

# Guideline versus practice in screening and monitoring of cardiometabolic risks in patients taking antipsychotic medications

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# Guidelines versus practice in screening and monitoring of cardiometabolic risks in patients taking antipsychotic medications: where do we stand?

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## INTRODUCTION

Despite the known benefits of antipsychotic medications, they have been associated with increased risks of cardiometabolic side effects. Antipsychotic-induced adverse cardiometabolic effects, such as weight gain, high blood pressure, alterations in glucose metabolism and lipid dysregulation, are well-recognised risk factors for cardiovascular diseases (CVDs) and diabetes.<sup>1</sup> Clinical guidelines call for regular physical health assessments and laboratory monitoring as a means to prevent and detect adverse cardiometabolic effects of antipsychotic medications. However, recent evidence suggests that cardiovascular conditions remain the key causes of death among people using antipsychotic medications, suggesting suboptimal screening and monitoring practices. Suboptimal cardiometabolic screening among antipsychotic users can hinder the early detection of high-risk people and delay receiving proper management.<sup>2</sup>

## ANTIPSYCHOTIC MEDICATIONS AND ADVERSE CARDIOMETABOLIC EFFECTS

Although the pathophysiological pathways underlying cardiometabolic side effects of antipsychotic treatment are not fully understood, antipsychotic-induced cardiometabolic side effects are attributed to multiple functional pathways. This involves the activation of the dopaminergic pathway ( $D_2$ ), with multiple inhibitions of serotonergic ( $5HT_2A$ ), adrenergic ( $\alpha_1$ ) and histamine ( $H_1$ ) pathways. These combined mechanisms suggest that cardiometabolic changes during antipsychotic treatment should be a net result of alterations in glucose and lipid regulations along with satiety signalling resulting in reduced energy expenditure.<sup>1</sup>

Notably, these cardiometabolic changes vary significantly across different antipsychotics. For example, clozapine, olanzapine, risperidone and quetiapine have been recognised as the antipsychotics with the highest metabolic liability. Moreover, evidences suggest that some antipsychotics, mainly aripiprazole and ziprasidone, demonstrate neutral cardiometabolic effects. However, caution is advised even when dealing with such agents, as these side effects can be unpredictable.<sup>1</sup>

While the available literature focuses mainly on the magnitude of the antipsychotic-induced cardiometabolic effects, little is known about the onset or duration of these changes. Preclinical studies reported the variability in the onset of some cardiometabolic changes. For example, the onset of some metabolic side effects such as glucose and lipid abnormalities with antipsychotics can be rapid, that is, occurring earlier than the onset of weight gain,<sup>1</sup> suggesting an independent relationship between the metabolic changes and weight gain. Besides, most records reported data from studies that were mostly conducted over a shorter duration, and little is known about these cardiometabolic changes over the long term.<sup>3</sup> It would be helpful to investigate such a relationship, as it would enable appropriate monitoring in patients vulnerable to cardiometabolic changes.

Although monotherapy is preferred over multiple antipsychotic therapies, there are growing enforcements for the use of antipsychotic augmented regimen, especially in cases of inadequate response to clozapine. Though the augmenting agent should meet the National Institute for Health and Care Excellence (NICE) eligibility criteria for antipsychotic combined therapy, such therapy may contribute to increased risks or



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increased mortality related to cardiometabolic issues.<sup>4</sup> With the increased applications of antipsychotic regimen, the risks of the associated cardiometabolic problems call for further attention.

### PRACTICAL CHALLENGES IN ANTIPSYCHOTIC THERAPY AND CARDIOMETABOLIC MONITORING

The patients' response to antipsychotic therapy has been the ultimate goal since the introduction of antipsychotic medications. Issues associated with antipsychotic treatment, such as treatment failure, may shift the attention entirely towards the efficacy of the antipsychotics. In clinical practice, the dose and course of antipsychotic therapy vary between patients, depending on patients' factors, including the acuity and course of the psychotic illness. Selecting antipsychotic medications can be challenging for many prescribers since the therapeutic response primarily drives the decision.<sup>3</sup> However, such decision must balance their benefits and the associated cardiometabolic risks. Selecting an initial agent with a favourable cardiometabolic profile is considered the best approach for those with or at higher risk of CVDs.<sup>3</sup> Guidelines recommend using new antipsychotics as initial therapy, though such an option may be inconvenient for many patients. As the antipsychotic efficacy of both antipsychotic classes (first and second generation antipsychotics) has been shown to be comparable, routine clinical decisions should be based on individual therapeutic response and tolerability, which can vary between individuals.<sup>5</sup>

