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# Physical Health and Drug Safety in Individuals with Schizophrenia

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## Abstract

**Background:** While antipsychotic medications are the mainstay of therapy for individuals with schizophrenia and psychotic disorders, their use is associated with adverse effects on physical health that require the attention and care of prescribers.

**Methods:** We used the ADAPTE process to adapt existing guideline recommendations from the National Institute for Health and Care Excellence (NICE) and Scottish Intercollegiate Guidelines Network (SIGN) guidelines on the dosing of antipsychotics and antipsychotic polypharmacy, screening for adverse effects of antipsychotics, and management of metabolic and extrapyramidal side effects to the Canadian context.

**Results:** Prescribers are encouraged to use the lowest effective dose and to avoid the routine use of multiple antipsychotics. Scheduled monitoring of body mass index, waist circumference, blood pressure, glucose, lipids, prolactin, electrocardiograms, and extrapyramidal symptoms is recommended. Lifestyle interventions are recommended to mitigate antipsychotic-induced weight gain. Prescribers should follow Canadian guidelines on the treatment of obesity, dyslipidemia, and diabetes. Recommendations on antipsychotic drug choice are made for users particularly concerned about extrapyramidal symptoms.

**Conclusion:** Careful monitoring and attention by prescribers may mitigate adverse effects associated with antipsychotic medications.

## Keywords

schizophrenia, antipsychotic polypharmacy, metabolic syndrome, extrapyramidal symptoms, ECG changes

While antipsychotic medications are the mainstay of therapy for individuals with schizophrenia and psychotic disorders, their use is associated with adverse effects on physical health that require the attention and care of prescribers. As the majority of individuals with schizophrenia require lifelong treatment, clinicians must maintain a high degree of vigilance for adverse effects on physical health. It is essential for the Canadian Schizophrenia Guidelines to include recommendations focusing on physical health of individuals with schizophrenia and the monitoring of drug safety in this population. Recommendations addressing the detection, prevention, and treatment of antipsychotic-induced adverse effects on physical health are provided.

## Methods

The methods for the Canadian Schizophrenia Guidelines are described in brief here; please see the Introduction and Methodology article in this issue for an in-depth description.

The Canadian Schizophrenia Guidelines were developed using the ADAPTE process.[1] Recognising that the development of guidelines requires substantial resources, the ADAPTE process was created to take advantage of existing guidelines and reduce duplication of effort.

The first phase of the ADAPTE process, the setup phase, involved preparing for the ADAPTE process. We assembled a national multidisciplinary panel from across Canada, including stakeholders with expertise in schizophrenia and mental health, health policy, patient advocacy, and lived

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**Table 1.** Clinical Practice Guidelines Used for the Canadian Schizophrenia Guidelines.

| Guideline Developer | Guideline Title | Year Published |
|---|---|---|
| National Collaborating Centre for Mental Health Commissioned by the National Institute for Health and Care Excellence (NICE) | NICE National Clinical Guideline Number 178. Psychosis and Schizophrenia in Adults. Treatment and Management[3] | 2014 |
| National Collaborating Centre for Mental Health Commissioned by the National Institute for Health and Care Excellence (NICE) | NICE National Clinical Guideline Number 155. Psychosis and Schizophrenia in Children and Young People: Recognition and Management[4] | 2013 |
| National Collaborating Centre for Mental Health Commissioned by the National Institute for Health and Care Excellence (NICE) | NICE National Clinical Guideline Number 120. Psychosis with Coexisting Substance Misuse: Assessment and Management in Adults and Young People[5] | 2011 |
| Scottish Intercollegiate Guidelines Network (SIGN) | SIGN 131. Management of Schizophrenia[6] | 2013 |
| European Psychiatric Association | European Psychiatric Association Guidance on the Early Intervention in Clinical High Risk States of Psychoses[7] | 2015 |
| American Psychiatric Association | American Psychiatric Association Practice Guidelines for Psychiatric Assessment of Adults[8] | 2016 |

experience with schizophrenia. Endorsement bodies for the guidelines include the Canadian Psychiatric Association and the Schizophrenia Society of Canada, which were also heavily involved in the dissemination and implementation strategy.

