Pharmacotherapy management of schizophrenia for family physicians

Japheth Bool Alex Crawley BSP ACPR Annabelle Wanson MD FRCPC
Breanna Davis MD CCFP FCFP Katelyn Halpape BSP ACPR PharmD BCPP

Canadian family physicians likely encounter 1 or 2 new patients per year with signs or symptoms of schizophrenia.[1] Although antipsychotic treatment of schizophrenia is generally the responsibility of a psychiatrist, family physicians play an important role in the long-term management of schizophrenia, including the management of antipsychotic adverse effects. Additionally, family physicians might initiate antipsychotic treatment for patients experiencing psychosis when immediate referral to a psychiatrist is not possible. Antipsychotic medications are the mainstay of schizophrenia management and attaining a stable medication regimen as soon as possible following diagnosis helps to prevent future disability.[2] Unfortunately, antipsychotic medication nonadherence and adverse effects are common in schizophrenia management, making the goal of attaining a stable medication regimen challenging to achieve. This article provides an overview of pharmacotherapy management of schizophrenia for family physicians through a case-based approach.

Case description: part 1

K.W. is a 25-year-old woman who presents to your medical office with a family member. She describes visual hallucinations of snakes coming out of a lake. She also has a delusion that "someone put an aneurysm in her head by laying hands on her at her workplace." K.W. has had these symptoms for the past month. Your electronic medical record tells you that 6 months ago, another physician in your clinic started K.W. on 15 mg of oral olanzapine once daily and referred her to a psychiatrist after she presented with suspected first-episode psychosis. K.W. states that the olanzapine caused excess sedation, so she stopped taking it. She did not follow up with the psychiatrist. She has no additional medical history and denies substance use. Collateral information from her family confirms that K.W. has never used substances.

Adherence to antipsychotic medications

More than half of patients with schizophrenia are nonadherent to their psychotropic medications, and this increases their risk of hospitalization, disease progression, and death.[3-6] In a retrospective study of patients with schizophrenia, 35% of nonadherent patients had a psychiatric hospitalization compared with 14% of adherent patients (number needed to harm of 4 over 3 years).[4]

One way to reduce the risk of antipsychotic medication nonadherence is to maximize tolerability. Most antipsychotic adverse effects are dose related; thus, avoiding overly rapid or premature dose escalations can improve tolerability.[7] This can be achieved by starting at low initial doses, such as those listed in **Table 1**,[8-16] and then increasing in increments equivalent to the initial dose.[7] To allow for assessment of tolerability and to avoid rapid dose escalations, the frequency of dose increases should depend on the duration of time a given antipsychotic takes to reach steady state.[7] For example, the initial suggested dose of aripiprazole for schizophrenia is 10 mg, and it takes 14 days of consecutive treatment for aripiprazole to reach steady state. Thus, an approach to aripiprazole initiation would be to start at 10 mg once daily for 2 weeks and then, if necessary, increase the dose by 10 mg at a time.

Most patients with first-episode psychosis respond well to approximately half the labeled maximum dose of an antipsychotic medication and dosing above the labeled maximum dose should only be done after specialist consultation.[7] This is important because the toxic range of antipsychotic medication is very close to the therapeutic range.[17] If patients do not demonstrate improvement while taking doses at or above the labeled maximum dose, the dose should be reduced and alternative antipsychotic therapy should be considered.[7] It might take as long as 2 to 4 weeks at a therapeutic antipsychotic dose for initial improvement in positive schizophrenia symptoms, such as delusions and hallucinations. An adequate antipsychotic medication trial is defined as 6 weeks of treatment with at least 80% of the labeled maximum dose.[7] Primary negative schizophrenia symptoms, such as avolition and anhedonia, are more challenging to treat and generally do not respond well to antipsychotic therapy.[17]

Back to the case

K.W. was initially started on 15 mg of olanzapine once daily but did not tolerate it. An initial regimen of 5 mg of olanzapine once daily might have increased the likelihood of tolerability. After 1 week the dose could then have been increased to half the labeled maximum dose (10 mg daily) and response assessed after 2 to 4 weeks.

