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Chris Aiken, MD
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IN THIS ISSUE

Focus of the Month:
Psychopharmacology Algorithms

Learning Objectives
After reading these articles, you should be able to:

1. Describe how to select an antipsychotic in schizophrenia.
2. Evaluate the safety and efficacy of pimavanserin for Parkinson's-related psychosis.
3. Identify ways that common practice patterns deviate from a research-based algorithm.
4. Summarize some of the current research on psychiatric treatment.

How to Choose an Antipsychotic in Schizophrenia

Rehan Aziz, MD. Associate Professor of Psychiatry and Neurology, Rutgers Robert Wood Johnson Medical School.

Dr. Aziz has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

It's been over a decade since the CATIE trial changed the way we look at antipsychotic drugs. Since then, the number of second-generation antipsychotics has about doubled, and the number of clinical trials has risen even more. Antipsychotics are not all the same, though, and when it comes to schizophrenia, a few stand out in ways that can help you fine-tune your selection. In this article, we'll look back at the past decade and highlight findings that could change clinical practice, while drawing from some new meta-analyses.

Highlights From This Issue

Schizophrenia is more likely to respond to clozapine if it's started early, and guidelines recommend considering clozapine after failure of 2 antipsychotics.

Antipsychotics are not very effective in Parkinson's-related psychosis, including the FDA-approved pimavanserin (Nuplazid).

David Osser, MD, explains why a few specific medications rise to the top for depression, bipolar disorder, and schizophrenia.

The CATIE trial

CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) was a double-blind, NIMH-sponsored study. It involved almost 1500 patients with chronic schizophrenia

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Q&A With the Expert

The Psychopharmacology Algorithm Project
David Osser, MD

General Editor of the Psychopharmacology Algorithm Project at the Harvard South Shore Psychiatry Residency Training Program and Associate Professor of Psychiatry at Harvard University.

Dr. Osser has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

TCPR: What would be the biggest change in practice if psychiatrists followed your algorithms?

Dr. Osser: One area is bipolar depression. This is a disorder where there is an exceptionally large deviation between what the evidence says and what people are doing, especially when it comes to antidepressants. They are still being used rampantly, even in patients with rapid cycling and mixed features, where there is virtually unanimous consensus among the experts that antidepressants should be avoided. For example, if you are a rapid cycler and you get put on an antidepressant, you have triple the chance of going into another depression than if you are not started on an antidepressant (El-Mallakh RS et al, *J Affect Disord* 2015;184:318–321).

TCPR: Why do we keep using antidepressants in bipolar depression?

Dr. Osser: That's a mystery. It seems people aren't aware of this evidence, or they feel that their clinical experience is more impressive, or maybe antidepressants are just easier to prescribe than the medications that are

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How to Choose an Antipsychotic in Schizophrenia

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studied under "real-world" conditions. Patients were initially randomized to receive olanzapine, quetiapine, risperidone, or ziprasidone. Later stages included open-label clozapine. The goal was to measure the effectiveness of second-generation antipsychotics vs each other and against a first-generation antipsychotic, perphenazine.

When the dust settled, olanzapine came out on top, at least when patients voted with their feet. Patients stayed on olanzapine longer than any other antipsychotic, suggesting its benefits outweighed its side effects. Those side effects were significant, though, as olanzapine had the highest rate of weight gain and metabolic problems. In the later stages of the study, clozapine was the champ—patients stayed on it twice as long as on olanzapine. Perhaps the most stunning finding was that despite all their fanfare, second-generation antipsychotics were no more efficacious or better tolerated than perphenazine (Lieberman JA and Stroup TS, *Am J Psychiatry* 2011;168(8):770–775).

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New findings

Although the CATIE trial suggests olanzapine should be the first choice for schizophrenia, it's often reserved as a second-line option because of its metabolic risks. Where, then, to start? The Harvard South Shore Psychopharmacology Algorithm Project (www.psychopharm.mobi) combines real-world scenarios with randomized controlled trials to help answer these kinds of questions. Medications in the project's flowcharts are chosen for their balance of efficacy, side effects, and cost. The project lists first-line treatments for schizophrenia as aripiprazole, risperidone, or ziprasidone. If cost is not an issue, cariprazine could be added to this list, since there is some evidence it improves negative symptoms. Second-line options include an alternate second-generation antipsychotic, risperidone if not already tried, olanzapine, or a first-generation antipsychotic. Clozapine is reserved for treatment-resistant cases, defined as failure to respond to 2 or more antipsychotics (Osser DN et al, *Harv Rev Psychiatry* 2013;21(1):18–40).

