CNS depression, serotonergic effects]. ADVICE: If using, consider decreasing amitriptyline and starting buprenorphine at a low dose; monitor for clinical signs of CNS depression. Additionally, monitor clinically for signs of serotonin syndrome. Stop both medicines if this syndrome is suspected.

- **Fluoxetine:** Major interaction [serotonergic effects], Moderate interaction [risk of QT prolongation]. Fluoxetine confers high-risk for QT interval prolongation and buprenorphine may increase this risk, though the evidence is unclear. ADVICE: monitor clinically for signs of serotonin syndrome. Stop both medicines if this syndrome is suspected. Monitor ECG if possible.

- **Haloperidol, risperidone, chlorpromazine, fluphenazine, clozapine, carbamazepine, diazepam:** Major interaction [risk of CNS depression]. ADVICE: Avoid using if concerns for risk of buprenorphine misuse. If using, consider decreasing other sedating medicines and starting buprenorphine at a low dose; monitor for clinical signs of CNS depression.

- **Lithium:** Major interaction [serotonergic effects]. ADVICE: Monitor clinically for signs of serotonin syndrome. Stop both medicines if this syndrome is suspected.

* Of note, the US FDA issued a safety announcement in 2017 regarding the use of methadone and buprenorphine with other sedating medications. While the risks of CNS sedation can be serious, they may be outweighed by the risk of other harms of untreated opioid use disorders. Thus, the US FDA does not recommend withholding opioid replacement therapy in the context of other sedating medications; cautious medication management is advised. United States Food and Drug Administration. Drug Safety and Availability - FDA Drug Safety Communication: FDA urges caution about withholding opioid addiction medications from patients taking benzodiazepines or CNS depressants: careful medication management can reduce risks. 2017. https://www.fda.gov/Drugs/DrugSafety/ucm575307.htm

PICO 5: CARDIOVASCULAR DISEASE

[The following table and information is summarized from drug-drug interaction searches using Lexi-Interact.]

- No interaction known or minor interaction
- Moderate interaction
- Major interaction

	Amitriptyline	Fluoxetine	Haloperidol	Risperidone	Chlorpromazine	Fluphenazine	Clozapine	Biperiden	Trihexyphenidyl	Lithium	Valproic acid	Carbamazepine	Diazepam
Bisoprolol	●	●	●	●	●	●	●	●	●	●	●	●	●
Atenolol	●	●	●	●	●	●	●	●	●	●	●	●	●
Metoprolol	●	●	●	●	●	●	●	●	●	●	●	●	●
Carvedilol	●	●	●	●	●	●	●	●	●	●	●	●	●
Glyceryl trinitrate	●	●	●	●	●	●	●	●	●	●	●	●	●
Isosorbide dinitrate	●	●	●	●	●	●	●	●	●	●	●	●	●
Verapamil	●	●	●	●	●	●	●	●	●	●	●	●	●
Digoxin	●	●	●	●	●	●	●	●	●	●	●	●	●
Amiodarone	●	●	●	●	●	●	●	●	●	●	●	●	●
Amlodipine	●	●	●	●	●	●	●	●	●	●	●	●	●
Enalapril	●	●	●	●	●	●	●	●	●	●	●	●	●
Hydrochlorothiazide	●	●	●	●	●	●	●	●	●	●	●	●	●
Losartan	●	●	●	●	●	●	●	●	●	●	●	●	●
Furosemide	●	●	●	●	●	●	●	●	●	●	●	●	●
Spironolactone	●	●	●	●	●	●	●	●	●	●	●	●	●
Aspirin	●	●	●	●	●	●	●	●	●	●	●	●	●
Clopidogrel	●	●	●	●	●	●	●	●	●	●	●	●	●
Simvastatin	●	●	●	●	●	●	●	●	●	●	●	●	●
Metformin	●	●	●	●	●	●	●	●	●	●	●	●	●

There are no known interactions between digoxin and medicines used for SMD.

BETA-BLOCKERS:

As a class, beta-blockers have significant interactions with multiple SMD medicines, most significantly the risk of hypotension or beta-blocker toxicity (including hypotension, bradycardia, and heart block/prolonged PR interval). There are some variations within this class.

