The role of mental health in obesity management

Clinical Practice Guideline
for the Management of Obesity in Adults in South Africa

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SOUTH AFRICAN METABOLIC MEDICINE AND SURGERY SOCIETY

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KEY MESSAGES FOR HEALTHCARE PROVIDERS

- Be aware of the links between mental health and obesity, and ensure that you manage weight-promoting medications used in the treatment of psychiatric conditions.
- Be aware that mental health can impact on obesity management efforts, and screen people living with obesity (PLWO) for potential mental illnesses that need to be addressed (with a focus on depression, binge-eating disorder [BED] and attention deficit hyperactivity disorder).
- Off-label (absence of approval by regulatory bodies) use of antipsychotics should be avoided, as significant metabolic adverse effects can occur even when these medications are prescribed at lower doses.
- When initiating antipsychotic treatment for the first time, avoid medications with higher metabolic risk, as individuals in their first episode respond well regardless of which medication is prescribed (and are at greatest risk for weight gain).
- Consider switching strategies to a lower metabolic liability antipsychotic in individuals with severe mental illness who gain weight on an antipsychotic treatment.
- For patients with severe mental illness who gain weight on antipsychotic treatments, metformin can be used in conjunction with behavioural obesity management interventions.
- For patients with severe mental illness who gain weight on antipsychotic treatments, glucagon-like peptide-1 (GLP-1) receptor agonists have the most safety and efficacy evidence among medications indicated for chronic obesity management. Cost and access may be a barrier for PLWO wishing to use this class of medications.
- Behavioural obesity management therapy, ideally as part of a multidisciplinary treatment approach, can be effective in managing weight in individuals with co-occurring mental illness. The intensity of the behavioural intervention will need to increase for individuals with more severe psychopathology in the context of obesity.
- The current approved obesity medications may be helpful in patients with a mental illness and should be used based on clinical appropriateness, safety, access and cost.
- For people with obesity and BED, evidence suggests that lisdexamfetamine, topiramate and second-generation antidepressants (duloxetine and bupropion) may be effective in reducing eating pathology. However, all are off-label pharmacological interventions in South Africa. While these medications are effective in reducing eating pathology, their effect on weight loss is less certain.
- Referral for more intense (i.e. long-term) and behavioural interventions, such as cognitive behavioural therapy (CBT), should be considered for individuals with significant binge-eating and depressive symptoms in the context of obesity.
- Individuals undergoing metabolic and bariatric surgery (MBS) should undergo a pre-surgical mental health screen by a qualified MBS clinician with experience in mental health to identify early risk factors for poor weight loss outcomes or mental health deterioration, and any mental health comorbidities. The presence of an active psychiatric disorder does not exclude patients from MBS, but warrants further assessment of potential impact on long-term weight loss.
- Assessment should continue following surgery and can include the use of either clinician-administered or patient self-report measures.
- PLWO should be monitored for alcohol and substance use changes, as well as self-harm and suicidal ideation, after MBS. They should be informed about altered alcohol metabolism following Roux-en-Y gastric bypass.

- We recommend psychiatric medication monitoring following MBS owing to potential changes in drug absorption and therapeutic effect, especially with malabsorptive surgical procedures. For psychiatric medications with a narrow therapeutic index, use of available protocols to manage perioperative levels is warranted.
- Postoperative behavioural and psychological interventions to support maintenance of weight loss and to prevent significant weight regain may be useful.
- For PLWO regaining weight after MBS, psychosocial interventions should be used to address comorbid psychiatric symptoms interfering with obesity management, such as depression and eating psychopathology, and to support behavioural change in the long term.
- MBS teams should focus on strategies to improve patient engagement during the post-surgery follow-up period, especially for high-risk patient groups.

KEY MESSAGES FOR PEOPLE LIVING WITH OBESITY

- There are clear links between mental illness and weight. Please ensure that your healthcare provider is aware of the treatments you are taking for your mental health issues.
- Individuals with co-occurring mental illness should receive behavioural therapy in combination with a biopsychosocial treatment approach to manage obesity.
- Antipsychotic medications should not routinely be prescribed (especially on a long-term basis) for issues like sleep and anxiety. Cognitive behavioural therapy or other psychological interventions should be the first-line treatment approach where appropriate.
- If you are gaining or have gained weight when taking an antipsychotic medication and changes in behaviour have not been sufficient, metformin can be used to help prevent further weight gain and/or reduce weight. Although evidence supports the use of metformin to prevent antipsychotic-related weight gain, it is not licensed for this indication in South Africa.
- Early studies suggest that, among medications approved for long-term obesity management in South Africa, weight loss medications of the GLP-1 (glucagon-like peptide-1) agonist class (such as liraglutide and semaglutide) have the most evidence to support their use to help reduce weight gained from antipsychotic medications.
- If you have gained weight while taking an antipsychotic medication, you can ask your doctor if there might be another antipsychotic with a lower weight gain risk. This should be a decision made together with your doctor, taking into careful consideration other potential side-effects/tolerability and the risk of mental health worsening.
- If you have binge-eating disorder, two medications (lisdexamfetamine and topiramate) can be helpful to reduce both binge episodes and weight, usually in conjunction with psychological treatments. These medications are not licensed for this indication in South Africa.
- If you are undergoing metabolic and bariatric surgery, early occurrence of psychiatric symptoms and eating difficulties after surgery could negatively influence your weight loss. All individuals living with obesity undergoing surgery should undergo mental health screening before surgery and have a multidisciplinary team identify and manage psychiatric symptoms and eating difficulties arising after surgery.
- For all individuals living with obesity who are undergoing metabolic and bariatric surgery, it is important to understand the increased risk of substance use problems (such as alcohol) and the potential risk of suicide after surgery. All these individuals should be aware of changes in how alcohol can affect them, changes in psychiatric medication absorption, and the importance of mental health monitoring after surgery.

