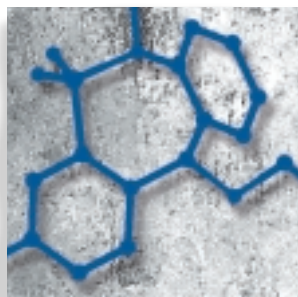


## Optimizing dosing in atypical neuroleptic monotherapy

Fabien Trémeau, MD; Leslie Citrome, MD, MPH



*Atypical neuroleptics have become the first line of treatment for psychotic disorders, but some questions remain: what are their optimal dosages and is more medication more efficacious? For clozapine, it is recommended to aim for a plasma level above 350 ng/mL for nonresponders and partial responders. It should be specified that this plasma level should be obtained exactly 12 h after the last dose. For risperidone, optimal daily doses range between 4 and 8 mg, and there is no indication that a higher dose would bring additional improvement. For olanzapine, a quite different situation is encountered. There is a good indication that daily doses of 30 and 40 mg can increase clinical response. It appears that plasma levels above 23 ng/mL may predict response. For quetiapine, reports on the utility of dosages greater than 800 mg/day are anecdotal at this point, and more studies should be conducted. For ziprasidone, dosages above 40 mg/day should be used, but daily doses above 200 mg have not yet been systematically investigated.*

Dialogues Clin Neurosci. 2002;4:438-443.

**Keywords:** atypical neuroleptic; monotherapy; dose–response relationship; optimal dose; schizophrenia

**Author affiliations:** Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY, USA

**Address for correspondence:** Fabien Trémeau, MD, Nathan Kline Institute for Psychiatric Research, 140 Old Orangeburg Rd, Orangeburg, NY 10962, USA (ftremeau@nki.rfmh.org)

The use of atypical neuroleptics in psychotic disorders has steadily increased since 1989, and atypical neuroleptics have become the first line of treatment for psychotic disorders. Since the marketing of clozapine in 1989 in the USA, several other atypical neuroleptics have become available to clinicians there, and this has extended and diversified the prescriptions of atypical neuroleptics. However, no newer atypical neuroleptic has yet shown greater efficacy than clozapine. In addition, many patients have improved only partially with these newer atypical neuroleptics. Clinicians often face difficult choices when patients do not respond or partially respond to these newer atypicals. Several strategic possibilities are then available to clinicians: (i) increasing the dosage of the antipsychotic; (ii) switching to another neuroleptic; (iii) augmenting treatment with a mood stabilizer; and (iv) using polypharmacy (meaning adding a second antipsychotic medication). Before adding any other medication, or changing to another neuroleptic, a fundamental question should be answered: has the current neuroleptic been optimally used? This question can be divided into two different questions: has the length of the medication trial been long enough, and has the patient received an optimal dosage?

In this presentation, we will focus on the second question: what is the optimal dosage for the atypical neuroleptics? We will limit the neuroleptics to the atypical agents currently available in the USA (clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole), and thus we will not discuss dosing issues regarding other atypicals such as sertindole or amisulpride.

### Lessons from typical neuroleptics

The issue of optimal dosage with typical neuroleptics has been the focus of frequent debates. For example, in the seventies, very high doses of haloperidol were routinely

used. However, it became clear that high doses can lead to more side effects and particularly to more extrapyramidal side effects (EPS). In the nineties, an opposite trend arose: it was considered that much lower doses than 30 mg/day were sufficient to obtain optimal efficacy. This was supported by positron emission tomography (PET) studies that showed that small daily doses such as 5 mg were sufficient to obtain more than 60% blockade of the dopamine D<sub>2</sub> receptors in the basal ganglia. Consequently, the average daily dosage of typical neuroleptics has decreased in clinical settings and in clinical research trials (eg, when haloperidol is used as a comparative treatment arm). One remaining issue is to identify patients who may need higher doses. Although it is commonly accepted that fast metabolizers need higher doses, there is very little evidence to support the use of high doses in other circumstances. Clinicians tend to increase neuroleptic doses, and sometimes up to high doses, for breakthrough symptoms and for a partial response. One study<sup>1</sup> found that patients who receive high doses of typical neuroleptics tend to show a more severe course of illness and more persistent symptoms, and some had a history of violence or regressed behavior.