Negative symptoms of schizophrenia have eluded treatment for decades. A meta-analysis looked at 168 trials involving more than 12,000 patients. Researchers found that many treatments reduced negative symptoms, including second-generation antipsychotics, antidepressants, and psychological interventions, but none resulted in clinically significant improvement (Fusar-Poli P et al, *Schizophr Bull* 2015;41(4):892–899). Cariprazine may offer some hope. In a single study, cariprazine decreased negative symptoms more than risperidone, though the effect size (0.31) was small (Nemeth G et al, *Lancet* 2017;389(10074):1103–1113). Risperidone also lost out to aripiprazole in a separate study, though aripiprazole-treated patients had more akathisia (Robinson DG et al, *Schizophr Bull* 2015;41(6):1227–1236).

Overall, the choice of a first antipsychotic is often based on side effects instead of efficacy. The "Side Effects of Atypical Antipsychotics" table below may help guide your decision making.

Treatment-resistant schizophrenia

Clozapine is still the gold standard in

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Side Effects of Atypical Antipsychotics

	Overall change in symptoms	Overall tolerability	Weight gain	Diabetes	Sedation	Akathisia and extrapyramidal symptoms	Hypotension
Aripiprazole	Med	Med	little to no risk	little to no risk	low risk	medium risk	low risk
Asenapine	Low	High	low risk	low risk	medium risk	medium risk	low risk
Brexpiprazole	Med	High	little to no risk	low risk	little to no risk	low risk	low risk
Cariprazine	Med	High	little to no risk	little to no risk	little to no risk	medium risk	low risk
Clozapine	High	Low	high risk	high risk	high risk	little to no risk	high risk
Iloperidone	Low	High	medium risk	medium risk	little to no risk	low risk	high risk
Lurasidone	Low	High	little to no risk	little to no risk	low risk	medium risk	low risk
Olanzapine	High	Low	high risk	high risk	medium risk	little to no risk	low risk
Paliperidone	Med	Med	medium risk	medium risk	little to no risk	medium risk	low risk
Quetiapine	Low	Med	medium risk	medium risk	high risk	little to no risk	high risk
Risperidone	Med	Med	medium risk	medium risk	low risk	medium risk	medium risk
Ziprasidone	Low	Med	little to no risk	little to no risk	low risk	little to no risk	low risk

= little to no risk; = low risk; = medium risk; = high risk

How to Choose an Antipsychotic in Schizophrenia

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treatment-resistant cases, but it needs to be started early. The likelihood of responding to clozapine drops by 8%–11% with every failed antipsychotic trial, and the chance of clozapine working goes down from 82% to 32% if it is started longer than 3 years after a first episode (John AP et al, *Can J Psychiatry* 2018;63(8):526–531; Yoshimura B et al, *Psych Res* 2017;250:65–70). Clozapine should be considered after failure of 2 antipsychotic trials, with failure meaning a lack of response—in contrast, treatment resistance in mood disorders is defined by lack of recovery. We don't expect full recovery right now in schizophrenia, though about 1 in 8 patients do come close and regain their functioning (Charlson FJ et al, *Schizophr Bull* 2018;44(6):1195–1203).

The US trails other nations in clozapine utilization, likely because of its risks. It's hard to feel good about starting a medication that can cause neutropenia, seizures, cardiotoxicity, and small bowel obstruction. Those risks must be balanced with the surprising fact that patients who take clozapine actually live longer than those taking other antipsychotics. In a meta-analysis of 24 studies covering over 200,000 life years, the mortality rate was 44% lower with clozapine than other antipsychotics, and that protective benefit disappeared soon after clozapine was discontinued (Vermeulen JM et al, *Schizophr Bull* 2019;45(2):315–329). A useful guide to managing clozapine's side effects is Jonathan Meyers' *The Clozapine Handbook* (2019).

