Web audio at CurrentPsychiatry.com

Dr. Graham: Switching patients back to antipsychotic monotherapy from polypharmacy

# When and why to initiate antipsychotic polypharmacy, and with which agents

**Elizabeth A. Jackson, PharmD, BCPS, BCPP, Aila J. Spiegel, PharmD, BCPP, and Rebecca L. Graham, PharmD, BCPP**

**Vicki L. Ellingrod, PharmD, FCCP**
Department Editor

Mr. C, age 31, who has a 7-year history of schizophrenia and is currently on perphenazine, 24 mg twice a day, presents for psychiatric admission after experiencing paranoid delusions. Notable symptoms include delusions of reference and persecution, along with affective flattening and intermittent suicidal ideation. Perphenazine is tapered, and he is started on quetiapine, titrated to 600 mg/d.

Past antipsychotic trials include aripiprazole, olanzapine, paliperidone, haloperidol, and ziprasidone. Because of his refractory symptoms and tolerability issues with other antipsychotics, Mr. C is switched to clozapine, 400 mg/d. His symptoms improve, but he experiences dose-limiting sialorrhea. Risperidone, 1 mg/d, is added to clozapine, which helps his psychosis and improves his functional status. Additionally, Mr. C develops enough insight to recognize his delusions and use skills learned in psychotherapy to cope with them.

Antipsychotic polypharmacy (APP), the concurrent use of ≥2 antipsychotics, is a topic of debate among mental health care providers. Studies indicate the prevalence of APP can reach upwards of 40%, with 1 systematic review citing more recent median APP prevalence in North America as 17%, an increase from a median of 12.7% in the 1980s.[1] Other studies cite more recent figures as around 20%.[2,3]

The literature lists several reasons for use of long-term APP, including:

- incomplete cross-titration
- accidental continuation of APP that was intended to be temporary
- monotherapy failure
- mitigation or enhancement of effects of other antipsychotics (***Table 1***).[1,4]

Other factors include direct-to-consumer advertising, external pressures to decrease hospital stays, and low doctor-to-patient ratios.[5] Although it can take as long as 16 weeks to see clinically significant improvement with an antipsychotic, prescribers might expect results

Drs. Jackson and Graham are Clinical Pharmacy Specialists–Mental Health, Veterans Affairs San Diego Healthcare System, San Diego, California. Dr. Spiegel is a Clinical Pharmacy Specialist–Mental Health, Veterans Affairs Central Texas Healthcare System, Austin, Texas.

**Disclosure**
The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

**Practice Points**

- Antipsychotic polypharmacy (APP) might be **appropriate in patients who have failed or cannot tolerate antipsychotic monotherapy**.
- Although evidence in the literature is mixed, **treatment-refractory patients could see improvement with the combination of clozapine plus risperidone**.
- **Safety data for APP are mixed**; several studies of clozapine plus risperidone or adjunctive aripiprazole suggest that these combinations generally are well tolerated.
- **Adding aripiprazole to existing antipsychotic therapy** could be beneficial for mitigating metabolic side effects and drug-induced hyperprolactinemia in patients who cannot be switched to another antipsychotic.

Savvy Psychopharmacology is produced in partnership with the College of Psychiatric and Neurologic Pharmacists
cpnp.org
mhc.cpnp.org (journal)

after 4 weeks of treatment.[6] Therefore, treatments could be labeled ineffective because trials did not last long enough, leading to premature use of polypharmacy. Combinations of a first- and second-generation antipsychotic (SGA) or 2 SGAs are most common.[2,7,8]

Treatment guidelines (***Table 2, page 52***)[9-17] suggest APP could be considered after several failures of monotherapy, including clozapine monotherapy, although some guidelines do not address the issue or recommend against APP because of lack of efficacy and safety data. Additionally, APP poses safety concerns (***Table 3, page 52***).[18-22] Recommendations for APP with combinations that do not include clozapine generally are not provided, because high-level evidence to support this strategy is lacking. Data on safety and efficacy of APP are mixed, with much of the literature dominated by case reports and uncontrolled studies.[19]

## *What* to initiate

**Clozapine.** Higher-level evidence is available for clozapine APP. The combination of clozapine and risperidone is one of the most thoroughly studied and, therefore, is a reasonable first choice. Randomized controlled trials (RCTs) examining clozapine plus risperidone[23-29] have yielded mixed results and have not provided conclusive information regarding benefit for positive vs negative symptoms.[24-28]