Antipsychotic medication selection

As all antipsychotic medications have comparable efficacy (except for clozapine, which is the most effective antipsychotic medication for schizophrenia treatment), choosing initial therapy based on the adverse effect profile is another strategy to promote adherence.[18-20] For this reason, first-generation antipsychotic medications are not

Table 1. Initial antipsychotic medication dosing and time to reach steady state: *A) Selected oral SGAs and B) selected long-acting injectable SGAs.*

A)				
GENERIC NAME (BRAND NAME)	**INITIAL DOSE[8]**	**LABELED MAXIMUM DOSE[8]**	**TIME TO STEADY STATE**	**COST RANGE (PER 30 d)**
Risperidone (Risperdal)	1 mg once daily	6 mg/d	5 to 6 d[9]	$25 to $41
Paliperidone (Invega)	3 mg once daily	12 mg/d	4 to 5 d[10]	$120 to $230
Olanzapine (Zyprexa)	5 mg once daily	20 mg/d	7 d[11]	$33 to $55
Extended-release quetiapine (Seroquel XR)	50 mg once daily (antipsychotic effect generally not seen until dose is ≥ 400 mg)	800 mg/d	1 to 2 d[12]	$57 to $99*
Aripiprazole (Abilify)	10 mg once daily	30 mg/d	14 d[13]	$45 to $52
Brexpiprazole (Rexulti)	1 mg once daily	4 mg/d	20 d[14]	$125
B)				
GENERIC NAME (BRAND NAME)	**INITIAL DOSE AND REQUIREMENT OF ORAL OVERLAP[8]**	**LABELED MAXIMUM DOSE[8]**	**TIME TO STEADY STATE**	**COST RANGE (PER 30 d)**
Once-monthly paliperidone (Invega Sustenna)	Day 1: 150 mg IM Day 8: 100 mg IM Then 75 mg IM every 4 wk No oral overlap needed	150 mg IM every 4 wk	4 to 5 mo[15]	$330 to $665
Risperidone (Risperdal Consta)	25 mg IM every 2 wk with 3 wk of oral risperidone overlap	50 mg IM every 2 wk	2 mo[9]	$368 to $708
Aripiprazole (Abilify Maintena)	400 mg IM every 4 wk with 2 wk of oral aripiprazole overlap	400 mg IM every 4 wk	4 mo[16]	$483

IM—intramuscular, SGA—second-generation antipsychotic medication.
*Immediate-release formulation is less costly, but requires twice-daily to 3-times-daily dosing, which is challenging for adherence.

usually recommended as first-line therapy, as they have higher discontinuation rates compared with second-generation antipsychotic medications (SGAs) owing to increased rates of extrapyramidal symptoms (EPS).[20,21] For example, in a 6-week study of patients after their first episode of psychosis, 8% of patients treated with risperidone withdrew due to adverse effects compared with 26% of patients treated with haloperidol.[22]

Antipsychotic medications differ substantially in their relative rates of EPS, weight gain, hyperprolactinemia, sedation, orthostatic hypotension, sexual dysfunction, and anticholinergic effects.[8,18] Clinicians might consider using a shared decision-making approach to select an antipsychotic medication that has the most acceptable adverse effect profile for each patient.[7]

Table 2 describes suggested management of SGA adverse effects.[7,8,18,23-25] In general, options for managing adverse effects include lowering the antipsychotic dose, changing administration times, using adjunctive medications, or switching to an alternate antipsychotic medication.[7]

Back to the case

From your assessment of K.W.'s current clinical presentation, you deem it appropriate for her to be admitted to an acute care facility for inpatient psychiatry treatment. On the inpatient psychiatry ward, she is diagnosed with schizophrenia and receives inpatient treatment for 1 month. She is discharged, taking 3 mg of risperidone orally at night and 150 mg of paliperidone intramuscularly every 4 weeks.

Long-acting injectable antipsychotic medications (LAIAs)

Long-acting injectable antipsychotic medications should be considered early in the course of schizophrenia to attempt to improve adherence.[26] For example, in the PRIDE (Paliperidone Palmitate Research in Demonstrating Effectiveness) study, 450 patients with schizophrenia were randomized to oral antipsychotic medications or a once-monthly paliperidone injection. After 15 months, treatment failure was 39.8% in the paliperidone injection group and 53.7% in the oral antipsychotic group (number needed to treat of 7).[27] Additionally, observational data of LAIA use in schizophrenia demonstrate a 20% to 30% reduction in risk of rehospitalization compared with oral antipsychotic medications.[28]

Unfortunately, LAIAs are typically much more expensive than oral agents are (eg, around $40 per month for oral risperidone vs around $400 per month for injectable risperidone) and drug coverage can be a challenge. Further, injection site reactions occur in up to 10% of patients.[15] However, the cost savings of reduced hospitalizations with LAIAs might offset the overall cost to the health care system.[29] If possible, patients should be involved in a shared decision-making process regarding the use of oral versus injectable antipsychotic treatment.

