BJPsych Open (2025)
11, e85, Page 1 of 3. doi: 10.1192/bjo.2025.34

Editorial

Latest findings challenge behavioural approaches to the management of antipsychotic-induced weight gain

Steve Kisely, Dan Siskind and Helene Speyer

Obesity is a major health problem among people with severe mental illness, linked to increased risk of chronic diseases and reduced life expectancy. This is attributable to a combination of factors, including lifestyle, social circumstances, medication side-effects and the illness itself. Second-generation antipsychotics are particularly associated with weight gain, affecting treatment adherence, symptoms and quality of life.

Keywords

Antipsychotics; lifestyle management; metformin; psychosis; weight gain.

Managing antipsychotic-induced weight gain is complex. Although lifestyle changes are often recommended, their effectiveness is limited. Switching medications or adding other drugs like metformin or glucagon-like peptide 1 (GLP-1) receptor agonists are options, but each has advantages and drawbacks.

Preventing antipsychotic-induced weight gain by choosing lower weight-gaining antipsychotics is ideal. Once weight gain occurs, collaborative decision-making with the person prescribed the antipsychotic is crucial. Recent qualitative findings highlight how patients often prefer early intervention and medication adjustments over lifestyle changes alone. Future research should involve people with severe mental illness (SMI) to develop more effective management strategies.

The public health importance of obesity in people with SMI

Obesity is a significant public health issue among individuals with SMI, being double that of the general population.[1] In turn, this increases the risk of cardiovascular disease, type 2 diabetes mellitus and cancer, leading to a threefold rise in standardised mortality rates and reducing life expectancy by 15 years compared with the general population.[2,3] The additional healthcare costs associated with managing obesity and associated complications are substantial, placing a financial burden on the healthcare system.

The role of antipsychotic-induced weight gain

The higher prevalence of obesity in this population comes from a combination of environmental, genetic and illness-specific factors.[4] These include sedentary lifestyles, poor dietary habits, social isolation, discrimination, inadequate management of psychotic symptoms and the side-effects of antipsychotic medications.[4] Second-generation antipsychotics (SGAs) are particularly associated with significant weight gain, which can negatively affect treatment adherence, worsen symptoms, lower quality of life and increase admissions to hospital.[4] Mechanisms include the interruption by SGAs (notably clozapine, olanzapine and quetiapine) of GLP-1, an intestinal peptide that modulates glucose regulation. In addition, there is antagonism of 5-HT2A or 5-HT2C serotonin receptors.[4] Most information concerns the 5-HT2C receptor, as olanzapine and clozapine are inverse agonists inducing more weight gain than ziprasidone and aripiprazole, which are partial agonists.[4] Some agents such as clozapine and olanzapine are also strong histamine (H1) receptor antagonists, leading to activation of hypothalamic AMP-related kinase (AMPK), which then stimulates appetite.[4]

The management of antipsychotic-induced weight gain is similarly varied and can include switching to agents with a lower tendency to cause weight gain, or lifestyle modification, as well as the addition of metformin or GLP-1 receptor agonists (GLP-1RAs).[4] Each of these have strengths and weaknesses.[4]

Prevention

Prevention is always the preferable option and entails choosing the agent least likely to case weight gain, such as aripiprazole, ziprasidone, lurasidone and amisulpride.[4] These agents have less affinity for H1 or 5-HT2C receptors and are less likely to increase AMPK activity.

Lifestyle interventions

Once antipsychotic-induced weight gain has occurred, other strategies have to be considered.[4] Lifestyle interventions, such as exercise, nutritional advice and cognitive–behavioural therapy, can result in statistically significant weight reduction,[5] although several clinical trials indicate that this may not reach clinically relevant loss.[6] This reflects findings in non-clinical populations where lifestyle counselling did not prevent cardiovascular disease, challenging the notion that behaviour can be changed solely through individual counselling and support.[7,8] In addition, focusing on individual responsibility ignores the fact that unhealthy lifestyle habits are closely associated to social determinants of health, and targeting these upstream determinants through public health

https://doi.org/10.1192/bjo.2025.34 Published online by Cambridge University Press

interventions may be a more effective way to tackle obesity.[9] This is of particular relevance to people with SMI, who are at greater risk of social isolation, educational disadvantage, unemployment and poor housing, thus making them an obvious case for structural changes.

Switching medication

In the case of olanzapine or quetiapine, switching to a more weight neutral agent is another option.[10] The weight gain potential of both the pre- and post-switch agent should be considered, but the best evidence is for changing to aripiprazole or ziprasidone.[10] However, changing agents entails the risk of relapse and is obviously not advisable when someone is psychiatrically unwell. In addition, it may not be possible for clozapine, which by definition, is prescribed in treatment-resistant cases where previous trials of alternative agents have been unsuccessful.[10] Furthermore, clinicians need to consider the correct approach to changing agents (e.g. cross-tapering as opposed to abrupt cessation), clinical severity, available support and any prior experiences of switching.[4]

Augmentation

In circumstances when switching is not feasible, augmentation with another agent may be an alternative.[4] Most information on augmentation concerns metformin, which is a biguanide anti-hyperglycaemic commonly used as a first-line treatment for type 2 diabetes.[4,11,12] Metformin acts by suppressing hepatic gluconeogenesis and increasing peripheral insulin sensitivity.[4] It can also reduce body weight in obese patients who are stabilised on olanzapine or clozapine, partly because it influences GLP-1.[4] This especially applies to clozapine and olanzapine, as both disrupt the GLP-1 pathway in the intestinal epithelium, reducing GLP-1 levels and therefore increases in body weight.[11] There is also increasing interest in GLP-1RAs.[4] These are synthesised in the intestinal mucosa and stimulate insulin secretion while decreasing glucagon secretion. There is evidence that two GLP-1RAs (exenatide and liraglutide) are effective for antipsychotic-associated body weight gain, especially in the case of clozapine or olanzapine.[4,13,14] Although all these approaches are generally well tolerated, there is always the risk of adverse consequences arising from polypharmacy. In the case of GLP-1RAs, there are additional concerns around cost, availability and the need for subcutaneous administration.