The second phase of the ADAPTE process, the adaptation phase, involves the process of identifying specific health questions; searching for and retrieving guidelines; assessing guideline quality, currency, content, consistency, and applicability; decision making around adaptation; and preparing the draft adapted guideline. We searched for guidelines on schizophrenia in guideline clearinghouses and on the websites of well-established guideline developers for mental health disorders, including the National Institute for Health and Care Excellence (NICE), the Scottish Intercollegiate Guidelines Network (SIGN), the American Psychiatric Association, the American Academy of Child and Adolescent Psychiatry, and the European Psychiatric Association. A MEDLINE search was also performed using the term *guideline* as the publication type and *schizophrenia* as the title or clinical topic. Inclusion criteria were that the guideline needed to be published after 2010, be written in English, and that recommendations had to be developed using a defined and systematic process. We identified 8 current guidelines that were potentially suitable for adaptation. These guidelines were reviewed and evaluated in duplicate using the Appraisal of Guidelines for Research & Evaluation II (AGREE II) tool,[2] an instrument to evaluate the methodological rigor and transparency in which a guideline is developed. Based on this evaluation, we determined that the 6 guidelines were of suitable quality and content for adaptation (see Table 1). Recommendations from each guideline were extracted and divided based on content and reviewed by the relevant working group. Following the ADAPTE process, working groups selected between guidelines and recommendations to create an adapted guideline. Each working group carefully examined each recommendation, the evidence from which the recommendation was derived, and the acceptability and applicability of the recommendation to the Canadian context. After reviewing the recommendations from the guidelines, the working groups decided which recommendations to accept and which to reject, and which recommendations were acceptable but needed to be modified. Care was taken when modifying existing recommendations not to change the recommendations to such an extent that they were no longer in keeping with the evidence upon which they were based. Please see Appendix 1 for how and why recommendations in this manuscript were modified from their original form.

Each working group developed a final list of recommendations from the included guidelines that were presented to the entire guideline panel at an in-person consensus meeting. Working group leaders presented each recommendation and its rationale to the panel. Anonymous voting by the entire panel using clicker technology was performed for each recommendation. Recommendations required agreement by 80% of the group to be included in the Canadian guidelines. If a recommendation did not receive 80% agreement, the group discussed the recommendation and if minor modifications to the recommendation would alter the likelihood that the recommendation would pass. In these situations, recommendations were modified (as described above) and the group revoted at a later date using an online anonymous survey. Whenever modifications in wording were made to original recommendations, the text "modified recommendation from" appears in the Canadian Schizophrenia Guidelines, and the source of each recommendation is written beside the recommendation statement. The strength or grade of the recommendation is provided in brackets if applicable, using the system from which the recommendation came. The grades of recommendation for each reference guideline and their meaning are explained in brief in Table 2 (see Introduction and Methodology article for a more detailed description). Once the voting and consensus process was completed, each working group created a separate manuscript that contains all the recommendations adapted from the included guidelines, with accompanying text explaining the rationale for each recommendation.

**Table 2.** Grade/strength of recommendation classification systems for included guidelines.[a]

National Institute for Health and Care Excellence (NICE)

**Strength of recommendations**
The wording used denotes the certainty with which the recommendation is made (the strength of the recommendation).
**Interventions that must (or must not) be used**
We usually use "must" or "must not" only if there is a legal duty to apply the recommendation. Occasionally, we use "must" (or "must not") if the consequences of not following the recommendation could be extremely serious or potentially life threatening.
**Interventions that should (or should not) be used: a "strong" recommendation**
We use "offer" (and similar words such as "refer" or "advise") when we are confident that, for the vast majority of patients, an intervention will do more good than harm and be cost-effective.
**Interventions that could be used**
We use "consider" when we are confident that an intervention will do more good than harm for most patients and be cost-effective, but other options may be similarly cost-effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation.

Scottish Intercollegiate Guidelines Network (SIGN) and European Psychiatric Association

**Levels of evidence**
1++: High-quality meta-analyses, systematic reviews of randomized controlled trials, or randomized controlled trials with a very low risk of bias; 1+: Well-conducted meta-analyses, systematic reviews, or randomized controlled trials with a low risk of bias; 1: Meta-analyses, systematic reviews, or randomized controlled trials with a high risk of bias
2++: High-quality systematic reviews of case control or cohort studies or high-quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal; 2+: Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal; 2: Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3: Nonanalytic studies (e.g., case reports, case series)
4: Expert opinion
**Grades of recommendation**
A: At least one meta-analysis, systematic review, or randomized controlled trial rated as 1++ and directly applicable to the target population *or* a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B: A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results *or* extrapolated evidence from studies rated as 1++ or 1+
C: A body of evidence including studies rated as 2+, directly applicable to the target population, and demonstrating overall consistency of results *or* extrapolated evidence from studies rated as 2++
D: Evidence level 3 or 4 *or* extrapolated evidence from studies rated as 2+
Good Practice Point: recommended best practice based on the clinical experience of the guideline development group

[a]This is a condensed table; please see the Introduction and Methodology paper for full details.