Antipsychotic Selection in Schizophrenia	
Step 1	Select the first antipsychotic based on tolerability, engaging the patient in the decision. Aripiprazole, risperidone, ziprasidone, and cariprazine are good starting places. If it's not tolerable, switch to an option with a different side effect profile (see the "Side Effects of Atypical Antipsychotics" table on page 2).
Step 2	If response to the first-line antipsychotic is inadequate after 4 weeks, move to olanzapine, risperidone, or a first-generation antipsychotic. The choice should be based on tolerability, though severe symptoms would point toward olanzapine.
Step 3	After 2 failures from lack of response, move to clozapine.

TCPR VERDICT: It could be argued that all of the second-generation antipsychotics outside of clozapine are equal, but we'll venture a recommendation. Start with aripiprazole or, if cost is not an issue, cariprazine. These stand out for their mild benefits in negative symptoms and favorable long-term side effect profiles. Olanzapine is a good second-line choice when efficacy is more of a consideration. After failure of 2 trials, move quickly to clozapine. See the "Antipsychotic Selection in Schizophrenia" table at left for more.

To learn more, listen to our 4/6/20 podcast, "Seven Clozapine Tips." Search for "Carlat" on your podcast store.

Expert Interview

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FDA approved in bipolar depression (see the "First-Line Medications for Bipolar Depression" table on page 4). In my own practice, I see case after case of people who are doing poorly with rapid-cycling depressions yet are on multiple antidepressants. It may feel counterintuitive to avoid antidepressants when the patient keeps cycling into depression, but rapid cycling includes those who only cycle into depression, as long as they have bipolar disorder and 4 or more distinct mood episodes in a year.

TCPR: How do the algorithms differ from other practice guidelines?

Dr. Osser: One of the problems with guidelines is that they tend to be too general and aren't as prescriptive as algorithms. Take the APA guidelines. For major depression, they have a whole range of treatments that are considered first line—the tricyclics, the SSRIs, various kinds of psychotherapy, and everything in between. Then they go through the treatments and give a massive literature review for each of them. But in the end, those guidelines never tell you which treatment to choose. We try to name specific medications that offer the best balance of efficacy, safety, and cost for each step.

TCPR: Is there a drawback to your approach?

Dr. Osser: Our algorithms could be misinterpreted as a rigid, black-and-white approach if readers only rely on the summary. The summaries are online so we can update them in real time (www.psychopharm.mobi), but to make good use of them you need to read the full description of the reasoning that is in the published papers. Those descriptions have all the nuances that allow you to tailor the treatment for the individual patient, as well as the evidence behind each decision.

TCPR: Let's get into that evidence. For major depression, you list three first-line options: bupropion, escitalopram, and sertraline. Why these?

Dr. Osser: There have been a few meta-analyses comparing the antidepressants. We drew from those as well as other interesting data like the CO-MED study, which compared escitalopram head-to-head with esteemed combinations like SSRI+bupropion and SSRI+mirtazapine. In that study, escitalopram did very well; it was equal to those combinations even when used alone. We also gave a lot of weight to side effects. Many patients don't want sexual side effects, in which case bupropion is the best first-line choice (Giakoumatos CI and Osser DN, *Harv Rev Psychiatry* 2019;27(1):33–52).

TCPR: The list gets longer once we're past the first-line options for depression,[1] and you suggest that patient preference should guide the selection of a second-line treatment. How would you talk to patients about their options?

Dr. Osser: I'd start by dividing the options into augmentation and switch strategies. We've listed five switches and five augmenters as second-line options. We were hoping a few would stand out, but there wasn't a meaningful difference in

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[1]*Editor's note:* **Second-line strategies for non-psychotic depression:** Switch to sertraline, escitalopram, bupropion, venlafaxine, mirtazapine, SAMe, or St. John's wort; or augment with quetiapine, risperidone, aripiprazole, bupropion, mirtazapine, lithium, T3, omega-3, L-methylfolate, NAC, or light therapy; or try rTMS.

