Selecting an Atypical Antipsychotic by Combining Clinical Experience With Guidelines From Clinical Trials

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Three atypical antipsychotics are currently considered to be first-line therapies for schizophrenia, namely risperidone, olanzapine, and quetiapine. Deciding which one of these agents to choose for any given patient can be a daunting task because head-to-head comparisons of these 3 agents are just beginning, and most published trials are comparisons with typical antipsychotics, not with another atypical antipsychotic. Furthermore, results from clinical trials often do not match findings from clinical practice. Thus, guidelines for selection and use of the atypical antipsychotics are evolving from controlled studies as well as from clinical judgment based on the practical use of these agents once they have entered clinical practice. The atypical properties of first-line atypical antipsychotics as well as clozapine are reviewed here, with clinical pearls and dosing tips for each based upon a consensus of information from both clinical trials and clinical practice. The conventional antipsychotic loxapine is also reviewed and proposed as a potentially valuable agent to augment atypical antipsychotics when patients do not experience an acceptable treatment response from monotherapy with an atypical antipsychotic. By integrating information from clinical trials and clinical practice, the prescriber can be in a better position to choose which atypical antipsychotic to select for any given patient. *(J Clin Psychiatry 1999;60[suppl 10]:31–41)*

WHAT IS AN ATYPICAL ANTIPSYCHOTIC?

The term *atypical antipsychotic* was coined when clozapine was discovered to have properties much different from those of the conventional "neuroleptic" antipsychotics, thus appearing to be "atypical."[1–19] Unlike conventional antipsychotics, clozapine has a far more complex pharmacology, including serotonin-2A (5-HT_{2A}) receptor antagonist properties as well as binding to several other neurotransmitter receptors. Clinically, clozapine is atypical in that it causes surprisingly few if any extrapyramidal side effects (EPS), does not appear to cause tardive dyskinesia, does not substantially elevate prolactin, and is especially efficacious in patients who fail to respond adequately to the conventional antipsychotics (Table 1).[3,8,20–37] Clarification of these atypical properties has spawned attempts to develop novel antipsychotics with atypical properties by incorporating, at a minimum, serotonin-dopamine antagonist properties into these new drugs.

As time has progressed, the term *atypical antipsychotic* has therefore been applied to several new antipsychotic agents, and the definition of this term has evolved to mean different things to different people.[7,8,38–40] Unfortunately, this can create confusion. For example, to a pharmacologist, *atypical antipsychotic* may mean "serotonin-dopamine antagonist" or "multiple neurotransmitter binding properties"; to a clinician worried about the side effects of an antipsychotic, it may mean "fewer EPS" or "less prolactin elevation"; to a clinician looking for optimal efficacy in schizophrenia, it may mean "better efficacy for negative symptoms" or even "better efficacy for cognitive symptoms, mood, and hostility"; to a family member of a patient with schizophrenia, it may mean "efficacy for treatment-resistant symptoms"; to a marketeer, it may mean "new and different, and better than the old antipsychotics"; to a managed care formulary committee, it may mean "expensive"; and to a pharmacoeconomist, it may mean "cost-effective."[7,8,38–40]

Here, I will explore how 5 different antipsychotics may meet many of these criteria, for there is no universally agreed upon definition. At a minimum, *atypical antipsychotic* will be used here to mean 5-HT_{2A}–dopamine-2 (D_2) receptor antagonism coupled with reduced EPS.

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Table 1. Clozapine: The Prototypical Atypical[a]

Serotonin-dopamine antagonist?	Yes
EPS fewer than with haloperidol?	Yes
Patients essentially never get EPS?	Yes[b]
Patients essentially never get tardive dyskinesia?	Yes
Prolactin increase less than with haloperidol?	Yes
Prolactin essentially never increases?	Yes
Negative symptoms treated better than with conventional antipsychotics?	Yes
Effective for symptoms refractory to conventional antipsychotics?	Yes

[a]Based on references 3, 8, and 20–37. Abbreviation: EPS = extrapyramidal side effects.
[b]Rare akathisia.

Table 2. Risperidone in Clinical Trials: How Does It Compare With Placebo and Haloperidol?[a]

Risperidone (R; 6 mg/d) versus haloperidol (H; 20 mg/d) and placebo (PBO) in schizophrenia
R beats H and PBO on overall psychosis ratings
R beats H and PBO on positive symptoms
R beats H and PBO on negative symptoms
R beats H and PBO on cognitive symptoms
R beats H and PBO on aggressive symptoms
R beats H and PBO on depression/anxiety symptoms
Conclusions
Best efficacy outcome for a new atypical antipsychotic against haloperidol and placebo
Doses higher than 6 mg/d not atypical in terms of EPS
Prolactin elevations same or more than with haloperidol

[a]Based on reference 41.

