



Obesity in Severe Mental Illness: Antipsychotic-Associated Weight Gain and the Metabolic Monitoring That Does Not Happen

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Abstract

People with severe mental illness carry a substantially raised burden of obesity and metabolic syndrome, and antipsychotic treatment contributes to it. Mean weight increase after starting antipsychotic treatment is reported at 4.85 kg, and metabolic syndrome prevalence differs markedly between agents, from 47.2 per cent with clozapine to 19.4 per cent with aripiprazole. The attribution is not simple. Meta-analysis reports metabolic syndrome in 20.2 per cent of unmedicated patients with schizophrenia, and prevalence rises across illness stages from 10 per cent in drug-naïve patients to 34.2 per cent in multi-episode patients, so illness and circumstance contribute alongside medication. International guidance on metabolic monitoring has been consistent for close to two decades and specifies weight, glucose, lipids and blood pressure. Audit repeatedly finds it incompletely performed. This review sets out the measured prevalence, what the comparisons between agents and stages support, and the gap between recommended and recorded monitoring.

Keywords: Severe mental illness; Antipsychotic medication; Metabolic syndrome; Metabolic monitoring; Cardiometabolic risk

Introduction

People with schizophrenia and bipolar disorder have markedly reduced life expectancy, and most of the excess mortality is cardiovascular rather than psychiatric [1,2,3]. Obesity, dysglycaemia and dyslipidaemia are more common in this population than in the general population, and antipsychotic treatment contributes to that burden [4,5,25,33]. Relative risks of diabetes, dyslipidaemia and hypertension in this population have been quantified in systematic review [33], and the epidemiology of diabetes in psychotic disorders described separately [34].

Antipsychotic medication is the foundation of treatment for these conditions, and decisions about which agent to use, and whether to continue it, rest with the treating psychiatrist and the patient [6,7]. This review does not address those decisions. Its subject is what has been measured about metabolic risk in this population and what is recorded about it in practice.

International guidance on metabolic monitoring has existed since the mid 2000s and is consistent across jurisdictions [8,9,10]. This review examines the measured prevalence, how far it can be attributed to medication, and the gap between recommended and recorded monitoring.

Material and Methods

Search strategy: PubMed and the archives of the major psychiatry, endocrinology and general medical journals were searched for studies of metabolic outcomes in severe mental illness. Search terms combined antipsychotic, schizophrenia and severe mental illness with weight gain, metabolic syndrome, diabetes and metabolic monitoring. Reference lists of the principal review [4] and monitoring guidance [8,9,10] were screened by hand for primary sources.

Eligibility: Studies were included if they reported prevalence or incidence of metabolic outcomes in defined populations with severe mental illness, compared agents or illness stages, or reported the completeness of metabolic monitoring. Guidance documents are cited for the measurements they specify and are identified as such.

Data extraction and handling: Population, treatment status, the definition of metabolic syndrome used and the reported estimate were extracted as published. Treatment status is stated alongside every prevalence figure, because unmedicated, first-episode and multi-episode populations differ substantially and comparisons between them bear directly on attribution. This review reports measured outcomes and monitoring rates. It offers no guidance on the management of weight and none on the choice, dose or continuation of psychotropic medication, which are matters for the treating clinician. No pooling or re-analysis was performed. Figures 1 to 6 and Tables 1 to 3 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

The scale of the excess: Patients with schizophrenia are reported to be 2.35 times more likely to have metabolic syndrome than the general population, and patients with bipolar disorder 1.98 times, with a prevalence of 37.4 per cent in the latter group. Within bipolar disorder, those taking antipsychotics had higher odds of metabolic syndrome than those who were not, at an odds ratio of 1.72 (Figure 5) [4,11].

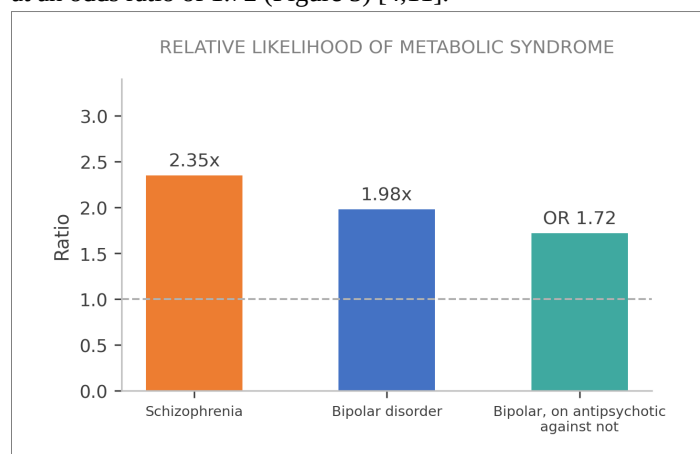


Figure 5: Relative likelihood of metabolic syndrome against the general population [4,11]

Weight change after starting treatment: Mean bodyweight increase following initiation of antipsychotic treatment is reported at 4.85 kg (Figure 4). Weight gain is also among the principal reasons given for discontinuing these medicines, so it bears on treatment adherence and readmission as well as on cardiometabolic risk [12,13].