Before initiation of a LAIA, tolerability with the oral equivalent must be established.[8] **Table 1** describes the overlap time required between oral antipsychotic medications and LAIAs.[8-16]

Case description: part 2

Four months after her discharge from the hospital, K.W. presents back to your office. She has been adherent to the risperidone and paliperidone prescribed in hospital. She has had no hallucinations, delusions, or paranoid thoughts since being discharged from hospital and she is managing well at home. She denies sexual dysfunction, anticholinergic adverse effects, or sedation. You assess her for EPS using the Simpson Angus Scale. On the Simpson Angus Scale, she scores a 2 on the gait criterion owing to noticeably decreased left arm swing with obvious rigidity.

Management of EPS

Extrapyramidal symptoms are a constellation of movement disorders that occur secondary to the use of dopamine receptor blocking agents such as antipsychotic medications.[8] One strategy to reduce the risk of EPS is to use the lowest effective antipsychotic dose (**Table 1**).[8-16]

The 4 main types of EPS, in order of typical onset, are as follows:

- acute dystonic reactions (usually occur within the first 2 weeks of treatment),[8]
- akathisia (usually begins within 2 to 4 weeks of treatment),[8]
- pseudoparkinsonism (usually seen within 3 to 6 weeks of treatment initiation but might also occur any time after),[8] and
- tardive dyskinesia (usually not seen until 3 months after treatment initiation).[8]

The goals of EPS treatment include resolution of symptoms and prevention of tardive dyskinesia. Although EPS occurs less frequently with SGAs compared with first-generation agents (aside from the higher incidence of akathisia with aripiprazole), EPS is still a concern with SGA use.[30,31] For example, it is reported that 7.2% of patients who receive a long-acting risperidone injection will develop an acute dystonic reaction.[32] Risk factors for EPS include the type of antipsychotic medication, high doses of antipsychotic medication, and history of previous EPS.[30,31] **Table 2** presents strategies to treat EPS.[7,8,18,23-25]

Case resolution

K.W. appears to have pseudoparkinsonism secondary to her antipsychotic regimen. She is currently taking 2 antipsychotic medications. Dual antipsychotic therapy can be appropriate when starting a long-acting injection to provide a temporary bridge until LAIA onset; however, long-acting injectable paliperidone is unique in that it is the only LAIA that does not require oral overlap on initiation. Additionally, long-acting injectable paliperidone achieves steady state in 4 to 5 months; thus, K.W. would now be at steady state levels. You recognize that she is taking the labeled maximum dose of long-acting injectable paliperidone despite this being her first time taking an antipsychotic consistently. She is responding well but the EPS she is experiencing are concerning. In consultation with her psychiatrist, you stop the risperidone, as it was unintentionally continued on hospital discharge, and decrease her dose of paliperidone to 100 mg every 4 weeks. Two months later you check in with K.W. and find that her EPS have resolved, and her schizophrenia remains controlled.

Switching antipsychotic medications

If K.W.'s pseudoparkinsonism had not improved, she might have needed to switch antipsychotic medications. Caution is required when switching antipsychotic medications to minimize the risk of a relapse and withdrawal symptoms. A crossover rotation approach is usually recommended, wherein the first medication is tapered down while the second medication is simultaneously titrated up. This process usually occurs over a minimum of 2 to 4 weeks for oral antipsychotic therapy. Switching LAIAs is more complex and the product monograph for the specific antipsychotic agents should be reviewed. A useful resource for cross-tapering can be found at **www.switchrx.com**. When considering switching, it is important to first consider confounding factors for nonresponse including nonadherence, substance use, and interactions between medications and substances (eg, cigarette smoking) that might alter antipsychotic pharmacokinetics.[8]

Conclusion

Treating patients living with schizophrenia is a complex task, as exemplified by K.W.'s case. Early intervention has a substantial effect on the long-term outcomes, and appropriate use of antipsychotic medications is the cornerstone of the management of schizophrenia.[2] It is important to consider the adverse effect profile, dosing, and patient preference when selecting a medication for schizophrenia treatment. Adherence to treatment is imperative in reducing the risk of psychotic relapse and, for this reason, LAIAs should be considered early in