Table 3. Olanzapine in Clinical Trials: How Does It Compare With Placebo and Haloperidol?[a]

Olanzapine (O; ≈ 5, 10, 15 mg/d) versus haloperidol (H ≈ 15 mg/d) and placebo (PBO) in schizophrenia
O equals H and beats PBO on overall psychosis ratings
O equals H and beats PBO on positive symptoms
O beats H and PBO on negative symptoms
O beats H and PBO on anxious/depressive symptoms
Conclusions
Comparable efficacy to haloperidol overall and for positive symptoms, but better than haloperidol for negative symptoms and anxious/depressive symptoms
Far more tolerable than haloperidol with occasional akathisia at low doses and much lower EPS ratings than haloperidol at high doses
Only occasional and transient prolactin elevation, much better than haloperidol

[a]Based on references 42 and 43.

ARE THE 3 NEW ANTIPSYCHOTICS "ATYPICAL"? FINDINGS FROM CLINICAL TRIALS

Three new antipsychotics—risperidone, olanzapine, and quetiapine—have entered clinical practice since clozapine was discovered to be atypical. In terms of efficacy, Tables 2 through 4 compare published clinical trials of the new atypical antipsychotics with haloperidol in placebo-controlled studies. Risperidone, olanzapine, and quetiapine are all superior to placebo (Tables 2–4).[41–46] There are differences, however, in how each of these 3 antipsychotics compares with haloperidol. For example,

Table 4. Quetiapine in Clinical Trials: How Does It Compare With Placebo and Haloperidol?[a]

Quetiapine (Q; 75–750 mg/d) versus haloperidol (H; 12 mg/d) or placebo (PBO) in schizophrenia
Q (150, 300, 600, and 750 mg/d) all equal H and beat PBO on overall psychosis ratings
Q (150, 300, 600, and 750 mg/d) all equal H and beat PBO on positive symptoms
Q (300 mg/d, but not 600 mg/d or 750 mg/d) equals H and beats PBO on negative symptoms
Q (all doses, especially 600 mg/d) beats H and PBO on hostility/aggression
Q (150 mg/d) beats H and PBO on anxiety/depression
Conclusions
Efficacy comparable to haloperidol for overall psychosis, positive symptoms, and negative symptoms
Efficacy better than haloperidol for hostility/aggression and anxiety/depression
Virtually no EPS observed throughout the dosing range
Virtually no prolactin elevations, even transient, observed throughout the dosing range
Not superior to haloperidol for negative symptoms. (However, proving greater efficacy than haloperidol in negative symptoms is more difficult for an antipsychotic with virtually no EPS, and also when compared with a low dose of haloperidol. As haloperidol dose rises, ratings of negative symptoms are raised because these symptoms are induced by the EPS that are caused at higher haloperidol doses. Thus, it is easier to beat haloperidol at high doses than at low doses. These studies used a lower dose of haloperidol than that used in studies with other atypicals.)

[a]Based on references 44–46.

although all 3 drugs are at least comparable to haloperidol, risperidone is the only drug to show efficacy superior to that of haloperidol for positive symptoms, and quetiapine is the only drug that fails to show efficacy superior to that of haloperidol for negative symptoms. Whether this translates into meaningful differences in clinical practice remains to be determined, because reported differences between an atypical antipsychotic and haloperidol in any given clinical trial can also be due to simple variability between trials, use of different rating instruments, type of statistics employed, and differences in the doses chosen both for haloperidol and for the new antipsychotic.

The conclusions as to whether each of the 3 new antipsychotics is atypical—and by which criteria—are given in Tables 5 through 7. Note that the degree of atypicality differs from one drug to another depending upon the factor of atypicality chosen and the quality of the evidence that exists so far. Available literature for risperidone,[41,47–91] olanzapine,[42,43,92–127] and quetiapine[44–46,128–137] was reviewed and is summarized in Tables 5–7.

OLD WINE IN A NEW BOTTLE? LOXAPINE IS A SEROTONIN-DOPAMINE ANTAGONIST, YET A CONVENTIONAL ANTIPSYCHOTIC

Loxapine is known as a conventional antipsychotic, but has recently been discovered to have 5-HT_{2A} antagonist properties like clozapine and the 3 new atypical antipsy-

Table 5. Risperidone: Is It Atypical?[a]

Serotonin-dopamine antagonist?	Yes
EPS fewer than with haloperidol?	Yes[b]
Patients essentially never get EPS?	No[b]
Reduced incidence of tardive dyskinesia?	Probably
Prolactin increase less than with haloperidol?	No[c]
Negative symptoms better than placebo?	Yes
Negative symptoms treated better than with 20 mg of haloperidol?	Yes
Effective for symptoms refractory to conventional antipsychotics?	Maybe

[a]Based on references 41 and 47–91.
[b]At low doses, EPS same as with placebo but occasionally seen; at high doses, EPS increased, but still fewer than with haloperidol.
[c]Prolactin increases same or more than with haloperidol.

