

# High-dose antipsychotics

A person in a dark suit stands with arms outstretched in a circular spotlight against a red background. The person is seen from behind, and the spotlight is a bright yellow circle in the center of the frame. The background is a deep red color with some faint, circular patterns.

For patients on the brink of the neuroleptic threshold, risks of high-dose antipsychotics may outweigh any benefit.

# Desperation or data-driven?

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**W**hen nothing else works, desperate clinicians are resorting to progressively more-tenuous and unpredictable treatments, trying to improve the lives of patients with refractory schizophrenia. High-dose antipsychotics is a common strategy.

Does boosting antipsychotic doses beyond the recommended range—but short of the neuroleptic threshold—enhance efficacy? This article attempts to answer that question by presenting the evidence on higher-than-recommended doses of atypical antipsychotics.

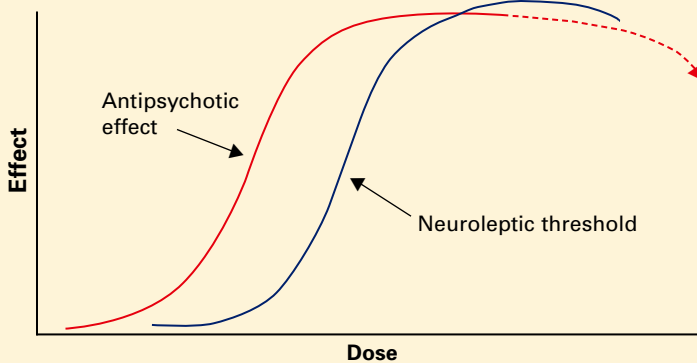
## LESSONS FROM NEUROLEPTICS

Up to 30% of patients with schizophrenia do not respond to antipsychotics and are considered “treatment refractory.”<sup>1</sup> Even among those who do respond, improving symptoms by 20%—as research defines “treatment response”—does not necessarily yield clinical or functional improvement. Clozapine is the only atypical antipsychotic with well-established efficacy in these chronically ill patients,<sup>2</sup> but its daunting side effects greatly curtail its use.

Before atypical antipsychotics, patients who did not respond to usual dosages of the typical

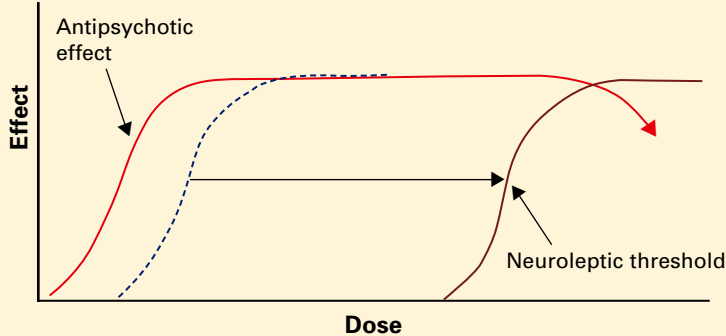


**Figure 1**  
**Typical antipsychotics' dose-response curve**



Narrow therapeutic window between antipsychotic effect and neuroleptic threshold. Dotted line indicates declining efficacy.

**Figure 2**  
**Atypical antipsychotics' dose-response curve**



Wider therapeutic window with atypicals, compared with typical antipsychotics, as neuroleptic threshold (dotted line) moves right.

neuroleptics were treated with higher dosages or switched to another drug class. Although many clinicians embraced high-dose neuroleptics, subsequent research discredited “rapid neuroleptization” in any clinical circumstance and showed that exceeding an antipsychotic’s neuroleptic threshold—the dose at which extrapyramidal side effects (EPS) occur—reduces its efficacy (Figure 1).<sup>3-5</sup> In

some instances, *reducing* neuroleptic dosages improves treatment-resistant patients’ symptoms and reduces drug-induced side effects.<sup>6</sup>

Atypical antipsychotics are defined by their relative lack of EPS at recommended dosages (Figure 2). Because these agents can cause EPS if dosed too high, however, our historical habit of testing this dose limit risks losing “atypicality” and encountering other untoward events (Figure 3, page 34).

What is the safest, most effective dosage? Consider the evidence for each atypical antipsychotic.