During the finalisation phase, the Canadian Schizophrenia Guidelines were externally reviewed by those who will be affected by its uptake: practitioners, policy makers, health administrators, and patients and their families. The external review asked questions about whether the users approve of the draft guideline, strengths and weaknesses, and suggested modifications. The process was facilitated through the *Canadian Journal of Psychiatry* and the Schizophrenia Society of Canada. The Canadian Psychiatric Association Clinical Practice Guidelines Committee reviewed and approved the guideline methodology process.

## Recommendations, Physical Health and Drug Safety

### *Antipsychotic Dosing and Polypharmacy*

Appropriate dosing of antipsychotic medication is at least equally important to the choice of medication. Recommended dosage ranges for antipsychotic medications are specified in product monographs and should be routinely adhered to. The available literature does not support exceeding the upper end of the dosage range on a routine basis.[9,10] The Canadian Agency for Drugs and Technology in Health review[10] found some evidence of increased harm with high-dose and combination strategies relative to standard-dose monotherapy, but evidence was inconclusive. Dold and colleagues[9] systematically reviewed randomised controlled trials (RCTs) comparing a dosage increase to continuation of standard-dosage antipsychotic monotherapy for nonresponders in the treatment of schizophrenia, schizoaffective disorder, or schizophreniform disorders and found no differences in any observed outcome measure. The study commented that a ceiling effect due to maximal occupancy of $D_2$ receptors may explain the lack of efficacy of high-dose strategies. Recent clinical practice guidelines[3,6,11] unanimously comment on the lack of evidence for high-dose antipsychotics. Guidelines typically recommend using the lowest effective dosage sufficient to control symptoms, reduce relapse, minimise side effects, and optimise a patient's subjective sense of well-being.

Dosage initiation should begin at the lower end of the dosage range and be adjusted in a cautious manner, allowing for sufficient time to observe for a response. Dosage adjustment intervals will vary with clinical urgency, patient preference, and patient or symptom characteristics such as age, comorbidities, potential drug interactions, and safety risk. Dosage adjustment may be informed clinically by the use of standardised rating scales and/or monitoring of several domains, including positive symptoms, negative symptoms, subjective well-being, side effects, and collateral information from health care staff, family, or other social contacts.

Determination of insufficient response (ranging from no improvement to partial response with persistent symptoms and functional impairment) to an antipsychotic monotherapy trial requires an adequate duration of treatment at either the upper end of the recommended dosage range or at the maximum tolerated dosage. An adequate duration of treatment will vary by medication and clinical circumstance, but a minimum of 2 weeks is generally recommended. Antipsychotic partial or nonadherence should also be a consideration for insufficient response. Subsequent strategies for medication treatment are discussed elsewhere in this guideline.

Antipsychotic polypharmacy (the concurrent use of 2 or more antipsychotics), similar to high-dose monotherapy, does not have a supportive evidence base and should not be routinely used. Studies consistently mention, however, that antipsychotic polypharmacy may be useful in select or treatment-refractory situations.[10,12,13] A study of antipsychotic polypharmacy in the treatment of schizophrenia in 2012 found an average prevalence approximating 20%.[14] The appropriateness of this rate is questionable as observed by Borlindo et al.,[15] in which approximately 80% of second antipsychotics were successfully discontinued in a population of patients with schizophrenia or schizoaffective disorder. While antipsychotic polypharmacy may be used in an attempt to either improve symptom control or decrease side effects through combination of low to moderate dosages, clinicians must be alert to cumulative equivalent dosages contributing to a high-dose scenario as well as additive side effects and increased risk for pharmacokinetic and pharmacodynamics drug interactions.[10]

### *Recommendation 1*

Health care professionals and service users should work together to find the most appropriate medication and the lowest effective dose. There should be detailed discussion with service users outlining the potential benefits and harms of individual medications. Service user preference should be elicited and taken into account.

[SIGN (Good Practice Point)]

### *Recommendation 2*

There should not be routine use of multiple antipsychotic medications. Where polypharmacy is being considered for an individual clinical situation, the benefits and harms should be discussed with the service user.

