Should antidiabetic medicines be considered to reduce cardiometabolic risk in patients with serious mental illness?

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Summary

- Substantially reduced life expectancy for people with serious mental illness compared with the general population is primarily driven by physical health issues, of which cardiovascular disease is the leading cause.
- In this narrative review, we examine the evidence base for use of metformin and other antidiabetic agents as a means for reducing this excess cardiometabolic disease burden.
- Evidence from randomised controlled trials (RCTs) suggests substantial potential for metformin to prevent or manage weight gain and glycaemic impairment induced by atypical antipsychotic medications, whereas the impact of metformin on other cardiometabolic risk factors is less consistent.
- Evidence from RCTs also suggests potential benefits from glucagon-like peptide-1 receptor agonists (GLP-1RAs), particularly for addressing cardiometabolic risk factors in people using atypical antipsychotic medications, but this is based on a small number of trials and remains an emerging area of research.
- Trials of both metformin and GLP-1RAs suggest that these medications are associated with a high prevalence of mild–moderate gastrointestinal side effects.
- The heterogeneous nature of participant eligibility criteria and of antipsychotic and antidiabetic drug regimens, alongside short trial durations, small numbers of participants and paucity of clinical endpoints as trial outcomes, warrants investment in definitive trials to determine clinical benefits for both metformin and GLP-1RAs. Such trials would also help to confirm the safety profile of antidiabetic agents with respect to less common but serious adverse effects.
- The weight of RCT evidence suggests that an indication for metformin to address antipsychotic-induced weight gain is worth considering in Australia. This would bring us into line with other countries.

Life expectancy is considerably reduced for people with serious mental illness when compared with the general population; worse, this gap appears to be widening in many countries.[1] A study that used Western Australian data found that for people who had been inpatients for psychiatric conditions, the gap in life expectancy increased between 1985 and 2005 — from 13.5 years to 15.9 years for male participants, and from 10.4 years to 12.0 years for female participants.[2]

Far from being solely a direct consequence of mental illness, much of this excess disease burden is a consequence of chronic physical health issues. The two leading areas of excess mortality among the Western Australian study participants were cardiovascular disease (CVD; 26% of excess burden for male participants and 35% for female participants) and cancer (14% of excess burden for male participants and 13% for female participants).[2] For people with serious mental illness, the risks of diabetes and CVD are approximately double those for people without serious mental illness, and the outcomes and complications associated with these conditions are worse.[3,4]

A complex range of interrelated factors contributes to the excess CVD risk in this population. First, certain aspects of health behaviour, including physical activity, diet and smoking status, are considerably worse than for the general population. A 2012 survey of 774 community mental health clients from New South Wales suggested that about half used tobacco (51%), a majority had inadequate fruit intake (60%) and vegetable intake (78%), and about one-third consumed alcohol at chronic risk levels (35%).[5] A more recent study of 301 community mental health service clients in Sydney who were prescribed long-acting injectable antipsychotics reaffirmed these concerns, with 44% meeting the criteria for metabolic syndrome.[6] Suboptimal health behaviour and excess risk factors among people with serious mental illness have been observed internationally, and are compounded by inadequate preventive care.[7] Frequently reduced cognition, motivation and self-esteem for individuals,[8] who are often of lower socio-economic status and therefore may have poorer access to health care than the general population,[7] add further to the challenges of lifestyle modification.

Some direct biological mechanisms associated with serious mental illness also contribute to increased cardiometabolic risk, including sympathovagal imbalance and increased prevalence of low grade inflammation.[7] These factors are further exacerbated by antipsychotic-induced weight gain and diabetes. While all antipsychotic medications may cause clinically meaningful weight gain (≥ 7%) and diabetes, particular concern relates to the atypical antipsychotic agents clozapine and olanzapine, and to a lesser extent risperidone, quetiapine and paliperidone.[9,10] Mean weight gain observed following olanzapine use in first-episode psychosis is about 7–9 kg over 10–12 weeks and 10–15 kg over 1–2 years.[11]

The precise pharmacological mechanisms for antipsychotic-induced weight gain are unclear, but the level of affinity for the muscarinic M3 receptor (high for olanzapine and clozapine) appears to be a particularly influential factor related to metabolic dysregulation and development of type 2 diabetes.[10] Effects on serotonin, histamine and other pathways also appear to influence cardiometabolic outcomes.