RECOMMENDATIONS

1. We recommend regular monitoring of weight, glucose and lipid profile in people with a mental health diagnosis who are taking medications associated with weight gain (Level 3, Grade C).[1,2]
2. Healthcare providers can consider both efficacy and effects on body weight when choosing psychiatric medications (Level 2a, Grade B).[3-15]
3. Metformin and psychological treatment, such as CBT, should be considered for prevention of weight gain in people with severe mental illness who are treated with antipsychotic medications associated with weight gain (Level 1a, Grade A).[16, 17]

Much like trying to untangle the aetiology of obesity, trying to understand the association between weight gain and mental illness is currently beyond our ability.[18] We are aware of vulnerabilities that increase risk, both of weight gain in those with mental illness and, conversely, mental health issues in those with weight issues, and we know the end result is that the presence of one illness can impact on the other.[19,20] We also know that unconscious bias, a factor that those with obesity and mental illness often face, is compounded when the conditions co-occur and can be especially damaging in medical settings.[21] This has profound effects on patient care and medical outcomes and, from a broader systems perspective, on healthcare costs and access to care.[22]

Although it is generally understood that individuals with mental illness, especially serious mental illness, have an increased risk of being obese and/or overweight,[23] the picture in South Africa (SA) is less clear. There is a paucity of local research on this topic, and the authors were unable to find robust literature on the interplay of obesity and major depressive disorder (MDD) or anxiety disorders in SA. A SANHANES-1 (South African National Health and Nutrition Examination Survey) study that reviewed the association of psychological distress (measured by the Kessler Psychological Distress Scale) with body mass index (BMI) found a weak association between poorer mental health and an unhealthy BMI. Indeed, psychological distress was associated with being underweight.[24] In a single case-controlled, cross-sectional study on serious mental illness and metabolic syndrome, Saloojee *et al.*[25] did not find individuals with serious mental illness to have significantly higher BMIs than controls. These findings were in keeping with those in a systematic review and meta-analysis of the international prevalence of obesity and severe mental illness in which Afzal *et al.*[23]

found a similar lack of data and a relatively lower risk of obesity with serious mental illness for the entire sub-Saharan Africa region. There may also be a lack of knowledge of the confluence of the two illnesses among clinicians.[2] In a study performed in a large metropole, fewer than 1% of attendees with severe mental illness at a district hospital had received any screening for metabolic syndrome.[26]

The evidence-based recommendations in this chapter are intended to serve as a guideline to ensure that healthcare providers (HCPs) are evidence informed and can provide the best care to an often complicated and marginalised patient group.

The mechanisms underlying the association between mental illness and early-onset and sustained weight gain are multifaceted and involve both biological and psychological factors, superimposed on the background of social health determinants, and medication and metabolic side-effects.[18] This association is supported by clinical and epidemiological research from North America reporting prevalence rates of overweight and obesity of 25 - 60% for bipolar disorder, 30 - 70% for schizophrenia and 20 - 50% for depression.[27,28] Links have also been made between overweight and obesity and binge-eating disorder (BED), attention deficit hyperactivity disorder (ADHD) and post-traumatic stress disorder (PTSD).[18,29] Given the high prevalence of mental health issues in people living with obesity (PLWO), it is not surprising that mental illness is more prevalent in those presenting with weight-related comorbidities and those seeking obesity management treatment. It is therefore critical that HCPs involved in the care of PLWO prioritise clients' mental health needs as well.[30]

Being aware of the association between mental illness and obesity is not simply an academic exercise. Individuals with mental illness have increased morbidity and mortality, in some cases with a risk of premature death of up to 15 years, because of medical comorbidities, many of which are linked to weight gain.[31] It can be challenging to address both the physical and mental health needs of this population, but given the interaction between the two conditions it should be considered a priority, both at an individual and a health systems level. Research has indicated that individuals with mental health issues often fall through the cracks, and this outcome can be prevented with a standardised screening approach.[32]

There is a clear and irrefutable link between psychiatric medications and weight gain. While this association has been most clearly studied and documented in respect of antipsychotics,[7] medications used in the treatment of bipolar disorder, MDD and anxiety have all been shown to be associated with significant weight gain.[7] While it is important that medication efficacy be the first priority, it is also important that tolerability be considered. There is significant premature mortality secondary to physical health problems documented in individuals with mental health problems. Also, weight gain secondary to medication use is a common cause of medication discontinuation in patients requiring psychotropic medications.[33] It is therefore important that HCPs be aware of the side-effect profile associated with different psychiatric medications, and consider both efficacy and tolerability in deciding on appropriate short-term and long-term psychopharmacology.