[SIGN (Good Practice Point)]

## Monitoring Cardiovascular Health and Metabolic Syndrome in Individuals with Schizophrenia

It is well established that a diagnosis of a major mental illness (e.g., depression, bipolar disorder, schizophrenia) carries with it an increased risk of premature death.[16] People with severe mental illness have a 2 to 3 times higher mortality rate and life expectancy 10 to 20 years less than the general population.[17,18] There are several putative causes, including lifestyle with known risk factors (smoking, diet, sedentary habits) occurring at higher rates than in the general population; use of medications that promote weight gain, dyslipidemia, and abnormal glucose metabolism; or reduced access to health care resources[19] and possible bias in use of health care resources for those with mental illness.

Cardiovascular conditions account for a major part of this excess mortality and represent significant modifiable risk factors.[16] These include smoking cessation, control of blood pressure, weight control/loss, glycaemic control, correction of lipid abnormalities, and increased physical activity. These factors, with the exception of smoking and physical activity, are subsumed in the concept of the metabolic syndrome, of central obesity, hypertension, low high-density lipoprotein (HDL), hyperglycemia, and elevated triglycerides. Several meta-analyses have shown higher rates of this syndrome in those with long-term mental illness.[16] Managing these factors is known to be challenging in the general population but is especially so in patients with long-lasting severe mental illness. There are several options for monitoring the cardiovascular status of patients. These include close liaison with primary care providers or cardiovascular specialty service, undertaking this responsibility in specialised psychiatric service, or a staged handover to primary care after an initial period of direct monitoring by a psychiatry specialty service.

### *Recommendation 3*

People with psychosis or schizophrenia, especially those taking antipsychotics, should be offered a combined healthy eating and physical activity programme by their mental health care provider.

[NICE (Strong)]

### *Recommendation 4*

Routinely monitor weight and cardiovascular and metabolic indicators of morbidity in people with psychosis and schizophrenia.

[Modified recommendation from NICE]

**Table 3.** Suggested Monitoring Schedule for Antipsychotic Medication.

| Test | Baseline | At 1 Month | At 3 Months | Annually |
|---|---|---|---|---|
| Individual and family history of physical illness | ✓ | | | ✓ |
| Smoking history | ✓ | | ✓ | ✓ |
| Body mass index/ weight/waist circumference | ✓ | ✓ | ✓ | ✓ |
| Blood pressure | ✓ | As clinically indicated | ✓ | ✓ |
| HbA1C/fasting glucose | ✓ | As clinically indicated | ✓ | ✓ |
| Random lipids/fasting lipids | ✓ | As clinically indicated | ✓ | ✓ |
| Prolactin | | As clinically indicated | | |
| History and examination for extrapyramidal symptoms | ✓ | ✓ | ✓ | ✓ |

### *Recommendation 5*

Suggested monitoring schedule for antipsychotic medication safety (Table 3).

[Modified recommendation from SIGN]

Despite the well-documented association between serious mental illness and increased risk of diabetes and cardiovascular disease, studies consistently demonstrate poor health screening and monitoring in this group of patients.[20,21] A systematic review and meta-analysis of pooled data from 5 countries, involving 218,940 patients with severe mental illness at baseline and 71,594 patients after guideline introduction, concluded that metabolic monitoring rates for patients with mental illness on antipsychotic medication were low.[20] The only parameters where rates of routine monitoring exceeded 50% were measurement of blood pressure and triglyceride levels.[20] Patients with first-episode schizophrenia have significant metabolic abnormalities early in their illness,[22] which emphasises the importance of initial screening and follow-up in the early stages of treatment. Regular long-term monitoring is equally important. In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, 88% of patients with dyslipidemia, 62% of those with hypertension, and 38% of people with diabetes received no treatment.[23] Almost a decade later, suboptimal treatment persists.[24] A 2016 review in the United States reports that up to 70% of patients taking antipsychotics remain unscreened and untreated.[25]

Low rates of screening and monitoring have been attributed in part to ambiguity about who is accountable for metabolic abnormalities.[26-28] As the responsible health professional starting treatment, psychiatrists should ensure the completion of baseline screening and that scheduled follow-up monitoring is provided within psychiatric care or by the patient's family physician.[20,29-31] The psychiatrist can conduct the monitoring or ensure that patients have access to and participate in systematic structured health monitoring through primary care. This is particularly important as people with severe mental illness are more likely to report difficulties accessing health care.[32] Even when patients do access health care, disparities persist. In a comparative review, more than 70% of studies found that people with psychiatric diagnoses received inferior medical care.[33] Thus, establishing monitoring protocols, with organised recording and interpretation of results, is essential. Computerised systems have been shown to improve patient monitoring.[21] This should be complemented with effective collaboration between mental health and primary care services to promote integrated care.[25]

### *Recommendation 6*

Local arrangements for physical health monitoring should be put in place at the time of antipsychotic prescribing.