Table 6. Olanzapine: Is It Atypical?[a]

Serotonin-dopamine antagonist?	Yes
EPS fewer than with haloperidol?	Yes
Patients essentially never get EPS?	Yes and no[b]
Reduced incidence of tardive dyskinesia?	Probably
Prolactin increase less than with haloperidol?	Yes
Prolactin essentially never increases?	No[c]
Negative symptoms treated better than with placebo?	Yes
Negative symptoms treated better than with about 15 mg of haloperidol?	Yes
Effective for symptoms refractory to conventional antipsychotics?	Maybe

[a]Based on references 42, 43, and 92–127.
[b]EPS unusual except occasional akathisia at up to 15 mg/d, but EPS occasionally seen at doses above usual prescribing range (ie, > 15 mg/d).
[c]Prolactin elevations in fewer patients compared to haloperidol and usually transient.

Table 7. Quetiapine: Is It Atypical?[a]

Serotonin-dopamine antagonist?	Yes
EPS fewer than with haloperidol?	Yes
Patients essentially never get EPS?	Yes
Reduced incidence of tardive dyskinesia?	Expected[b]
Prolactin increase less than with haloperidol?	Yes
Prolactin essentially never increases?	Yes
Negative symptoms treated better than with placebo?	Yes
Negative symptoms treated better than with 12 mg of haloperidol?	No[c]
Effective for symptoms refractory to conventional antipsychotics?	Maybe

[a]Based on references 44–46 and 128–137.
[b]Studies in progress.
[c]The lower the dose of haloperidol, and the fewer EPS caused by an atypical, the harder it may be to beat haloperidol due to the lack of haloperidol-induced negative symptoms at low doses.

Table 8. Loxapine: How Does It Compare With Conventional Antipsychotics?[a]

No fixed-dose comparative trials
No consistent differences between loxapine and conventional antipsychotics, but in 5 comparison studies with haloperidol, EPS comparable to haloperidol at generally higher doses of loxapine in 3 studies and EPS fewer than with haloperidol at generally lower doses of loxapine in 2 studies
No study of negative symptoms. However, of 21 older studies comparing loxapine and a conventional antipsychotic using older rating scales (BPRS and NOSIE), 6 showed statistically superior efficacy for loxapine on negative symptom–related items, 14 showed no differences, and 1 showed superiority of a comparator over loxapine
No treatment-refractory studies, but study of loxapine augmentation for 18–52 weeks of 7 clozapine partial responders after 9 months of clozapine treatment showed no change in blood clozapine levels, with all patients improving somewhat, 2 improving remarkably
Conclusions
- Typical properties of a conventional antipsychotic in recommended dosage range of 60–250 mg/d
- Efficacy comparable to haloperidol for overall psychosis and for positive symptoms
- No clearly atypical features in the recommended dosage range, but EPS may be fewer than with haloperidol, although prolactin elevations same as with haloperidol
- Inadequate studies of negative symptoms and treatment-refractory patients
- No low-dose studies in the 5- to 50-mg/d range, where it may hypothetically have potentially atypical properties

[a]Based on references 1, 7, 8, 38–40, and 138–184. Abbreviations: BPRS = Brief Psychiatric Rating Scale, NOSIE = Nurses' Observation Scale for Inpatient Evaluation.

Table 9. Loxapine: Is It Atypical?[a]

Serotonin-dopamine antagonist?	Yes
EPS fewer than with haloperidol?	Maybe[b]
Patients essentially never get EPS?	No[c]
Reduced incidence of tardive dyskinesia?	No[c]
Prolactin increase less than with haloperidol?	No[c]
Negative symptoms treated better than with placebo?	Maybe[d]
Negative symptoms treated better than with haloperidol?	Maybe[d]
Effective for symptoms refractory to conventional antipsychotics?	Maybe[e]

[a]Based on references 1, 7, 8, 38–40, and 138–184.
[b]Some but not all studies show lower EPS than with haloperidol.
[c]EPS and elevated prolactin at doses of 60 mg/d or more; no studies less than 20 mg/d.
[d]No proper study of negative symptoms, but some studies show lower negative symptom–related items than with conventional antipsychotics.
[e]No monotherapy study, but improved symptoms unresponsive to clozapine when loxapine added as an augmenting agent.

chotics risperidone, olanzapine, and quetiapine.[39] Because it was introduced prior to the discovery of clozapine's atypical antipsychotic properties, why wasn't loxapine the first atypical antipsychotic?

Firstly, all atypical antipsychotics are serotonin-dopamine antagonists, but this does not mean that every serotonin-dopamine antagonist will be an atypical antipsychotic. Indeed, Tables 1–7 show that the known serotonin-dopamine antagonists may differ substantially on the various factors of atypicality. On the other hand, loxapine was tested in a prior era, with trials not designed to show superiority to haloperidol in terms of EPS, efficacy for negative symptoms, or efficacy for treatment-refractory symptoms. Furthermore, Glazer's[40] retrospective review of loxapine's potentially atypical properties indeed provides some hints of atypicality. Since loxapine may have efficacy at low doses, it is possible that atypical properties may be more prominent if lower doses are used. Is loxapine the "Cinderella" antipsychotic awaiting invitation to the low-dose atypical ball?