- **Risperidone, chlorpromazine, fluphenazine, clozapine:** Moderate interaction for most beta-blockers [risk of hypotension] ADVICE: Monitor therapy.
- **Fluoxetine (with carvedilol and metoprolol only):** Moderate interaction with carvedilol, Major interaction with metoprolol. [Elevated levels of beta blocker via CYP2D6 inhibition] ADVICE: Consider alternative. If using, monitor for signs of beta blocker toxicity; adjust dosing accordingly.
- **Carbamazepine (with bisoprolol only):** Major interaction [reduced levels and efficacy of bisoprolol via CYP3A4 induction]. ADVICE: Consider alternative. If using, monitor for reduced efficacy of bisoprolol.

GLYCERYL TRINITRATE:

- **Amitriptyline, haloperidol, risperidone, chlorpromazine, fluphenazine, clozapine, biperiden, trihexyphenidyl:** Moderate interaction [reduced absorption of sublingual glyceryl trinitrate due to dry mouth from anticholinergic effects]. ADVICE: If dry mouth develops, utilize strategies such as artificial saliva and chewing gum

ISOSORBIDE DINITRATE:

- **Risperidone, chlorpromazine, clozapine:** Moderate interaction [elevated risk of hypotension] ADVISE caution and monitor.
- **Carbamazepine:** Major interaction [reduced levels and efficacy of isosorbide dinitrate] ADVICE: Consider alternative.

VERAPAMIL:

Verapamil may elevate the levels of multiple medicines due to P-glycoprotein, CYP3A4, or CYP1A2 inhibition.

- **Haloperidol, risperidone, clozapine:** Moderate interaction [elevated levels of antipsychotic via CYP3A4, P-glyocoprotein, or CYP1A2 inhibition] ADVICE: Monitor for toxicity of antipsychotic
- **Chlorpromazine:** Moderate interaction [elevated risk of hypotension] ADVICE: Monitor blood pressure and adjust doses accordingly
- **Lithium:** Moderate interaction [increased risk of neurotoxicity from lithium; unclear effect on levels] ADVICE: Monitor clinically, as well as via laboratory levels
- **Diazepam:** Moderate interaction [increased levels of diazepam via CYP3A4 inhibition] ADVICE: Monitor for signs of diazepam toxicity
- **Carbamazepine (CBZ):** Major interaction [reduced levels and efficacy of verapamil via CYP3A4 induction, elevated levels of CBZ via CYP3A4 inhibition] ADVICE: Consider another mood stabilizer

AMIODARONE:

- **Fluoxetine, haloperidol, risperidone, chlorpromazine, clozapine:** Major interaction [QT prolongation] ADVICE: Avoid using
- **Amitriptyline, lithium:** Major interaction [QT prolongation] ADVICE: If able, avoid using. If using, monitor for QT-prolongation and arrythmias on ECG.
- **Carbamazepine:** Major interaction [reduced levels and efficacy of amiodarone] ADVICE: Consider another mood stabilizer. If using, monitor for reduced efficacy of amiodarone.

AMLODIPINE:

- **Risperidone, chlorpromazine, clozapine:** Moderate interaction [risk of hypotension] ADVICE: Monitor blood pressure and adjust doses accordingly
- **Carbamazepine:** Major interaction [reduced levels and efficacy of amlodipine via CYP3A4 induction] ADVICE: Consider another mood stabilizer. If using, monitor for reduced efficacy of amlodipine and adjust doses accordingly.

ENALAPRIL, LOSARTAN:

- **Risperidone, chlorpromazine, clozapine:** Moderate interaction [risk of hypotension] ADVICE: Monitor blood pressure and adjust doses accordingly
- **Lithium:** Moderate interaction with losartan, Major interaction with enalapril. [Elevated levels of lithium] ADVICE: Consider decreasing lithium when starting losartan or enalapril. Monitor for signs of lithium toxicity clinically and via laboratory testing.
- **Carbamazepine (with losartan only):** Major interaction [reduced levels and efficacy of losartan via CYP3A4 induction] ADVICE: Consider another mood stabilizer. If used, monitor for reduced efficacy of losartan.