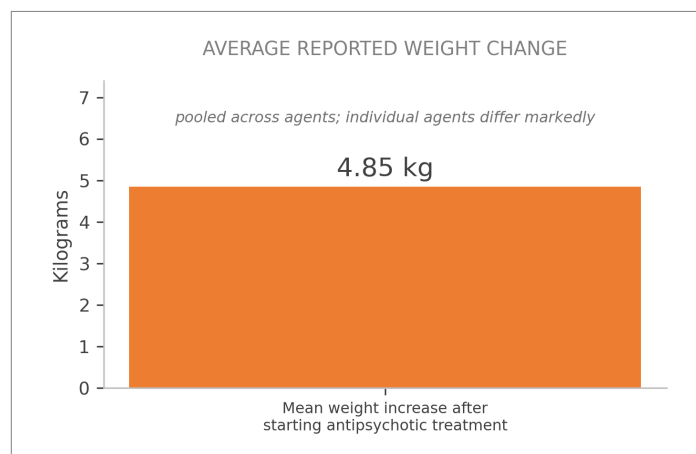


Figure 4: Average reported weight change after starting antipsychotic treatment [12]

Differences between agents: Reported metabolic syndrome prevalence differs considerably by agent: 47.2 per cent with clozapine, 37.3 per cent with quetiapine, 36.2 per cent with olanzapine, 22.8 per cent with amisulpride and 19.4 per cent with aripiprazole (Figure 1) [4,14]. Clozapine and olanzapine are consistently ranked highest for weight gain and for glucose dysregulation, followed by quetiapine and risperidone [12,15,16,25]. Cardiometabolic risk on first exposure has been examined in children and adolescents [26].

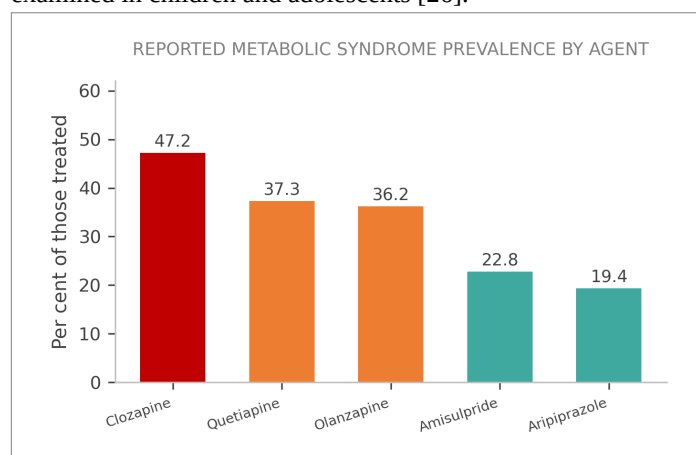


Figure 1: Reported metabolic syndrome prevalence by antipsychotic agent [4,14]

The unmedicated comparison: A meta-analysis reported metabolic syndrome in 51.9 per cent of patients receiving clozapine, 28.2 per cent receiving olanzapine and 27.9 per cent receiving risperidone, against 20.2 per cent of unmedicated patients with schizophrenia (Figure 2) [17,18]. A clozapine clinic in Australia reported 58.3 per cent meeting criteria [18].

Prevalence rises with illness stage: Metabolic syndrome prevalence was 10 per cent in drug-naïve patients, 15.9 per cent in first-episode patients and 34.2 per cent in multi-episode patients, a difference that persisted after correction for age ($p < 0.001$) (Figure 3) [4,19]. Estimated diabetes prevalence in antipsychotic-naïve patients is 2.9 per cent, and treatment duration is associated with higher rates [4,20].

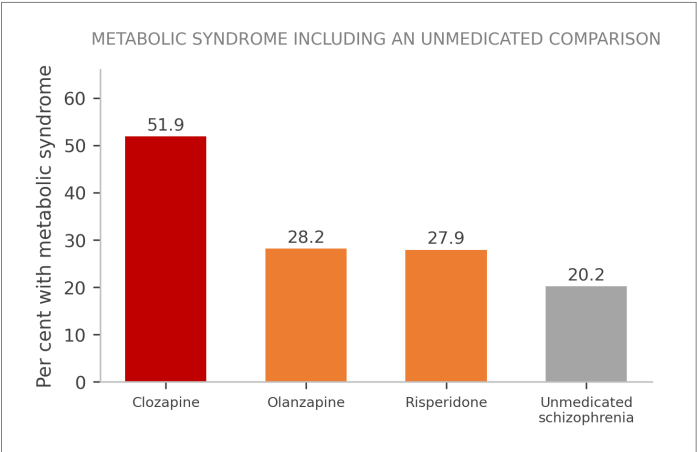


Figure 2: Metabolic syndrome by agent including an unmedicated comparison [17,18]