Second-generation antipsychotics are approved by the US Food and Drug Administration (FDA), and in SA by the South African Health Products Regulatory Authority (SAHPRA), for the treatment of schizophrenia, bipolar disorder and depression under drug-specific circumstances. While second-generation antipsychotics have been argued to have a lower propensity to cause extrapyramidal side-effects compared with their first-generation counterparts when used on-label, they are indisputably associated with significant metabolic sequelae, including weight gain, glucose dysregulation and dyslipidaemia.[34,35]

Off-label use of antipsychotic medications: What are the safety and efficacy implications for metabolic comorbidity?

The rate of off-label use of antipsychotics in SA is unknown. In Canada, prescription of antipsychotic medications doubled, exceeding seven million prescriptions annually, between 2005 and 2012.[36] Concerningly, the most rapid increases in prescription patterns were attributed to use in off-label indications for which clinical evidence is less certain, including ADHD, anxiety, dementia, eating disorders, insomnia, obsessive-compulsive disorder, personality disorders, PTSD, substance use disorders and Tourette syndrome. A meta-analysis and several individual studies reported significant occurrence of metabolic adverse effects in the context of off-label antipsychotic use, including increased appetite and weight gain, increased triglyceride abnormalities, and an increased risk of precipitating diabetes.[37,38] In elderly patients with dementia, use of antipsychotics has been associated with an increased risk of mortality and cardiovascular events.[39-41]

Pharmacological interventions in mental illness and comorbid overweight or obesity

While behavioural interventions are first-line approaches for addressing metabolic comorbidities, these are often not sufficient on their own, and pharmacological interventions must be considered. Pharmacological interventions approved for treatment of obesity in the general population are likely to have a place in the management of PLWO with mental illness, keeping in mind population-specific considerations of efficacy and safety. For example, the combination naltrexone/bupropion may not be the first-line choice for patients with bipolar disorder owing to the risk of mania induction.[42]

Because mechanisms driving obesity may be different in patients with severe mental illness compared with the general population (i.e. psychotropic medications affect neurotransmitters associated with metabolic homeostasis), treatments not approved by licensing bodies for obesity treatment have been studied off-label in this population. Because antipsychotics, as well as antidepressants and mood stabilisers, carry a differential weight gain risk, lower-liability medications can also be considered as a strategy to target metabolic comorbidity in this population.[43,44]

Although antipsychotics are the psychotropics typically associated with the highest risk of weight gain, where switching these agents has been studied with regard to weight-related effects, prevention of further weight gain (as opposed to reversal of weight effects) tends to be found.[45] In a recent meta-analysis of randomised controlled trials (RCTs) and uncontrolled before-and-after studies, switching to aripiprazole was only associated with significant average reductions in weight of –5.52 kg in RCTs and –2 kg in before-and-after studies. Although a worsening of psychotic symptoms was not observed in these studies, average study duration may have been too short to adequately observe significant changes.[46]

Therefore, particularly when moving from high-risk agents (e.g. olanzapine), one of the primary benefits of switching is by effecting a plateau of weight gain, and the largest benefit is likely to be gained when switching is undertaken early in antipsychotic treatment.[45] While switching strategies has a place in clinical practice, the decision to switch antipsychotic drugs must be considered on a case-by-case

basis in the context of efficacy of the current regimen, tolerability of both current and potential new antipsychotic, and patient choice. Furthermore, since dose reduction alone has not been clearly effective in reversing weight gain associated with antipsychotic use, it is not a recommended strategy in this context.[43,44,47]

In other words, where weight loss is deemed necessary, additional interventions (such as pharmacological treatments) will probably be required in addition to switching of psychotropic medications. Please refer to specialist psychiatric resources, such as the Maudsley Prescribing Guidelines, for information on effective medications with a lower associated risk of weight gain. Ensuring that medication changes are carefully monitored and appropriate will be best served by ongoing collaboration with the patient's current mental HCPs.[45]

How effective are pharmacological interventions for obesity in patients with mental illness?

Agents currently approved for the treatment of obesity in SA include liraglutide (Saxenda®) and semaglutide (Wegovy®), both glucagon-like peptide-1 (GLP-1) receptor agonists (RAs); naltrexone/bupropion (Contrave®); phentermine (Duramine®); and orlistat (Xenical®). Below is a summary of those interventions that, in randomised controlled studies, show significant and consistent results (most interventions show small to medium effect sizes).[48] None of these agents is licensed in SA specifically for the management of weight gain induced by psychotropic medication, nor have they been extensively researched in individuals with comorbid mental illness. Furthermore, since obesity is a complex illness requiring a multidisciplinary approach, we would caution mental HCPs against prescribing medications for the treatment of obesity without the support of a multidisciplinary team. (See the chapter 'Pharmacotherapy in obesity management'.)