DIURETICS (HCTZ, FUROSEMIDE, SPIRONOLACTONE):

Diuretics have significant interactions with multiple SMD medicines, including the risk of hypotension.

- **Risperidone, chlorpromazine, clozapine:** Moderate interaction [risk of hypotension] ADVICE: Monitor blood pressure and adjust doses accordingly
- **Amitriptyline, haloperidol, fluphenazine, biperiden, trihexyphenidyl, risperidone, chlorpromazine, clozapine (with HCTZ only):** Moderate interaction [increased levels of HCTZ due to effects on gut motility] ADVICE: Monitor for side effects of HCTZ
- **Fluoxetine, carbamazepine (with HCTZ only):** Moderate interaction [increased risk of hyponatremia] ADVICE: Monitor for clinical signs of hyponatremia including headache, dizziness, nausea, confusion, seizures
- **Lithium (with HCTZ only):** Moderate interaction [increased lithium levels] ADVICE: Consider decreasing lithium dose when HCTZ is started. Monitor for signs of lithium toxicity clinically and via laboratory testing.
- **Risperidone with furosemide only:** Major interaction [increased risk of mortality in patients with dementia] ADVICE: Consider another antipsychotic. If using, monitor carefully, especially hydration status.

ASPIRIN:

- **Amitriptyline, fluoxetine:** Major interaction [increased risk of bleeding, especially gastrointestinal bleeding] ADVICE: Monitor for signs of bleeding
- **Valproic acid:** [VPA] Moderate interaction [elevated levels of VPA] ADVICE: Monitor for toxicity of VPA clinically and via laboratory testing if possible

CLOPIDOGREL:

- **Fluoxetine:** Major interaction [reduced levels of active metabolite of clopidogrel via CYP2C19 inhibition] ADVICE: Consider another antidepressant. If using, monitor for reduced efficacy of clopidogrel.

SIMVASTATIN:

- **Risperidone:** Moderate interaction [increased risk of myopathy and rhabdomyolysis] ADVICE: Monitor clinically for any concerning symptoms
- **Carbamazepine:** Major interaction [reduced levels and efficacy of simvastatin via CYP3A4 induction] ADVICE: Consider another mood stabilizer. If using, monitor for reduced efficacy of simvastatin.

METFORMIN:

- **Fluoxetine:** Moderate interaction [increased potency of anti-diabetic medicine]. ADVICE: Monitor blood glucose control and adjust dosing of anti-diabetic medicine.
- **Risperidone, Clozapine:** Moderate interaction [decreased efficacy of anti-diabetic medicine]. ADVICE: Monitor glycaemic control and adjust dosing of anti-diabetic medicine.

PICO 6: DIABETES

[The following table and information is summarized from drug-drug interaction searches using Lexi-Interact.]

- No interaction known or minor interaction
- Moderate interaction
- Major interaction

	Amitriptyline	Fluoxetine	Haloperidol	Risperidone	Chlorpromazine	Fluphenazine	Clozapine	Biperiden	Trihexyphenidyl	Lithium	Valproic acid	Carbamazepine	Diazepam
Metformin	🟢	🟡	🟢	🟡	🟢	🟢	🟡	🟢	🟢	🟢	🟢	🟢	🟢
Gliclazide	🟡	🟡	🟢	🟡	🟢	🟢	🟡	🟢	🟢	🟢	🟢	🟢	🟢
Insulin	🟢	🟡	🟢	🟡	🟢	🟢	🟡	🟢	🟢	🟢	🟢	🟢	🟢

METFORMIN, INSULIN:

- **Fluoxetine:** Moderate interaction [increased potency of anti-diabetic medicine]. ADVICE: Monitor blood glucose control and adjust dosing of anti-diabetic medicine.
- **Risperidone, Clozapine:** Moderate interaction [decreased efficacy of anti-diabetic medicine]. ADVICE: Monitor glycaemic control and adjust dosing of anti-diabetic medicine.

GLICLAZIDE:

- **Amitriptyline, Fluoxetine:** Moderate interaction [increased potency of anti-diabetic medicine]. ADVICE: Monitor blood glucose control and adjust dosing of anti-diabetic medicine.
- **Risperidone, Clozapine:** Moderate interaction [decreased efficacy of anti-diabetic medicine]. ADVICE: Monitor glycaemic control and adjust dosing of anti-diabetic medicine.

