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 salivation. 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. 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...
after 4 weeks of treatment. 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.

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.

Treatment guidelines (Table 2, page 52) 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). 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.

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 have yielded mixed results and have not provided conclusive information regarding benefit for positive vs negative symptoms.

One RCT reported a significant change in Brief Psychiatric Rating Scale (BPRS) total and positive symptom scores. 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. In terms of cognition, this combination provided no additional benefit. 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.

Data from 1 study 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) 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. Surprisingly, 1 literature review found no association between APP and increased risk of orthostasis. Increased occurrence of sedation, hyper-
Clinical Point

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

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### Table 2

<table>
<thead>
<tr>
<th>Organization (year)</th>
<th>Findings and recommendations</th>
</tr>
</thead>
</table>
| American Psychiatric Association (2004) | • Clozapine APP is reasonable for patients who have an inadequate response to clozapine  
• 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  
• 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  
• 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

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### 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
- Difficulty 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
Adjunctive aripiprazole, a dopamine partial agonist, could reduce elevated prolactin levels caused by other antipsychotics.

**Clinical Point**

**Table 4**

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>N</th>
<th>Results</th>
</tr>
</thead>
</table>
| 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  
  • 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  
  • Secondary analysis: significantly greater improvement for negative symptoms (BPRS, SANS) but not positive symptoms with aripiprazole  
  • 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  
  • 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)  
  • 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

**Table 5**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target dosage (mg/d)</th>
<th>Maximum dosage (mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>10 to 15</td>
<td>30</td>
</tr>
<tr>
<td>Asenapine</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Clozapine</td>
<td>300 to 600</td>
<td>900</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>6 to 12</td>
<td>24</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>40 to 120</td>
<td>160</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>10 to 20</td>
<td>20</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>6 to 12</td>
<td>12</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>300 to 800</td>
<td>800</td>
</tr>
<tr>
<td>Risperidone</td>
<td>4 to 8</td>
<td>16</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>80 to 160</td>
<td>160</td>
</tr>
</tbody>
</table>

Source: References 13,40

prolactinemia, and an elevated fasting blood glucose level have been found for clozapine plus risperidone compared with clozapine monotherapy.14-26,28

**Aripiprazole.** Adjunctive aripiprazole, a dopamine partial agonist, could reduce elevated prolactin levels caused by other antipsychotics.22 In a study27 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 RCTs28,29 of patients taking clozapine or olanzapine suggest adjunctive aripiprazole could improve weight and metabolic profile. Therefore, adding aripiprazole to existing antipsychotic regimens is...
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 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, therefore, an adequate trial period within the target dosage range is advised for all antipsychotics (Table 5, page 53).

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.

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.

References
10. Barnes TRE. Schizophrenia Consensus Group of the...