Metformin

Across several published meta-analyses of RCTs in patients with schizophrenia spectrum disorders, metformin consistently emerges as an effective and safe intervention resulting in modest weight loss compared with placebo (average of 3.5 kg), as well as improvements in lipid and insulin sensitivity parameters.[16,17,49,50] A meta-analysis that included individuals with mood disorders receiving mood stabilisers found similar beneficial effects of metformin over placebo.[51] Similar findings have been reported in two meta-analyses that assessed all RCTs investigating metformin for antipsychotic-induced weight gain. The effect of metformin may be greater in first-episode patients compared with chronically ill populations.[17,52] As noted by the authors who adapted this guideline for Ireland, the ability of metformin to induce a weight gain plateau early during antipsychotic treatment may be its most significant benefit.[45] The plateau of weight gain on antipsychotic treatment may otherwise take months (olanzapine) to years (clozapine) to occur, and is as yet unknown for many other antipsychotics.[53,54] Please refer to prescribing guidelines for further information on the recommended use of metformin for this indication.[55]

GLP-1 receptor agonists

Three RCTs have examined GLP-1 RAs (liraglutide) in PLWO with schizophrenia spectrum disorders taking antipsychotic medications.[56-58] Data from these trials were recently analysed in a participant-level data meta-analysis (N=141 participants). Endpoint weight for GLP-1 RAs was 3.61 kg lower than for controls. BMI, glycated haemoglobin (HbA1c), fasting glucose and visceral adiposity were all lower for the GLP-1 RA group. Weight loss in the GLP-1 RA group appeared to be greater for participants on clozapine or olanzapine, and for longer study endpoints. GLP-1 RAs were well tolerated, with no safety concerns apart from more common reports of nausea in the treatment group.[56] This study did not include enough participants or continue over a long enough period to detect uncommon effects that may be associated with GLP-1 RAs in the general population. However, to date, neuropsychiatric effects have not been noted in the use of these agents in a larger study,[59] and indeed, emerging evidence suggests that these agents may in fact have positive neuropsychiatric effects.[60] Access to this class of drugs is limited in SA, and cost is often a barrier to use.

Naltrexone/bupropion

Naltrexone/bupropion was examined in males with obesity and schizophrenia who were smokers, and showed no differences in weight change or smoking cessation rates compared with placebo.[61] In patients with schizophrenia using olanzapine, naltrexone alone (a component of naltrexone/bupropion), when compared with placebo in a small double-blind randomised clinical trial, was not associated with differences in BMI over a 12-week treatment period.[62] In 25 women with obesity and MDD, naltrexone/bupropion was found to modestly reduce both weight and depression scores.[63]

Orlistat

Orlistat was examined in a double-blind RCT in patients with schizophrenia spectrum or bipolar disorder taking antipsychotics.[64] The data did not show a significant difference in body weight between groups.

Topiramate

Topiramate, approved in SA only for epilepsy and migraines, represents a component of the topiramate-phentermine combination approved in the USA by the FDA for obesity treatment. A recent meta-analysis of RCTs examined the use of topiramate in patients with schizophrenia spectrum disorders and reported superiority of topiramate compared with placebo with regard to weight (3.76 kg) and BMI (1.62 kg/m^2) reduction.[65] Overall, the side-effect profile was comparable to control groups, with the exception of paraesthesia, which was more common in topiramate-treated patients. The topiramate group also had small improvements in psychopathology. Similarly, a meta-analysis examining RCTs conducted in mixed populations of schizophrenia spectrum and mood disorders (bipolar disorder) found topiramate to be associated with weight loss compared with placebo (3.95 kg), with no safety concerns reported.[51] Although cognitive disturbances have been linked with topiramate use (particularly in epilepsy populations),[66] these have not been sufficiently studied in schizophrenia spectrum disorders[65] but are clearly an issue to be aware of in assessing tolerability. An open-label trial in patients with anxiety disorders who experienced weight gain with selective serotonin reuptake inhibitors (SSRIs) also found topiramate to be associated with weight loss and reported no safety concerns.[67] Of note, however, a recent year-long observational study on the use of anti-obesity medications in individuals with mental illness noted a persisting increase in both depressive symptoms and suicidal thinking in those who took topiramate. Although the numbers were small, this was a consistent finding in only the topiramate-treated group and would necessitate special attention and monitoring on the part of the prescribing clinician when considering using this agent.[68]

In summary, adjunctive off-label use of topiramate appears to be modestly effective to mitigate weight gain in the context of schizophrenia spectrum illnesses, although mood and suicidality may be an emerging concern.[16,49,51,65,68] However, larger studies of

extended treatment, and more detailed examination of potential adverse effects on cognition and mood, are required before topiramate can be recommended for routine use in the management of obesity in mental illness.

Phentermine

Although registered in SA as a weight loss medication, phentermine is only licensed for short-term use (<3 months) and is contraindicated, per the drug monograph, in individuals with 'agitated states or a history of psychiatric disorders including anorexia nervosa and depression' or a 'history of drug/alcohol abuse or dependence'.[69] It is therefore not recommended as a weight loss agent in those with mental illness.

Other off-label obesity interventions that may be effective in the treatment of antipsychotic-associated weight gain and obesity include aripiprazole and H_2 (histamine) receptor agonists such as nizatidine. However, the quality of the evidence for these interventions is low, making the effects uncertain.[16,49,50] A published meta-analysis investigating H_2 agonists in antipsychotic-induced weight gain failed to find differences in weight reduction compared with placebo.[70] Recommendations on the use of most pharmacological agents are limited by the small number of studies utilising the agents, variability in the studies testing the same agent, and variable intensity and duration of the studies using the same interventional agent. Making a consensus statement on these treatments is currently challenging. We would caution against off-label prescribing of the majority of these agents until such time as the registration of these agents changes or further evidence emerges to robustly support their use in this population. Preference should be given to the use of metformin and GLP-1 RAs where applicable.

How effective are behavioural interventions for obesity in patients with mental illness?