One RCT reported a significant change in Brief Psychiatric Rating Scale (BPRS) total and positive symptom scores.[27] Other RCTs have shown a non-significant trend toward greater change in total, positive, and negative symptom scores with the clozapine-risperidone combination compared with clozapine monotherapy.[25,28] In terms of cognition, this combination provided no additional benefit.[23] Response, defined as ≥20% reduction in total BPRS or Positive and Negative Syndrome Scale (PANSS) scores, for clozapine plus risperidone range from 13% to 83%, compared with 8% to 29% for clozapine plus placebo.[24,25,27,29]

**Table 1**

### Broad rationale among clinicians for instituting antipsychotic polypharmacy

| |
|---|
| Obtain pharmacodynamic synergy: Adding an FGA to an SGA might increase D2 receptor occupancy above a threshold level |
| Broaden the range of receptor activity |
| Decrease total antipsychotic dosage burden |
| Gain a greater and more rapid response |
| Cross-taper |
| Manage particularly challenging symptoms |
| Decrease persistent positive symptoms (rationale for adding an FGA) |
| Optimize pharmacokinetic effects |
| Counteract adverse effects (aripiprazole) |
| Treat breakthrough psychotic symptoms (as-needed agent) |
| Counteract a patient's refusal to take clozapine or sidestep a contraindication to clozapine |
| Respond to pressure to decrease length of hospitalization |
| Manage a low physician-to-patient ratio |

FGA: first-generation antipsychotic; SGA: second-generation antipsychotic

**Source:** References 1,4

Data from 1 study[27] suggest a number needed to treat of 4 to achieve at least a 20% improvement in BPRS scores with clozapine plus risperidone vs clozapine monotherapy. Across these studies, the average risperidone dosage was 4 mg/d, although using the lowest effective dosage is encouraged. A small number of RCTs and articles examining other APP combinations (***Table 4, page 53***)[30-33] have yielded mixed results.

Overall, APP appears to be well-tolerated, although it is associated with an increased risk of adverse effects, including sedation, extrapyramidal symptoms, hyperprolactinemia, sexual dysfunction, cognitive impairment, anticholinergic effects, hyperlipidemia, and diabetes.[23,24,34-36] Surprisingly, 1 literature review[36] found no association between APP and increased risk of orthostasis. Increased occurrence of sedation, hyper-

**Clinical Point**

**Treatment guidelines suggest APP could be considered after several failures of monotherapy, including clozapine monotherapy**

Discuss this article at www.facebook.com/CurrentPsychiatry

## Clinical Point

**The combination of clozapine and risperidone is one of the most thoroughly studied and, therefore, is a reasonable first choice**

Table 2

### Treatment guidelines for antipsychotic polypharmacy in schizophrenia

| Organization (year) | Findings and recommendations |
|---|---|
| American Psychiatric Association (2004) | • Clozapine APP is reasonable for patients who have an inadequate response to clozapine<br>• Evidence for (or against) the use of non-clozapine APP is minimal |
| British Association for Psychopharmacology (2011) | • Clozapine APP can be considered after 3 months of clozapine monotherapy<br>• Effectiveness of non-clozapine APP has not been assessed enough to support a recommendation over antipsychotic monotherapy |
| National Institute for Health and Care Excellence (2014) | If the patient has an inadequate response to clozapine at an optimized dosage, consider measuring the serum drug level before adding a second antipsychotic |
| Texas Medication Algorithm Project (2008) | • Clozapine APP is recommended after failure of 2 FGAs, 2 SGAs, or clozapine monotherapy<br>• Non-clozapine APP is recommended after failure of clozapine monotherapy and clozapine in combination with another antipsychotic |
| World Federation of Societies of Biologic Psychiatry (2012) | Combination of clozapine with another SGA (possibly risperidone) might have some advantage compared with monotherapy |
| The Schizophrenia Patient Outcomes Research Team (2009) | Studies of clozapine APP have failed to document sufficient efficacy and safety to support a recommendation in people with treatment-resistant schizophrenia |
| Canadian Psychiatric Association (2005) | APP is the last treatment strategy to be employed |
| Royal Australian and New Zealand College of Psychiatrists (2004) | APP should not be used except during transitional periods when switching antipsychotics; there is little evidence for the effectiveness of APP, and the practice increases the side-effect burden |
| Scottish Intercollegiate Guidelines Network (2013) | A trial of clozapine augmentation with a second SGA should be considered for patients whose symptoms have not responded adequately to clozapine monotherapy |