The risk of relapse of psychotic illness represents an additional obstacle for dose or drug alteration. Likewise, resistance to antipsychotic therapy remains a significant issue that continues to provoke debate over its clinical management.<sup>3</sup> To date, clozapine is the only approved agent for refractory conditions, and the role of augmented antipsychotic therapy is less advocated as routine practice. Not surprisingly, these obstacles in antipsychotic therapy can often deviate clinical decisions away from the adverse outcomes profile, as they direct the attention more toward treatment efficacy and less to treatment safety, resulting in suboptimal monitoring.

### IMPORTANCE OF OPTIMAL MONITORING

Regular monitoring for metabolic issues among high-risk individuals is considered a crucial first step in determining the treatment plan.<sup>6</sup> In the UK, the NICE/Royal College of Psychiatrists provides the guidance for baseline and ongoing monitoring of people taking antipsychotic medications. Specifically, the recommendations include monitoring of factors such as personal and family history, anthropometric measures and body compositions (weight, body mass index (BMI), waist circumference (WC) and blood pressure (BP)), fasting plasma glucose (HbA1c) and lipid profile.<sup>4</sup> Similarly, international clinical guidelines on the same subjects were introduced<sup>4,5,7-12</sup> (table 1).

It is important to note that not all guidelines provide explicit recommendation standards for the monitoring of adverse cardiometabolic effects of antipsychotics, yet they all propose physical examination for people with severe mental illness (SMI). Available guidelines also differ in terms of the timing and extent of monitoring and the scope of physical health domains that are to be monitored. In terms of monitoring indications, most guidelines recommend 'frequent' monitoring mainly in the presence of risk factors,<sup>5,7,8,10,11</sup> while others state frequent monitoring after initiating or changing antipsychotic medications.<sup>7,11</sup>

Despite the guidelines emphasising the importance of monitoring practices, although inconsistent, monitoring practices are reported to be suboptimal. This was parallel with the findings of a systematic review assessing metabolic screening practices among antipsychotic users, as the authors concluded the rates of metabolic monitoring were 'generally inadequate' except for body weight (75.9%) and BP (75.2%).<sup>2</sup> Similarly, other studies showed significant variations in monitoring status of the cardiometabolic outcomes in antipsychotics users, as some anthropometric variables, mainly blood pressure, were frequently measured in 56.1% of subjects, while WC was rarely recorded.<sup>6,12,13</sup> Literature also demonstrated variations in monitoring practices according to patient demography. Certain patients' groups, such as the older populations, appeared to be more frequently tested for CVDs in some studies. For example, the overall monitoring rate of different metabolic components in people with SMI attending primary care tended to be higher among older people.<sup>6</sup>

Currently, there are variations regarding what extent of monitoring can be called the 'optimal' level of monitoring. For example, one study defined 'adequate monitoring' when 70% of the patients received cardiometabolic monitoring for each outcome,<sup>12</sup> while similar definition was expressed in another study as 'comprehensive recording' when all modifiable risk factors had been recorded at least once during the treatment period.<sup>1</sup> Collectively, these reports suggest that there should be room to improve the monitoring of patients receiving antipsychotic medication in primary care. Also, further research assessing the level of adherence to the available guidelines for cardiometabolic monitoring in patients with SMI using antipsychotics in primary care is highly recommended.