In individuals with comorbid depression and obesity, behavioural obesity therapy has been studied alone and in combination with other treatments. Two RCTs comparing behavioural obesity therapy in combination with an additional psychological treatment, namely a behavioural intervention or cognitive behavioural therapy (CBT), resulted in comparable weight loss between groups and showed no advantage of combination treatment.[71,72] The addition of depression-specific interventions, such as behavioural activation therapy, to a behavioural lifestyle intervention aimed at weight loss may provide additional benefit compared with treatment with a behavioural lifestyle intervention alone for reducing depressive symptoms in PLWO.[71]

Significant research exists on the efficacy of behavioural treatments for PLWO with severe mental illness, including patients with psychotic illness and severe mood disorders. Interventions focused primarily on physical activity have shown inconclusive results related to weight loss in two meta-analyses.[73,74] A comprehensive meta-analysis by Caemmerer *et al*.[75] evaluated the effectiveness of non-pharmacological interventions for obesity management in individuals with severe mental illness across 17 included studies. This review consisted of CBT, psychoeducational interventions and nutrition and exercise interventions, with treatments lasting a mean of 19.6 weeks. The review demonstrated a mean difference in weight of –3.12 kg and a BMI reduction of –0.94 kg/m^2 overall across studies, with some studies showing sustained benefits at 8- to 52-week follow-up post intervention. CBT had a smaller effect than nutrition and/or exercise programmes. Analysis of moderating variables showed no difference between prevention versus treatment studies, studies with interventions more or less than 3 months' duration, and individual versus group treatments. A second meta-analysis also confirmed the above results related to overall weight loss. However, it showed that prevention trials were slightly more effective than treatment interventions for obesity in severe mental illness.[76]

An additional meta-analysis focusing on pharmacological and behavioural interventions to improve cardiovascular risk factors in adults with severe mental illness analysed 10 studies using behavioural interventions, which included either lifestyle interventions or CBT.[77] Behavioural interventions resulted in a mean difference of –3.13 kg. A more recent meta-analysis involving 17 studies using a behavioural intervention for weight loss in PLWO with severe mental illness showed that interventions of <6 months' and >12 months' duration led to comparable weight loss.[78] For these long-term behavioural interventions (>12 months), patients had more than 60% greater odds of achieving clinically significant weight loss (>5% weight loss) compared with controls. Bruins *et al*.[79] also evaluated the efficacy of behavioural interventions for PLWO and severe mental illness in a meta-analysis and showed improvements in specific cardiometabolic risk factors, namely waist circumference, triglycerides, fasting glucose and insulin. No effects were observed for blood pressure and cholesterol levels.

More recently, Speyer *et al*.[80] performed a systematic review, meta-analysis and meta-regression analysis looking at the mediators and moderators of treatment effects of lifestyle interventions for weight in individuals with serious mental illness. This work replicated other meta-analyses confirming that lifestyle interventions can lead to statistically significant weight loss, but concluded that these may not be clinically significant at a group level (average of 2.2 kg lost), and there was no effect on secondary cardiovascular outcomes. Heterogeneity was significant, study duration was generally short, and few of the trials were conducted outside Western countries.[80]

In summary, the results of these meta-analyses suggest that behavioural interventions, including lifestyle, nutrition and physical activity changes, result in an average weight loss at a group level of 2.2 kg and a BMI reduction of –0.63 kg/m^2. Research is needed to further elucidate the optimal duration, type and intensity of behavioural interventions for weight loss in patients with severe mental illness. Negative results for weight loss from the STEPWISE study, which used group psychoeducation and behaviour-focused sessions, suggest that more intense and multidisciplinary interventions may be needed for long-term weight loss, especially for individuals with schizophrenia spectrum disorders.[81]

This raises the question of whether behavioural and lifestyle interventions alone are adequate to address obesity in individuals with severe mental illness, which may mirror the waning enthusiasm with which lifestyle interventions are recommended as a single stand-alone approach to obesity in individuals without mental illness.[82] However, it must be kept in mind that although the gains of lifestyle interventions for those with severe mental illness may not be clinically significant at the group level, some individuals may benefit significantly from these interventions and further excessive weight gain may be prevented.[80] Furthermore, physical activity has been shown to have positive preventive as well as treatment effects across a broad spectrum of mental disorders and may contribute to a general improvement in health apart from a weight loss effect.[83] We would therefore recommend that education and lifestyle interventions continue to be offered to this population until such time as the gaps in the research on this topic are addressed or better alternatives become available.

How effective are pharmacological treatments for obesity in binge-eating disorders?

Several studies have explored the effectiveness of various pharmacological interventions (antidepressants, appetite suppressants, stimulants and anticonvulsants) in patients with BED. Peat *et al*.'s[84] meta-analysis of placebo-controlled RCTs reported a significantly greater reduction in binge eating and related psychopathology for second-generation antidepressants (bupropion, SSRIs and duloxetine), lisdexamfetamine (a central nervous system stimulant originally marketed for ADHD) and topiramate (an anticonvulsant). Only topiramate and lisdexamfetamine (but not antidepressants) reduced weight compared with placebo in patients. Review of comparative effectiveness suggested that lisdexamfetamine was better at inducing binge abstinence compared with second-generation antidepressants. Weight as an outcome was not compared. In their meta-analysis of the efficacy of psychological and medical treatments for BED, Hilbert *et al*.[85] found that lisdexamfetamine positively affected both weight and binge-eating outcomes compared with placebo.