This is only a hypothetical possibility that must await further investigation. Currently, it is prudent to consider

Table 10. Risperidone Versus Olanzapine in Head-to-Head Clinical Trials[a]

Measure	Lower Dose Trial[b] (R ≈ 4.8 mg/d; O ≈ 12.5 mg/d)	Higher Dose Trial[c] (R ≈ 7.2 mg/d; O ≈ 17.2 mg/d)
Efficacy		
Overall psychosis ratings[d]	R = O	R = O
Positive symptoms	R beats O	R = O
Negative symptoms	R = O	O beats R
Cognitive symptoms[d]	R = O	R = O
Aggressive symptoms[d]	R = O	R = O
Depression/anxiety	R beats O	R = O
Response maintenance	Not reported	O beats R
Response rate	R beats O (for > 30% response)	O beats R (for > 40% response)
Side effect		
EPS	R = O	O beats R
Weight gain[d]	R beats O	R beats O
Prolactin[d]	O beats R	O beats R
Conclusions		
Dose matters		
Two conflicting trials require independent replication for a tie-breaker		
Risperidone may be a better drug at lower doses; olanzapine may be a better drug at higher doses		

[a]These are the only 2 head-to-head placebo-controlled trials of 2 atypical antipsychotics (both atypicals beat placebo).
[b]Sponsored by Janssen Pharmaceutica Inc. (see reference 53).
[c]Sponsored by Eli Lilly and Company (see reference 107).
[d]Where both trials agree.

Table 11. Findings From Clinical Practice That Confirm Clinical Trials

Atypicals undoubtedly cause fewer EPS compared with conventionals
Atypicals probably reduce negative symptoms of schizophrenia better than the conventionals, but this may in part be secondary to fewer EPS
Atypicals possibly reduce cognitive and affective symptoms in schizophrenia, which may also be secondary to fewer EPS
The magnitude of these properties makes atypicals first-line therapies for psychosis, and conventional antipsychotics second-line

Table 12. Perceptions From Clinical Practice That Differ From Clinical Trials

Different atypical antipsychotics often have clinically distinctive effects in different patients (unlike conventional antipsychotics)
Optimal doses derived from clinical trials do not match optimal doses used in clinical practice
Atypical antipsychotics do not always seem to work as fast as conventional antipsychotics
Atypical antipsychotics can appear to be less effective than conventional antipsychotics in treating acute psychosis, especially in the first few days
Atypical antipsychotics can appear to be less effective than conventional antipsychotics in treating agitation (especially if acute)
Efficacy of new atypical antipsychotics in treating patients refractory to conventional antipsychotics is not dramatic. Clozapine is still the gold standard
To switch from ongoing treatment to a new drug, some clinical trials recommended "stop-start," whereas in practice, patients are usually "cross-tapered" (ie, the immediate discontinuation of ongoing treatment followed by the immediate starting of a new atypical drug can lead to rebound psychosis, withdrawal reactions, and rehospitalizations. Instead, the dose of ongoing treatment can be tapered down, while the dose of the new atypical drug is simultaneously tapered up.)
Occasional patients may actually respond better to conventional antipsychotics than to atypical antipsychotics

loxapine to be a bit unusual perhaps, but still a conventional antipsychotic as it is normally used in clinical practice. The findings for loxapine from clinical trials and an overview of the status of its potentially atypical properties are given in Tables 8 and 9. Literature reviewed for loxapine was collated for Tables 8 and 9.[1,7,8,38–40,138–184]

IS ONE ATYPICAL ANTIPSYCHOTIC SUPERIOR TO ANOTHER? LIES, DAMN LIES, AND STATISTICS FROM CLINICAL TRIALS

Most published clinical trials for the atypical antipsychotics are studies of one atypical versus one conventional antipsychotic, usually haloperidol. Head-to-head comparisons of 2 atypical antipsychotics in placebo-controlled multicenter trials are just now emerging. Two studies have been presented comparing risperidone with olanzapine and have generated considerable controversy (Table 10).[53,107] There are no published head-to-head placebo-controlled comparisons between quetiapine and either risperidone or olanzapine.

The problem of relying on head-to-head comparisons of 2 drugs as a basis for choosing to prescribe one over the other is exemplified by the situation, shown in Table 10, where 2 different studies purport to compare risperidone with olanzapine. The results of these 2 clinical trials of the same atypical antipsychotics can seem to say opposite things, depending upon one's perspective. In one study, risperidone appears to have efficacy superior or equal to that of olanzapine, whereas in the other, olanzapine seems to have efficacy superior or equal to that of risperidone.