### RISPERIDONE

**Recommended dosage too high?** When using atypicals at recommended doses, you are most likely to encounter the neuroleptic threshold with risperidone, with EPS risk increasing substantially at >6 mg/d.<sup>7</sup> Post-approval studies set the most effective and safest dosage at approximately 4 mg/d, though this dosage was not studied in North American pre-approval trials. Dosages of 2 to 4 mg/d have been associated with more-favorable outcomes, suggesting that the initial recommendation to titrate to 6 mg/d within the first 3 days was ill-advised.<sup>8</sup>

In our study of patients with treatment-refractory schizophrenia,<sup>9</sup> those treated with risperidone, 6 mg/d, improved significantly more after 4 weeks than did those receiving haloperidol, 15 mg/d, based on Brief Psychiatric Rating Scale (BPRS) scores. No additional benefit was seen after risperidone was increased to >6 mg/d at 8 weeks. Akathisia and tardive dyskinesia occurred significantly more often in the haloperidol group.

**Conclusion.** Some patients respond to higher-dose

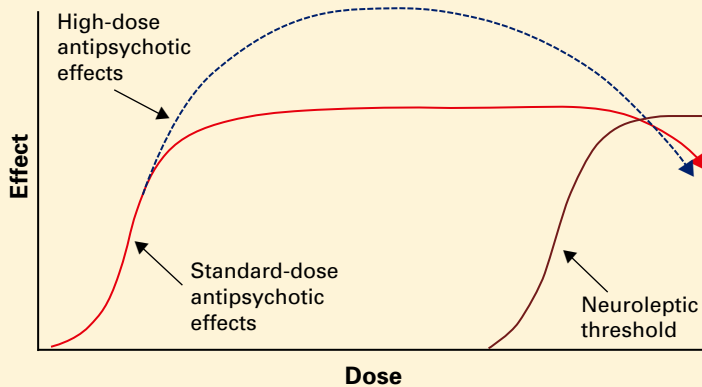
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Figure 3

### Unknown effects of high-dose atypical antipsychotic therapy



Dotted line indicates potential for greater antipsychotic effect with increasing dose.

risperidone, but emerging EPS suggest the need to reduce the dosage rather than add an antiparkinsonian agent.

### OLANZAPINE

**Mixed results.** Case reports suggest that some patients who did not respond to previous antipsychotic trials or olanzapine, 20 mg/d, improved significantly—without substantial side effects—when olanzapine was increased up to 60 mg/d.<sup>10-14</sup> Other case studies, however, report EPS, increased heart rate, increased transaminases, hyperprolactinemia, and prolonged QTc interval with high-dose olanzapine.<sup>14-16</sup>

**In an open-label trial,**<sup>17</sup> 43 patients with schizophrenia received olanzapine, up to 40 mg/d, after inadequate response to neuroleptics and risperidone or clozapine. Olanzapine was titrated to 20 mg/d by week 4 and increased 5 mg every 2 weeks if symptoms did not improve. After 14 weeks, improvement was modest and only 17% of patients met response criteria. However, >20 mg/d reduced symptoms more than did <20 mg/d, suggesting that high-dose olanzapine was more effective.

**In a randomized trial,**<sup>18</sup> patients who did not respond to at least one atypical antipsychotic then received 8 weeks of fixed, standard-dose treatment with (mean dosages):

- haloperidol, 18.9 mg/d
- risperidone, 7.9 mg/d
- olanzapine, 19.6 mg/d
- clozapine, 401.6 mg/d.

Flexible dosing was then allowed for 6 weeks, and mean dosages were:

- haloperidol, 25.7 mg/d
- risperidone, 11.6 mg/d
- olanzapine, 30.4 mg/d
- clozapine, 526.6 mg/d.

Symptoms improved modestly at best for all medications, although patients taking olanzapine or clozapine

improved significantly more than those treated with haloperidol as shown by mean changes in total Positive and Negative Syndrome Scale (PANSS) scores.

PANSS scores for olanzapine-treated patients showed additional improvement at week 14—when higher dosages were used—compared with week 8. This was not the case for the other medications, for which response plateaued. These findings suggest that high-dose risperidone and haloperidol are incrementally ineffective, but high-dose olanzapine could help some patients with refractory symptoms.