An issue with this work is that the studies predominantly included middle-aged females of white ethnicity living with overweight or obesity. Questions of generalisability beyond this population, and data on how long an individual might need to remain on treatment, remain unanswered. Furthermore, lisdexamfetamine (Vyvanse) and topiramate are not approved for treatment of BED in SA. Lisdexamfetamine is a central nervous system stimulant; efficacy and safety may not be generalisable to patients with a history of substance use disorders, suicide attempts, bipolar disorder or psychosis, as these populations could be more susceptible to abuse or mental deterioration. We recommend that use of these medications for the treatment of BED in individuals with obesity should be limited to clinicians with experience in the management of eating disorders. Non-pharmacological interventions for BED are also effective and should be considered early in the treatment of BED as well.[86]

Given the high prevalence of psychiatric disorders in PLWO,[87] several studies have explored the impact of the bidirectional relationship of obesity and mental illness on the efficacy of behavioural interventions for weight loss and improvement in metabolic outcomes. Given that the most highly prevalent psychiatric disorders in obesity include MDD and BED, several studies have focused on the impact of behavioural and related psychosocial interventions in individuals with these comorbid mental illnesses.

How effective are behavioural interventions for patients with comorbid binge eating disorder and obesity?

Several studies have explored the effectiveness of behavioural interventions in patients with BED and obesity. However, a meta-analysis by Peat *et al*.[84] was limited to a qualitative analysis of study trials owing to heterogeneity in treatment outcome measures. Nonetheless, this review reported a significantly greater reduction in BMI with behavioural obesity therapy compared with therapist-led CBT, although this benefit was only found at the end of treatment, and the difference in BMI disappeared at follow-up. Moreover, behavioural obesity therapy had inconclusive and inferior results in comparison with CBT in terms of abstinence from binge eating and improvement in binge-eating frequency, respectively. In a meta-analysis by Hilbert *et al*.,[85] psychotherapy and self-help interventions (largely CBT-based therapies) did not significantly affect weight loss or BMI in individuals with BED, although the effects on binge-eating pathology were significant with large effect sizes. The dose of behavioural therapy may also influence the effectiveness of therapy in reducing binge-eating severity in obesity, with current evidence indicating that high-moderate doses, consisting of 16 to 24 sessions, may be needed to adequately address binge eating.[88]

What is the impact of 'food addiction' on obesity?

Evidence from animal models suggests that ingredients from highly processed foods can result in addictive-like biological and behavioural responses,[89-91] such as food craving.[92,93] However, there is ongoing controversy about the construct, and the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), 5th edition (DSM-5), has not recognised food addiction as an official diagnosis. Researchers have cautioned against equating obesity with food addiction[94] and have highlighted the need to better understand the impact of the 'food addiction' label for PLWO in terms of stigma, ethics and health policy issues.[95] (See the chapter 'The science of obesity'.)

How does mental illness affect metabolic and bariatric surgery outcomes?

Studies have demonstrated high lifetime rates of psychiatric illness in metabolic and bariatric surgery (MBS) patients, with rates approximating 70% when using structured psychiatric interviews.[87,96] According to the Ontario Bariatric Network registry, rates of a current psychiatric diagnosis were found to be 51%.[97] In a meta-analysis of 52 studies reporting prevalence data, rates of any current mood disorder, BED and anxiety were 23%, 17% and 12%, respectively.[98] There are few data available on the mental health aspects of individuals seeking MBS in the SA context. Van der Merwe *et al*.[99] reported on the gender-specific prevalence of 'neuropsychiatric symptoms' in their preoperative population in a private clinic. Diagnoses were made by the attending psychiatrist using DSM-IV-TR (4th edition, text revision) criteria, and it was found that 53% of females and 25% of males were depressed and 14.2% and 6.7%, respectively, suffered from anxiety. The authors commented that a history of eating disorders (including BED) was 'relatively low', but no further information or figures were included. Kruger-Steyn *et al*.[100] found a 22% rate of depression in a preoperative SA population at a state-funded institution. Depression was diagnosed and graded by the attending clinician, and the lack of universal rating and diagnostic criteria decreased validity. Although both studies noted rates of mental illness that were higher than the lifetime population prevalence of depression (9.8%) and any anxiety disorder (15.8%),[101] these findings are difficult to interpret owing to the lack of clarity surrounding diagnostic methodology. There are no data on mental health outcomes in SA postoperative populations.

Following MBS, data from the Longitudinal Assessment of Bariatric Surgery (LABS) Research Consortium have shown a significant reduction in any axis I psychiatric disorder (as per DSM IV-TR) at year two (16.8%) and year three (18.4%) after surgery, compared with pre-surgery rates (30.2%).[102] Moreover, MBS can result in improvements in cognition, most commonly memory and attention/executive function.[103] Only post-surgery eating disorder symptoms have been associated with less weight loss after MBS in multiple studies.[102,104]

Increases in suicide and self-harm have been noted after MBS.[105,106] A meta-analysis identified a pooled prevalence of suicide of 0.3%, compared with 1.8% for the pooled prevalence of all-cause mortality after surgery.[107] A Canadian population-based study examining self-

harm emergencies 3 years before and after MBS showed an increase in self-harm emergencies after surgery (3.63 v. 2.33 per 1 000 patient-years), with intentional overdose being the most common method.[105] Risk factors for self-harm included individuals aged 35 years or older, lower income status, and living in rural areas.