APP: antipsychotic polypharmacy; FGA: first-generation antipsychotic; SGA: second-generation antipsychotic

**Source:** References 9-17

Table 3

### What are the concerns about antipsychotic polypharmacy?

| |
|---|
| Prescribing total dosages of antipsychotics higher than is necessary or recommended |
| Increased risk of side effects, including metabolic syndrome and extrapyramidal symptoms |
| Increased risk of drug–drug interactions |
| Difficultly assessing response to individual medications when ≥2 agents are given concomitantly |
| Could contribute to worsened medication adherence because of greater treatment complexity |
| Could be associated with increased mortality |
| Might produce a decline in cognitive functioning |
| Might be associated with longer hospitalization |

**Source:** References 18-22

Table 4

## Studies of antipsychotic polypharmacy

| Study | Type | N | Results |
|---|---|---|---|
| CADTH (2012) | Review article examining combination and high-dose antipsychotic therapies for schizophrenia | 30 RCTs | • Clozapine APP was associated with improvement in CGI scores and reduction in metabolic side effects, but also with a higher rate of hyperprolactinemia, akathisia, and treatment withdrawal compared with patients taking clozapine monotherapy<br>• Because of the dearth of high-level evidence in the literature, RCTs for non-clozapine APP were limited |
| Chang et al (2008) | 8-Week randomized double-blind, placebo-controlled trial of aripiprazole augmentation of clozapine | 62 | • No significant difference in BPRS total score between aripiprazole and placebo<br>• Secondary analysis: significantly greater improvement for negative symptoms (BPRS, SANS) but not positive symptoms with aripiprazole<br>• No differences in adverse effects |
| Kane et al (2009) | 16-Week multicenter, double-blind, placebo-controlled study of aripiprazole or placebo added to quetiapine or risperidone | 323 | • Similar mean change in PANSS total score between adjunctive aripiprazole and placebo groups<br>• Similar incidence of treatment-emergent adverse effects, including EPS, in all groups |
| Velligan et al (2015) | Analysis of Medicaid data for adult patients initiated on APP or clozapine monotherapy between July 2006 and January 2009 | 2,919 | • Clozapine monotherapy was associated with lower odds of mental illness-related emergency department visits compared with patients on APP (odds ratio = 0.75)<br>• Both disease-specific and all-cause health care costs were lower in patients receiving clozapine monotherapy (of note, not all APP patients in the study were receiving clozapine APP) |

APP: antipsychotic polypharmacy; BPRS: Brief Psychiatric Rating Scale; CADTH: Canadian Agency for Drugs and Technology in Health; CGI: Clinical Global Impression; EPS: extrapyramidal symptoms; PANSS: Positive and Negative Syndrome Scale; RCT: randomized controlled trial; SANS: Scale for the Assessment of Negative Symptoms

**Source:** References 30-33

prolactinemia, and an elevated fasting blood glucose level have been found for clozapine plus risperidone compared with clozapine monotherapy.[24-26,28]

**Aripiprazole.** Adjunctive aripiprazole, a dopamine partial agonist, could reduce elevated prolactin levels caused by other antipsychotics.[32] In a study[37] of 56 patients taking haloperidol who had hyperprolactinemia, prolactin levels normalized in 88.5% of patients taking adjunctive aripiprazole, 30 mg/d, compared with 3.6% of those with added placebo. Furthermore, results from 2 RCTs[38,39] of patients taking clozapine or olanzapine suggest adjunctive aripiprazole could improve weight and metabolic profile. Therefore, adding aripiprazole to existing antipsychotic regimens is

Table 5

## Oral dosages of second-generation antipsychotics for adult patients with schizophrenia

| Drug | Target dosage (mg/d) | Maximum dosage (mg/d) |
|---|---|---|
| Aripiprazole | 10 to 15 | 30 |
| Asenapine | 10 | 20 |
| Clozapine | 300 to 600 | 900 |
| Iloperidone | 6 to 12 | 24 |
| Lurasidone | 40 to 120 | 160 |
| Olanzapine | 10 to 20 | 20 |
| Paliperidone | 6 to 12 | 12 |
| Quetiapine | 300 to 800 | 800 |
| Risperidone | 4 to 8 | 16 |
| Ziprasidone | 80 to 160 | 160 |

**Source:** References 13,40

### Clinical Point

**Adjunctive aripiprazole, a dopamine partial agonist, could reduce elevated prolactin levels caused by other antipsychotics**

## Related Resource

- Kontos N, Freudenreich O, Querques J. Reducing polypharmacy: when less is more. Current Psychiatry. 2010;9(3):80.