[SIGN (Good Practice Point)]

### *Recommendation 7*

General practitioners (GPs) and other primary health care professionals should monitor the physical health of people with psychosis or schizophrenia at least annually. The health check should be comprehensive, including a cardiovascular risk assessment.

[Modified recommendation from NICE]

## Prevention and Management of Metabolic Side Effects Associated with Antipsychotic Medications

While schizophrenia has been identified as an independent risk factor for diabetes, long-term antipsychotic use adds to this risk.[34-36] With the initiation of antipsychotic treatment, patients often experience a marked increase in appetite and early triglyceride elevation followed by new or worsened dyslipidemia and glucose dysregulation. Weight gain can onset early and continue for months or years, promoting treatment refusal, reduced self-esteem, stigma, and physical health problems other than metabolic and cardiovascular disease, including osteoarthritis, sleep apnea, gallbladder disease, and obesity-related cancers.[37]

There is a range among antipsychotic agents of their effects on markers of metabolic and cardiovascular risk. The CATIE trial demonstrated that olanzapine was of greatest concern. Rates of treatment discontinuation due to weight gain or metabolic adverse effects were olanzapine (9.2%), quetiapine (3.6%), ziprasidone (3.2%), risperidone (1.8%), and perphenazine (1.1%) in the first phase of the study.[38] A

**Table 4.** Antipsychotic Risk for Clinically Important Weight Gain.

| Category | Risk of Clinically Important Weight Gain, %[a] | Antipsychotic |
|---|---|---|
| Lower | <12 | Aripiprazole, asenapine, and ziprasidone |
| Intermediate | 10-24 | Lurasidone, other FGAs, paliperidone, perphenazine, quetiapine, and risperidone |
| Higher | >24 | Chlorpromazine, clozapine, and olanzapine |

FGA, first-generation antipsychotic.
[a]Estimated are rates of clinically important weight gain (equaling a net weight gain of 7% or greater from baseline weight) within ~9 months of treatment.

subgroup of participants in the second phase of CATIE were treated with clozapine or other antipsychotics, including olanzapine. Clozapine was also associated with an average gain in weight, although it was smaller than that observed with olanzapine.[39] Recent reviews of selected first- and second-generation antipsychotics support categorising individual agents as having lower, intermediate, and higher propensity for clinically relevant weight gain (Table 4).[40,41] The analyses confirm that longer durations of treatment are associated with greater weight gain among all agents.

The range of change in weight is remarkable among patients taking the same antipsychotic. For example, with lurasidone, 16% and 18% experience clinically important weight gain and weight loss, respectively, over 9 months of treatment.[41] Some lose weight rapidly, often when switching from a more obesogenic antipsychotic to a less obesogenic antipsychotic.[38,40] Others gain weight rapidly and continually, leading to experiences of 25 to 50 kg of weight gain within 6 to 12 months of initiating treatment. It is important to recognise this variability, especially with the use of antipsychotics reported to have low average weight gain as patients often experience clinically relevant changes in weight despite a low average mean change across patients.

The mechanism by which antipsychotic agents cause weight gain is unknown, but several hypotheses have been proposed. One of the strongest associations with weight gain is the antipsychotic's binding affinity for H1 receptors, which is associated with a change in eating behaviours and a decreased sensation of satiety.[42] Genetic studies suggest that an interaction between genetic susceptibility and antipsychotic pharmacology predicts weight gain.[43-46]

A proactive, preventative approach is needed in the mitigation of leading physical health problems in people with schizophrenia regardless of treatment status. This is warranted based on the excessive rates of metabolic and cardiovascular morbidity and mortality compared with the general population.[16,23,24,47] Increased physical activity and a healthy diet are recommended for all people with schizophrenia, albeit without a substantial evidence base of how to best implement these recommendations or how to best achieve the related clinical and surrogate outcomes of improved cardiovascular and metabolic health.[3]

Intervention studies promoting increased physical activity and healthy eating have used psychoeducation/information-based approaches. Specific intervention programs that have been studied include Achieving Healthy Lifestyles in Psychiatric Rehabilitation (ACHIEVE), behavioural weight loss treatment, Diabetes Awareness and Rehabilitation Training (DART), early behavioural intervention, healthy lifestyle intervention, lifestyle wellness program, nutrition education sessions, Passport 4 Life programme, psychoeducation class—Solutions of Wellness modules, psychoeducational intervention with referral to a nutritionist, Psychoeducational Program (PEP) for weight control, and Recovering Energy Through Nutrition and Exercise for Weight Loss (RENEW).[3] In the absence of stronger evidence, no specific intervention can be supported over another. As for exercise and diet interventions in the general population, overall study results have been encouraging but are limited in their generalisability, study duration, outcome measures, and size of benefit observed.