### What doses do clinicians prescribe?

In the USA, clinical use of atypicals began in 1989 with clozapine. At that time, it was commonly accepted that the average daily dose should be around 500 to 600 mg. It is of note that, in the last 5 years, publications report that in Europe the average daily dose of clozapine has been much lower (around or below 300 mg), and at the same time, the average daily dose of clozapine has decreased in the USA, as seen in psychiatric hospitals operated by the State of New York (Table I).<sup>2</sup> State hospitals in the USA are dedicated to the treatment of people with mental illness who have minimal or no insurance, and who need longer hos-

pital stays. For these reasons, patients in state hospitals are mostly those with schizophrenia or schizoaffective disorder, and who also have frequent relapses, or who do not show a good and fast response to therapy, and are thus the most challenging patient population to treat. The average daily doses of clozapine and risperidone have decreased in the last 5 years, while the average daily dose of olanzapine has increased, almost reaching the maximal recommended dose. This current practice does not seem specific to New York State. Stahl<sup>3</sup> reported that, in California, the average daily dose in 2002 was 4.0 mg for risperidone, 20.5 mg for olanzapine, and 316 mg for quetiapine (for patients aged 18 to 44). Although the patient populations were not quite comparable between these two reports, it appears that clinicians use a lower daily dose of risperidone than before, whereas they use higher doses of olanzapine.

### Evidence for an optimal dose of atypical neuroleptics

For all atypicals, studies have shown that very low doses are no better than placebo, so the question of finding the optimal dose can be summarized as: is more medication more efficacious? There are two ways to measure the quantity of medication each patient receives: daily dose and plasma level. Usually, when plasma levels are studied, the question that researchers try to answer is: is there a drug plasma level that should be reached in order to obtain an optimal response? To answer this, a specific statistical tool is used: the receiver operating characteristics (ROC) curves. These curves are obtained by ranking each patient from the highest plasma level to the lowest plasma level. Each case is then plotted on a graph: the y axis represents the cumulative percentage of responders (which is also the sensitivity of the cutoff point), while the x axis represent the cumulative percentage of nonresponders (which will give the specificity of the cutoff point, by subtracting

Antipsychotic	Daily doses recommended by the FDA (mg)	New York State Hospitals Mean daily dose used (mg)	
		1997 (1st quarter)	2001 (3rd quarter)
Clozapine	300-450; maximum: 900	586.3 (N=845)	494.7 (N=851)
Risperidone	4-8; maximum: 16	7.1 (N=1320)	4.9 (N=1552)
Olanzapine	10-15; maximum: 20	15.6 (N=1057)	18.9 (N=1662)
Quetiapine	300-500; maximum: 800	Not available	518.4 (N=782)
Ziprasidone	40-160; maximum: 200	Not available	132.4 (N=129)

**Table I.** Recommended daily doses of neuroleptics, and neuroleptic doses used in New York State Hospitals. FDA, Food and Drug Administration. Data taken from reference 2.

# Pharmacological aspects

this number from 1). From the curve, a cutoff point is determined, and a chi-square analysis is undertaken to determine whether the percentage of responders among patients with a plasma level above the cutoff point is significantly different from the rate of responders with a plasma level under the cutoff point. We will now review the evidence for high dosing for each atypical neuroleptic.

## Clozapine

Several studies<sup>4-10</sup> have tried to determine a threshold for the clozapine plasma level, above which a response could be predicted (Table II). Comparison between these studies is made difficult as they vary greatly in their methodologies. For example, some used a fixed dose, while others did not (which leads to a lower percentage of responders in the high doses, and thus makes it difficult to identify a threshold). However, it can be concluded that 350 ng/mL can be considered as a plasma threshold for optimal clozapine therapy. Moreover, several remarks need to be made:

- 350 ng/mL is not a “magical” number. A good percentage of patients do improve even with plasma levels lower than 350 ng/mL. This means that for patients who do not respond or partially respond to clozapine, and who have a plasma level below 350 ng/mL, efforts should be made to obtain a clozapine plasma level above 350 ng/mL, before establishing that these patients are clozapine nonresponders.
- The dosage of clozapine plus norclozapine does not add precision in the determination of a threshold compared with clozapine plasma level alone.
- Clozapine plasma levels vary greatly between individuals. This is quite important, and some patients with a daily dose of 900 mg may not achieve a plasma level of 350 ng/mL, while some patients even with a low daily dose may show a plasma level a good deal higher than 350 ng/mL.
- A higher plasma level is associated with a higher risk of seizures.
- The dosing schedule should be taken into consideration. As clozapine has an average half-life of 12 h, a daily dos-

Reference	N	Duration (weeks)	Fixed dosage (mg/day)	Mean dosage (mg/day)	Criteria for improvement	Cutoff plasma level (ng/mL)	Response rate	Sensitivity/specificity	Remarks
Perry et al, <sup>4</sup> 1991	29	4	400	384±42	BPRS ≥20%	350	64% vs 22% P=0.03	64%/78%	Dose given at bedtime
Hasegawa et al, <sup>5</sup> 1993	59	26	No	444±270	BPRS ≥20%	370	73% vs 38% P=0.01	53%/73%	Level at D29 to D2288
Potkin et al, <sup>6</sup> 1994	58	12	400 for 6 weeks	Then 400 or 800	BPRS ≥20%	420	60% vs 8% at W4 73% vs 23% at W12	74%/NA	Frequency?
Kronig et al, <sup>7</sup> 1995	45	6	500 for 3 weeks	623±203	BPRS ≥20%	350	55% vs 20% P<0.04	80%/54%	Dose given BID
VanderZwaag et al, <sup>8</sup> 1996	56	12	NA	Plasma: 50-150, 200-300, 350-450	BPRS ≥20% ≥33%	>200-300	60% vs 39% NS 42% vs 6% P=0.04		BID or TID
Spina et al, <sup>9</sup> 2000	45	12	No	309±63	BPRS ≥20%	350	62% vs 21% P<0.02	72%/70%	BID or TID
Llorca et al, <sup>10</sup> 2002	37	18	No	486	PANSS ≥20%	550	NS	64%/51%	QD or BID (at 6 PM and 8 PM)

**Table II.** Studies of clozapine plasma levels and response rates. BPRS, Brief Psychiatric Rating Scale; NA, not available; NS, not significant; PANSS, Positive and Negative Syndrome Scale.

ing schedule of 400 mg at night will lead to a higher plasma level than a dosing schedule of 200 mg twice a day, even if levels are drawn 12 h after the last dose in both cases. This may explain some discrepancies between the results of the studies examining plasma levels.

- In all these studies, blood was drawn 12 h after the last clozapine dose. Clinicians should make sure that plasma levels are checked exactly 12 h after the last clozapine dose. Again, as the half-life of clozapine is around 12 h, a plasma level of 350 ng/mL at 12 h, will drop to 310 ng/mL at 13 h. Although this might not be a difficult problem to resolve with inpatients, it can be quite a challenge with outpatients.

### Risperidone

Risperidone was released commercially in the USA in 1994. Two major studies, one North American<sup>11</sup> and one European,<sup>12</sup> compared different doses of risperidone. Both favored mid-range daily doses: 6 mg for the North American study, and 4 and 8 mg in the European study. These two studies did not give any indication that higher doses would bring a better response rate. The absence of a dose–response relationship for risperidone has been further confirmed by biological studies. One study<sup>13</sup> could not find any significant correlation between the plasma concentration of risperidone and clinical response. However, it has been shown that higher doses of risperidone lead to a higher frequency of EPS, and thus they lose the one great advantage that atypicals have brought, ie, the low frequency of EPS.