PICO 7: HIV/AIDS

[The following table and information is summarized from drug-drug interaction searches using Lexi-Interact.]

- No interaction known or minor interaction
- Moderate interaction
- Major interaction

	Amitriptyline	Fluoxetine	Haloperidol	Risperidone	Chlorpromazine	Fluphenazine	Clozapine	Biperiden	Trihexyphenidyl	Lithium	Valproic acid	Carbamazepine	Diazepam
Dolutegravir	●	●	●	●	●	●	●	●	●	●	●	●	●
Efavirenz	●	●	●	●	●	●	●	●	●	●	●	●	●
Emtricitabine	●	●	●	●	●	●	●	●	●	●	●	●	●
Lamivudine	●	●	●	●	●	●	●	●	●	●	●	●	●
Tenofovir disoproxil fumarate (TDF)	●	●	●	●	●	●	●	●	●	●	●	●	●

There are no known interactions between **emtricitabine, lamivudine**, or **tenofovir disoproxil fumarate (TDF)** and medicines used for SMD.

DOLUTEGRAVIR (DTG):

Major interaction with carbamazepine (CBZ).

- **CBZ** may reduce the level and efficacy of DTG. ADVICE: Double the dose of DTG if patient not on integrase inhibitors before. If resistance suspected to DTG (or similar drug in the same class), choose another mood stabilizer.

EFAVIRENZ:

There are multiple interactions between Efavirenz and medicines used for SMD, specifically involving the risk of QT interval prolongation, the risk of CNS depression (ex: sedation, confusion, decreased respiratory drive), and/or enzymatic induction.

- **Amitriptyline:** Moderate interaction [QT prolongation, risk of CNS depression]. ADVICE: If using, monitor for QT-prolongation and arrhythmias on ECG if possible and monitor for signs of CNS depression.
- **Lithium:** Moderate interaction [QT prolongation]. ADVICE: If using, monitor for QT-prolongation and arrhythmias on ECG if possible
- **Fluphenazine, Diazepam:** Moderate interaction [risk of CNS depression]. ADVICE: If using, monitor for signs of CNS depression.
- **Haloperidol, risperidone, chlorpromazine, and clozapine:** Major interaction [QT prolongation]. ADVICE: If able, avoid using efavirenz with these medicines. If using, monitor for QT-prolongation and arrythmias on ECG.
- **Fluoxetine:** Major interaction [high risk of QT prolongation]. ADVICE: Avoid using.
- **Carbamazepine:** Major interaction. Efavirenz and carbamazepine may reduce the levels (and efficacy) of each other. ADVICE: Avoid using.

* For details as to interactions between second-line and third-line antiretroviral and psychiatric medicines, please refer to (Annex 13: Key drug-drug interactions for antiretroviral drugs), which is available online at the following link: http://apps.who.int/iris/bitstream/handle/10665/208825/9789241549684_eng.pdf?sequence=1

PICO 8: TUBERCULOSIS

[The following table and information is summarized from drug-drug interaction searches using Lexi-Interact.]

- No interaction known or minor interaction
- Moderate interaction
- Major interaction

	Amitriptyline	Fluoxetine	Haloperidol	Risperidone	Chlorpromazine	Fluphenazine	Clozapine	Biperiden	Trihexyphenidyl	Lithium	Valproic acid	Carbamazepine	Diazepam
Isoniazid	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟡	🟡	🟢
Rifampin/ Rifampicin	🟡	🟡	🔴	🟡	🟢	🟢	🔴	🟢	🟢	🟢	🔴	🔴	🔴
Pyrazinamide	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Ethambutol	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Levofloxacin	🟡	🟡	🔴	🔴	🔴	🟢	🔴	🟢	🟢	🟡	🟢	🟢	🟢
Cycloserine	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Bedaquiline	🟡	🟡	🔴	🔴	🔴	🟢	🔴	🟢	🟢	🟡	🟢	🔴	🟢
Delamanid	🟡	🟡	🔴	🔴	🔴	🟢	🔴	🟢	🟢	🟡	🟢	🔴	🟢
Linezolid	🔴	🔴	🟡	🟡	🟡	🟡	🟡	🟢	🟢	🔴	🟢	🔴	🟢

There are no known interactions between pyrazinamide, ethambutol, or cycloserine and medicines used for SMD.