Expert Interview

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the numbers needed to treat (NNT), which were in the 5–10 range. Patients usually know whether they'd prefer to switch or augment, and they tend to be right. The ones who've improved on the initial drug prefer to augment. Once you clarify a patient's preference, you can refine the choice based on whether the patient prefers a natural supplement, a prescription medication, or repetitive transcranial magnetic stimulation (rTMS). Side effects also play a key role. The second-generation antipsychotics may have more studies than other options, but they don't have an impressive NNT—it's around 8. But if a patient wants one of those and will put up with the side effects, I'd go with it. By the way, psychotherapy is a legitimate option at each of these steps, but these are psychopharmacology algorithms, so they do not review the evidence on that.

TCPR: Your algorithms for bipolar and unipolar depression both place electroconvulsive therapy at the top when there is an urgent need for recovery or when the depression fails to resolve after 2 medication trials. You give less weight to rTMS, which only shows up as an option after failure of 1 antidepressant in unipolar depression.

Dr. Osser: Yes. The FDA approved rTMS after failure of 1 antidepressant trial, but not after the patient fails 2 antidepressants, and there's a good reason for that. In the data submitted to the FDA, rTMS was not significantly more effective than sham after 2 or more failed trials (Giakoumatos CI and Osser DN, *Harv Rev Psychiatry* 2019;27(1):33–52). A lot of practitioners believe rTMS is more effective than medication for treatment-resistant cases, but this is an area where clinical experience doesn't match with the evidence.

TCPR: Why the mismatch?

Dr. Osser: One reason might be that there's a large placebo effect with new technologies like rTMS. In addition, the patient comes in for treatment 5 days a week, which will further boost the placebo effect. The placebo effect of sham rTMS has caused some studies to fail, and in everyday practice, that effect can color our experience. We can also be fooled by the natural course of illness. We see that in bipolar depression, where the episodes usually last 2–3 months. So let's say it takes a month for the patient to come see us. Then we start an antidepressant and the patient gets better in 1–2 months. That patient probably would have gotten better without the medication, but we might attribute the recovery to the antidepressant.

TCPR: The algorithms don't seem to give special preference to FDA-approved medications or limit their reviews to randomized controlled trials (RCTs). Otherwise the second-generation antipsychotics would have risen to the top of the list for treatment-resistant depression.

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> **"If you have rapid-cycling bipolar disorder and you get put on an antidepressant, you have triple the chance of going into another depression than if you are not started on an antidepressant."**
>
> David Osser, MD

First-Line Medications for Bipolar Depression

	Dose	Pros	Cons
Lamotrigine (Lamictal)	Effective dose: 50–200 mg qam Start: 25 mg qam x14 days, 50 mg qam x14 days then 100 mg qd	Best tolerated; good preventative effects for depression	Slow to work (6–12 weeks) Stevens-Johnson syndrome (1 in 3,000) Does not treat mania
Lithium	Optimal level: 0.6–0.8 mmol/L Start: ER 300 mg 1 po qhs x4–7 days, 2 po qhs x4–7 days then 3 po qhs Lower levels (0.4–0.6 mmol/L) work in elderly; higher levels may be needed in mania	Best preventative effects against mania, depression, suicide, and hospitalization; may prevent dementia, stroke, and cardiac disease	Nephrotoxicity (lessened by keeping level ≤ 0.8 mmol/L), hypothyroidism (10%–20%), arrhythmias, toxicity (especially with drug interactions), diabetes insipidus (10%–15%) Tremor, imbalance, nausea, thirst, acne, affective flattening
Second-generation antipsychotics			
Cariprazine (Vraylar, brand only)	Effective dose: 1.5 mg qd Start: 1.5 mg qod x7–14 days then 1.5 mg qd	Effective in mania (3–6 mg qd) and depression	Worse for akathisia; better for fatigue and metabolic effects[1] Lower effect size in depression than other second-generation antipsychotics
Lurasidone (Latuda, brand only)	Effective dose: 20–120 mg qd (usual range 40–80 mg) Start: 20 mg 1/2 qd x4–7 days, 1 qd x4–7 days then 40 mg qd (take with ≥ 350 cal meal)	Among the atypicals, best balance of efficacy and tolerability Approved in pediatrics (13–17 for schizophrenia, 10–17 for bipolar depression) May improve cognition	Worse for akathisia; better for fatigue and metabolic effects[1]
Quetiapine (Seroquel)	Effective dose: 300 mg qhs Start: 50 mg qhs x 1–4 days, 100 mg qhs x 1–4 days, 200 mg qhs x 1–4 days, then 300 mg qhs	Best acute efficacy in depression; good preventative effects Best evidence in bipolar II, insomnia, & anxiety Effective in mania (400–800 mg qd) and depression	Worse for metabolic and cardiac/QTc risks, fatigue, and orthostasis; better for akathisia[1] The XR version has less orthostasis but more next-day sedation

