

Dose Response and Dose Equivalence of Antipsychotics

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Abstract: We review evidence from randomized, placebo-controlled studies of patients with schizophrenia or schizoaffective disorder, which compared 2 or more doses of an antipsychotic to calculate the dose-response curve for each first-generation (typical) antipsychotic (FGA) or second-generation (atypical) antipsychotic (SGA) and as a group (based on dose equivalence). We identified the near-maximal effective dose (ED; ie, the threshold dose necessary to produce all or almost all the clinical responses for each drug).

In randomized, fixed-dose studies of SGAs, the near-maximal efficacy dose for olanzapine may be greater than 16 mg; for risperidone, it is 4 mg; and for ziprasidone, it is 120 mg. Risperidone at 2 mg daily is 50% less efficacious than higher doses. Olanzapine at about 6 mg is approximately 33% less effective than higher doses. Aripiprazole at 10 mg daily was fully efficacious. Doses of clozapine well above 400 mg are necessary for optimal treatment of many schizophrenia patients. We found 3.3 to 10 mg haloperidol to be the near-maximal ED range. We find no evidence that doses higher than these are more effective. We failed to find that high doses of haloperidol (or all other first-generation comparison drugs converted to equivalent doses) were less effective than medium doses (3.3 to 10 mg). While high-dose FGAs are not less effective, we feel it is important not to avoid using high dose to avoid excessive toxicity.

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Although chlorpromazine antipsychotic properties were discovered 50 years ago, the dose-response curve for most antipsychotics has yet to be determined. Because most antipsychotics cause serious and uncomfortable side effects, produce only partial remission in most patients, and have a somewhat unclear end point, determining the dose range to produce a near-maximal response with minimal side effects is clinically important. Previously, Davis¹ constructed an empirically-based antipsychotic drug equivalency report based

on double-blind, random-assignment studies which found the dose of 2 drugs equally efficacious. This was replicated by Wyatt and Torgow.² However, these studies used flexible doses and overestimated the near-maximal effective doses (EDs) to varying degrees. Most dose guidelines have been compiled using clinical impression and have differed from each other and over time.^{3–14} These differences are large enough to be clinically significant (often 2-fold to 3-fold and sometimes more). At one time, very high-loading “industrial strength” doses were widely promoted in the United States to treat exacerbated schizophrenia.^{15–19} The dosage question has rarely been addressed, although there was a seminal review in 1988 by Baldessarini et al²⁰ and one meta-analysis conducted 9 years ago by Bollini et al,²¹ restricted to maintenance medication. In this article, (a) we challenge the concept of dose equivalence as inaccurate, as it ignores the dose-response curves, but is accepted in current practice and guidelines; (b) we devise a new method to estimate dose-response curves for first-generation antipsychotics (FGAs) and use this to recalculate dose equivalency; (c) using results from our meta-analysis, we calculate dose-response curves based on randomized, double-blind studies of different doses of both FGAs and second-generation antipsychotics (SGAs); and (d) we test the hypothesis that exceedingly high doses of FGAs are less efficacious than medium doses (the concept of the therapeutic window). We critique the concept of dose equivalency and also include additional methodology, tables, a substantial amount of statistical as well as graphical data (such as many Forrest plots, discussions, and sensitivity analyses) in greater detail on our website (herein referred to as Web): http://www.psych.uic.edu/faculty/davis/dose_response.pdf. One of our goals is to amass the dose-response data in one location, so as to provide easy availability.