It is not clear if specific metabolic monitoring clinics for patients taking antipsychotics achieve better outcomes than other approaches, such as collaborative or shared care models in which patient care plans are centralised and provided by a team of health providers, including mental health and primary care providers. Due to access differences from one community to the next, local health care providers will need to collectively determine how to best provide support for physical activity and healthy eating to people with schizophrenia.

Metformin has been investigated as a leading pharmacological option for managing weight during antipsychotic treatment. It has been relatively well investigated, especially in first-episode psychosis patients, and offers a tolerability advantage over alternatives.[48] Data demonstrate the possibility of substantial weight loss for many patients during antipsychotic treatment within 3 months of starting metformin. An additional advantage to metformin over other pharmacological weight loss options is its demonstrated effect at reducing the rate of new-onset diabetes in patients with dysglycemia.[49]

### *Recommendation 8*

Lifestyle interventions (incorporating physical activity, dietary change, and behavioural components) should be considered for service users who are experiencing weight gain on antipsychotic medications.

[SIGN (Grade A)]

### *Recommendation 9*

Metformin should be considered for service users who are experiencing weight gain on antipsychotic medications.

[SIGN (Grade B)]

### Recommendation 10

If a person has rapid or excessive weight gain, abnormal lipid levels, or problems with blood glucose management, offer interventions in line with relevant Canadian guidelines:

- Canadian Task Force on Preventive Health Care Obesity Guidelines[50]
- Canadian Cardiovascular Society Guidelines for the Diagnosis and Treatment of Dyslipidemia[51]
- Canadian Diabetes Association Guidelines[34]

[Modified recommendation from NICE (Strong)]

## Antipsychotic Medications and Arrhythmias

Among the most serious of antipsychotic side effects are arrhythmias and sudden cardiac deaths (SCDs). Torsade de pointes is a malignant ventricular arrhythmia that is associated with syncope and sudden death and is associated with prolonged $QT_c$, which can occur with antipsychotics and other medications.[52]

A large retrospective cohort analysis of 93,300 users of antipsychotics demonstrated that both typical and atypical antipsychotics had rates of sudden cardiac death that were double that of nonusers (incidence rate ratio, 1.99; 95% confidence interval [CI], 1.68-2.34).[53] While there was no significant difference in rates between typical and atypical agents, there was a dose-dependent increase in SCDs. Among users of the typical agents, the incidence rate ratios increased from 1.31 (95% CI, 0.97-1.77) for persons taking low doses to 2.42 (95% CI, 1.91-3.06) for those taking high doses ($P < 0.001$ for dose-response relationship). Among users of the atypical drugs, the incidence rate ratios increased from 1.59 (95% CI, 1.03-2.46) for persons taking low doses to 2.86 (95% CI, 2.25-3.65) for those taking high doses ($P = 0.01$ for dose-response relationship).[53]

Given this dose-incidence relationship for SCDs, pharmacokinetic drug interactions are another potential factor for elevating drug concentration and risk of SCDs.[54] A study of 1437 outpatients with schizophrenia determined that female gender (odds ratio [OR], 1.83; 95% CI, 1.28-2.56) and cytochrome P450 (CYP) 3A4-metabolised drugs (OR, 1.56; 95% CI, 1.05-2.30) were associated with an increased risk of $QT_c$ prolongation.[55] Antibiotics and foods such as grapefruit juice are potent inhibitors of CYP3A4 and can potentially contribute inadvertently to elevated antipsychotic drug levels by decreasing the rate of drug metabolism and clearance, increasing the risk for arrhythmias and SCDs.[54] Different antipsychotic agents prolong $QT_c$ to different degrees. A multiple-treatments network analysis of 212 clinical trials and 43,049 participants determined $QT_c$ prolongation risk of most commonly used antipsychotics.[56] Lurasidone, aripiprazole, paliperidone, and asenapine were not associated with significant $QT_c$ prolongation compared with placebo. Drugs with significant risk compared to placebo, in decreasing order, were sertindole, amisulpiride, ziprasidone, iloperidone, risperidone, olanzapine, quetiapine, and haloperidol.[56]