There is less evidence for other augmentation agents. For instance, H2 antagonists such as nizatidine, famotidine and ranitidine may be slightly effective, as well as other agents such as reboxetine and fluoxetine.[12] Topiramate and orlistat are less well tolerated and/or of limited benefit.[4,12]

Perspectives of those prescribed antipsychotics

In the discussion of how best to manage this issue, the views of those who are most affected, those with SMI, are rarely considered. The paper by Fitzgerald and colleagues on the views of people prescribed antipsychotics concerning antipsychotic-induced weight gain is thus a welcome addition to the literature.[15] The authors make the very valid point that most current clinical guidelines have minimal input from people on antipsychotic medication. In this well-designed qualitative study, 17 participants were asked about their experiences of antipsychotic-induced weight gain management, as well as their values and preferences on the issue.[15] They reported being unaware of, or having difficulty in accessing, appropriate interventions, and also felt that clinicians largely overestimated the manageability of antipsychotic-induced weight gain through behavioural changes, as well as underestimating the physical and psychological impacts. They did not favour behavioural change as first-line management and, if applied, diet and physical activity programmes should be tailored to antipsychotic-induced weight gain, rather than using generic approaches to weight gain that have been developed for the general population.

Participants highlighted barriers to effective behavioural change, including the effects of psychiatric symptoms and medication on their motivation, cognition and capacity, as well as the intensity of the food cravings they experienced when on antipsychotics and the rapidity of weight gain. Furthermore, they felt that psychiatric services often lacked the resources to support these interventions, and their effectiveness varies depending on whether high- or low-risk antipsychotics are used. In their experience, many dietary and lifestyle interventions were largely ineffective, reflecting research that shows minimal clinical impact. Additionally, participants expressed a preference for collaborative prevention and/or early intervention that considered antipsychotic choice and the use of augmentation agents. Of interest is the fact that these preferences are also backed by the available research evidence.

Participants stated that to be patient-centred, interventions for antipsychotic-induced weight gain should be proactive, personalised, comprehensive and involve teamwork. They suggested that to make this happen, there should be changes in the training and guidance that clinicians received, as well as how mental health services are delivered. They also mentioned the need for more support in implementing strategies that could help change individual behaviours, while also addressing the broader structural factors that might prevent the success of patient-centred interventions in these settings. This includes poverty, inadequate or insecure accommodation and factors that predispose to sedentary behaviour.

This is an admittedly small qualitative study ($n = 17$) from one health service in Ireland, and the findings need replication in larger studies from more than one location.[15] However, the results potentially challenge orthodox practice and highlight the need for greater involvement of people who are prescribed antipsychotics in the development of guidelines on the management of antipsychotic-induced weight gain. Any behavioural component should be specific to antipsychotic-induced weight gain as opposed to generic interventions for weight gain in the general population.

In conclusion, the management of antipsychotic-induced weight gain is complex and cannot solely rely on lifestyle modification, given the limited evidence and potential stigmatising effect on people with SMI. At an individual level, clinicians should initially prioritise the use of agents with the least potential for weight gain. When not possible, a shared approach should be negotiated and implemented in collaboration with those affected. These could include switching antipsychotic medication, dose reduction or augmentation with metformin or GLP-1RAs. At a population level, interventions should address relevant social determinants of health. At a policy level, further research is needed to better inform clinical guidelines that are specific to antipsychotic-induced weight gain. Combining all of these strategies can create a comprehensive plan that addresses antipsychotic-induced weight gain from multiple angles. Pharmacological interventions can provide more immediate effects, while addressing lifestyle and social determinants of health can offer long-term benefits.

Most importantly, the paper by Fitzgerald and colleagues reminds us about the importance of co-production. Including people with lived experience as equal partners in the development of clinical guidelines may not only provide epistemic justice, but also be necessary to create innovative approaches and improve

https://doi.org/10.1192/bjo.2025.34 Published online by Cambridge University Press

equity in health. Their involvement ensures that interventions are tailored to individuals' needs and preferences, thereby increasing the likelihood of success.

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First received 6 Aug 2024, final revision 10 Jan 2025, accepted 10 Feb 2025

Author contributions

S.K. and H.S. had the original idea for the paper. S.K. wrote the first draft. This was then revised critically for important intellectual content by H.S. and D.S., before S.K. incorporated amendments to produce the final draft, which was then approved by the other authors.

Funding

This study received no specific grant from any funding agency, commercial or not-for-profit sectors.

Declaration of interest

S.K. is a member of the International Editorial Board of the *British Journal of Psychiatry*, *BJPsych Open* and *BJPsych International*. S.K. did not take part in the review or decision-making process of this submission to *BJPsych Open*. D.S. is a member of the International Editorial Board of the *British Journal of Psychiatry*. H.S. is a member of the Editorial Board of the *Community Mental Health Journal*, *Psychiatric Rehabilitation Journal* and *American Journal of Psychiatric Rehabilitation and Psychiatric Services*.

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