**Drug Brand Names**

| | |
|---|---|
| Aripiprazole • Abilify | Olanzapine • Zyprexa |
| Asenapine • Saphris | Paliperidone • Invega |
| Clozapine • Clozaril | Perphenazine • Trilafon |
| Haloperidol • Haldol | Quetiapine • Seroquel |
| Iloperidone • Fanapt | Risperidone • Risperdal |
| Lurasidone • Latuda | Ziprasidone • Geodon |

**Clinical Point**

**Clozapine APP, especially with risperidone, has the most substantial evidence to support it**

reasonable for patients with drug-induced symptomatic hyperprolactinemia or metabolic effects and who cannot be easily switched to another antipsychotic.

## *When* to initiate

Most treatment guidelines[9-17] recommend clozapine only after monotherapy with at least 2 other antipsychotics fails. It is reasonable to add an antipsychotic to clozapine in patients who have shown a partial response to clozapine after a minimum of 3 months. Non-clozapine APP should be considered when:

- a patient derives no benefit from clozapine
- refuses clozapine
- clozapine is contraindicated
- APP is initiated to mitigate side effects from another antipsychotic.

Antipsychotics could take up to 16 weeks to achieve full efficacy,[6] therefore, an adequate trial period within the target dosage range is advised for all antipsychotics (***Table 5, page 53***).[13,40]

## *Why* initiate

Based on available data, partial response to maximum recommended dosages of antipsychotic monotherapy, including clozapine, or inability to tolerate higher dosages, provides a reason for initiating APP. Non-clozapine APP generally should be considered only in patients who refuse, cannot tolerate, or do not respond to clozapine. Consider using validated rating scales to track treatment outcomes (ideally, a ≥20% symptomatic reduction on the BPRS or PANSS), although there is no formal guidance regarding their use or benefit in APP.

## Summing up

APP is a fairly common prescribing practice, even though safety and efficacy data are mixed. The issue of APP has become prevalent enough that regulatory bodies are involved in its monitoring and documentation.[41]

Clozapine APP, especially with risperidone, has the most substantial evidence to support it. Although APP generally is well tolerated, the overall dearth of conclusive safety and efficacy data indicates that this practice should be reserved for patients who have not responded adequately to monotherapy, including clozapine. Adjunctive aripiprazole could be considered for addressing symptomatic hyperprolactinemia or other metabolic effects caused by other antipsychotics.

An adequate trial as long as 16 weeks is advised before assessing the efficacy of any antipsychotic regimen. If APP provides inadequate response, or if there is no clear indication for APP, consider switching the patient back to monotherapy.[42-44]

**References**


1. Gallego JA, Bonetti J, Zhang J, et al. Prevalence and correlates of antipsychotic polypharmacy: a systematic review and meta-regression of global and regional trends from the 1970s to 2009. Schizophr Res. 2012;138(1):18-28.
2. Gören JL, Meterko M, Williams S, et al. Antipsychotic prescribing pathways, polypharmacy, and clozapine use in treatment of schizophrenia. Psychiatr Serv. 2013;64(6):527-533.
3. Sun F, Stock EM, Copeland LA, et al. Polypharmacy with antipsychotic drugs in patients with schizophrenia: trends in multiple health care systems. Am J Health Syst Pharm. 2014;71(9):728-738.
4. Tapp A, Wood AE, Secrest L, et al. Combination antipsychotic therapy in clinical practice. Psychiatr Serv. 2003;54(1):55-59.
5. Ananth J, Parameswaran S, Gunatilake S. Antipsychotic polypharmacy. Curr Pharm Des. 2004;10(18):2231-2238.
6. Stahl SM. Antipsychotic polypharmacy: evidence based or eminence based? Acta Psychiatr Scand. 2002;106(5):321-322.
7. Botts S, Hines H, Littrell R. Antipsychotic polypharmacy in the ambulatory care setting, 1993-2000. Psychiatr Serv. 2003;54(8):1086.
8. Santone G, Bellantuono C, Rucci P, et al. Patient characteristics and process factors associated with antipsychotic polypharmacy in a nationwide sample of psychiatric inpatients in Italy. Pharmacoepidemiol Drug Saf. 2011;20(5):441-449.
9. American Psychiatric Association. Practice guideline for the treatment of patients with schizophrenia, second edition. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/schizophrenia.pdf. Updated September 2009. Accessed September 20, 2014.
10. Barnes TRE; Schizophrenia Consensus Group of the