ISONIAZID (INH):

- **Valproic acid:** Moderate interaction. INH can increase valproic acid levels. ADVICE: If using, monitor for valproic acid toxicity clinically and via laboratory testing of levels, if possible, especially when starting, stopping, or adjusting INH.
- **Carbamazepine (CBZ):** Moderate interaction. INH can increase CBZ levels and CBZ may increase the hepatotoxicity of INH. ADVICE: If using, monitor for clinical signs of CBZ toxicity and hepatotoxicity.

RIFAMPIN/RIFAMPICIN:

There are multiple interactions between rifampin and medicines used for SMD due to rifampin's ability to induce multiple enzymes (rifampin is a strong inducer of CYP3A4 and CYP2C9).

- **Amitriptyline:** Moderate interaction [reduced levels and efficacy of amitriptyline]. ADVICE: Monitor clinically for efficacy of amitriptyline.
- **Fluoxetine:** Moderate interaction [reduced levels and efficacy of fluoxetine]. Mechanism: CYP2C9 induction. ADVICE: Monitor clinically for efficacy of fluoxetine.
- **Risperidone:** Moderate interaction [reduced levels and efficacy of risperidone]. Mechanism: CYP3A4 induction. ADVICE: Monitor clinically for efficacy of risperidone and adjust dosing accordingly.
- **Haloperidol:** Major interaction [reduced levels and efficacy of haloperidol]. Mechanism: CYP3A4 induction. ADVICE: Consider another antipsychotic medication. If using, monitor for clinical efficacy of haloperidol and adjust dosing as needed.

- **Clozapine:** Major interaction [reduced levels and efficacy of clozapine]. Mechanism: CYP3A4 induction. ADVICE: Avoid using. If using, monitor for efficacy clinically and via clozapine levels and adjust dosing as needed.
- **Valproic acid (VPA):** Major interaction [reduced levels and efficacy of VPA]. ADVICE: Monitor for efficacy clinically and via VPA levels if possible, especially with dosing changes of rifampin; adjust VPA dosing accordingly.
- **Carbamazepine (CBZ):** Major interaction [reduced levels and efficacy of carbamazepine]. Mechanism: CYP3A4 induction. ADVICE: Consider another mood stabilizer. If using, monitor for clinical efficacy of CBZ and adjust dosing as needed.
- **Diazepam:** Major interaction [reduced levels and efficacy of diazepam]. Mechanism: CYP2C19 and CYP3A4 induction. ADVICE: Consider another medicine. If using, monitor for clinical efficacy of diazepam and adjust dosing as needed.

LEVOFLOXACIN:

There are multiple interactions between levofloxacin and medicines used for SMD due to increased risk for QT-prolongation (levofloxacin confers moderate risk).

- **Amitriptyline, fluoxetine, lithium:** Moderate interaction [increased risk for QT-prolongation]. ADVICE: Monitor for QT-prolongation and arrhythmias by ECG.
- **Haloperidol, risperidone, chlorpromazine, clozapine:** Major interaction [risk of QT prolongation]. ADVICE: Avoid using if possible. If using, monitor for QT-prolongation and arrhythmias on ECG.

BEDAQUILINE & DELAMANID:

There are multiple interactions between bedaquiline and delamanid with medicines used for SMD due to increased risk for QT-prolongation (both bedaquiline and delamanid confer moderate risk) and induction by CYP3A4.

- **Amitriptyline, fluoxetine, lithium:** Moderate interaction [increased risk for QT-prolongation]. ADVICE: Monitor for QT-prolongation and arrhythmias by ECG.
- **Haloperidol, risperidone, chlorpromazine, clozapine:** Major interaction [risk of QT prolongation]. ADVICE: Avoid using if possible. If using, monitor for QT-prolongation and arrhythmias on ECG.
- **Carbamazepine (CBZ):** Major interaction [reduced levels and effectiveness of bedaquiline or delamanid]. ADVICE: Consider another mood stabilizer.