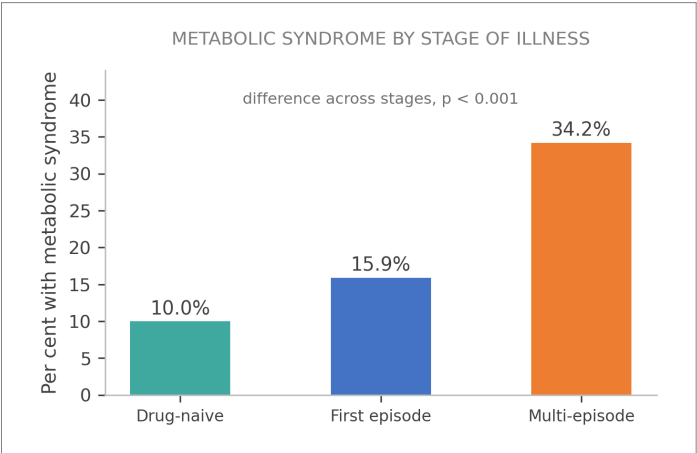


Figure 3: Metabolic syndrome prevalence by stage of illness [4,19]

Population	Metabolic syndrome	Source
Drug-naïve	10%	Review of prevalence [4,19]
First episode	15.9%	Review of prevalence [4,19]
Multi-episode	34.2%	Review of prevalence [4,19]
Unmedicated schizophrenia	20.2%	Meta-analysis [17]
Receiving clozapine	47.2% to 51.9%	Review and meta-analysis [4,17]

Table 1: Reported prevalence by treatment status, as published by the original investigators

Attribution is not straightforward: A study of patients with treatment-resistant schizophrenia examined metabolic outcomes in those treated with clozapine against those on other antipsychotics, and reported that metabolic problems in this group were not unique to clozapine [18]. Since treatment-resistant illness is itself associated with greater metabolic burden, comparisons between agents in observational data are confounded by the severity of illness that led to the agent being chosen [17,18].

What monitoring guidance specifies: Guidance issued from the mid 2000s onwards specifies recording weight at baseline and repeatedly thereafter, together with blood glucose or glycated haemoglobin, lipid profile, blood pressure, waist

circumference and personal and family history (Figure 6) [8,9,21]. Baseline measurement is described as particularly important when an antipsychotic is first prescribed and when a patient is switched to an agent with higher metabolic liability [21]. A position paper from the European Psychiatric Association, supported by the European Association for the Study of Diabetes and the European Society of Cardiology, sets out comparable recommendations, as do national guidelines in Australia, Canada, France and Sweden [9,21,22].

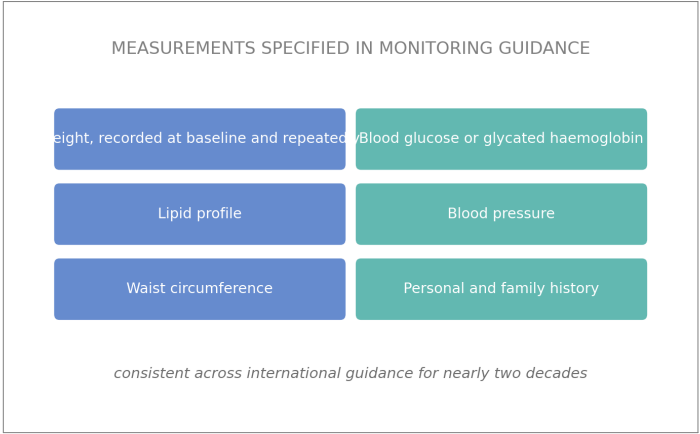


Figure 6: Measurements specified in international monitoring guidance [8,9,21]

Measurement	When guidance specifies it
Weight	Baseline and repeatedly thereafter [8,21]
Glucose or glycated haemoglobin	Baseline and periodically [9,21]
Lipid profile	Baseline, then annually rather than less often [21]
Blood pressure	Baseline and periodically [8,9]
Waist circumference	Baseline and periodically [8,9]

Table 2: Components of metabolic monitoring as set out in guidance [8,9,21]

What is recorded in practice: National clinical audit of psychosis services reports incomplete recording of these measurements, and the discrepancy between guidance and practice has been a recurring finding since monitoring recommendations were first issued [10,23,24]. A commission on protecting physical health in mental illness reached the same conclusion across conditions [27]. Obtaining fasting blood samples is acknowledged in the guidance literature as practically difficult in this population, which contributes to the shortfall [21].