**Results were different** in a randomized, double-blind, 16-week, crossover study,<sup>19</sup> when 13 patients with inadequate response to neuroleptics, risperidone, or conventional-dose olanzapine then received olanzapine, 50 mg/d, or clozapine, 450 mg/d. No olanzapine-treated patients and 20% of clozapine-treated patients met criteria for treatment response (20% improvement in BPRS score and final BPRS score <35 or 1-point improvement on Clinical Global Impressions-Severity of Illness scale).

Box

## Thinking about high-dose antipsychotics? Consider these caveats first

### Negative results don't make headlines.

Published clinical trials and case reports are subject to selective reporting of positive outcomes. Cases in which high-dose therapy proved ineffective may outnumber positive results but are less likely to be published.

**Numbers don't lie.** Using high doses will almost always increase side effect risk and drug therapy costs, contributing to a poor risk-benefit ratio when efficacy remains unchanged. Resorting to an "if-it's-not-working, double-it" strategy may seem reasonable, but two times zero is still zero.

**Desperation warps perception.** Clinicians tend to rely on observational experience. The desperation inherent in treating refractory patients, however, often creates a strong desire for improvement and therefore a potentially biased perception of outcome.

Likewise, patients may inaccurately portray themselves as improved to avoid disappointing their doctors. Controlled trials reduce these biases to better assess efficacy.

### Antipsychotics work in 6 to 8 weeks.

Improvements seen when pushing medications beyond recommended dosing may not be an effect of dose but of additional time on the medication. Antipsychotics usually take 6 to 8 weeks to produce maximal response, so high-dose therapy should not be started during this initial phase. This pace may not satisfy pressures

for expedient stabilization and hospital discharge, but it is unrealistic to expect antipsychotics to work more quickly than they do.

### Oversedation does not equal improvement.

Patients who become excessively sedated from high-dose therapy or adjunctive medications may appear less psychotic but may not be so. The family or hospital staff may desire such sedation, but it can adversely affect the patient's quality of life or medication adherence.

**Polypharmacy clouds the issue.** Many patients treated with high-dose antipsychotics are taking multiple agents, making it difficult to attribute improvement (or side effects) to any single one. A well-designed study of high-dose therapy would therefore:

- control for time
- examine concomitant medications' effects
- determine whether "improvements" are related to sedation or reduced psychosis.

**Medication may not need to change.** When a patient decompensates, many forces pressure clinicians to change or add medications or increase dosages. Change may not be necessary, however, as nonadherence or substance abuse often trigger psychotic exacerbations. For example, Steingard et al<sup>27</sup> added fluphenazine or placebo to antipsychotic regimens of newly hospitalized patients and found that increasing antipsychotic dosage did not improve outcome.

Subjects switching from clozapine to olanzapine tended to worsen, whereas those switching from olanzapine to clozapine tended to improve. Olanzapine-treated patients experienced more anticholinergic side effects and more weight gain than did clozapine-treated subjects.<sup>20</sup>

**Conclusion.** These mixed findings on high-dose olanzapine suggest questionable efficacy in patients with treatment-resistant schizophrenia and an uncertain risk of increased toxicity.

## QUETIAPINE

Early placebo-controlled studies of quetiapine in schizophrenia concluded that statistically significant improvement begins at 150 mg/d and falls off after 600 mg/d.<sup>21</sup> Although few high-dose quetiapine cases have been presented, clinical opinion holds that:

- most patients with chronic schizophrenia require 400 to 800 mg/d
- some treatment-refractory patients might benefit from >800 mg/d.

continued





One patient responded to quetiapine, 1,600 mg/d, after not responding to olanzapine, 40 mg/d, and quetiapine, 800 mg/d. Constipation was the only reported side effect.<sup>22</sup>

Our group<sup>23</sup> reported a series of 7 patients who responded (by clinician report) to quetiapine, 1,200 to 2,400 mg/d, after not responding to quetiapine, 800 mg/d, or to neuroleptics, risperidone, or olanzapine. Six responded to high-dose quetiapine and 1 to high-dose quetiapine plus risperidone, 2 mg/d; 4 received adjunctive divalproex sodium, 1,500 to 3,000 mg/d. Psychopathology, violence, and behavioral disturbances were reduced throughout 5 to 14 months of monitoring. Side effects included sedation, orthostasis, and dysphagia.