### Olanzapine

Olanzapine has been commercially available in the USA since 1996. As we have seen, clinicians tend to use higher and higher daily doses of olanzapine. However, one would like to have evidence from clinical trials showing that patients, or at least some patients, improve to a greater degree with high doses. Several lines of evidence can be found in the literature. First, in their pivotal randomized clinical trial, Beasley et al<sup>14</sup> found that 48% of patients improved with a mean daily dose of 5 mg, while 58% improved with 10 mg and 66% with 15 mg. This leads to the following question: will more patients improve as we continue to increase the dosage of olanzapine? Several case reports have been published describing a better response with an increment of olanzapine dosage above

20 mg/day. A recently published double-blind study<sup>15</sup> has shed more light on this issue. In the first 8 weeks of this study, patients received a fixed daily dose of clozapine (500 mg), olanzapine (20 mg), risperidone (8 mg), or haloperidol (20 mg). In the subsequent 6 weeks, doses were adjusted clinically, although clinicians remained blind to medication. At the end of the study, the average daily dose was 30 mg for olanzapine, 530 mg for clozapine, 12 mg for risperidone, and 26 mg for haloperidol. Interestingly enough, only the patients who were on olanzapine continued to improve as their dose was increased. This tends to show that doses of olanzapine above the maximal recommended dose may be beneficial for optimizing olanzapine treatment. This finding awaits replication.

One study<sup>16</sup> tried to determine a plasma level threshold for olanzapine using the ROC methodology outlined earlier. In this study, several fixed arms were used, and a cut-off point of 23 ng/mL was shown to be an olanzapine plasma level threshold in order to obtain an optimal response.

### Quetiapine

Quetiapine was released commercially in the USA in 1997. Quetiapine has a rather unique receptor profile. Like clozapine, quetiapine is a low-potency dopamine D<sub>2</sub> blocker, and one study<sup>17</sup> showed that quetiapine leads to transient high D<sub>2</sub> occupancy, which decreases to very low levels after 12 h. Two major studies<sup>18,19</sup> compared various daily doses of quetiapine from 75 mg to 750 mg. It appears that doses above 75 mg are necessary to obtain a response superior to placebo. These studies did not give any indication of a clear dose–response relationship. However, some case reports have indicated that a daily dose above 800 mg brought a better response for some symptoms. For this reason, some clinical trials comparing usual doses of quetiapine with higher than recommended daily doses (up to 1200 mg) are planned.

### Ziprasidone

Ziprasidone was released commercially in the USA in 2001. Two placebo-controlled studies compared different daily doses of ziprasidone in acute schizophrenia. The first one<sup>20</sup> compared ziprasidone 40 mg/day with ziprasidone 120 mg/day. A daily dose of 40 mg led to a 37% response rate, and a daily dose of 120 mg to a response rate of 49%. In the second study,<sup>21</sup> 29% of the patients improved with a daily dose of 80 mg, versus 31% of the patients on 160 mg. In

# Pharmacological aspects

each of the two pivotal trials, the higher dose of ziprasidone resulted in a greater efficacy than the lower dose. Dosages greater than 40 mg/day are recommended. This was confirmed in a 1-year, placebo-controlled clinical trial.<sup>22</sup> After 1 year, 43% of patients on 40 mg/day had relapsed versus 35% of the patients on 80 mg/day, and 36% of the patients on 160 mg/day. Systematic trials using dosages of 200 mg/day have not yet been reported. It is possible that higher doses of ziprasidone may lead to higher rates of response.

## Aripiprazole

Aripiprazole has been available in the USA since November 2002. For this reason, experience is very limited. The recommended daily dosage is from 10 to 30 mg. From the phase 3 clinical trials, high dosages of 30 mg/day were no more effective than lower dosages of 10 or 15 mg/day. It will be interesting to see whether clinical usage of this compound will confirm this finding. The efficacy of dosages above 30 mg/day is not known.

## Conclusions

The determination of an optimal dosage for each atypical neuroleptic is an important issue for the clinical

treatment of patients with schizophrenia. For clinicians, it is linked to another important question: when can we consider that a patient has not responded to a specific antipsychotic? In this presentation, it appeared that (i) for most atypical neuroleptics, little is known; and (ii) for each atypical neuroleptic, a different answer should apply.