Pharmacodynamic drug interactions can also result in cardiac risk from additive effects of antipsychotics (or other drugs) on $QT_c$.[57] Thus, greater vigilance is required when co-prescribing antipsychotics, with the use of *pro re nata* (PRN) antipsychotic medications, and during crossover titration periods when patients may be exposed to multiple agents, with additive effects on QTc prolongation. Age is another factor that is associated with decreased clearance and thus elevated plasma levels of antipsychotic, and thus more caution and greater monitoring vigilance should occur in older adults.[58] A recent study determined the prevalence of prolonged QTc in psychiatric inpatients by analysing admission electrocardiograms (ECGs) over a 5-year period. Among 6790 inpatients, 27.3% had an abnormal ECG, 1.6% had a long QT, and 0.9% qualified as drug-induced long QT case subjects.[59] Thus, approximately 1/100 patients may have prolonged QTc. With respect to acceptable QTc intervals, in clinical trials, Health Canada suggests drug discontinuation for QTc >500 ms or an increase of >60 ms from baseline, but "the exact criteria chosen for a given trial will depend on the risk-tolerance level considered appropriate for the indication and patient group in question."[60] In clinical practice, normal QTc is often considered to be <450 ms for men and <460 ms for women.[61,62]

### Recommendation 11

Before initiating or changing antipsychotic medication, depending on the medication being considered and the clinical situation, an ECG is suggested particularly if

- specified in the summary of product characteristics,
- a physical examination has identified specific cardiovascular risk (such as diagnosis of high blood pressure),
- there is a personal history of cardiovascular disease, or
- if there is a family history of QT prolongation.

[Modified recommendation from NICE]

## Extrapyramidal Side Effects Associated with Antipsychotic Medications

Extrapyramidal side effects associated with antipsychotic medications include medication-induced acute dystonia, medication-induced acute akathisia, neuroleptic-induced parkinsonism, tardive dyskinesia, tardive dystonia, and tardive akathisia. Criteria for these disorders are listed in the *DSM-5*.[63]

Acute dystonia, or an acute dystonic reaction, is seen within days of starting or increasing the dose of an

antipsychotic medication. Dystonic movements are repetitive muscle contractions causing twisting, involuntary movements or abnormal postures. In acute dystonia associated with antipsychotic use, the cranial, neck, and trunk muscles are preferentially affected, with typical acute dystonic reactions consisting of retrocollis, extension of the trunk, deviation of the eyes, forced jaw opening, and tongue protrusion. Acute akathisia is a state of excessive restlessness with a need to move. Symptom relief occurs with movement. Individuals with akathisia experience feelings of inner tension or restlessness, and they engage in movements such as shaking or rocking the legs and trunk, pacing, rubbing the face, or vocalising to relieve their discomfort. Neuroleptic-induced parkinsonism consists of neurological signs that can be indistinguishable from idiopathic Parkinson disease, including tremor, rigidity, slowness of movement, or shuffling of gait. Symptoms can be unilateral or asymmetric. The term *tardive dyskinesia* is used traditionally to describe repetitive, choreiform movements of the mouth, lips, and tongue, in a pattern that resembles chewing, sucking, or lip pursing. Repetitive movements of the fingers and toes and respiratory dyskinesias can also occur. Tardive dystonia is a subtype of tardive dyskinesia used to describe sustained, slow, involuntary movements or postures affecting the limbs, trunk, neck, or face. Common manifestations of generalised dystonia include retrocollis, facial grimacing affecting the lower face, opisthotonic trunk extension, and hyperpronation of the arms. Focal forms are also seen, such as blepharospasm and cervical dystonia. Tardive akathisia is a persistent form of akathisia that is present for at least 1 month when the patient is on a constant dose of antipsychotic. The phenomenology is similar to acute akathisia.