The inconsistent monitoring practices reported in the literature may be a consequence of 'hidden factors' that may prevent the prescribed population from receiving comprehensive cardiometabolic care. A recent review of qualitative evidences attempted to address barriers for cardiometabolic monitoring among people using antipsychotics. The review revealed numerous barriers, including lack of knowledge and understanding of the physical health issues, unconcerned attitude of the patients and healthcare professionals, the elusive nature of the psychotic disease, financial constraints, fragmentation of

**Table 1** Guidelines for cardiometabolic risk factor monitoring in patients treated with antipsychotic medications

Guideline	Origin	Focus of the guideline	Recommended cardiometabolic components
Consensus Statement on Antipsychotic Drugs and Obesity and Diabetes <sup>7</sup>	USA	<ul style="list-style-type: none"> <li>▶ Monitoring of metabolic adverse events associated with antipsychotics</li> <li>▶ Focusing mainly on SGAs</li> </ul>	<ul style="list-style-type: none"> <li>▶ Physical health monitoring: anthropometrics and body compositions (BP, WC and BMI)</li> <li>▶ Biochemical examination: fasting glucose and lipids</li> <li>▶ Baseline follow-up: 4–8 weeks, quarterly, then annually</li> </ul>
Monitoring for Metabolic Disorders in Patients Taking Antipsychotic Drugs <sup>8</sup>	New Zealand	<ul style="list-style-type: none"> <li>▶ Monitoring of metabolic adverse events associated with antipsychotics</li> </ul>	<ul style="list-style-type: none"> <li>▶ Physical health monitoring: body compositions (body weight and BMI)</li> <li>▶ Biochemical examinations: fasting glucose and lipids</li> <li>▶ Cardiovascular examination: ECG</li> <li>▶ Baseline follow-up: quarterly, then annually (frequency increased in high-risk groups)</li> </ul>
World Federation of Societies of Biological Psychiatry Guidelines for Biological Treatment of Schizophrenia <sup>9</sup>	Global	<ul style="list-style-type: none"> <li>▶ Management of schizophrenia and related disorders</li> <li>▶ General recommendations including general health monitoring</li> </ul>	<ul style="list-style-type: none"> <li>▶ Physical health monitoring: anthropometrics and body compositions (BP, body weight, WC and BMI)</li> <li>▶ Biochemical examinations: fasting glucose and lipids</li> <li>▶ Cardiovascular examination: ECG</li> <li>▶ Baseline follow-up: 4–8 weeks, quarterly, then annually</li> <li>▶ Personal/family history (lifestyle and smoking)</li> </ul>
NICE Guidelines: Psychosis and Schizophrenia in Adults <sup>4</sup>	UK	<ul style="list-style-type: none"> <li>▶ Management of schizophrenia and related disorders</li> <li>▶ Evidence-based recommendations for optimising treatment and prognosis</li> <li>▶ General recommendations including general health monitoring</li> </ul>	<ul style="list-style-type: none"> <li>▶ Personal/family history (lifestyle and smoking)</li> <li>▶ Physical health monitoring: anthropometrics and body compositions (BP, body weight, WC and BMI)</li> <li>▶ Biochemical examination: fasting glucose and lipids</li> <li>▶ Baseline follow-up: 4–6 weeks, quarterly, then annually</li> </ul>
The Royal Australian and New Zealand College of Psychiatrists Guidelines for the Management of Schizophrenia and Related Disorders <sup>10</sup>	Australia and New Zealand	<ul style="list-style-type: none"> <li>▶ Management of schizophrenia and related disorders</li> <li>▶ General recommendations including general health monitoring</li> <li>▶ Focusing mainly on SGAs</li> </ul>	<ul style="list-style-type: none"> <li>▶ Physical health monitoring: anthropometrics and body compositions (BP, body weight, WC and BMI)</li> <li>▶ Biochemical examination: fasting glucose and lipids</li> <li>▶ Managing any existing metabolic comorbidities</li> </ul>
The Maudsley Prescribing Guidelines in Psychiatry <sup>11</sup>	UK	<ul style="list-style-type: none"> <li>▶ Evidence-based recommendations for optimising treatment and prognosis</li> <li>▶ General recommendations including general health monitoring</li> </ul>	<ul style="list-style-type: none"> <li>▶ Physical health monitoring: anthropometrics and body compositions (BP, body weight, WC and BMI)</li> <li>▶ Biochemical examination: fasting glucose and lipids</li> <li>▶ Cardiovascular examination: ECG</li> <li>▶ Early on-treatment monitoring: during dose titration</li> <li>▶ Baseline follow-up: quarterly, then annually</li> </ul>
SIGN Guidelines: Management of Schizophrenia <sup>5</sup>	Scotland	<ul style="list-style-type: none"> <li>▶ Evidence-based recommendations for optimising treatment and prognosis</li> <li>▶ General recommendations including general health monitoring</li> </ul>	<ul style="list-style-type: none"> <li>▶ Personal/family history (lifestyle and smoking)</li> <li>▶ Physical health monitoring: anthropometrics and body compositions (BP, body weight, WC and BMI)</li> <li>▶ Biochemical examination: fasting glucose and lipids</li> <li>▶ Pretreatment screening</li> <li>▶ Baseline follow-up: quarterly, then annually</li> </ul>

