The Management of Obesity in People with Severe Mental Illness: An Unresolved Conundrum

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Introduction

There can be little doubt in anyone's mind that obesity is a major global public health challenge. The prevalence has steadily risen over recent decades to the point where overweight and obesity now affect more than two billion people or 30% of the world's population, a rate that has tripled since 1975 [1]. Obesity comes at a huge personal cost through a range of medical illnesses from metabolic conditions such as diabetes, through musculoskeletal disorders to cardiovascular disease and various cancers as well as impaired mental well-being and reduced life chances. In terms of the societal cost, the economic impact of obesity was estimated at USD 2 trillion in 2014, through increased health expenditure, lost productivity and disability [2].

At its core, the cause of obesity appears simple, namely, consuming more calories than are expended but experience dictates that the causes are much more complex

and include both individual and societal factors. Dietary patterns have changed with an increased intake of energy-dense foods that are rich in fat and refined sugars, while physical activity has dropped both at work and leisure. Although, some might view these as personal responsibility, the observation that obesity affects the most socially disadvantaged people, at least in high-income countries, would argue that a lack of governmental policy has contributed to the epidemic by failing to create a healthy environment through transport and urban planning and support for healthy food choices.

Obesity in People with Severe Mental Illness

People with severe mental illness have been disproportionately affected by the obesity epidemic; in contrast to historical descriptions of an "asthenic" body habitus, recent studies indicate that obesity rates have increased substantially among people with severe mental illness and at a quicker rate than the general population [3, 4]. Changes in body composition are recognised early in the natural history with people with first-episode psychosis being more likely to have overweight and obesity [5]. Rapid

weight gain occurs after treatment initiation with antipsychotics, however, and this continues, albeit at a slower rate, in the following years [5–7]. Overall the prevalence of overweight and obesity is 2- to 3-fold higher than that in the general population [3].

All antipsychotics can lead to substantial weight gain with 37–86% of those with first-episode psychosis experiencing more than 7% of body weight gain during the first year of treatment [5, 8]. The propensity to weight gain differs between drugs with the greatest weight gain observed with olanzapine and clozapine [9]. Although much of the focus of research in this area has been on second-generation antipsychotics, weight gain may also occur with first-generation antipsychotics with chlorpromazine being associated with the most weight gain [10].

Although there is a marked inter-individual variation in weight change with antipsychotic treatment ranging from weight gain to loss [11], several demographic and clinical features are associated with more weight gain. These include antipsychotic-naïve younger people with first-episode psychosis, florid psychotic features, lower initial body mass index, non-white European ethnicity, a tendency to overeat at times of stress and concomitant cannabis usage [3]. The best predictor of long-term antipsychotic-induced weight gain, however, is rapid weight gain in the first 6 weeks of treatment [6].

The precise mechanisms by which antipsychotics induce weight gain are not fully understood. Although antipsychotics decrease energy expenditure [12, 13] and alter the gut microbiome in ways that could lead to weight gain [14], the effects of antipsychotics on appetite and food intake are the predominant mechanism [3]. Appetite regulation is complex and involves multiple neuropeptides, some of which are affected by antipsychotics [15]. The most important receptor interactions are with the 5-hydroxytryptamine_{2C} (5-HT_{2C}) receptor [12], histamine H₁ receptors [16] and dopamine receptors [17].

Antipsychotics, however, do not provide the whole explanation as unhealthy food choices, physical inactivity and social deprivation are also important aetiological factors in the development of obesity in this population [18, 19]. Disease-specific factors such as altered neuro-endocrine functioning may also play a role [3].

Obesity is an important contributor to the excess morbidity and mortality experienced by people with severe mental illness and may also worsen self-esteem and lead to further stigmatisation of those taking antipsychotics [20]. Weight gain may be one reason why people discontinue antipsychotic treatment with the risk of relapse and hospi-

talisation. There is a clear and pressing need to develop interventions for people with severe mental illness to support weight loss and a reduction in health inequality.

Challenges of Obesity Management

Everyday experience would suggest that managing overweight and obesity is challenging, and it is important to recognise that obesity is a long-term condition for which we have no cure, only treatments, and even these are not that effective. As Arya Sharma, past-Chair in Obesity Research and Management at the University of Alberta, Edmonton, so insightfully remarked, “Telling someone with obesity to lose weight is about as effective as telling someone with depression to cheer up” [21]. Weight rebound all too frequently occurs after behavioural interventions as the body has powerful homeostatic mechanisms to protect against weight loss [22, 23]. These include diminished signals from the gastro-intestinal tract to indicate nutrient ingestion, impaired signalling from fat stores and increased brain responses to food cues [24]. Even after bariatric surgery, the most effective treatment for obesity, some individuals do not lose weight [25].