Studies have also identified an association between substance use disorders and MBS.[105] Rates of a lifetime substance use disorder in MBS candidates are 35.7%, with alcohol use disorder being observed in 33.2% of surgery candidates.[87] In a systematic review, the proportion of new-onset substance use after surgery among MBS patients ranged from 34.3% to 89.5%.[108] In this review, the most reliable predictor of postoperative substance use was a preoperative history of substance use.

Cigarette smoking and alcohol use disorders are common in MBS candidates. Cigarette smoking is problematic after surgery owing to risks of post-surgical ulcers. Although studies suggest that 28.6% of patients who were smoking before surgery quit after surgery, approximately 12% of PLWO were new-onset cigarette smokers after surgery.[108] In contrast, several studies have demonstrated an increased prevalence of new-onset alcohol use disorder after MBS. Rates of new-onset alcohol use disorder following Roux-en-Y gastric bypass (RYGB), for example, approximate 7 - 8% at 2 years after surgery.[109,110] RYGB is associated with a higher risk of alcohol use disorder after surgery compared with laparoscopic adjustable gastric banding.[111] This study showed an adjusted hazard ratio (AHR) of 2.08 for incident alcohol use disorder after surgery, and an AHR of 1.76 for incident illicit drug use. It has been suggested that increased alcohol use disorders may be related to altered alcohol pharmacokinetics after RYGB versus other surgeries.[112]

Limited data are available on opioid use disorders related to MBS, but preliminary data suggest that 4% of patients could become chronic opioid users after MBS.[113,114] Risk factors for chronic post-surgery opioid use are higher pre-surgery total days of opioid use, and pre-surgery use of non-analgesics, anti-anxiety medications and tobacco.[113,114] Further research is needed to clearly elucidate rates and predictors of opioid use in MBS populations.

How do psychiatric symptoms affect weight loss after MBS?

Several studies have attempted to assess mental health and eating psychopathological predictors of MBS outcomes. A meta-analysis did not find an association between pre-surgery psychiatric disorders and weight loss outcomes after MBS.[98] Moreover, a review suggests that pre-surgery psychosocial variables such as cognitive impairment and personality variables (e.g. high neuroticism) may be associated with reduced weight loss after MBS, although the latter may be more closely linked to eating pathology than weight loss directly.[115] Depressive symptoms after MBS have also been associated with reduced weight loss after surgery. However, results from additional studies have shown conflicting results.[116-118] In addition, conflicting results suggest that pre-surgical complex psychiatric illness is not clearly associated with poor weight loss outcomes after surgery.[115,119] There are therefore limited data on clear pre-surgery psychosocial predictors of weight loss outcomes related to MBS.

Further, studies have identified preliminary evidence suggesting that early adaptation to the eating changes required with MBS may be an early indicator of weight loss. This is reinforced by 3-year data from a large multi-site study demonstrating that, although overall eating pathology declines after surgery, those individuals who had higher eating pathology after surgery experienced less weight loss after MBS.[120] These findings were replicated in a postoperative cohort study in Canada that showed that binge-eating symptoms at 1 year after surgery were a predictor of reduced total percentage weight loss at 2 years after surgery.[104] Additional longitudinal studies are needed, but existing data suggest that MBS programmes should continue with ongoing monitoring of eating-related symptoms after surgery.

What tools can assist with assessment of psychiatric conditions before MBS and post-surgery monitoring?

Recent guidelines recommend a comprehensive psychosocial assessment before MBS to identify risk factors and for proactive identification of potential postoperative challenges that could be problematic after surgery. It is further recommended that such assessments be performed by a mental health clinician with experience in the care of MBS patients.[121] Psychosocial assessment should be conducted using a clinical interview and can be guided by such resources as the Boston Interview for Gastric Bypass assessment.[122] In addition, an interprofessional risk assessment tool called the Toronto Bariatric Interprofessional Psychosocial Assessment Suitability Scale (BIPASS) can provide a standardised approach to pre-surgery psychosocial assessment and can inform risk stratification before surgery.[123] Moreover, ongoing psychosocial monitoring is recommended given the influence of postoperative psychopathology on weight loss and psychiatric outcomes.

Patient self-reporting tools can be used to assist with pre- and post-surgery assessment of psychiatric symptoms. Currently, there is no single robust assessment tool that assesses all psychosocial domains during the preoperative assessment.[124] In a 2015 systematic review, the Master Questionnaire, a 56-item true/false questionnaire, was identified as the only tool that assessed multiple eating behaviour domains in PLWO.[124] In this same review, the Binge Eating Scale was identified as having the most support for assessing binge-eating symptoms in patients undergoing MBS.[124] A second review of patient self-report measures recommended the use of the Binge Eating Scale, the Night Eating Questionnaire and the Eating Disorder Examination Questionnaire to assess eating psychopathology in patients undergoing MBS.[125] The PHQ-9 (Patient Health Questionnaire-9) and the Alcohol Use Disorders Identification Test are recommended for assessing depressive symptoms and alcohol use, respectively, in MBS candidates.[125,126] However, further research is needed to fully establish self-report patient measures with robust psychometric properties in assessing eating psychopathology in MBS patient populations, especially in the unique post-surgery context.[127]

How are psychiatric medications affected by MBS?