Table 2. Antipsychotic medication adverse effects, monitoring, and management

ADVERSE DRUG EFFECT	MOST LIKELY CAUSATIVE SGA[8,18]	ASSESSMENT TOOLS	SCHEDULE FOR MONITORING[23]	MANAGEMENT STRATEGIES[7,8,23]
Sedation	Olanzapine Clozapine Quetiapine	NA	Baseline and at each visit	• Change administration time to before bedtime • Slow down the titration if in titration phase • Lower the dose (if appropriate) • Switch to an alternative such as risperidone, paliperidone, aripiprazole, or brexpiprazole
Anticholinergic effects (eg, xerostomia, constipation, dry eyes)	Clozapine Quetiapine	NA	Standard monitoring schedule*	• Lower the dose (if appropriate) • Add an adjunctive medication based on symptom† • Switch to an alternative such as risperidone, paliperidone, aripiprazole, or brexpiprazole
Orthostatic hypotension	Clozapine Quetiapine Olanzapine	Orthostatic blood pressure monitoring	Standard monitoring schedule*	• Change administration time to before bed • Slow down the titration if in titration phase • Nonpharmacologic measures: get up slowly, increase fluids. If other strategies are ineffective, can try medications such as midodrine or fludrocortisone[24] • Switch to an alternative such as risperidone, paliperidone, aripiprazole, or brexpiprazole
Sexual dysfunction	Olanzapine Quetiapine Risperidone Paliperidone	NA	Baseline, during titration, and annually thereafter	• Lower the dose (if appropriate) • Can wait 1 to 3 mo to assess for tolerance • Switch to an alternative such as aripiprazole or brexpiprazole • Adjunctive medication based on symptom‡
Metabolic effects (eg, weight gain, dyslipidemia, glucose intolerance)	Olanzapine Clozapine Quetiapine	Weight, BMI, fasting blood glucose level, hemoglobin A_{1c} level, lipid panel	Standard monitoring schedule*	• Behaviour modification (diet, exercise) • Add 850 to 1000 mg metformin twice daily • Switch to an alternative such as risperidone, paliperidone, aripiprazole, or brexpiprazole
Hyperprolactinemia	Risperidone Paliperidone	Prolactin levels	If symptoms of hyperpro-lactinemia are present	• Lower the dose (if appropriate) • Switch to an alternative such as aripiprazole or brexpiprazole • Add 3 to 6 mg/d adjunctive aripiprazole§
Acute dystonia (sudden muscle contraction)	Risperidone Paliperidone	Simpson-Angus Scale‖	Standard monitoring schedule*	• Lower the dose (if appropriate) • Use IM benztropine or diphenhydramine for shortest duration possible • Switch to an alternative such as aripiprazole, olanzapine, quetiapine, or brexpiprazole
Pseudoparkinsonism (eg, tremor, cogwheel rigidity, shuffling gait)	Risperidone Paliperidone	Simpson-Angus Scale‖	Standard monitoring schedule*	• Lower the dose (if appropriate) • Switch to an alternative such as quetiapine, aripiprazole, brexpiprazole, or clozapine • Add 0.5 to 2 mg oral benztropine daily to twice daily for the shortest duration possible
Akathisia (inner feeling of restlessness)	Aripiprazole Olanzapine Risperidone	Barnes Akathisia Rating Scale	Standard monitoring schedule*	• Lower the dose (if appropriate) • Switch to an alternative such as quetiapine or paliperidone • Add 10 to 20 mg oral propranolol 3 times daily
Tardive dyskinesia (involuntary repetitive muscle movement usually involving orofacial muscles)	Risperidone Paliperidone	Abnormal Involuntary Movement Scale	Standard monitoring schedule*	• Slowly taper off the causal antipsychotic medication, as tardive dyskinesia can be irreversible, and switch to clozapine or quetiapine (less risk of tardive dyskinesia) • Add tetrabenazine

BMI—body mass index, IM—intramuscular, NA—not applicable, SGA—second-generation antipsychotic medication.
*Baseline, every 1 to 2 wk during titration, at 3 mo, and annually thereafter.
†For example, laxatives can be used for constipation or artificial saliva can be used for dry mouth.
‡For example, phosphodiesterase 4 inhibitors can be used for erectile dysfunction.
§Partial agonist activity of aripiprazole overcomes D_2 blockade–induced hyperprolactinemia in the tuberoinfundibular pathway.[25]
‖Available from **https://wbma.cc/wp-content/uploads/2018/01/Simpson_Angus_scale.pdf**.

schizophrenia management. Initiation of LAIAs requires confirmation of oral antipsychotic tolerability and an appropriate period of overlap with oral antipsychotic medications. Prescribers of antipsychotic medications should monitor for adverse drug effects continuously, with more rigorous monitoring at times of antipsychotic initiation or dose changes. Monitoring should include assessment of symptom improvement, sedation, metabolic status, EPS, sexual dysfunction, and hyperprolactinemia. Early identification and management of these adverse effects can promote adherence and thereby decrease the risk of psychotic episodes and hospitalizations.