What is the meaning of these results? The answer may lie in the different doses selected, because risperidone seems to look more efficacious at low doses, whereas olanzapine seems to look more efficacious at high doses. The studies agree only in the area of side effects: both find more prolactin elevation with risperidone and more weight gain with olanzapine.

Statistically significant differences between 2 drugs in how they improve certain symptoms in a population of patients may not meaningfully translate into clinically significant differences between these same 2 drugs for any given individual patient. Indeed, interindividual variation is often much greater than the size of the mean differences between 2 large groups derived from clinical trials. The randomized trial is capable of showing that 2 outcomes are different from each other. However, these trials do not always show differences of a magnitude and consistency that provide clear guidelines on how to select one atypical antipsychotic over another for any given individual patient. Thus, these findings in Table 10 should be weighed in the

Table 13. Factors in Choosing an Atypical Antipsychotic: Weight Gain[a]

No change or weight loss
Loxapine
Molindone
Increasing likelihood of weight gain
Ziprasidone (the least weight gain)
Thiothixene
Fluphenazine
Haloperidol
Risperidone
Chlorpromazine
Sertindole
Quetiapine
Thioridazine
Olanzapine
Zotepine
Clozapine (the most weight gain)

[a]Based on references 72–78.

Table 14. Frequency of Augmentation of an Atypical Antipsychotic With a Second Antipsychotic in Clinical Practice[a]

Drug	% of All Prescriptions
Risperidone	
Survey 1	4.2
Survey 2	4.6
Survey 3	7.1
Olanzapine	
Survey 1	25.1
Survey 2	15.4
Survey 3	6.1
Quetiapine	
Survey 1	11.4
Survey 2	21.5
Survey 3	6.4
Clozapine	
Survey 1	9.7
Survey 2	12.5
Survey 3	12.3

[a]Survey 1: National Disease and Therapeutic Index (NDTI) survey for the second quarter of 1998, IMS HEALTH, Plymouth Meeting, Pa.; Survey 2: NDTI survey for the third quarter of 1998, IMS HEALTH, Plymouth Meeting, Pa.; Survey 3: Scott-Levin Physician Drug & Diagnosis Audit (PDDA) for the third quarter of 1998, Scott-Levin, a division of PMSI Scott-Levin, Inc.

selection of risperidone versus olanzapine, but other factors outlined below should also factor into that decision.

AN OVERVIEW OF ATYPICAL ANTIPSYCHOTICS IN CLINICAL PRACTICE

Tables 2, 3, 4, and 10 have summarized results from clinical trials of the atypical antipsychotics. As there has now been considerable experience with each of these drugs in clinical practice, it may be useful to review the areas of agreement and disagreement between clinical trials and clinical practice. These are summarized in Tables 11 and 12. Specific information from clinical practice that applies to 5 antipsychotic drugs will be detailed in the following section. These drugs are clozapine, risperidone, olanzapine, quetiapine, and loxapine.

Table 15. Choice of Augmenting Agent When Coprescribing Atypical Antipsychotics With a Second Antipsychotic in Clinical Practice[a]

	Distribution of Antipsychotic Cotherapy From Table 14	
Drug	% Augmentation With Conventional	% Augmentation With 2nd Atypical
Risperidone		
Survey 1	88	12
Survey 2	70	30
Survey 3	55	45
Olanzapine		
Survey 1	83	17
Survey 2	34	66
Survey 3	91	9
Quetiapine		
Survey 1	50	50
Survey 2	17	83
Survey 3	25	75
Clozapine		
Survey 1	0	100
Survey 2	43	57
Survey 3	26	74

[a]Survey 1: NDTI survey for the second quarter of 1998, IMS HEALTH, Plymouth Meeting, Pa.; Survey 2: NDTI survey for the third quarter of 1998, IMS HEALTH, Plymouth Meeting, Pa.; Survey 3: Scott-Levin PDDA for the third quarter of 1998, Scott-Levin, a division of PMSI Scott-Levin, Inc.

Weight is often ignored by clinicians, with body weight and body mass index not monitored during long-term treatment. Since many of the atypical antipsychotics in frequent use may increase body weight by 20 to 50 lb (9–22 kg) with long-term maintenance, the selection of an atypical antipsychotic may be influenced by its actual or potential effects on weight gain (Table 13).[72–78] Regardless of which antipsychotic is chosen, monitoring body weight and preventing obesity should be a priority for antipsychotic prescribers. New data document better than ever the increased health risks of obesity, such as new-onset diabetes mellitus and especially accelerated cardiovascular mortality. This may be particularly relevant for the treatment of schizophrenic patients who are likely to have disproportionately high levels of other cardiovascular risk factors such as smoking (up to 80% of schizophrenic patients), sedentary lifestyle, and unhealthy diet.