[1]Second-generation antipsychotics share common risks of tardive dyskinesia, metabolic syndrome, akathisia, orthostasis, anticholinergic effects, QT interval prolongation, temperature dysregulation, neuroleptic malignant syndrome, and increased mortality in dementia. Only relative differences in those risks are noted above.

Nuplazid: Novel Mechanism, Modest Benefits

Randall Moore, MD, JD. Clinical Associate Professor, Department of Psychiatry and Behavioral Sciences at Texas A & M University Health Science Center College of Medicine. Chris Aiken, MD. Editor-in-Chief of TCPR. *Practicing psychiatrist, Winston-Salem, NC.*

Dr. Moore and Dr. Aiken have disclosed that they have no relevant financial or other interests in any commercial companies pertaining to this educational activity.

Psychosis can be a paralyzing dilemma for patients with Parkinson's disease (PD). Most antipsychotics worsen the motor symptoms of PD, while the dopaminergic drugs that treat PD can worsen the psychosis. Psychosis afflicts up to 60% of patients with PD, and it is the leading cause of nursing home placement in these patients (Hacksell U et al, *Neurochem Res* 2014; 39(10):2008–2017).

In 2016, the FDA approved pimavanserin (Nuplazid) for Parkinson's-related psychosis. This medication does not worsen the motor symptoms of Parkinson's. Pimavanserin is a highly selective 5-HT2A inverse agonist that binds minimally with dopaminergic, histaminergic, and muscarinic receptors. Research suggests that overactive 5-HT2A signaling contributes to psychosis in PD (Hawkins T et al, *Neurol Clin Pract* 2017;7:157–162). Clinical evidence for this concept comes from clozapine, which, in low doses, blocks 5-HT2A receptors with minimal dopamine blockade. A review found that low doses of clozapine have proven efficacious in treating Parkinson's psychosis (Cook K et al, *Mov Disord* 2017;32(S2)).

Safety and efficacy

Pimavanserin's benefits in Parkinson's psychosis are real, but very modest. In a meta-analysis of four randomized controlled trials, pimavanserin led to a 2.3 point reduction in psychotic symptoms compared to placebo on a 100-point rating scale, the SAPS H+D, a modified version of the Scale for the Assessment of Positive Symptoms (Yasue I et al, *J Alzheimers Dis* 2016;50:733–740). This 2-point difference could be achieved by resolution of a mild delusion, an improvement that may not always be clinically significant.

There was also a concerning risk of bias in these studies. Problems included neglecting to report the primary outcome in one of the treatment arms, leaving out important details about the randomization and blinding, relying on an unvalidated rating scale, and excluding patients with cognitive impairment (Mini Mental Status Exam < 21) (Cummings J et al, *Lancet* 2014;383(9916):533–540).

Outside of pimavanserin, clozapine is the best-studied antipsychotic for Parkinson's psychosis. In low doses (12.5–50 mg), clozapine outperformed placebo without worsening motor symptoms in two randomized controlled trials. However, clozapine's numerous medical risks make it a difficult choice for this syndrome. Quetiapine and ziprasidone also have low levels of extrapyramidal side effects, though the evidence for their efficacy in Parkinson's psychosis is minimal or mixed (Cook K et al, *Mov Disord* 2017;32(S2)).

Like other antipsychotics, pimavanserin's benefits build up over about 2 weeks. The recommended dose is 34 mg daily. Assess the patient's psychotic symptoms carefully before and after prescribing it, and consider discontinuing it if there is no clear improvement. Monitor for side effects, which include nausea, imbalance, and peripheral edema. Although pimavanserin is indicated for delusions and hallucinations, it can also cause new hallucinations (the rate was 5% with pimavanserin vs 3% with placebo). Other psychiatric side effects include aggression and confusional states.