Mr Bool is a pharmacy student at the University of Saskatchewan in Saskatoon. **Mr Crawley** is Associate Director of RxFiles Academic Detailing in the College of Pharmacy and Nutrition at the University of Saskatchewan. **Dr Wanson** is Assistant Professor in the College of Medicine at the University of Saskatchewan and Inpatient Psychiatry Lead in the Irene and Leslie Dube Centre at the Royal University Hospital in Saskatoon. **Dr Davis** is Assistant Professor in the Department of Academic Family Medicine at the University of Saskatchewan and a family physician in Prince Albert, Sask. **Dr Halpape** is Assistant Professor in the College of Pharmacy and Nutrition at the University of Saskatchewan and a clinical psychiatric pharmacist in Saskatoon.

Competing interests
RxFiles Academic Detailing Program is funded through a grant from Saskatchewan Health to the University of Saskatchewan; additional "not for profit; not for loss" revenue is obtained from sales of books and online subscriptions. No financial assistance was obtained for this publication. **Dr Halpape** reports that she has previously received an honorarium as a chapter editor of the *Clinical Handbook of Psychotropic Drugs*, 23rd edition. All other authors have no competing interests to disclose.

Correspondence
Dr Katelyn Halpape; e-mail **Katelyn.halpape@usask.ca**

References

1. Anderson KK, Archie S, Booth RG, Cheng C, Lizotte D, MacDougall AG, et al. Understanding the role of the family physician in early psychosis intervention. *BJPsych Open* 2018;4(6):447-53.
2. Sami MB, Shiers D, Latif S, Bhattacharyya S. Early psychosis for the non-specialist doctor. *BMJ* 2017;357:j4578.
3. Semahegn A, Torpey K, Manu A, Assefa N, Tesfaye G, Ankomah A. Psychotropic medication non-adherence and associated factors among adult patients with major psychiatric disorders: a protocol for a systematic review. *Syst Rev* 2018;7(1):10.
4. Gilmer TP, Dolder CR, Lacro JP, Folsom DP, Lindamer L, Garcia P, et al. Adherence to treatment with antipsychotic medication and health care costs among Medicaid beneficiaries with schizophrenia. *Am J Psychiatry* 2004;161(4):692-9.
5. Nasrallah HA. For first-episode psychosis, psychiatrists should behave like cardiologists. *Curr Psychiatr* 2017:16(8):4-7.
6. Tiihonen J, Tanskanen A, Taipale H. 20-Year nationwide follow-up study on discontinuation of antipsychotic treatment in first-episode schizophrenia. *Am J Psychiatry* 2018;175(8):765-73. Epub 2018 Apr 6.
7. Keepers GA, Fochtmann LJ, Anzia JM, Benjamin S, Lyness JM, Mojtabai R, et al. The American Psychiatric Association practice guideline for the treatment of patients with schizophrenia. *Am J Psychiatry* 2020;177(9):868-72.
8. Procyshyn RM, Bezchlibynk-Butler KZ, Jeffries JJ, editors. *Clinical handbook of psychotropic drugs*. 23rd ed. Boston, MA: Hogrefe Publishing; 2019.
9. *Risperdal (risperidone)* [product monograph]. Titusville, NJ: Janssen Inc; 2020.
10. *Invega (paliperidone extended-release tablets)* [product monograph]. Toronto, ON: Janssen Inc; 2018.
11. *Zyprexa (olanzapine tablets)* [product monograph]. Indianapolis, IN: Eli Lilly and Company; 2020.
12. *Seroquel XR (quetiapine fumarate extended-release tablets)* [product monograph]. Mississauga, ON: AstraZeneca Canada Inc; 2019.
13. *Abilify (aripiprazole)* [product monograph]. Tokyo, Japan: Otsuka Pharmaceutical Co, Ltd; 2014.
14. *Rexulti (brexpiprazole tablets)* [product monograph]. Tokyo, Japan: Otsuka Pharmaceutical Co, Ltd; 2019.
15. *Invega Sustenna (paliperidone palmitate prolonged-release injectable suspension)* [product monograph]. Toronto, ON: Janssen Inc; 2020.