Although clinical trials are conducted in patients taking only one antipsychotic drug, in practice up to one fourth of patients are taking 2 (Tables 14 and 15). The data in Tables 14 and 15 come from prescription surveys, with the first a National Disease Therapeutic Index (NDTI) survey for the second quarter of 1998 (IMS HEALTH, Plymouth Meeting, Pa.), the second an NDTI survey for the third quarter of 1998 (IMS HEALTH, Plymouth Meeting, Pa.), and the third a Physician Drug & Diagnosis Audit (PDDA) for the third quarter of 1998 (Scott-Levin, a division of PMSI Scott-Levin, Inc.). Physicians were surveyed concerning all concomitant medications that they gave with each atypical antipsychotic they prescribed. The frequency of

Table 16. Factors in Choosing an Atypical Antipsychotic: Managing Inadequate Treatment Responses to Antipsychotic Drugs

Monotherapy with an atypical is considered to be inadequate in up to 20% of patients who also receive augmentation with a second antipsychotic drug
If one of these 3 atypical agents (risperidone, olanzapine, quetiapine) generates an unsatisfactory treatment response at normal doses, try one of the other atypical antipsychotics before augmenting
If the second drug is also unsatisfactory, try the third
If all 3 atypicals are unsatisfactory, consider higher doses than usual, a trial of clozapine, or various augmentation strategies
Augmentation can be with a conventional antipsychotic such as loxapine or haloperidol, with a benzodiazepine such as lorazepam, or with a mood stabilizer such as valproic acid

Table 17. Clozapine Pearls[a]

Most efficacious but most dangerous
May reduce violence and aggression in difficult cases
Reduces suicide in schizophrenia
May improve tardive dyskinesia
Clinical improvements may continue slowly over several years
Not a first-line/first-break treatment choice in most countries
Can cause agranulocytosis (0.5%–2%)
Requires monitoring of blood counts weekly for 6 months, then every 2 weeks
Dose-related increased risk of seizures
Over 550 mg/d may require concomitant anticonvulsant
Can cause significant weight gain
Sedation and sialorrhea (especially at night) may be bothersome

[a]Based on references 3, 8, and 19–37.

Table 18. Risperidone Pearls[a]

Well accepted for treatment of agitation and aggression in elderly demented patients
Well accepted for treatment of bipolar disorders
Many anecdotal reports of utility in children, treatment-refractory cases, and for positive symptoms of psychosis in disorders other than schizophrenia
Only atypical antipsychotic that elevates prolactin levels, but this is of unproven and uncertain clinical significance
Although low doses cause no more EPS than placebo, that does not mean they never cause EPS
Less weight gain than some other antipsychotics, but this does not mean no weight gain

[a]Based on references 8, 41, and 47–91.

Table 19. Risperidone Dosing Tips[a]

Less may be more: By lowering dose, side effects often reduced without loss of efficacy
Thus, doses used in clinical practice are *lower* than doses suggested from early clinical trials
Target dose for best efficacy/best tolerability may be 2–6 mg/d (average = 4.5 mg/d) except in children or elderly, who should get 0.5–2.0 mg/d
Patients who respond to these doses may have lowest drug costs among the atypicals
Low doses may not be adequate in difficult patients
Rather than raise dose above these levels in agitated patients, in partial responders, or in acutely ill patients requiring sudden antipsychotic effects, consider augmentation with a benzodiazepine or conventional antipsychotic, orally or i.m.
Can use once-daily dosing
May wish to use twice-daily dosing for the elderly and children during dosage titration
Only atypical antipsychotic with liquid dosage formulation
Tablets as small as 0.25 mg and 0.5 mg soon available
Working on new formulation that dissolves on tongue
Working on depot palmitate formulation for monthly administration of 9-hydroxy metabolite
Compliance monitoring at point of care for presence of drug in saliva or urine available soon

[a]Based on references 8, 41, and 47–91.

Table 20. Olanzapine Pearls[a]

Well accepted for use in schizophrenia and bipolar disorders, including difficult cases
Many anecdotal reports of utility in children, treatment-refractory cases, and for positive symptoms of psychosis in disorders other than schizophrenia
Documented efficacy as augmenting agent to SSRIs in nonpsychotic treatment-resistant major depressive disorder
Muscarinic antagonist properties theoretically unfavorable for cognition in schizophrenia, and in the elderly, but cognitive symptoms of schizophrenia may improve in some clinical trials
Same EPS as placebo does not mean never, but EPS unusual at low to mid doses
More weight gain than other antipsychotics does not mean every patient gains weight
Not necessary to monitor liver function tests except in significant liver disease

[a]Based on references 8, 42, 43, and 92–127. Abbreviation: SSRI = selective serotonin reuptake inhibitor.

use of another antipsychotic in these surveys is given in Table 14. The breakdown as to how many of these prescriptions were for a conventional antipsychotic or for another atypical antipsychotic is given in Table 15.