LINEZOLID:

There are multiple interactions between linezolid and medicines used for SMD due to serotonergic effects, dopamine antagonism, and monoamine oxidase inhibition. Signs of serotonin syndrome include confusion, neuromuscular excitability (ex: myoclonus and hyperreflexia), and dysautonomia (ex: flushing, sweating, diarrhoea, high blood pressure and heart rate, and fever). Signs of neuroleptic malignant syndrome include confusion, muscle rigidity, and dysautonomia (ex: high fever, heart rate, or labile blood pressures).

- **Amitriptyline:** Major interaction [serotonergic effects, risk of serotonin syndrome]. ADVICE: Do not use concurrently. Stop amitriptyline at least two weeks before starting linezolid. If linezolid is necessary in an emergency situation, stop amitriptyline and monitor clinically for signs of serotonin syndrome for at least two weeks after amitriptyline is stopped (while linezolid treatment is ongoing) or until one day after linezolid is stopped.
- **Fluoxetine:** Major interaction [serotonergic effects, risk of serotonin syndrome]. ADVICE: Do not use concurrently. Stop fluoxetine at least five weeks before starting linezolid. If linezolid is necessary in an emergency situation, stop fluoxetine and monitor clinically for signs of serotonin syndrome for at least five weeks after fluoxetine is stopped (while linezolid treatment is ongoing) or until one day after linezolid is stopped.
- **Haloperidol, risperidone, chlorpromazine, fluphenazine:** Moderate interaction [serotonergic effects and dopamine antagonism, risk of serotonin syndrome and neuroleptic malignant syndrome]. ADVICE: Monitor clinically for signs of serotonin syndrome and neuroleptic malignant syndrome.
- **Clozapine:** Moderate interaction [serotonergic effects, dopamine antagonism, myelosuppressive effects, risk of serotonin syndrome and neuroleptic malignant syndrome, risk of neutropenia]. ADVICE: Monitor clinically for signs of serotonin syndrome and neuroleptic malignant syndrome. Monitor neutrophil count closely.
- **Lithium:** Major interaction [serotonergic effects, risk of serotonin syndrome]. ADVICE: Do not use concurrently. Stop lithium at least two weeks before starting linezolid. If linezolid is necessary in an emergency situation, stop lithium and monitor clinically for signs of serotonin syndrome for at least two weeks after lithium is stopped (while linezolid treatment is ongoing) or until one day after linezolid is stopped.
- **Carbamazepine:** Major interaction [risk of increased monoamine oxidase inhibition by linezolid]. ADVICE: Do not use concurrently. Do not use carbamazepine for two weeks after stopping linezolid.

PICO 8: HEPATITIS B/C

[The following table and information is summarized from drug-drug interaction searches using Lexi-Interact.]

- No interaction known or minor interaction
- Moderate interaction
- Major interaction

	Amitriptyline	Fluoxetine	Haloperidol	Risperidone	Chlorpromazine	Fluphenazine	Clozapine	Biperiden	Trihexyphenidyl	Lithium	Valproic acid	Carbamazepine	Diazepam
Tenofovir	●	●	●	●	●	●	●	●	●	●	●	●	●
Entecavir	●	●	●	●	●	●	●	●	●	●	●	●	●
Sofosbuvir	●	●	●	●	●	●	●	●	●	●	●	●	●
Daclatasvir	●	●	●	●	●	●	●	●	●	●	●	●	●
Ribavirin	●	●	●	●	●	●	●	●	●	●	●	●	●
Ledipasvir	●	●	●	●	●	●	●	●	●	●	●	●	●

There are no known interactions between **tenofovir**, **entecavir**, or **ribavirin** and medicines used for SMD.

SOFOSBUVIR:

- **Carbamazepine (CBZ):** Major interaction. Levels and efficacy of sofosbuvir may be reduced by intestinal P-glycoprotein inducers. CBZ may or may not be an inducer of intestinal P-glycoprotein; this effect is unclear. ADVICE: Do not use.