Antipsychotics may have only modest benefits in Parkinson's psychosis, but other interventions that can help (Schubmehl S et al, *Am J Geriatr Psychiatry* 2018;26(10):1014) include:

1. Reduce dopaminergic medications
2. Teach caregivers how to redirect patients
3. Keep the lights on during the day to minimize visual hallucinations
4. Play soothing music and address any hearing loss or tinnitus to minimize auditory hallucinations

Expanding use

Since its approval for Parkinson's psychosis, pimavanserin has been tested in a variety of other conditions, including schizophrenia, Alzheimer's disease with psychosis, depression, and antidepressant-induced sexual dysfunction. The majority of the available studies for off-label uses constitute low-quality and often negative evidence.

In major depression, pimavanserin successfully augmented an SSRI or SNRI in patients who had failed to respond to the antidepressant (n = 207). Pimavanserin separated from placebo at 1 week in this 10-week study, with a medium effect size (0.5–0.6). It's a promising result, but the study needs replication (Fava M et al, *J Clin Psychiatry* 2019;80(6)).

Costs and coverage

Without insurance, pimavanserin costs over $3,000 per month. Most Medicare plans and commercial insurers cover it, though prior authorizations are often required. CoverMyMeds.com can assist with prior authorizations, and the Nuplazid website has a handy program (www.nuplazid.com/nuplazidconnect) that quickly checks coverage. Commercial insurers benefit from a $0 copay card, but the copay can be prohibitive for patients who are on governmental insurance.

TCPR VERDICT: Antipsychotics are not particularly effective in Parkinson's psychosis. Pimavanserin has FDA approval for this condition, but its benefits are modest and the price is high. Low-dose clozapine, though not FDA approved, is also helpful. For many of these patients, the psychosis will persist despite antipsychotic therapy. Other options, including minimizing dopaminergics and non-pharmacologic interventions, are an essential part of the plan.

To learn more, listen to our 4/27/20 podcast, "Serotonin 2A and the New Psychotropics." Search for "Carlat" on your podcast store.

Research Update IN PSYCHIATRY

MEDICATION

Antipsychotics Fall Short in Delirium

REVIEW: Oh ES et al, *Ann Intern Med* 2019;171(7):474–484; Nikooie R et al, *Ann Intern Med* 2019;171(7):485–495

STUDY TYPE: Systematic reviews of randomized controlled trials and prospective studies

Delirium is common and costly. With an incidence rate approaching 50% in hospitalized older adults, the condition poses a burden that is anticipated to grow as the largest elderly population in human history enjoys increasing life expectancy. For patients, delirium heightens the risk of physical and cognitive decline and overall mortality.

Antipsychotics remain a mainstay of delirium treatment despite significant concerns about their safety and efficacy. A pair of reports recently evaluated the evidence on their use in delirium. The first investigated antipsychotics for the prevention of delirium in high-risk (vulnerable) patients. The other report looked at whether antipsychotics can improve symptoms of delirium after it develops.

The reports employed a rigorous protocol developed with input from a panel of experts. They included randomized controlled trials as well as prospective observational studies with comparison groups. All studies used standard diagnostic instruments, and five outcomes were selected for data extraction: cognitive functioning, hospital length of stay, delirium severity, sedation, and inappropriate continuation of antipsychotics. Other outcomes included delirium incidence and duration, mortality, and cardiac and neurological adverse effects.

The prevention analysis included 14 randomized controlled trials, totaling 4281 patients. Most of the studies involved postsurgical interventions. The majority used haloperidol (10 studies), while the other four studies used olanzapine, risperidone, and ziprasidone. No differences were found between haloperidol and placebo in delirium incidence, duration, hospital length of stay, and mortality. Little to no evidence supported haloperidol over placebo in cognitive functioning, delirium severity, sedation, and inappropriate continuation. Second-generation antipsychotics, but not haloperidol, showed a slightly reduced incidence of delirium. However, this difference only proved significant in a pooled analysis of three studies, indicating a weak association.