BMI, body mass index; BP, blood pressure; ECG, electrocardiogram; NICE, National Institute for Health and Care Excellence; SGAs, second generation antipsychotics; SIGN, Scottish Intercollegiate Guidelines Network; WC, waist circumference.

care, lack of specialised training and limited resources to perform the monitoring.<sup>14</sup>

Better liaison between different healthcare sectors is imperative. The transition in mental healthcare from secondary care to community-based care has been accompanied by some challenges that indirectly influence physical healthcare delivered to patients using antipsychotics.<sup>14</sup> To resolve this, there is a need to facilitate this transition in order to enhance the level and quality of care delivered to patients prescribed antipsychotic medications. Also, integrating other medical care into psychiatric teams, particularly those concerned with managing vulnerable groups such as those with cardiometabolic comorbidities, is paramount.

There is a scope to develop a treatment algorithm to detect antipsychotic-induced weight gain and metabolic dysregulations, which can be used as a guidance for pretreatment assessment for patients who would recently start antipsychotic treatment. Such tools may allow rapid, comprehensive, systematic collection and assessment of these adverse outcomes if integrated as part of routine care.

### PROMISING ROLE OF PHARMACISTS

Pharmacists are in a unique position to enhance the quality of antipsychotic medication uses with the potentials to reduce adverse drug-related outcomes. In the context of mental health, pharmacists can improve cardiometabolic monitoring by being an active part of the monitoring process. Previously, a preliminary study demonstrated pharmacists' ability to contribute to the cardiometabolic risk assessment and monitoring of patients prescribed antipsychotics.<sup>13</sup> In another study of pharmacist-led cardiovascular risk-reduction strategy in the USA, pharmacists were able to identify patients with SMI at high risks of cardiovascular issues by closely reviewing their lab profiles and make appropriate decisions, including starting medications and ordering relevant laboratory tests.<sup>15</sup> These findings revealed the capability of pharmacists in performing appropriate screening of patients with SMI as they demonstrated fair competency to make decisions and order laboratory tests for general comorbidities such as diabetes in patients with SMI when necessary. Additionally, the literature suggests that pharmacists can indirectly improve cardiometabolic monitoring by providing focused education on adverse cardiometabolic outcomes of psychotropic medications for patients and other healthcare professionals. Healthcare professionals including pharmacists should also offer advices and interventions to address other known modifiable risk factors related to cardiometabolic health when counselling patients in relation to antipsychotic medicines.

Also, pharmacists can function as a bridge that facilitates care transitions between acute and community-based care settings since they work closely with patients and other healthcare providers at different levels. Such roles can improve patients' clinical outcomes by allowing

continuity of care, improving medication adherence, assessing therapeutic outcomes, optimising medication regimens, and ordering and evaluating monitoring parameters.<sup>15</sup> Further randomised controlled trials (RCTs) are necessary to investigate the clinical outcomes following pharmacist interventions regarding monitoring adverse metabolic outcomes associated with antipsychotic use. It is also important to understand patients' perspectives regarding the services delivered by pharmacists and the associated effects on their health outcomes. This can be achieved using qualitative study designs.

### CONCLUSIONS

While guidelines have attempted to emphasise frequent monitoring for cardiometabolic risks in antipsychotic users, monitoring adverse outcomes in these patients remains suboptimal. There is a need to investigate potential factors influencing the adoption of monitoring guidelines, and a need to develop and evaluate interventions aiming to incorporate the roles of other healthcare professionals, such as pharmacists, in the care of patients prescribed antipsychotic medications.

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