Whether the concomitant administration of 2 antipsychotic drugs in the patients from these surveys is rational (due to poor treatment response to an atypical antipsychotic) or irrational polypharmacy is not represented in these tables. Presumably there is some of both. Given that treatment nonresponsiveness is well documented in 5% to 25% of schizophrenic patients,[27,31] however, the numbers deriving from clinical practice are consistent with use of 2 antipsychotics for patients who have an unsatisfactory treatment response to an atypical antipsychotic. These surveys excluded patients being tapered or cross-tapered with one of these agents.

It is a sorry fact that there are no large-scale studies of which patients are most likely to benefit from an atypical antipsychotic augmented with a second antipsychotic. It is not known whether patients receiving an atypical antipsychotic with a conventional antipsychotic would be better off on treatment with the conventional antipsychotic alone. It is not known whether the use of 2 atypicals simultaneously (from 9% to 100% of the time depending upon the survey; see Table 15) is cost-effective, especially considering that use of 2 atypical agents can double or quadruple the cost of drug therapy. Studies are sorely needed to determine a rational approach to treatment with 2 antipsychotics that has a positive risk-benefit ratio and that is also cost-effective. Until these studies are available, it

Tables 21. Olanzapine Dosing Tips[a]

More may be more: By raising dose above recommended levels of 15 mg/d, can be useful for acutely ill and agitated patients, and even some treatment-resistant patients, gaining efficacy without many more side effects
Thus, doses used in clinical practice (> 15 mg/d) often *higher* than those suggested from clinical trials (ie, usually 10 mg/d)
Patients who respond to higher doses will have higher drug costs, but this may be justified if the patient is severely ill and other options fail
Higher doses given in the acute period or while agitated can sometimes be reduced later when patient stabilized
Rather than raising doses to high level in difficult cases, consider augmentation with a benzodiazepine or conventional antipsychotic orally or i.m.
Women may require lower doses than men since plasma levels higher in women than in men at comparable doses
Once-daily administration for all applications
4 dose sizes: 2.5 mg, 5 mg, 7.5 mg, and 10 mg
No scored tablets, so cannot break in half
Each tablet costs about the same, so a single dose size will allow 2.5, 5, 7.5, or 10 mg/d; price can double for 2 dosage sizes (required for 12.5, 15, 17.5, or 20 mg/d); price can triple for 3 dosage sizes (required for 22.5, 25, 27.5, or 30 mg/d)
A 15-mg and a 20-mg tablet may become available to reduce drug costs
An i.m. dosage formulation for acute administration is in development

[a]Based on references 8, 42, 43, and 92–127.

Table 22. Quetiapine Pearls[a]

Some patients respond to quetiapine who have failed to respond to other atypicals
Anecdotal reports of usefulness for treatment-refractory cases, bipolar disorder, and for positive symptoms of psychosis in disorders other than schizophrenia
Early studies support use in adolescents, elderly, and for hostility/aggression, cognition, and affective symptoms in schizophrenia
Beats placebo (but not haloperidol) on negative symptoms, yet least likely to cause negative symptoms secondary to EPS
Never say never, but essentially no EPS or prolactin elevation at any dose
Cataracts caused at high doses in dogs but not monkeys or humans, possibly due to species-specific inhibition of cholesterol biosynthesis in the lens of dogs
However, in US, FDA precaution to monitor for development of cataracts every 6 months (similar to precaution for carbamazepine and HMGCoA reductase inhibitors of cholesterol biosynthesis)
Not necessary to get eye exams until dose stabilized and planned for long-term use

[a]Based on references 8, 44–46, and 128–137.

would be prudent to use 2 antipsychotics reluctantly and only for patients whose inadequate treatment responses to a single atypical antipsychotic are clearly improved by the addition of a second antipsychotic. Judicious use of low doses of a conventional antipsychotic added on to the most cost-effective dose of an atypical antipsychotic is the most inexpensive approach. Given the pharmacologic properties of loxapine, and numerous case reports of its enhancement of clozapine efficacy, this agent, particularly in low doses, should be considered when augmentation of an atypical antipsychotic with another antipsychotic is being tried (Table 16).

Table 23. Quetiapine Dosing Tips[a]

Clinical trials suggest effective dose range is 75–400 mg bid for schizophrenia (except lower doses in the elderly, namely 25–75 mg bid)
Clinical practice suggests target doses of 150–200 mg bid for schizophrenia
Some clinical trials done tid, but in clinical practice, doses are given bid, and may even transition to once daily, especially for total daily doses of 400 mg or less, and after stabilized for long-term treatment
More may be more: Raising dose can be useful for acutely ill and agitated patients, and even some treatment-resistant patients, gaining efficacy without essentially any more side effects, especially over 200 mg bid
3 dose sizes: 25, 100, and 200 mg
No scored tablets so cannot break in half
Recommended titration to 300–400 mg/d by the fourth day requires 2 doses/d and changing combinations of 25-mg, 100-mg, and 200-mg tablets
In practice, aim for 200 mg bid on the fifth day, whether initiating new patients or switching while cross-titrating down with another antipsychotic, eg, 50 mg on day 1 (25 mg bid or 50 mg qhs), 150 mg on day 2 (50 mg q am and 100 mg qhs), 200 mg on day 3 (100 mg bid), 300 mg on day 4 (100 mg q am and 200 mg qhs), and 400 mg on day 5 (200 mg bid); this regimen uses a total of four 25-mg tablets, four 100-mg tablets, and one 200-mg tablet in the first 4 days, then two 200-mg tablets daily thereafter
At 200 mg bid may be a lower cost atypical, but other doses higher or lower may be more expensive (more than twice the cost) and require complicated combinations of multiple tablets and multiple dosage sizes (up to 10 tablets/d and all 3 dosage strengths)