DACLATASVIR:

- **Risperidone:** Moderate interaction. Daclatasvir may increase levels of risperidone via P-glycoprotein/ABCB1 inhibition. ADVICE: Monitor for risperidone toxicity and adjust dose accordingly.
- **Carbamazepine (CBZ):** Major interaction. CBZ may reduce the levels and efficacy of daclatasvir via CYP3A4 induction. ADVICE: Do not use.

LEDIPASVIR:

- **Risperidone:** Moderate interaction. Ledipasvir may increase levels of risperidone via P-glycoprotein/ABCB1 inhibition. ADVICE: Monitor for risperidone toxicity and adjust dose accordingly.
- **Carbamazepine (CBZ):** Major interaction. Levels and efficacy of ledipasvir may be reduced by intestinal P-glycoprotein inducers. CBZ may or may not be an inducer of intestinal P-glycoprotein; this effect is unclear. ADVICE: Do not use.

Glossary

Bipolar disorder:
A person with bipolar disorder experiences episodes in which their mood and activity levels are significantly disturbed. They may experience periods of elevated mood and increased energy and activity (mania), as well as periods of low mood and decreased energy and activity (depression).

Collaborative care:
A model of care in which physical and mental health services are integrated. It is a multi-professional approach to patient care with a structured management plan, scheduled patient follow-up, and enhanced inter-professional communication.

Cognitive behavioural therapy:
Cognitive behavioural therapy (CBT) aims to address negative feelings by understanding thoughts and behaviours that lead to these feelings. A CBT therapist helps a person identify distorted thoughts and maladaptive behaviours.

Contingency management therapy:
Contingency management therapy is a form of therapy that involves encouraging positive, desired behaviours through rewards. Examples of desired behaviours include participating in treatment and reducing harmful substance use. It is recommended as a form of therapy for persons with alcohol or drug use disorders.

Depression, moderate to severe:
A person with moderate to severe depression typically may experience low mood, loss of interest or pleasure in activities, or low energy for at least two weeks or more. Additional symptoms may include reduced concentration and attention, reduced self-esteem and self-confidence, excessive feelings of guilt or unworthiness, bleak or pessimistic views of the future, disturbed sleep, diminished appetite, or ideas or attempts of self-harm or suicide.

Fixed-dose combination:
A fixed-dose combinations (FDC) is a combination of two or more medications in one pill, the goal of which is to simplify medication regimens. FDCs have been shown to increase adherence, decrease prescribing mistakes, and streamline procurement.

Glycaemic control:
Refers to control of blood sugar levels in patients with diabetes mellitus.

GRADE methodology:
Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology is an internationally agreed upon standard for rating the quality of studies included in a systematic review according to study design, risk of bias, inconsistency, indirectness, imprecision, and publication bias.

Iatrogenic effects:
Refer to the unintended side effects or health consequences of prescribed medication or other healthcare interventions.

Motivational interviewing or motivational enhancement therapy:
Motivational interviewing or motivational enhancement therapy is a type of therapy that engages a person in a discussion about their behaviour and what they perceive as the benefits and harms of this behaviour, with the goal of supporting behaviour change.

Noncommunicable diseases:
Noncommunicable diseases (NCDs) encompass all diseases that are not infectious in origin. The term NCDs commonly refers to mental disorders, cardiovascular diseases, diabetes, respiratory illnesses, and cancers.

Obese:
Excess weight, defined by a body-mass-index (BMI) of greater than or equal to 25 and less than 30.

Overweight:
Excess weight, defined by a body-mass-index (BMI) of greater than or equal to 30.

Severe mental disorders:
A group of conditions that include moderate to severe depression, bipolar disorder, and schizophrenia and other psychotic disorders

Schizophrenia:
Schizophrenia is a chronic psychotic disorder, which is characterized by distortions of thinking and/or perception. Schizophrenia may manifest by disorganized thinking, paranoia or suspiciousness, delusional beliefs, altered perceptions or hallucinations, limited range of emotions, and/or impaired functioning.

Social determinants of health:
Defined as the social circumstances across a lifetime in which people are born, raised, and live their lives. Inequitable distribution of resources impact these conditions and subsequently impact numerous health outcomes.

Universal health coverage:
Universal health coverage (UHC) is a principle by which all persons have access to essential health care without onerous out-of-pocket expenditures.

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