For clozapine, it is recommended to aim for a plasma level above 350 ng/mL for nonresponders and partial responders. It should be specified that this plasma level should be obtained exactly 12 h after the last dose. For risperidone, optimal dosages range between 4 and 8 mg/day, and there is no indication that a higher dose would bring additional improvement. For olanzapine, a quite different situation is encountered. There is good indication that dosages of 30 and 40 mg/day can increase clinical response. It appears that plasma levels above 23 ng/mL may predict response. For quetiapine, reports on the utility of dosages greater than 800 mg/day are anecdotal at this point, and more studies should be conducted. For ziprasidone, dosages above 40 mg/day should be used, but daily doses above 200 mg have not yet been systematically investigated. For aripiprazole, experience is very limited, but it seems that daily dosages of 10 or 15 mg are as effective as 30 mg. □

## REFERENCES

1. Krakowski MI, Kunz M, Czobor P, Volavka J. Long-term high-dose neuroleptic treatment: who gets it and why? *Hosp Community Psychiatry*. 1993;44:640-644.
2. Citrome L, Volavka J. Optimal dosing of atypical antipsychotics in adults: a review of the current evidence. *Harv Rev Psychiatr*. 2002;10:280-291.
3. Stahl S. Fiscal pharmacology of the atypical antipsychotics: getting the biggest bang out for the buck. Neuroscience Education Institute, University of California, San Diego, Calif; 2001.
4. Perry PJ, Miller DD, Arndt SV, Cadoret RJ. Clozapine and norclozapine plasma concentrations and clinical response of treatment-refractory schizophrenic patients. *Am J Psychiatry*. 1991;148:231-235.
5. Hasegawa M, Gutierrez-Esteinou R, Way L, Meltzer HY. Relationship between clinical efficacy and clozapine concentrations in plasma in schizophrenia: effect of smoking. *J Clin Psychopharmacol*. 1993;13:383-390.
6. Potkin SG, Bera R, Gulasekaram B, et al. Plasma clozapine concentrations predict clinical response in treatment-resistant schizophrenia. *J Clin Psychiatry*. 1994;55(suppl B):133-136.
7. Kronig MH, Munne RA, Szymanski S, et al. Plasma clozapine levels and clinical response for treatment refractory schizophrenic patients. *Am J Psychiatry*. 1995;152:179-182.
8. VanderZwaag C, McGee M, McEvoy JP, Freudenreich O, Wilson WH, Cooper TB. Response of patients with treatment-refractory schizophrenia to clozapine within three serum level ranges. *Am J Psychiatry*. 1996;153:1579-1584.
9. Spina E, Avenoso A, Facciola G, et al. Relationship between plasma concentrations of clozapine and norclozapine and therapeutic response in patients with schizophrenia resistant to conventional neuroleptics. *Psychopharmacology*. 2000;148:83-89.
10. Llorca PM, Lancon C, Disdier B, Fariße J, Sapin C, Auquier P. Effectiveness of clozapine in neuroleptic-resistant schizophrenia: clinical response and plasma concentrations. *J Psychiatry Neurosci*. 2002;27:30-37.
11. Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. *Am J Psychiatry*. 1994;151:825-835.
12. Peuskens J. Risperidone in the treatment of patients with chronic schizophrenia: a multi-national, multi-centre, double-blind, parallel-group study versus haloperidol. Risperidone Study Group. *Br J Psychiatry*. 1995;166:712-726.
13. Spina E, Avenoso A, Facciola G, et al. Relationship between plasma risperidone and 9-hydroxyrisperidone concentrations and clinical response in patients with schizophrenia. *Psychopharmacology*. 2001;153:238-243.
14. Beasley CM Jr, Tollefson G, Tran P, Satterlee W, Sanger T, Hamilton S. Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. *Neuropsychopharmacology*. 1996;14:111-123.