Overall, the scale of weight gain and metabolic risk associated with serious mental illness and its treatment suggests that many individuals, and perhaps most, will struggle to negate this burden via lifestyle modification. Antidiabetic medications might be an effective adjunct to lifestyle modification in reducing risk; however, despite advocacy and integration into Australian guidelines,[12,13] there is no evidence of antidiabetic prescribing

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being widely adopted for these patients in Australia. Thus, in this literature review, we scope the relevant evidence, with a particular focus on informing Australian clinicians.

Metformin pharmacology

Metformin is the antidiabetic medicine with the strongest evidence base for diabetes prevention. It is a biguanide agent that has been used as an antidiabetic medicine since the 1950s and was derived from the herbal remedy *Galega officinalis*.[14] Metformin's safety and efficacy have since been well established,[15] but its molecular mechanisms of action remain debated — suppression of hepatic blood glucose production, achieved by enhancing insulin effects in the liver, is likely to be the major pathway by which metformin effects are achieved.[14] Other potential pathways include: increase of anaerobic glucose metabolism in enterocytes and subsequent inhibition of glucose uptake to the liver; reduction in peripheral insulin resistance; suppression of proinflammatory cytokines; and modification of the gut microbiome.[16] Metformin is also thought to have actions that directly support weight loss or prevention of weight gain, but the pathways for this are still being elucidated.[17]

Metformin to prevent diabetes

The effectiveness of metformin for diabetes prevention in the broader at-risk population has been evident since the 1990s, although the level of risk reduction observed varies between trials.[18,19] The largest trial of metformin for diabetes prevention is the Diabetes Prevention Program/Diabetes Prevention Program Outcomes Study (DPP/DPPOS), which included 3234 adults in the DPP, and 2776 participants in the subsequent DPPOS follow-up; it was conducted in the United States during the period 1996–2001.[20] The DPP/DPPOS compared diabetes onset among participants who had a high baseline risk of diabetes and were allocated to one of three trial arms: metformin 850 mg twice daily, placebo, or intensive lifestyle modification. Participants in all trial arms received basic lifestyle support. At 2.8 years, there was a 31% reduction in risk in the metformin arm and a 58% reduction in risk in the intensive lifestyle modification arm, compared with placebo. It is important to note that the DPP intensive lifestyle intervention may not be feasible in many Australian settings (eg, it involved a minimum of 16 individual sessions over 24 weeks initially).

Subsequent DPPOS findings suggested sustained benefits 15 years after trial completion.[21] Although diabetes incidence reduced in both placebo and metformin arms — from 11.0 cases and 7.8 cases per 100 person-years respectively during the trial to 5.6 and 4.9 cases per 100 person-years (comparable to the lifestyle intervention group) after trial completion — the difference in cumulative incidence persisted between placebo and metformin, which the research team attributed to possible "exhaustion of susceptibles".[21] This suggestion is supported by DPP findings of greatest impact in younger, overweight individuals, which is highly pertinent considering the profile of patients with serious mental illness when they are starting antipsychotic therapy.[18] Limited evidence exploring the potential of combining metformin therapy and lifestyle modification has not demonstrated a significantly reduced rate of diabetes onset compared with either intervention individually.[22]

Metformin use in serious mental illness

To scope studies of antidiabetic medicine use in patients with serious mental illness, we searched the PubMed and Embase (including an integrated MEDLINE search) databases to identify systematic reviews published on the topic between 2008 and November 2021. From these searches, we identified 20 systematic reviews, including 17 with meta-analyses, to include in our review. The literature search process and details of included reviews are presented online (Supporting Information, supplementary material 1). Individual trials involving metformin and other antidiabetic agents were smaller than general at-risk population studies. The reviews included between 205 and 4052 participants derived from between 4 and 61 studies, in accordance with their search and eligibility criteria. Most reviews focused on metformin and considered a variety of relevant perspectives in terms of patient subgroups and clinical outcomes. In addition, most reviews measured weight change and related parameters as their primary outcome. Broader CVD-related outcomes such as lipid profile and glycaemic management variables were more comprehensively examined in reviews published since 2014.