The treatment analysis included 16 randomized controlled trials and 10 prospective studies (a total of 5607 adult inpatients with delirium). No differences were found between haloperidol and second-generation antipsychotics vs placebo for sedation, delirium duration, hospital length of stay, or mortality. More importantly, there was insufficient evidence to support any antipsychotic over placebo in delirium severity and cognitive functioning. For second-generation antipsychotics, evidence was generally lacking for most outcomes, but there were no differences in overall mortality.

Neither report found evidence of neurological harms associated with short-term antipsychotic use, such as extrapyramidal side effects. However, a higher frequency of cardiac adverse effects (eg, QT interval prolongation) was noted. Both studies had similar limitations, including high variability in patient characteristics, treatment context, antipsychotic dosing, and outcome reporting.

TCPR'S TAKE

Antipsychotics are not a panacea for all agitated or psychotic states, and their expansion into delirium is not supported by the evidence. Patients at risk for delirium are also more likely to develop problems on these medications, such as QT prolongation, hypothermia, hypotension, and anticholinergic effects like urine retention, constipation, and (frankly) delirium.

—Adrienne Grzenda, MD. Dr. Grzenda has disclosed that she has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

Expert Interview

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Dr. Osser: That's right. Treatments that are FDA approved or backed by a dozen RCTs don't always have the biggest effect size or the most favorable side effect profile. There are also limitations to RCTs. They are usually short term, and they tend to include a select population that may not represent the patients we're actually seeing in our office. Sometimes they use designs that inflate the results, like with enriched samples. That's why we also emphasize real-world observational studies in the algorithms, which can lead to conclusions that are different from those of the industry-sponsored RCTs.

TCPR: What's an example where the observational data lead you in a different direction?

Dr. Osser: Schizophrenia is one. When the industry-sponsored trials are meta-analyzed, they find very little difference in the efficacy of the antipsychotics, except for clozapine. However, when you look at real-world studies that randomized anyone who was hospitalized with acute schizophrenia to open-label treatment with different antipsychotics, you see a difference. In those studies, the more effective treatments tend to be olanzapine, risperidone, and the first-generation antipsychotics like haloperidol and perphenazine. In contrast, quetiapine, ziprasidone, and aripiprazole tend to be significantly less effective at getting the patient out of the hospital in the shortest possible time (Osser DN et al, *Harv Rev Psychiatry* 2013;21(1):18–40).

TCPR: Back to bipolar disorder. You recommend two first-line medications for the manic side: lithium for classic, euphoric mania; and quetiapine for dysphoric mania and mixed states. Tell us why.

Dr. Osser: We started out with the idea that we should have two lines of treatment for mania: one for severe mania and one for mild to moderate mania. For severe cases, we were going to suggest haloperidol, which has the largest

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CME Post-Test

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This page is intended as a study guide. Please complete the test online at www.TheCarlatReport.com. Learning Objectives (LO) are listed on page 1.

1. What is the recommended dose of pimavanserin for Parkinson's-related psychosis? (LO #2)
   [ ] a. 18 mg/day [ ] b. 25 mg/day [ ] c. 28 mg/day [ ] d. 34 mg/day
2. Olanzapine is often considered a second-line antipsychotic for schizophrenia due to its metabolic risks. (LO #1)
   [ ] a. True [ ] b. False
3. According to Dr. Osser, the Psychopharmacology Algorithm Project recommends which antidepressants as first-line in major depression? (LO #3)
   [ ] a. Bupropion, duloxetine, and escitalopram
   [ ] b. Bupropion, escitalopram, and sertraline
   [ ] c. Escitalopram, fluoxetine, and sertraline
   [ ] d. Escitalopram, duloxetine, and venlafaxine
4. Besides pimavanserin, which medication has the best evidence in Parkinson's-related psychosis? (LO #2)
   [ ] a. Clozapine
   [ ] b. Nuedexta (dextromethorphan-quinidine)
   [ ] c. Ziprasidone
   [ ] d. Olanzapine
5. In a 2019 study evaluating antipsychotics for prevention of delirium in adults, the rate of mortality was greater with haloperidol than it was for second-generation antipsychotics. (LO #4)
   [ ] a. True [ ] b. False
6. According to Dr. Osser, antipsychotics can cause significant harm to patients with which condition? (LO #3)
   [ ] a. Sleep apnea
   [ ] b. Depression
   [ ] c. Alzheimer's disease
   [ ] d. Obsessive-compulsive disorder