Examination for extrapyramidal symptoms includes observation of spontaneous movement, assessment of tone, and performance of repetitive tasks. Clinicians should observe for evidence of hyperkinetic movements suggestive of akathisia, dyskinesia, or tremor while the patient is at rest and for evidence of poverty of movement to suggest drug-induced parkinsonism. Limbs should be moved by the clinician passively to examine for cogwheel rigidity. Limbs should be held in a posture and actively moved through a range of motion to assess for postural and kinetic tremor. Repetitive movements of the hands, arms, and feet should be performed such as pronation supination movements of the arms, opening and closing of the hands, or foot tapping to examine for bradykinesia. There are a number of validated rating scales to screen for extrapyramidal symptoms. The use of standardised scales may be useful to the clinician as they provide a general structure on how the examination should be performed and allows abnormalities to be quantified to facilitate comparison between visits. The Extrapyramidal Symptom Rating Scale[64] assesses for all types of antipsychotic-induced movement disorders. It consists of 4 subscales and 4 clinical global impression severity scales for parkinsonism, akathisia, dystonia, and tardive dyskinesia. An explicit scoring system for ratings on each scale is provided. Interrater reliability is high, with mean item correlation coefficients of 0.80 to 0.97. Other rating scales include the Abnormal Involuntary Movement Scale (AIMS)[65] for assessment of tardive dyskinesia, the Simpson Angus Scale (SAS)[66] for assessment of antipsychotic-induced parkinsonism, and the Barnes Akathisia Scale[67] for assessment of akathisia. While choosing between scales should be based on physician preference, the Extrapyramidal Symptom Rating Scale is a logical choice since it assess for all types of extrapyramidal symptoms while the other scales only evaluate a single symptom domain.

## Recommendation 12

Service users should be informed of the risk of extrapyramidal side effects and encouraged to report any symptoms suggestive of extrapyramidal side effects (at every visit). Health care professionals should be vigilant for the presence of extrapyramidal side effects, even if this is not mentioned by the service user, for example, by use of a validated side effect scale (at least annually).

[Modified recommendation from SIGN (Good practice point)]

The risk of extrapyramidal side effects varies depending on the antipsychotic medication used and its receptor binding profile. A recent multiple-treatment meta-analysis compared 15 orally administered antipsychotic drugs for schizophrenia with respect to their comparative efficacy, risk of all-cause discontinuation, and major side effects, including extrapyramidal side effects.[56] The use of antiparkinson drugs as a measure of extrapyramidal side effects was used and compared between drugs. As expected, the odds of extrapyramidal side effects was highest with first-generation antipsychotics, with an OR of 4.76 (95% CI, 3.70-6.04) with haloperidol and 2.65 (95% CI, 1.33-4.76) with chlorpromazine. ORs for extrapyramidal side effects were significantly higher compared to placebo for lurasidone (2.46), risperidone (2.09), paliperidone (1.81), and ziprasidone (1.61; 95% CI, 1.05-2.37). The risk of extrapyramidal side effects was significantly lower with clozapine compared to placebo (OR, 0.3; 95% CI, 0.12-0.62). The remaining medications (olanzapine, quetiapine, aripiprazole, and asenapine) all had 95% CIs that crossed 1 and therefore were not significantly different from placebo. Although it was not demonstrated in this analysis, likely due to the way the outcome was defined, the use of aripiprazole is associated with the development of akathisia. A Cochrane review of aripiprazole versus placebo for schizophrenia found a relative risk of akathisia of 1.78 (95% CI, 1.16-2.74) with aripiprazole compared to placebo.[68]

## Recommendation 13

If extrapyramidal side effects are of particular concern to a service user, then second-generation antipsychotics (SGAs),

especially olanzapine, quetiapine, clozapine, or asenapine, or low-potency first-generation antipsychotics (FGAs) should be considered.

[Modified from SIGN (Grade B)]

A systematic review of 12 trials published from 2004 to 2008 ($n = 28,051$, age 39.7 years, 59.7% male, 70.9% white, followed for 463,925 person years) found that the annualised tardive dyskinesia incidence was 3.9% (95% CI, 3.6-4.3) for SGAs and 5.5% (95% CI, 5.1-6.1) for FGAs.[69]

### *Recommendation 14*

Where tardive dyskinesia is a specific concern, an SGA should be considered.

[SIGN (Grade B)]

## Conclusion

Careful monitoring and attention by prescribers may mitigate adverse effects associated with antipsychotic medications. Existing evidence suggests that monitoring of adverse effects of antipsychotic medications in psychiatric patients is infrequently performed, despite evidence-based guidelines that such monitoring procedures are necessary. Physicians who prescribe antipsychotics must become champions of antipsychotic safety and take responsibility for both the mental and physical well-being of the patients they treat. Using the structured and evidence-based recommendations on appropriate screening measures, antipsychotic safety monitoring is both feasible and relevant. Several evidence-based strategies can be employed to promote weight loss and decrease the risk of extrapyramidal symptoms. Suggested areas of further research include interventions designed to improve the uptake of drug safety monitoring procedures by physicians and economic studies of the cost of physical health impacts of antipsychotics relative to screening and prevention programs.

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### Supplementary Material

Supplementary material is available for this article online.

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