Antidepressants are the most commonly prescribed psychotropic medication in MBS candidates, with accounts of up to 35% of a cohort of 2 146 patients in the LABS-2 study.[128] MBS procedures, whether restrictive or malabsorptive, can have an impact on drug absorption, distribution metabolism or excretion.[129]

Although the literature is far from robust, antidepressants are the most studied class of psychotropic medications in the MBS population. Despite small sample sizes, studies have demonstrated evidence of reduced bioavailability after surgery, specifically with malabsorptive procedures such as RYGB. Antidepressants such as sertraline and duloxetine have shown reduced antidepressant plasma concentration following MBS compared with controls.[130] HCPs therefore have to be vigilant and make sure that MBS patients do not exhibit discontinuation symptoms or worsening of depressive

symptoms, especially in the course of at least the first postoperative year.[131]

The impact of psychiatric medications on patient outcomes varies with the type of psychiatric medication and the therapeutic index of the medication. Anecdotal reports indicate that individuals may be at risk of antidepressant discontinuation syndrome due to drops in therapeutic levels of antidepressant early on after surgery. These symptoms are significant, as they may be mistaken as dumping syndrome, and they should be assessed in the early postoperative phase.[132]

In addition, mood stabilisers require special attention owing to the frequent comorbidity of obesity and mood disorders and the significant risk of acute relapse with subtherapeutic levels. Owing to its narrow therapeutic index, management of lithium could be challenging in the MBS population because of unpredictable absorption, preoperative liquid diets, possible fluid and salt shifts, and postoperative limited oral intake. Cases of lithium toxicity as well as subtherapeutic levels have been described in the literature, and perioperative lithium protocols have therefore been developed to improve clinician management of the drug.[133]

Data on use of antipsychotics in the MBS population are limited to case reports. However, it is important for clinicians to be aware of possible pharmacokinetic changes due to MBS procedures, as well as the metabolic adverse effects of these medications. For example, individuals taking ziprasidone or lurasidone may have inconsistent absorption owing to low calorie intake in the perioperative period.[134]

HCPs should work collaboratively with patients' existing mental HCPs to ensure that alternative antipsychotic options have been explored when preparing for MBS. Antipsychotics associated with a high risk of weight gain should be reviewed if already prescribed and avoided where possible in patients with a history of MBS.[45]

What is the evidence for psychosocial interventions to support weight loss after MBS?

There are some contrasting results regarding the impact of psychological interventions on weight loss after MBS. While studies have examined the effectiveness of pre-surgery behavioural and structured psychological interventions on weight loss outcomes, results have been inconclusive in the pre-surgery phase. For example, psychological support focused on behaviour change and modifying cognitions before and after surgery had no impact on weight loss as measured by BMI.[135] In a systematic review, behavioural interventions delivered with MBS improved weight loss outcomes, and although the number of studies was limited, the data suggest that postoperative psychological interventions had a greater effect.[136] Moreover, a meta-analysis of five studies also showed greater weight loss after surgery when surgery was combined with postoperative behavioural interventions.[137] The optimal time to initiate adjunctive behavioural interventions is therefore after surgery, but before significant weight regain has occurred.[138]

Specific psychological treatment modalities have been examined in MBS patient populations. These interventions include CBT (in person or remotely delivered via telephone),[118,139] acceptance commitment therapy,[140] mindfulness-based therapies,[141] and other psychological modalities that have improved eating pathology and psychological distress after surgery in the short term. Despite these symptom benefits, these psychological treatments have not translated to long-term post-surgery improvements in weight loss outcomes.

What factors affect adherence and engagement in MBS aftercare?

Poor adherence to post-surgical aftercare continues to challenge surgical practices. Regular postoperative follow-up for MBS patients is important to detect nutritional deficiencies and post-surgery eating difficulties, and to optimise weight loss.[142,143] Despite high rates of attrition from MBS aftercare programmes, only a few studies have explored the reasons for non-attendance. Studies report high follow-up loss rates ranging from 10% to 80%, with estimates approximating 50% in the first postoperative year and only 41% attending year two follow-up appointments.[144-146] Possible factors associated with poor postoperative appointment attendance include higher preoperative weight, younger age, family-related problems, work problems or unemployment, lack of insurance coverage, avoidant attachment (relationship) style, and longer distance to travel.[142,145-148]

Although there is no consensus regarding the reasons for patient non-adherence to recommended follow-up after MBS, a qualitative study exploring factors influencing patients' decisions to attend postoperative aftercare identified several variables.[149] Patients who stopped attending post-surgery follow-up appointments:

- Had greater confidence in their primary care physician's ability to manage their MBS care
- Had challenges with travel distance in terms of time and financial implications
- Felt that they failed to achieve weight-loss goals
- Perceived that follow-up had limited utility to their current care.

Additional studies are needed to further identify potential factors contributing to follow-up attrition.

Difficulties with patients' adherence to behavioural changes and the postoperative regimen have also been studied in the literature. Poor dietary adherence has been associated with baseline depressive symptoms and the presence of BED.[150] Moreover, higher attachment (relationship) anxiety and younger age (i.e. adolescents) have also been associated with poor adherence to postoperative vitamins.[148,150] Interventions to improve patient engagement and adherence to MBS follow-up recommendations have not been well studied. Interventions that have the potential to improve collaborative engagement between MBS multidisciplinary teams and general care/primary services could be helpful.[45]

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