[a]Based on references 8, 44–46, and 128–137.

Table 24. Loxapine Pearls[a]

Recently discovered to be a serotonin-dopamine antagonist (binding studies and PET scans)
Active metabolites also serotonin-dopamine antagonists
Developed as a conventional antipsychotic, ie, reduces positive symptoms, but causes EPS and prolactin elevations
Lower EPS than haloperidol in some studies, but no fixed-dose studies and no low-dose studies
Causes less weight gain than other antipsychotics, both atypical and conventional, and may even be associated with weight loss
Norepinephrine reuptake blocking properties suggest potential utility for depressive symptoms
No formal studies of negative symptoms, but some studies show superiority to conventional antipsychotics for emotional withdrawal and social competence
Best use may be as a low-cost augmentation agent to atypical antipsychotics, eg, enhances efficacy in clozapine partial responders when given concomitantly with clozapine
For previously stabilized patients with "breakthrough" agitation or incipient decompensation, "top up" the atypical antipsychotic with prn i.m. or oral single doses of loxapine
For patients maintained on 2 antipsychotics, use loxapine to augment 1 atypical
For the greater than one third of patients on doses of an atypical antipsychotic above the documented atypical/cost-effective ranges, consider lowering atypical antipsychotic dose and augmenting with loxapine 5–60 mg/d
Loxapine has only 10%–25% the cost of atypical antipsychotics

[a]Based on references 1, 8, and 138–184.

LIES, DAMN LIES, AND IN MY CLINICAL JUDGMENT: CLINICAL PEARLS AND DOSING TIPS FOR ANTIPSYCHOTICS

In this section, clinical pearls and dosing tips derived both from clinical trial experience and from the effects of

Table 25. Loxapine Dosing Tips[a]

Has conventional antipsychotic properties at originally recommended doses (ie, starting at 10 mg bid, maintenance 60–100 mg/d, maximum 250 mg/d given in divided doses)
Binding studies, PET studies, and anecdotal clinical observations suggest that loxapine may be atypical at lower doses (perhaps 5–60 mg/d), but further studies needed
Anecdotal evidence that many patients can be maintained at 20–60 mg/d as monotherapy
Available as 5-mg and 10-mg capsules for low-dose use and as 25-mg and 50-mg capsules for routine use
Available as a liquid dosage formulation
Only serotonin-dopamine antagonist available for acute intramuscular administration (50 mg/mL)
Loxapine i.m. may have faster onset of action and superior efficacy for agitated/excited and aggressive behavior than i.m. haloperidol
Give 25–50 mg i.m. (0.5–1.0 mL of 50 mg/mL solution) with onset of action within 60 minutes in the acute situation
When initiating therapy with an atypical antipsychotic in an acute situation, consider i.m. loxapine to "lead in" to orally administered atypical; eg, initiate oral dosing of an atypical antipsychotic with 25–50 mg loxapine bid to tid i.m. short-term as necessary for antipsychotic effects without EPS and sedation
When using loxapine to "top up" previously stabilized patients now decompensating, may use loxapine as single 25- to 50-mg doses prn as i.m., or oral liquid or tablets
To augment partial responders to an atypical antipsychotic, consider doses of loxapine as low as 5–60 mg/d, but use full doses if necessary

[a]Based on references 1, 8, and 138–184.

atypical antipsychotics in clinical practice are detailed in several tables. These include clozapine (Table 17),[3,8,19–37] risperidone (Tables 18 and 19),[8,41,47–91] olanzapine (Tables 20 and 21),[8,42,43,92–127] quetiapine (Tables 22 and 23),[8,44–46,128–137] and loxapine (Tables 24 and 25).[1,8,138–184]

SUMMARY

In summary, combining statistics and science from clinical trials with art and anecdote from clinical practice may assist the prescriber in selecting an atypical antipsychotic.

Drug names: carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), clozapine (Clozaril), fluphenazine (Prolixin and others), haloperidol (Haldol and others), lorazepam (Ativan and others), loxapine (Loxitane and others), molindone (Moban), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), thioridazine (Mellaril and others), thiothixene (Navane), valproic acid (Depakene and others).

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