

## Choosing an Optimal Antipsychotic Dose for Relapse Prevention

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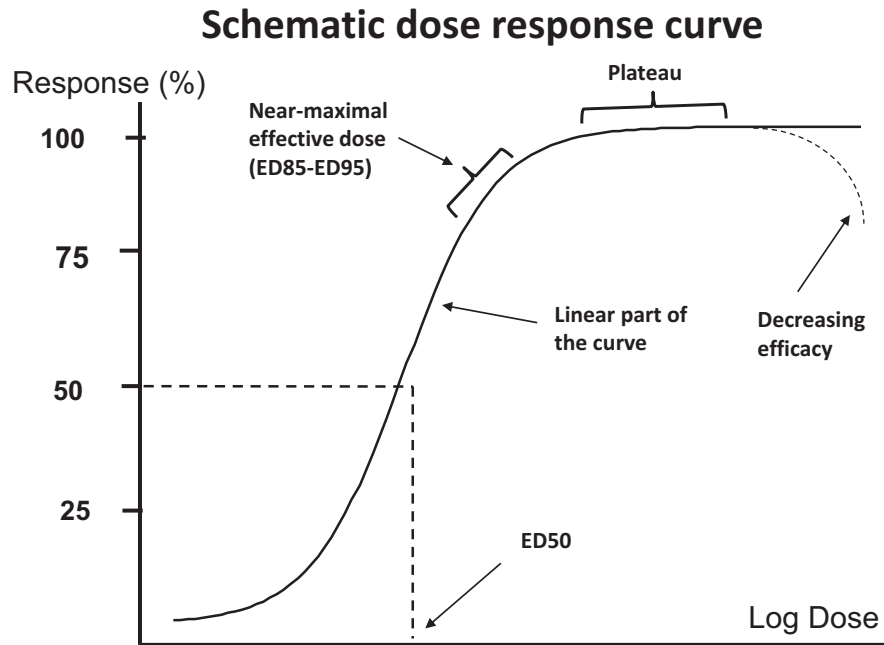
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Taipale et al.<sup>1</sup> (this issue) investigated optimal antipsychotic dose for the maintenance treatment of schizophrenia by linking the Hospital Discharge registry of Finland with the prescription register 1995 to 2017 from which they estimated dose for each prescribing period classified in the WHO Defined Daily Dose (DDD) categories <0.6, 0.6–0.9, 0.9–1.1, 1.1–1.4, 1.4–1.6, ≥1.6. The DDD was developed as a tool for drug utilization research that reflects common doses used to treat schizophrenia with 1 DDD unit being an average dose (eg, 10 mg olanzapine is 1 DDD unit, 0.6 DDD is 6 mg, 1.6 DDD is 16 mg). The DDD corresponds approximately to efficacious doses found in short-term trials of schizophrenia.<sup>2</sup> The analysis estimates the rate of relapse (using within-subject Cox regression) occurring at the various doses in DDD units. Relapse was defined as rehospitalization. Each analysis was restricted to patients who received just monotherapy with one of the 15 antipsychotics and had several relapses preceded by different maintenance doses. Compared to nonuse of antipsychotics within the same individual, 13 of the 15 antipsychotics investigated showed a U- or J-shaped dose–response curve usually with the best prevention of relapse at 0.9–1.1 DDD. The lowest preventive effect was seen at the highest dose (1.6 DDD or greater). An increase in relapses was also seen with the lowest dose (less than 0.6 DDD units) for some drugs.

In a companion study, the Tiihonen group<sup>3</sup> applied the same DDD categories for all antipsychotics as a class providing a more comprehensive dose analysis because patients could be on monotherapy with different antipsychotics at different times or the same time (polypharmacy). The researchers analyzed data starting from the first episode of schizophrenia and followed up for about 5 years. Forty-three percent of patients did not have a relapse and 57% had one or more relapses. The dose prescribed to those who relapsed was increased both

over time and in those with more relapses. Compared to nonuse of antipsychotics, virtually all doses prevented relapses. The U-shaped dose–response curve was observed for individuals with 1 or 2 relapses, and there was a poor relapse preventative effect with doses of less than 0.6 DDD, best preventive effect at doses of 0.9–1.1 DDD, a fair preventative effect with doses from that to 1.4–1.6 DDD units, but a very poor preventative effect at 2.4 or more DDD units. Those with 3 or more relapses had the best preventative effects at 1.4–1.6 DDD units, the next best with 0.9–1.1 DDD units, fair preventive effects up till 2.4 DDD units, but poor effect at doses 2.4 DDD or greater.

These results should be considered with the general pharmacology principle that most drugs have a sigmoidal dose–response curve where there is a linear portion where the magnitude of response is proportional to the log dose (see [figure 1](#)) but the dose–response becomes a horizontal line at both ends indicating a plateauing of drug response. The drug response increases proportionally with increasing dose to a threshold (ED85–95), after which the response gradually diminishes though side effect may continue to increase. Davis and Chen,<sup>3</sup> Leucht et al.<sup>2,4,5</sup> have examined the dose–response curves of antipsychotics used for acute treatment and for maintenance finding they follow the sigmoidal dose–response curve. In our opinion, the best data to dose comes from the double-blind randomized control trial (RCT) where patients are assigned randomly to different doses. Randomization and blinding prevent both known and unknown biases. RCTs have shown that efficacy plateaus for almost all drugs, and there was no tendency for high doses to yield lower efficacy although higher doses would be associated with excessive side effects. But there are only a few papers that study different doses, especially for a study period of longer than one year. Of those that exist, all are done