Despite these challenges, some people can lose weight through lifestyle interventions whether these are undertaken individually or provided commercially or within health settings. One of the most impressive recent trials was the Diabetes Remission Clinical trial (DiRECT), which employed a low-calorie total diet replacement followed by stepped food reintroduction and support in people with type 2 diabetes. After 1 year, nearly a quarter of participants had lost more than 15 kg in weight and by 2 years, an average weight loss of 10 kg was maintained [26, 27]. The authors attribute their success to four key criteria: (1) an initial assessment using defined criteria for suitability of the individual to the programme; (2) an integrated programme with a focus on long-term behaviour change and strategies for relapse management, which should be introduced at the start of the programme; (3) protocols for management of anti-diabetes and anti-hypertensive medications and; (4) prospective data collection and audit for continuous programme improvement [28]. Other important mediators of success reported in the wider literature include higher levels of autonomous motivation, greater self-efficacy and self-regulation as well as positive body image and social support [29, 30], issues that surely affect people with severe mental illness to a greater extent than the general population.

Lifestyle Interventions in People with Severe Mental Illness

There has been a widespread feeling of nihilism towards lifestyle interventions in people with severe mental illness; the argument goes along the lines that if the general population cannot lose weight with lifestyle change, what hope is there of success in people with severe mental illness. Despite this pessimism, a considerable amount of work has been undertaken to develop appropriate lifestyle interventions in this population and initially suggested that, contrary to expectation, lifestyle interventions could be effective. In 2012, Caemmerer et al. [31] published a meta-analysis of 17 studies including 810 people receiving antipsychotics, which showed that lifestyle interventions led to a mean weight reduction of just over 3 kg, alongside improvements in other cardiovascular risk factors. The conclusions were, however, limited by the short duration of most trials (12–16 weeks) and the low number of participants (median 53, range 15–110). The National Institute of Health and Clinical Excellence (NICE) produced an expanded literature review of 24 studies in 2014 and came to broadly the same conclusions [32]. NICE, however, was more critical of the evidence; again, it noted the short duration of follow-up and small numbers but also commented on the high risk of bias and substantial heterogeneity of effect size between studies. Further concern about the effectiveness of lifestyle interventions was raised in a meta-analysis by Naslund et al. [33]. Although the authors reported an overall significant weight reduction in the 6 studies that lasted longer than a year, it is noteworthy that only 2 studies achieved a statistically significant weight loss and both of these included a diverse population of people receiving antipsychotics.

Despite the inconsistencies in the literature, national and international guideline groups have been quick to recommend the provision of lifestyle interventions for people with severe mental illness. For example, NICE recommends that “people with psychosis or schizophrenia, especially those taking antipsychotics, should be offered a combined healthy eating and physical activity programme by their mental healthcare provider,” while the World Federation of Societies of Biological Psychiatry recommends psychosocial interventions to treat weight gain [32, 34]. Healthcare providers are, however, left in the quandary of being required to provide services for people with severe mental illness without knowing exactly what these should involve.

Given the uncertainty in the literature and the resources currently being dedicated towards lifestyle intervention in people with severe mental illness, the meta-analysis by Speyer et al. [35] published in this issue is both timely and instructive. The meta-analysis, which is the largest to date, included 41 randomised controlled trials and 4,267 participants. The interventions reduced mean BMI by 0.63 kg/m², equivalent to a weight loss of 2.2 kg in association with a reduction of waist circumference. Intervention participants were 50% more likely to lose weight than control participants. This effect size is smaller than earlier reports and, as a 5% weight loss is generally recommended to improve health, is likely not to be clinically relevant.

When reported, the lifestyle intervention had no effect on quality of life, other cardiovascular risk factors, mortality or hospitalisation, although these negative findings likely reflect inadequate power as most trials were of too short duration to assess hard long-term outcomes.

There was considerable heterogeneity between trials, and it is noteworthy that Asian trials were more effective than trials undertaken in the USA, which in turn were better than European trials. It seems likely that these differences result from a number of confounding factors, such as provision of healthcare delivery and consultation style, rather than geographical location. Individual sessions were more effective than group sessions. Together, these two factors explained almost two-thirds of the heterogeneity. Interestingly, neither duration nor intensity of the intervention predicted its outcome. More recent and rigorous studies were less likely to demonstrate a beneficial effect, which may explain the smaller effect size than in earlier meta-analyses.

Complex Interventions

So where does this leave us regarding the management of overweight and obesity in people with severe mental illness? Before abandoning lifestyle interventions in favour of other interventions, it is worth considering again the heterogeneity both within and between trials. In the STEPWISE trial, the range of weight change was from 30 kg weight gain to 25 kg weight loss, suggesting that some individuals respond to lifestyle interventions while others do not [19]. We need to know much more about the predictors of success so that clinicians can assess an individual's suitability for any programme offered [28].