16. *Abilify Maintena (aripiprazole for prolonged release injectable suspension)* [product monograph]. Tokyo, Japan; Otsuka Pharmaceutical Co, Ltd; 2014.
17. Correll CU, Schooler NR. Negative symptoms in schizophrenia: a review and clinical guide for recognition, assessment, and treatment. *Neuropsychiatr Dis Treat* 2020;16:519-34.
18. Huhn M, Nikolakopoulou A, Schneider-Thoma J, Krause M, Samara M, Peter N, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet* 2019;394(10202):939-51. Epub 2019 Jul 11. Erratum in: *Lancet* 2019;394(10202):918.
19. Williams R, Malla A, Roy MA, Joober R, Manchanda R, Tibbo P, et al. What is the place of clozapine in the treatment of early psychosis in Canada? *Can J Psychiatry* 2017;62(2):109-14. Epub 2016 Jul 9.
20. Crockford D, Addington D. Canadian schizophrenia guidelines: schizophrenia and other psychotic disorders with coexisting substance use disorders. *Can J Psychiatry* 2017;62(9):624-34.
21. Zhang JP, Gallego JA, Robinson DG, Malhotra AK, Kane JM, Correll CU. Efficacy and safety of individual second-generation vs. first-generation antipsychotics in first-episode psychosis: a systematic review and meta-analysis. *Int J Neuropsychopharmacol* 2013;16(6):1205-18. Epub 2012 Dec 3.
22. Emsley RA; Risperidone Working Group. Risperidone in the treatment of first-episode psychotic patients: a double-blind multicenter study. *Schizophr Bull* 1999;25(4):721-9.
23. Stroup TS, Gray N. Management of common adverse effects of antipsychotic medications. *World Psychiatry* 2018;17(3):341-56.
24. Lu L, Stone S, Regier L. *Orthostatic hypotension (OH): considerations for management*. Saskatoon, SK: RxFiles; 2014. Available from: **https://www.rxfiles.ca/RxFiles/uploads/documents/OrthoHypo-QandA.pdf**. Accessed 2021 Mar 19.
25. Tewksbury A, Olander A. Management of antipsychotic-induced hyperprolactinemia. *Ment Health Clin* 2016;6(4):185-90.
26. Remington G, Addington D, Honer W, Ismail Z, Raedler T, Teehan M. Guidelines for the pharmacotherapy of schizophrenia in adults. *Can J Psychiatry* 2017;62(9):604-16. Epub 2017 Jul 13.
27. Alphs L, Benson C, Cheshire-Kinney K, Lindenmayer JP, Mao L, Rodriguez SC, et al. Real-world outcomes of paliperidone palmitate compared to daily oral antipsychotic therapy in schizophrenia: a randomized, open-label, review board-blinded 15-month study. *J Clin Psychiatry* 2015;76(5):554-61.
28. Tiihonen J, Mittendorfer-Rutz E, Majak M, Mehtälä J, Hoti F, Jedenius E, et al. Real-world effectiveness of antipsychotic treatments in a nationwide cohort of 29 823 patients with schizophrenia. *JAMA Psychiatry* 2017;74(7);686-93.
29. Kane JM, Schooler NR, Marcy P, Correll CU, Achtyes ED, Gibbons RD, et al. Effect of long-acting injectable antipsychotics vs usual care on time to first hospitalization in early-phase schizophrenia: a randomized clinical trial. *JAMA Psychiatry* 2020;77(12):1217-24. Erratum in: *JAMA Psychiatry* 2020;77(12):1310.
30. Divac N, Prostran M, Jakovcevski I, Cerovac N. Second-generation antipsychotics and extrapyramidal adverse effects. *BioMed Res Int* 2014;2014:656370. Epub 2014 Jun 3.
31. D'Souza RS, Hooten WM. *Extrapyramidal symptoms.* Treasure Island, FL: StatPearls Publishing; 2020.
32. Kamishima K, Ishigooka J, Komada Y. Long term treatment with risperidone long-acting injectable in patients with schizophrenia. *Jpn J Psychiatry Neurol* 2009;12:1223-44.

This article is eligible for Mainpro+ certified Self-Learning credits. To earn credits, go to **www.cfp.ca** and click on the Mainpro+ link.

Can Fam Physician 2021;67:350-4. DOI: 10.46747/cfp.6705350

La traduction en français de cet article se trouve à **www.cfp.ca** dans la table des matières du numéro **de mai 2021** à la **page e115**.