British Association for Psychopharmacology. Evidence-based guidelines for the pharmacological treatment of schizophrenia: recommendations from the British Association for Psychopharmacology. http://www.bap.org.uk/pdfs/Schizophrenia_Consensus_Guideline_Document.pdf. Updated 2011. Accessed September 20, 2014.

11. National Institute for Health and Care Excellence. Psychosis and schizophrenia in adults: prevention and management. http://www.nice.org.uk/guidance/cg178. Published February 2014. Accessed September 20, 2014.
12. Texas Medication Algorithm Project. Schizophrenia treatment algorithms. http://www.jpshealthnet.org/sites/default/files/tmapalgorithmforschizophrenia.pdf. Updated April 2008. Accessed September 20, 2014.
13. Hasan A, Falkai P, Wobrock T, et al; World Federation of Societies of Biological Psychiatry (WFSBP). World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia, part 1: update 2012 on the acute treatment of schizophrenia and the management of treatment resistance. World J Biol Psychiatry. 2012;13(5):318-378.
14. Canadian Psychiatric Association. Clinical practice guidelines: treatment of schizophrenia. https://ww1.cpa-apc.org/Publications/Clinical_Guidelines/schizophrenia/november2005/index.asp. Updated November 2005. Accessed February 26, 2016.
15. Royal Australian and New Zealand College of Psychiatrists. Clinical practice guidelines for the treatment of schizophrenia and related disorders. http://www.ranzcp.org/Files/ranzcp-attachments/Resources/Publications/CPG/Clinician/CPG_Clinician_Full_Schizophrenia-pdf.aspx. Updated May 2005. Accessed February 26, 2016.
16. Scottish Intercollegiate Guidelines Network. Management of schizophrenia: a national clinical guideline. http://www.sign.ac.uk/guidelines/fulltext/131/index.html. Updated March 2013. Accessed September 20, 2014.
17. Buchanan RW, Kreyenbuhl J, Kelly DL, et al; Schizophrenia Patient Outcomes Research Team (PORT). The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. Schizophr Bull. 2010;36(1):71-93.
18. Correll CU, Gallego JA. Antipsychotic polypharmacy: a comprehensive evaluation of relevant correlates of a long-standing clinical practice. Psychiatr Clin North Am. 2012;35(3):661-681.
19. Tranulis C, Skalli L, Lalonde P, et al. Benefits and risks of antipsychotic polypharmacy: an evidence-based review of the literature. Drug Saf. 2008;31(1):7-20.
20. Barnes TR, Paton C. Antipsychotic polypharmacy in schizophrenia: benefits and risks. CNS Drugs. 2011;25(5):383-399.
21. Lochmann van Bennekom MW, Gijsman HJ, Zitman FG. Antipsychotic polypharmacy in psychotic disorders: a critical review of neurobiology, efficacy, tolerability and cost effectiveness. J Psychopharmacol. 2013;27(4):327-336.
22. Weinmann S, Read J, Aderhold V. Influence of antipsychotics on mortality in schizophrenia: systematic review. Schizophr Res. 2009;113(1):1-11.
23. Akdede BB, Anil Yağcioğlu AE, Alptekin K, et al. A double-blind study of combination of clozapine with risperidone in patients with schizophrenia: effects on cognition. J Clin Psychiatry. 2006;67(12):1912-1919.
24. Anil Yağcioğlu AE, Kivircik Akdede BB, Turgut TI, et al. A double-blind controlled study of adjunctive treatment with risperidone in schizophrenic patients partially responsive to clozapine: efficacy and safety. J Clin Psychiatry. 2005;66(1):63-72.
25. Freudenreich O, Henderson DC, Walsh JP, et al. Risperidone augmentation for schizophrenia partially responsive to clozapine: a double-blind, placebo-controlled trial. Schizophr Res. 2007;92(1-3):90-94.
26. Honer WG, Thornton AE, Chen EY, et al; Clozapine and Risperidone Enhancement (CARE) Study Group. Clozapine alone versus clozapine and risperidone with refractory schizophrenia. N Engl J Med. 2006;354(5):472-482.