Obesity interventions are plagued with high drop-out rates, and consistent with general population lifestyle in-

intervention trials, Speyer's meta-analyses highlights that ~15% of participants discontinued their trial [36]. This is unsurprising as people are quick to recognize a lack of treatment effect and become discouraged; further work is needed to understand how to keep people engaged in these programmes as long-term attendance can predict greater weight loss.

Another challenge facing clinicians and researchers is the poor description of interventions. By definition, these are complex and it is not easy to assess what are the "active ingredients" of any one intervention. Given the lack of detail, it would be challenging for any clinician to faithfully replicate an intervention. Much better reporting is needed in future and perhaps should be made mandatory by journal editors, particularly now that it is so easy to publish supplementary material on the journal website.

Alternatives to Lifestyle Management

Switching Antipsychotics or Treatments

Given the different propensity between antipsychotics to induce weight gain, switching to an antipsychotic with less weight gain appears a sensible approach. Unfortunately, there is little evidence to support this; nevertheless, a few studies have reported that switching from olanzapine to aripiprazole or quetiapine may be beneficial, although any switch must balance the risk of a deterioration in mental health [37]. Adding aripiprazole to clozapine or olanzapine has also been shown to result in a modest weight reduction of ~2 kg [38]. As there is little evidence of an antipsychotic dose response with regard to weight gain, lowering the antipsychotic dose rarely achieves weight loss.

Alternatives to antipsychotics can be considered for bipolar illness or depression but weight gain may also occur with these treatments. Again, there appears to be a hierarchy of risk with antidepressants with paroxetine, amitriptyline and mirtazapine being associated with the most weight gain; by contrast, bupropion is associated with weight loss, while fluoxetine and sertraline appear weight neutral [39].

Pharmacotherapy

Although metformin has very little effect on body weight in the general population, this drug is the most extensively studied in the context of severe mental illness and is associated with a mean reduction in body weight of 3.3 kg over 3–6 months [40]. Nevertheless, the lack of long-term stud-

ies means it is unclear whether this weight loss would be maintained over the years of antipsychotic treatment. Many other drugs have been studied, of which orlistat, reboxetine and topiramate are associated with a small reduction in weight; however, none has the evidence base to recommend their routine use, not least because of the adverse effects of these drugs [41]. The most promising new drug class is the glucagon-like peptide-1 (GLP-1) receptor agonists. These drugs are used to treat diabetes and cause weight loss as well as improved glucose control. Liraglutide is also licensed as an obesity medication at a higher dose [42]. Three trials of GLP-1 receptor agonists have been completed in people taking antipsychotics, two of which demonstrated a weight reduction of over 5 kg [42–44]. A further trial of the obesity dose of liraglutide in people with schizophrenia is currently ongoing (Universal Trial Number U1111-1203-0068; EudraCT: 2017-004064-35).

Surgery

There is little experience of bariatric surgery in people with severe mental illness, but psychosis should not be seen as a contraindication where an individual has severe obesity and where otherwise surgery would be recommended [45].

Mitigating the Effects of Weight Gain

In a previous editorial in this journal, Fava and Rafanelli [46] applied the concept of "cascade iatrogenesis" to discuss how a series of multiple medical complications can be set in motion by a seemingly innocuous first event. In their editorial, they discussed the long-term effects of initiating antidepressants, but this concept can be applied equally well to antipsychotics, given the long-term sequelae of weight gain.

It is important that measures are taken from the onset of treatment to prevent weight gain. Although Speyer's meta-analysis included studies of lifestyle interventions to prevent weight gain, few have been conducted in very early psychosis. One study, however, from Australia suggests that a comprehensive approach to body and mind in early psychosis may attenuate weight gain [47].

Guidelines consistently recommend that weight is monitored regularly during the early phases of treatment to identify those individuals who gain weight rapidly after treatment initiation to whom interventions can be targeted [48]. The guidelines also advocate regular laboratory measurement to screen for diabetes and cardiovascular risk.

One Size Does Not Fit All

There is an urgent clinical need to develop robust interventions to address overweight and obesity in people with severe mental illness. It is clear that we are a long way from the ideal solution and much more work is needed to understand how best to tackle this problem. Given the complexity of obesity, it is likely that one approach will not suit all individuals. Within the general population, obesity guidelines recommend a tiered approach beginning with lifestyle and moving through pharmacotherapy to bariatric surgery for those with the most severe and intractable disease [49–51]. Perhaps the time has come where future research into managing obesity in people with severe mental illness should also examine care pathways rather than just the individual components.

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