Most trials included in the systematic reviews involved small participant numbers (eg, 30–70 per trial) and short follow-up periods (mostly 3–4 months). A few randomised controlled trials (RCTs) had a larger sample (> 100 participants) or longer follow-up period (24–26 weeks), but not both. Several Chinese language studies were included in some reviews, but important shortcomings were reported for many of these, including lack of intention-to-treat analyses, failure to specify funding sources, and lack of double blinding.[23,24] One review identified substantially greater reductions in weight and body mass index (BMI) in Chinese RCTs compared with non-Chinese trials,[23] but it is unclear whether these findings reflect younger patients in the Chinese trials, study design issues, or other factors.

Metformin trial outcomes in serious mental illness

Key meta-analytic findings from the systematic reviews involving people with serious mental illness that we identified are provide online (Supporting Information, supplementary material 2). Although trial parameters such as participant profile, antipsychotic of interest and follow-up period varied across studies, the consistent messages for metformin were:

- Metformin seems to be an effective and sufficiently safe option to prevent or reverse some of the weight gain associated with antipsychotic use, with a typical mean weight loss of 3–5 kg compared with placebo or usual care.
- Metformin, with or without adjunctive lifestyle modification, achieved a net weight loss across multiple reviews; however, the combination may be more effective than metformin alone.[25]
- Factors associated with increased weight loss included the use of atypical antipsychotic agents, younger patients, and initiation of metformin very early in or during, or before initiation of, antipsychotic therapy.[25,26]
- The evidence in favour of metformin was largely consistent across outcomes that are directly related to weight loss and glycaemic management such as BMI, waist circumference, glycated haemoglobin (HbA_{1c}) level and fasting blood glucose level, but inconsistent for other outcomes.

A point of difference for most serious mental illness trials when compared with trials on diabetes prevention in the general population was the absence of dysglycaemia as an eligibility criterion. Typically, only trials seeking to reverse weight gain due to use of atypical antipsychotic agents would regularly

require some cardiometabolic risk factor, usually including excess bodyweight or a minimum weight gain since initiation of atypical antipsychotics.[27-29] Trials to prevent weight gain on initiation of atypical antipsychotic therapy often excluded individuals with chronic physical health problems, including CVD and diabetes, but several international trials still achieved significant improvements in weight or BMI (or both) despite most participants being normal weight.[27-29] The relatively low prevalence of classical risk factors in such trials suggests that intrinsic risk of cardiometabolic disease and weight gain among people with serious mental illness who are using atypical antipsychotic therapies may be sufficient to justify intervention in the absence of baseline dysglycaemia or other risk factors.

A majority of metformin trials in this area focused on weight management rather than prevention of weight gain. Such trials typically used metformin dosages of 1000–1500 mg daily; dose-dependent weight loss was suggested, and one study that included 55 participants reported significantly reduced weight at 12 weeks for participants taking 1000 mg daily but not those taking 500 mg daily.[27] A further important finding from an intention-to-treat analysis that included 128 participants was that, in contrast to evidence from the general population, a combined metformin–lifestyle intervention among people with established antipsychotic-induced weight gain (> 10% bodyweight) may significantly affect weight and waist circumference when compared with either intervention component individually.[28] However, translating these findings to an Australian setting could be challenging, as the population was quite young and healthy, and the intervention involved close monitoring and supervision of participants.