In this schematic dose-response curve response to treatment is plotted versus log of the dose administered. On the log-linear portion (x), a log unit increase in dose corresponds to a linear unit increase in response. As the curve approaches maximum efficacy, the curve asymptotes, approaches a plateau, and flattens out. Here, an incremental increase in log dose corresponds to a progressively small increase in clinical response until it essentially merges with the plateau. We call this region “plateau.” The near-maximal dose range is roughly the ED85–ED95, where the curve is beginning to flatten out. The ED50 is the dose where 50% of the maximum efficacy is obtained. The dotted line presents a bell-shaped curve where high doses lead to decreasing efficacy (modified from Davis and Chen 2004)

**Figure 1.** In this schematic dose–response curve, response to treatment is plotted versus log of the dose administered. On the log-linear portion (x), a log unit increase in dose corresponds to a linear unit increase in response. As the curve approaches maximum efficacy, the curve asymptotes, approaches a plateau, and flattens out. Here, an incremental increase in log dose corresponds to a progressively small increase in clinical response until it essentially merges with the plateau. We call this region “plateau.” The near-maximal dose range is roughly the ED85–ED95, where the curve is beginning to flatten out. The ED50 is the dose where 50% of the maximum efficacy is obtained. The dotted line presents a bell-shaped curve where high doses lead to decreasing efficacy (modified from Davis and Chen<sup>4</sup>).

on cooperative volunteers. Observational studies provide data on what occurred long term, in the real world and in noncompliant individuals. However, both known and unknown biases can influence observational studies. One cannot infer causation from an observational study. Showing “A is correlated with B” does not differentiate whether “A causes B,” “B causes A,” “both A and B cause each other,” or “both A and B are caused by something else.” The within-subject design uses the same subject on different doses at different times so that many variables associated with that subject such as genetics, or the initial severity of illness are held constant. It would be reasonable to assume that if the patient is becoming increasingly unstable, the clinician would increase the dose, or the clinician might try a higher dose after a relapse to prevent the next episode. The patient’s worsening state might be the reason for a high dose causing the poor drug response and not the higher dose itself. It is important not to draw conclusions from observational studies as if they were randomized studies because observational studies are prone to bias. It would be reasonable to assume that a clinician might have reduced the dose to a very low dose in individuals t doing well, but the fact that more relapses

occurred overrides this bias and suggests that a low dose might really be too low. It was once thought that the maintenance dose should be much lower than the acute treatment dose. Leucht et al.<sup>5</sup> examined the controlled trials of maintenance medication and found the dose–response curves were roughly comparable to the dose–response curves of acute treatment. The Correll group<sup>6</sup> did a meta-analysis, finding that a standard dose produced a better reduction of the relapse rate than that of low doses. There is a good agreement between these meta-analysis of RCTs<sup>5,6</sup> and the observational studies<sup>1,3</sup> that substantially lower than acute treatment doses are less effective.

The random assignment trials show the dose–response curve plateaus, and high doses do not increase efficacy. These observation studies<sup>1,3</sup> suggest that ultra-high doses have considerably less preventive efficacy (i.e., not plateauing). Our speculation of explaining this contradiction is due to high doses being given to unstable patients in the observational studies. An exception may be Risperidone which was found to be less efficacious at high doses in several controlled studies.<sup>4</sup> Both random assignment studies and the observational studies show that ultra-high doses do not increase efficacy and should be avoided. Since

individuals with schizophrenia differ in body size, drug metabolism, fluctuations in the illness, and possible sensitivity to drugs, it would be reasonable to expect that the optimal dose may differ from person to person, and some individual might need a slightly higher or lower than usual dose. For almost all drugs, there was a wide range of doses that show roughly similar efficacy and clearly better efficacy than for those at too low or too high dosage end. There were some interesting exceptions that DDD of 0.9–1.1 produced best efficacy. Depot Olanzapine produced its best efficacy at 1.4–1.6 DDD units, and doses lower than 1.1 DDD yielded very poor efficacy. This is consistent with the randomized study, showed that it has not plateaued at the high dose used (300 mg biweekly).<sup>5</sup> Perphenazine showed best efficacy at the lowest dose (less than 0.6 mg DDD or 18 mg) and much worse efficacy at most doses, ie at the 0.9–1.1 DDD or above. (The Perphenazine dose used in CATIE was 20.8 mg/day.) Based on these findings, the authors<sup>1</sup> suggest that some DDD should be revised. We agree. We recommend considering the finding of the primary randomized dose–response RCTs, and meta-analysis of them as well as these 2 observational studies for selection of dose. There is good consensus that high doses are not more efficacious than medium doses and should be avoided.

What should be done when some patients become unstable or have frequent relapses? Since inappropriate dosing can substantially influence drug efficacy, comparison of drug efficacy should only compare doses in the more efficacious range. The Tiihonen group<sup>1</sup> in their Table 1 list the drug and dose combinations which are most efficacious at preventing relapse. As a crude approximation, we average the mean HR of the 3 most efficacious doses, finding the drugs which best prevented relapse were the

following: olanzapine LAI, clozapine, risperidone LAI. All the other 3 LAIs, and oral olanzapine, had an average HR of 0.40. The other oral drugs had an average HR of 0.67. Since depot drugs are used frequently in patients who have frequent relapses and suspected of non-compliance and clozapine is used for treatment-resistant patients, the favorable results observed occur despite the likely bias. These suggest that when a patient seems unstable or has had frequent relapses, the clinician should avoid ultra-high doses and consider switching to an LAI or to a different oral medication such as clozapine.

## References

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