Expert Interview

Continued from page 6

effect size in mania. But our expert reviewers presented convincing evidence that the major treatment difference is whether the patient has mixed mania or classic, euphoric mania. For mixed mania, lithium is not as effective as second-generation antipsychotics and mood-stabilizing anticonvulsants, particularly valproate (Depakote). Lithium is ranked third after those two. The second-generation antipsychotics are also effective in mixed mania, and we settled on quetiapine because it had the best evidence for both mania and depression. The big risk with mania is that patients are going to switch into depression, and depressions make up over 75% of the time that bipolar patients suffer a mood episode. Other second-gens do have slightly greater efficacy than quetiapine in mania, such as risperidone and olanzapine, but we stayed with quetiapine because we want to prevent those subsequent depressions. As for haloperidol, we actually ended up dropping it altogether from the algorithm. It may be very effective for mania, but it also has the greatest risk of precipitating a post-manic depression (Mohammad O and Osser DN, *Harv Rev Psychiatry* 2014;22(5):274–294).

TCPR: Cariprazine (Vraylar) recently joined quetiapine as the second atypical antipsychotic to gain FDA approval in both mania and depression. Where does it fit?

Dr. Osser: It's the new kid on the block. Lurasidone (Latuda) and olanzapine-fluoxetine combination (Symbyax) are the other two with FDA approval in bipolar depression, but neither of them have any studies in mania. Cariprazine does have some advantages over quetiapine, like fewer metabolic side effects and less sedation. We are waiting for more studies on it to see where it fits in the algorithm, but currently it has at least one drawback (besides cost): Its efficacy was about half of the other options in a meta-analysis. Specifically, it had an NNT of 10 for response in bipolar depression, compared to 6 for quetiapine, 5 for lurasidone, and 4 for olanzapine-fluoxetine combination (Citrome L, *Int J Clin Pract* 2019;73(10):e13397; Wang D and Osser DN, *Bipolar Disord* 2019. doi:10.1111/bdi.12860). That's a concerning signal, but those numbers might be explained by quirks in the studies, and we go into those subtleties more in the full description of the algorithm.

TCPR: Olanzapine-fluoxetine combination consistently rises to the top for efficacy in bipolar depression, and some experts recommend it first-line there. What made it sink to the bottom in your bipolar depression algorithm?

Dr. Osser: That one's simple. We give strong consideration to the harms, especially the long-term harms, and olanzapine's metabolic side effects are pretty dire. Those are not acceptable risks for a first-line treatment.

TCPR: Thank you for your time, Dr. Osser.

Editor's note: A summary of the 10 psychopharmacology algorithms is available at www.psychopharm.mobi, and a book with their full descriptions is slated for publication in 2020 (Wolters Kluwer).

To learn more, listen to our 4/13/20 podcast, "A Practical Guide to Psychopharmacology." Search for "Carlat" on your podcast store.

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PSYCHIATRY
P.O. Box 626
Newburyport, MA 01950

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Psychopharmacology Algorithms
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Next Issue:
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In Brief

Singulair and Suicide: FDA Strengthens Warning. After a rise of adverse psychiatric reports on montelukast (Singulair), an oral leukotriene inhibitor used for asthma and allergies, the FDA added a black box warning in March 2020 about mood and behavior changes including suicide. There were 82 reports of completed suicide associated with the drug. Earlier research has linked montelukast to depression (odds ratio 7), aggression in children (odds ratio 30), and psychosis (Haarman MG et al, *Pharmacol Res Perspect* 2017;5(5):e00341). Given these risks, the FDA recommends reserving montelukast for serious symptoms that haven't responded to other options.

Research Theme Park: Med Updates. This month's bonus podcast will feature a roundup of recent clinical trials in psychiatry (***"Research Theme Park: Med Updates,"*** 4/20/20). Search for "Carlat" on your podcast store.

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