2. Correll CU, Solmi M, Veronese N, Bortolato B, Rosson S, Santonastaso P, et al. "Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness". World Psychiatry 16(2017):163-180.

Observation	What it bears on
Prevalence rises from drug-naïve to multi-episode	Illness and exposure both contribute [4,19]
Unmedicated prevalence already 20.2%	Medication is not the whole explanation [17]
Metabolic problems not unique to clozapine	Severity confounds agent comparisons [18]
Guidance consistent for two decades	The gap is implementation, not knowledge [8,9,21]

Table 3: Findings bearing on how the metabolic burden should be attributed

Discussion

Two things are established and worth separating. The metabolic burden in severe mental illness is large, and antipsychotic treatment adds to it: mean weight increase after initiation is reported at 4.85 kg, prevalence of metabolic syndrome differs more than twofold between agents, and within bipolar disorder those receiving antipsychotics had higher odds than those who were not [4,11,12].

But the medication is not the whole explanation, and the data make that clear. Metabolic syndrome was present in 20.2 per cent of unmedicated patients with schizophrenia, against roughly 20 to 25 per cent in general populations of comparable age, and prevalence rose from 10 per cent in drug-naïve patients through 15.9 per cent at first episode to 34.2 per cent in multi-episode illness [4,17,19]. Duration of illness, duration of treatment, and the social and material circumstances that accompany long-standing severe mental illness are all bound together in that gradient, and observational data cannot separate them.

The comparison between agents carries the same difficulty in a sharper form. Clozapine shows the highest reported prevalence, and clozapine is reserved for treatment-resistant illness. The study that examined this directly found metabolic problems in treatment-resistant schizophrenia were not unique to clozapine, which suggests that some of what is attributed to the agent belongs to the population receiving it [18]. That does not mean the differences between agents are illusory, since randomised data also show them, but it does mean observational prevalence figures overstate the contrast.

The finding this review is named for is the least ambiguous. Guidance specifying what should be measured has been consistent internationally for close to two decades, is endorsed by cardiology and diabetes bodies as well as psychiatric ones, and asks for measurements that are neither expensive nor technically demanding [8,9,21,22]. Audit continues to find it incompletely done [10,23,24]. This is not a gap in knowledge about what to measure.

Two practical observations follow, and both concern measurement rather than treatment. The guidance literature notes that fasting samples are difficult to obtain in this population, which argues for measurements that do not require fasting where

those are acceptable [21]. And weight is the one measurement requiring no laboratory at all, is specified at baseline and repeatedly, and is the parameter that changes earliest. A service unable to achieve complete biochemical monitoring can still record weight, and the audit evidence suggests that even this is inconsistently done [10,23].

Study limitations

The limitations belong to the underlying literature. Prevalence estimates are drawn from observational studies in which treatment is not randomly allocated, so confounding by indication is pervasive and is most severe precisely where the differences between agents appear largest [17,18]. Definitions of metabolic syndrome differ between criteria sets and over time, which affects reported prevalence independently of the population [4,19]. Comparisons with the general population are sensitive to the age and socioeconomic composition of the comparator, which is inconsistently reported [1,4]. The unmedicated and drug-naïve groups are small in most studies and may differ from treated patients in illness duration and severity [17,19]. Monitoring audits report recorded measurements rather than measurements performed, so under-recording and under-measurement cannot be distinguished [10,23]. Much of the guidance predates the agents most recently introduced [8,21]. And this literature reports associations between medication and metabolic outcome; it does not establish what should follow clinically, which depends on the individual patient and lies outside its scope [6,7,30]. Trials of structured lifestyle education, pharmacological approaches to weight gain associated with these medicines, and meta-reviews of interventions to improve physical health in schizophrenia have all been published, and are noted here as existing literature rather than as recommendations [28,29,31,32].

Conclusion

Obesity and metabolic syndrome are substantially more common in severe mental illness than in the general population, and antipsychotic treatment contributes, with a mean weight increase of 4.85 kg after initiation and prevalence differing more than twofold between agents. Attribution to medication alone is not supported: a fifth of unmedicated patients with schizophrenia already meet criteria for metabolic syndrome, prevalence climbs with illness stage, and the agent associated with the highest prevalence is the one reserved for the most refractory illness. What is unambiguous is the monitoring gap. The measurements have been specified consistently for nearly twenty years, they are inexpensive, and audit keeps finding them incompletely recorded. Weight alone requires no laboratory and changes earliest, and it is not reliably captured.

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Conflict of Interest

The authors declare no competing interests.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

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