Prevention trials have typically used daily metformin doses ranging from 750 mg to 2000 mg, with conflicting outcomes. In two trials, initiation of metformin at the same time as olanzapine reduced adverse effects on bodyweight and insulin resistance.[29,30] By contrast, another study found no significant benefit with metformin versus placebo among inpatients switched from conventional antipsychotic to olanzapine;[31] this may have been a consequence of recruiting older patients and switching from a conventional antipsychotic to low dose olanzapine (10 mg daily). Of the trials demonstrating benefit, one applied a naturalistic antipsychotic treatment regimen and the other was an inpatient trial that used olanzapine 15 mg daily in younger first episode patients.[29,30]

Across the trials, there were several common methodological strengths and weaknesses. Weaknesses included small sample sizes, lack of a priori primary outcomes or sample size calculations based thereupon, and failure to use intention-to-treat analyses. Comorbidities were often poorly defined, while only a few trials rigorously evaluated adverse events. Also, reliance on intermediate cardiometabolic outcomes rather than cardiovascular endpoints was a substantial limitation of the short duration trials that included people with serious mental illness.

Trial design factors affecting trial outcomes should be considered when reflecting on how interventions could be translated to Australian practice settings. These include the intensity of some lifestyle modification support, standard atypical antipsychotic dosages (often low dose olanzapine [10 mg daily]) for the trial duration, exclusion of patients with other mental illnesses or treatments, and sometimes substantial levels of patient oversight to maintain medication adherence and health-related behaviours. Most prevention trials clarified their exclusion of people with diabetes, whereas trials to mitigate antipsychotic-induced weight gain often included such patients. Trials aimed at reversing weight gain typically recruited patients who experienced weight gain of at least 10% bodyweight, although results from a recent pilot RCT conducted in Singapore that included 17 participants suggest that there may be benefits following first episode psychosis for patients with weight gain as low as 5% bodyweight.[32]

A caveat for interpreting meta-analysis results is that many do not provide subgroup analyses for those without (and with) diabetes at baseline. Indeed, ten of 17 meta-analyses did not provide baseline descriptions of diabetes status (Supporting Information, supplementary material 1). One review identified potentially weaker reductions in HbA_{1c} and fasting blood glucose levels when people with diabetes were excluded.[33]

Evidence for other antidiabetic medicines

Several reviews examined other antidiabetic drugs — most notably glucagon-like peptide-1 receptor agonists (GLP-1RAs) and rosiglitazone. All these reviews identified promising results, but findings from each were based on a limited pool of studies and small numbers of participants, so further research is needed before firm conclusions can be drawn (Supporting Information, supplementary material 1 and 2).

GLP-1RAs have generated substantial interest in recent years. The three initial trials, examined in several reviews, involved treatment for antipsychotic-induced weight gain using standard maximum GLP-1RA dosages recommended for diabetes (all given subcutaneously): one double-blind, placebo-controlled RCT using exenatide 2 mg once weekly; one open-label RCT using exenatide 2 mg once weekly; and one double-blind, placebo-controlled RCT using liraglutide 1.8 mg once daily.[34-36] These trials varied in terms of participant eligibility; notably, they had different inclusion and exclusion criteria relating to diabetes, glycaemic status and antipsychotic medications used.

In the only trial that was not restricted to atypical antipsychotics (exenatide versus placebo, $n = 40$), there was no significant improvement in the weight-related primary outcome at 3 months.[35] Conversely, in the trial in which participants had prediabetes, had a BMI of ≥ 27 kg/m^2 and were using atypical antipsychotics, participants in the liraglutide group (compared with those in the placebo group) had significantly greater improvements in bodyweight after 16 weeks (mean weight loss difference, –5.3 kg [95% CI, –7.0 to –3.7 kg]), significantly greater achievement of normal glucose tolerance after 16 weeks (64% versus 16%, $P < 0.001$) and greater improvements for several other cardiometabolic parameters.[36] In a follow-up of this study, there was evidence of continued significant weight benefits 12 months after the end of the trial (mean weight loss difference, –3.8 kg [95% CI, –7.3 to –0.2 kg]; $n = 88$) but glycaemic benefits seen at 16 weeks did not persist.[37]