27. Josiassen RC, Joseph A, Kohegyi E, et al. Clozapine augmented with risperidone in the treatment of schizophrenia: a randomized, double-blind, placebo-controlled trial. Am J Psychiatry. 2005;162(1):130-136.
28. Weiner E, Conley RR, Ball MP, et al. Adjunctive risperidone for partially responsive people with schizophrenia treated with clozapine. Neuropsychopharmacology. 2010;35(11):2274-2283.
29. Zink M, Kuwilsky A, Krumm B, et al. Efficacy and tolerability of ziprasidone versus risperidone as augmentation in patients partially responsive to clozapine: a randomized controlled clinical trial. J Psychopharmacol. 2009;23(3):305-314.
30. Canadian Agency for Drugs and Technology in Health. Current utilization of antipsychotic agents for schizophrenia: combination and high-dose therapies. https://www.cadth.ca/sites/default/files/pdf/H0503_AAP-Current-Utilization-Report_e.pdf. Published August 2012. Accessed February 26, 2016.
31. Chang JS, Ahn YM, Park HJ, et al. Aripiprazole augmentation in clozapine treated patients with refractory schizophrenia: an 8-week, randomized, double blind, placebo-controlled trial. J Clin Psychiatry. 2008;69(5):720-731.
32. Kane JM, Correll CU, Goff DC, et al. A multicenter, randomized, double-blind, placebo-controlled, 16-week study of adjunctive aripiprazole for schizophrenia or schizoaffective disorder inadequately treated with quetiapine or risperidone monotherapy. J Clin Psychiatry. 2009;70(10):1348-1357.
33. Velligan DI, Carroll C, Lage MJ, et al. Outcomes of medicaid beneficiaries with schizophrenia receiving clozapine only or antipsychotic combinations. Psychiatr Serv. 2015;66(2):127-133.
34. Citrome L, Jaffe A, Levine J, et al. Relationship between antipsychotic medication treatment and new cases of diabetes among psychiatric inpatients. Psychiatr Serv. 2004;55(9):1006-1013.
35. Correll CU, Frederickson AM, Kane JM, et al. Does antipsychotic polypharmacy increase the risk for metabolic syndrome? Schizophr Res. 2007;89(1-3):91-100.
36. Gallego JA, Nielsen J, De Hert M, et al. Safety and tolerability of antipsychotic polypharmacy. Expert Opin Drug Saf. 2012;11(4):527-542.
37. Shim JC, Shin JG, Kelly DL, et al. Adjunctive treatment with a dopamine partial agonist, aripiprazole, for antipsychotic-induced hyperprolactinemia: a placebo-controlled trial. Am J Psychiatry. 2007;164(9):1404-1410.
38. Fan X, Borba CP, Copeland P, et al. Metabolic effects of adjunctive aripiprazole in clozapine-treated patients with schizophrenia. Acta Psychiatr Scand. 2013;127(3):217-226.
39. Henderson DC, Fan X, Copeland PM, et al. Aripiprazole added to overweight and obese olanzapine-treated schizophrenia patients. J Clin Psychopharmacol. 2009;26(2):165-169.
40. Drug Information Handbook, 22th ed. Hudson, OH: Lexi-Comp, Inc.; 2013:1143-1147.
41. The Joint Commission. Specifications Manual for Joint Commission National Quality Measures (v2013A1). https://manual.jointcommission.org/releases/TJC2013A/. Accessed on May 13, 2015.
42. Essock SM, Schooler NR, Stroup TS, et al; Schizophrenia Trials Network. Effectiveness of switching from antipsychotic polypharmacy to monotherapy. Am J Psychiatry. 2011;168(7):702-708.
43. Godleski LS, Kerler R, Barber JW, et al. Multiple versus single antipsychotic drug treatment in chronic psychosis. J Nerv Ment Dis. 1989;177(11):686-689.
44. Suzuki T, Uchida H, Tanaka KF, et al. Revising polypharmacy to a single antipsychotic regimen for patients with chronic schizophrenia. Int J Neuropsychopharmacol. 2004;7(2):133-142.

## Clinical Point

**If APP provides inadequate response, or if there is no clear indication for APP, consider switching the patient back to monotherapy**