

Initial Dosing and Clinical Titration of Antipsychotic Drugs in Schizophrenia

Antipsychotic	a. Typical dose in mg/day b. (Usual Dosage Range)	Starting Dose (mg/day)			Comments
		Medically Uncomplicated	First Episode	Elderly	
Aripiprazole	a. 15 b. (10-30)	15	10	10	72 hour half-life; no evidence of improved efficacy > 20 mg/day
Clozapine	b. (200-500)	25	N/A	12.5	Response associated with plasma level >350 ng/ml
Haloperidol	a. 5-8(2-3 for 1 st episode) b. (5-20)	10	5	2	Monitor for EPS, blood levels may be helpful
Olanzapine	a. 15 b. (10- 25)	15	10	5	30-40 mg/day may be more effective in refractory patients
Quetiapine	a. 400 b. (300- 850)	50	50	25	Safety and benefit of high doses (>800 mg/day) not yet established
Risperidone	a.3-5 b. (2-8)	2	1	0.5	Increased EPS without improved efficacy above 6 mg/day
Ziprasidone	a. 120 b. (80-160)	40	40	20	Administered with meals; safety and benefits of high doses (>160 mg/day) not yet established

Conventional antipsychotics

Dosing

Optimal dosing with conventional antipsychotic agents involves the selection of a moderate initial dose (Table), followed by careful clinical titration to maximize antipsychotic efficacy while minimizing extrapyramidal symptoms (EPS). (If EPS develop on a typical drug, consider decreasing dose or adding an anticholinergic drug or switching to an atypical, if possible). Sedation also may be dose-limiting with lower-potency conventional antipsychotics.

Agitation during acute phase is best treated with co-administration of a benzodiazepine, such as oral or intramuscular lorazepam as needed.¹ Because compliance with conventional antipsychotics is often poor, clinicians must first determine that the unresponsive or partially-responsive patient is taking the medication as prescribed before making adjustments to the dose onset of action. While sedation occurs within hours,

and increased muscle tone, tremor or other EPS within the first few days, full antipsychotic response is usually not realised until 3-10 days, sometimes not until 4-8 weeks after initiating antipsychotic treatment.² Clinicians must avoid the temptation or pressure for too rapid a rate of dosage increase in an effort to bring psychosis under control rapidly. The antipsychotic response is delayed in comparison with the sedative response.

PET studies of striatal dopamine D2 receptor occupancy indicate that antipsychotic efficacy with atypical antipsychotics roughly corresponds with D2 occupancy greater than 65%, whereas EPS are associated with occupancy greater than about 80 percent.³ ⁴ Excessive doses of conventional agents may be associated with poorer clinical outcome, as antipsychotic effects are unlikely to improve above an optimal therapeutic dose range, possibly causing secondary negative symptoms.

Whereas clinical titration of efficacy against neurological side effects remains the most appropriate approach to dosing, measurement of trough blood levels of haloperidol may be helpful in cases of non-response, to assess compliance, and when co-prescribing agents that may affect hepatic metabolism. Although not entirely consistent, plasma concentrations between five and fifteen (5-15) mg/ml of haloperidol have been associated with optimal therapeutic response.⁵ ⁶

Drug Interactions:

Most conventional antipsychotic agents are primarily metabolized in the liver by the microsomal CYP 2D6 enzyme.⁷ Based on genetic polymorphism status, individuals may differ substantially in their metabolism of conventional antipsychotics; blood levels may vary by more than ten-fold between rapid and slow metabolizers. In addition, the 2D6 enzyme may be inhibited by co-administration of other psychotropic agents, particularly certain selective serotonin reuptake inhibitors. For example, fluoxetine was shown to elevate blood levels of haloperidol and fluphenazine by 20% and 65%, respectively. ⁸ Anticonvulsants, such as carbamazepine and diphenylhydantoin may decrease haloperidol levels below a therapeutic threshold and, thus, require increases in doses.⁹

Atypical antipsychotics:

Clinical trials conducted by the manufacturers identified dose ranges for the atypical agents which produce, on average, good clinical efficacy with reduced extrapyramidal side effects (Table). However, the optimal dose for several agents for some clinical indications remains uncertain. Higher doses may be more effective in treatment resistant patients. These have not yet been systematically examined for olanzapine,

quetiapine, and ziprasidone. In addition, unlike the conventional antipsychotics, the atypical agents often do not produce dose-related neurological side effects which can guide dosing. Sedation may be dose-limiting for some agents, and EPS may appear at higher doses, particularly with risperidone. Clozapine may be used at doses up to 900 mg/day if tolerated. In general, risperidone should not be prescribed at doses above 6 mg/d since fixed dose studies have not identified improved efficacy and EPS are more frequent and severe at doses ≥ 6 mg than lower doses.¹⁰ In contrast, olanzapine has displayed evidence for increasing efficacy between 10- 25 mg daily.¹¹ Preliminary evidence from one study suggests that some partially-responsive patients may derive modest benefit from increases of olanzapine to 30- 50 mg/d ¹² but studies show more robust improvement. Whereas doses of quetiapine between 350- 600 mg/d have demonstrated superior efficacy compared to lower doses, higher doses have not been adequately studied.¹³ Ziprasidone has shown efficacy at daily doses between 80-160 mg/d, but higher doses have not been studied.^{14, 15, 16} In contrast, aripiprazole appears to produce maximal efficacy in most patients at a daily dose of 15 mg/d; doses of 20 and 30 mg/d have not been associated, on average, with greater efficacy. With the exception of clozapine, relationships between blood levels and clinical outcome currently are not sufficiently established to guide dosing with the atypical agents. Clozapine plasma concentrations above 350 mg/ml have been associated with a greater likelihood of response.¹⁷

Risperidone is metabolized by the CYP isoenzyme, 2D6, but because its primary metabolite, 9-hydroxyrisperidone is active, alterations of 2D6 activity by pharmacokinetic interactions do not appear to result in clinically-significant effects.¹⁸ The other atypical agents are metabolized by multiple hepatic microsomal enzymes and few significant drug-drug interactions have been reported—possibly due to the existence

of alternative metabolic pathways. However, addition of 3A4 inhibitors, such as fluvoxamine, are reported to increase clozapine serum concentrations by as much as four-fold.¹⁹

All Antipsychotics:

Considerable variability is expected in optimal dose ranges between individual patients; typical therapeutic ranges are provided in the Table. Lower doses are generally recommended in first-episode patients, who tend to be more responsive and more sensitive to side effects and in the elderly, who may metabolize antipsychotic drugs at substantially lower rates and are also more sensitive to side effects,. In addition, lower doses may be effective for maintenance treatment compared to doses required for treatment of acute psychosis, although this has not been well-studied yet with atypical agents. In patients who display no response or only partial response, the dose should be gradually increased but only if compliance has been established and in the absence of dose-limiting side effects (particularly EPS).

(Goff and Meltzer)

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