When Nelson et al<sup>24</sup> treated 13 subjects for 14 weeks with quetiapine, 1,000 to 1,400 mg/d, mean weight, glucose, total cholesterol, prolactin, and QTc interval duration did not change significantly. Heart rate increased significantly (though not to tachycardia), and headache, constipation, and lethargy were the most frequent side effects.

**Summary.** Although encouraging, these reports are preliminary, unpublished, and lack peer review. Controlled trials of high-dose quetiapine's efficacy and safety are needed.

### ZIPRASIDONE AND ARIPIPRAZOLE

No studies of high-dose ziprasidone or aripiprazole have been published. In premarketing trials:

- ziprasidone was studied at 200 mg/d and released with a maximum recommended dosage of 160 mg/d
- aripiprazole, 30 mg/d, was not more effective than 15 mg/d.<sup>25</sup>

Deutschman et al<sup>26</sup> reviewed the charts of 31 patients who received ziprasidone, 240 to 320 mg/d, after an "incomplete" response to 160 mg/d. At the higher dosing:

- psychosis, affective symptoms, or anxiety improved in nearly one-half of patients

- 15% reported sedation, but most reported no side effects
- none developed QTc intervals >500 msec.

### CAVEATS AND PRECAUTIONS

These uncontrolled case reports and open-label studies do not "prove" efficacy or safety but reflect clinical practice. More than anything, they show that we need controlled trials to gauge high-dose antipsychotic therapy's efficacy and safety and to curb our collective habit of relying on anecdotal experience and idiosyncratic beliefs.

Despite its side-effect profile, clozapine remains the treatment of choice for refractory schizophrenia. Given high-dose antipsychotic therapy's uncertain efficacy and unknown risks, the evidence supports a clozapine trial before higher-than-recommended dosing is attempted.

Because educated guesswork plays a role in premarketing dosing studies, a medication's optimal dose may be:

- overestimated (as with risperidone)
- underestimated (as perhaps with olanzapine and quetiapine).

Keep in mind some important caveats when you consider giving a patient high-dose antipsychotic therapy (*Box, page 35*).<sup>27</sup> Of course, nonadherence is often the cause of apparent medication nonresponse. Increasing the dosage of a medication a patient is not taking rarely improves adherence. Interventions to enhance adherence—careful assessment, psychoeducation, and using long-acting intramuscular medication—may be useful.

**For more information on this topic,  
see page 38 for a commentary by  
Sheldon H. Preskorn, MD**

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## Related resources

- ▶ Marder SR, Essock SM, Miller AL, et al. The Mount Sinai Conference on the pharmacotherapy of schizophrenia. *Schizophrenia Bull* 2002;28:5-16.
- ▶ Practice guideline for the treatment of patients with schizophrenia (2nd ed). *Am J Psychiatry* 2004;161(suppl):1-56.
- ▶ Texas Medication Algorithm Project antipsychotic algorithm. <http://www.mhmr.state.tx.us/centraloffice/medicaldirector/timascz.lalgo.pdf>

### DRUG BRAND NAMES

Aripiprazole • Abilify  
Clozapine • Clozaril  
Divalproex • Depakote  
Fluphenazine • Prolixin

Haloperidol • Haldol  
Olanzapine • Zyprexa  
Quetiapine • Seroquel  
Risperidone • Risperdal  
Ziprasidone • Geodon

### DISCLOSURES

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Dr. William Wirshing receives research support from, is a consultant to, and/or is a speaker for Bristol-Myers Squibb Co., Pfizer Inc., Eli Lilly & Co., Janssen Pharmaceutica, and AstraZeneca Pharmaceuticals.

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High-dose antipsychotic therapy is commonly tried because our ability to treat schizophrenia is limited. Preliminary reports suggest high antipsychotic dosages may help some patients, but evidence supports trying clozapine first, before higher-than-recommended dosing.

**BottomLine**