### Optimización de la dosis en monoterapia de neurolépticos atípicos

Los neurolépticos atípicos han llegado a ser el tratamiento de primera línea para los trastornos psicóticos, pero persisten algunas preguntas: ¿cuáles son sus dosis óptimas? y ¿la mayor cantidad de medicación es más eficaz? Para la clozapina se recomienda alcanzar un nivel plasmático por sobre los 350 ng/mL en los no respondedores o respondedores parciales. Se debe especificar que este nivel plasmático se debe obtener exactamente 12 horas después de la última dosis. Para la risperidona, el rango de dosis óptima es entre 4 mg y 8 mg y no hay indicación que una dosis mayor produzca una mejoría adicional. Para la olanzapina se ha encontrado una situación completamente diferente. Existe un buen fundamento para que dosis de 30 mg y 40 mg puedan aumentar la respuesta clínica. Al parecer los niveles plasmáticos por sobre 23 ng/mL pueden predecir la respuesta. Para la quetiapina los datos disponibles hasta el momento sobre la utilidad de dosis mayores a 800 mg/día son anecdóticos, y se requiere que se realicen más estudios. Para la ziprasidona se deben usar sobre 40 mg/día, pero dosis diarias sobre 200 mg no se han investigado sistemáticamente hasta la fecha.

### Optimisation de la posologie d'une monothérapie neuroleptique atypique

Les neuroleptiques atypiques sont devenus le traitement de choix des troubles psychotiques, mais quelques questions persistent : quelle est leur posologie optimale ? Une posologie supérieure est-elle plus efficace ? En ce qui concerne la clozapine, viser une concentration plasmatique au-dessus de 350 ng/ml est recommandé chez les non-répondeurs et les sujets partiellement répondeurs, en spécifiant que ces concentrations doivent être obtenues exactement 12 heures après la dernière dose. Pour la risperidone, les doses optimales se situent entre 4 et 8 mg/j, et rien n'indique qu'une posologie plus élevée apporterait une amélioration supplémentaire. On est confronté à une situation tout à fait différente avec l'olanzapine. Tout indique que des posologies entre 30 et 40 mg/j peuvent augmenter la réponse clinique. Il semble qu'on puisse prévoir une réponse avec des concentrations plasmatiques au-dessus de 23 ng/ml. Pour la quetiapine, l'utilité de doses supérieures à 800 mg/j n'est attestée que de façon anecdotique actuellement, et plus d'études sont nécessaires. Pour la ziprasidone, il faut utiliser des doses supérieures à 40 mg/j, mais des doses quotidiennes supérieures à 200 mg n'ont pas été encore systématiquement étudiées.

15. Volavka J, Czobor P, Sheitman B, et al. Clozapine, olanzapine, risperidone, and haloperidol in the treatment of patients with chronic schizophrenia and schizoaffective disorder. *Am J Psychiatry*. 2002;159:255-262.
16. Perry PJ, Lund BC, Sanger T, Beasley C. Olanzapine plasma concentrations and clinical response: acute phase results of the North American Olanzapine Trial. *J Clin Psychopharmacol*. 2001;21:14-20.
17. Kapur S, Zipursky R, Jones C, Shammi CS, Remington G, Seeman P. A positron emission tomography study of quetiapine in schizophrenia: a preliminary finding of an antipsychotic effect with only transiently high dopamine. D<sub>2</sub> receptor occupancy. *Arch Gen Psychiatry*. 2000;57:553-559.
18. Arvanitis LA, Miller BG. Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. *Biol Psychiatry*. 1997;42:233-246.
19. Small JG, Hirsch SR, Arvanitis LA, Miller BG, Link CG. Quetiapine in patients with schizophrenia: a high- and low-dose double-blind comparison with placebo. *Arch Gen Psychiatry*. 1997;54:549-557.
20. Keck P Jr, Buffenstein A, Ferguson J, et al. Ziprasidone 40 and 120 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 4-week placebo-controlled trial. *Psychopharmacology (Berl)*. 1998;140:173-184.
21. Daniel DG, Zimbroff DL, Potkin SG, Reeves KR, Harrigan EP, Lakshminarayanan M. Ziprasidone 80 mg/day and 160 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 6-week placebo-controlled trial. *Neuropsychopharmacology*. 1999;20:491-505.
22. Arato M, O'Connor R, Meltzer HY, on behalf of the ZEUS Study Group. A 1-year, double-blind, placebo-controlled trial of ziprasidone 40, 80 and 160 mg/day in chronic schizophrenia: the Ziprasidone Extended Use in Schizophrenia (ZEUS) study. *Int Clin Psychopharmacol*. 2002;17:207-215.