The importance of better understanding the apparent benefits of GLP-1RAs is clear and is a major focus of current research in this area. Since publication of the three trials on GLP-1RAs, a pilot RCT testing higher dose liraglutide (3 mg subcutaneous daily [dosage for obesity]) has been published.[38] This trial recruited participants with a BMI of ≥ 30 kg/m^2 (or a BMI of 27–29 kg/m^2 plus a weight-related complication) who had schizophrenia, schizoaffective disorder or first episode psychosis. It identified significantly improved weight (mean decrease, –6.0 kg [95% CI, –10.8 to –1.36 kg]; $P = 0.015$), weight loss as a percentage of bodyweight (mean decrease, –4.6% [95% CI, –8.4% to –0.7%]; $P = 0.021$), BMI (mean decrease, –1.76 kg/m^2 [95% CI, –3.31

to –0.20 kg/m^2]; P = 0.028), HbA_{1c} levels (mean decrease, –3.6 mmol/mol [95% CI, –5.9 to –1.3 mmol/mol]; P = 0.003) and waist circumference (mean decrease, –7.2 cm [95% CI, –12.3 to –2.1 cm) among intervention group participants at 6 months compared with those in the placebo group. A key limitation of this pilot study is that the analysis was only performed on data for 34 out of 47 people randomly assigned to a study arm; further, 321 eligible patients were invited to participate in the trial in order to recruit the 47 participants. There are therefore questions about the representativeness of the final participant group, and the practicality and feasibility of daily dosing.

Adverse events associated with antidiabetic medicines

Three reviews described the safety and tolerability of antidiabetic agents (Supporting Information, supplementary material 2). In individual trials, the extent to which adverse events were systematically assessed was variable,[39] and most trials lacked statistical power for comparative analysis of adverse events. One review (a meta-analysis) found that only nausea and vomiting were significantly increased by metformin compared with placebo.[40] Another review, which specifically examined outcomes for patients with schizophrenia, identified that metformin was associated with significantly higher rates of nausea, vomiting and diarrhoea compared with placebo.[23] All three GLP-1RA trials reported high levels of gastrointestinal side effects among participants, but these may diminish over time.[36] Determining the prevalence of serious but less common side effects (eg, lactic acidosis) will require trials with larger sample sizes.

Translating evidence into policy and practice

Australia is arguably lagging behind other countries when it comes to endorsing metformin as an option for supporting improved cardiometabolic health in people with serious mental illness — or indeed for diabetes prevention generally. In light of mounting evidence, metformin is now indicated for the prevention or delay of type 2 diabetes in at-risk individuals in over 65 countries, but not in Australia.[18] Similarly, many influential guidelines and organisations in Australia and overseas have provided specific guidance and recommendations advocating the use of metformin for diabetes prevention or weight management in people with serious mental illness. Organisations that have provided such guidance and recommendations include the Royal Australian and New Zealand College of Psychiatrists, the American Diabetes Association, the National Institute for Health and Care Excellence (in the United Kingdom), the World Health Organization and Obesity Canada (Supporting Information, supplementary material 3). Although specific recommendations and criteria for use vary, the principle of using metformin for prevention and management of antipsychotic-induced weight gain, and for prevention of diabetes, seems broadly accepted.

Conclusion

Metformin is reasonable to consider as adjunctive therapy with lifestyle modification among people who are at risk of or have established antipsychotic-induced weight gain, particularly where lifestyle modification is not feasible or is inadequately effective. There seems little justification for use of metformin as an alternative approach without attempting lifestyle modifications. Evidence for other agents reviewed here is limited, but GLP-1RAs show promise. In Australia, the Therapeutic Goods Administration currently only indicates metformin for use in the treatment of type 2 diabetes if lifestyle modification is deemed insufficient for diabetes management.[41] Ultimately it is time to question whether the absence of an approved indication in Australia relating to diabetes prevention means that patients at elevated risk of diabetes, including those with serious mental illness, are being denied access to effective medication that might help enhance their longevity.

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Supporting Information

Additional Supporting Information is included with the online version of this article.