The Concept of the Dose-Response Curve

The dose-response curve is a plot of the response on the y-axis versus the log dose on the x-axis (see Fig. 1A or Fig. 1B chlorpromazine). The sigmoidal curve shows a minimal response at low doses, followed by a log-linear region with the steepest slope where an increase of log dose produces a proportionally linear increase in response, with the curve approaching an asymptote in a plateau at the upper flatter portion. On the plateau portion of the curve, with each

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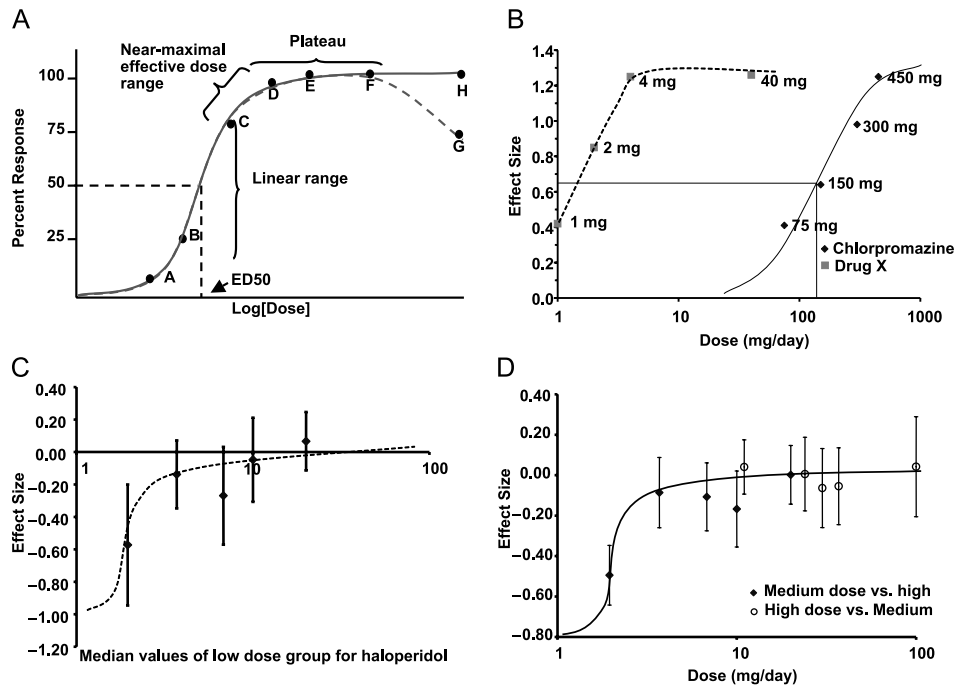


FIGURE 1. A, A schematic dose-response curve showing response versus log of the dose administered. On the log-linear portion, a log unit increase in dose corresponds with a linear unit increase in clinical response. As the curve approaches maximum efficacy, the curve asymptotes, approaching a plateau, 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 label this region "plateau." The near-maximal dose range is roughly the ED_{85} – ED_{95} , where the curve is beginning to flatten out. B, Dose-response curves of chlorpromazine and a hypothetical drug X. We plot the log-linear dose-effect studies of chlorpromazine from the multiple fixed-dose studies. The curve to the left represents a dose-response curve of a hypothetical drug X. Note that both 4 and 40 mg drug X are on the flat part of the dose-response curve, and 4 mg is in the near-maximal effect dose range. If the 40-mg dose was interpreted as the near-maximal ED and the clinical trials were carried out at this dose, this would be used in calculation of the dose equivalence, which would be a 1 to 10 conversion (40 mg drug X to approximately 400 mg of chlorpromazine). Actually, the equivalent conversion based on ED_{50} is about 1 to 100. C, Haloperidol dose-response curve. We use the method of successive approximations to calculate this figure. We averaged all studies within a given dose range with each study's effect size entered. We compared these as a deviation from reference point as described in "METHODS." We calculate the dose-response curve for the various doses (1–3.2, 3.3–4.0, 4.1–8.0, 8.1–12.0, >12 mg/d) using the high dose in each study as a reference point. The slight increase in response at 3.3 to 4 is likely due to a first-episode study. (These patients respond to slightly lower doses.) But note that the other studies in the range were on typical multiple-episode patients. We also performed a meta-analysis with log-dose as a continuous variable for all studies with doses above the near-maximal effective range of 3.3 to 10 mg. The slope of the log-dose versus response relationship is equal to zero and is not significantly different from zero ($P =$ not significant). D, Dose-response curve of all drugs using haloperidol equivalent doses. Patients were randomized to 2 doses—one higher than the other. We initially used the high dose as a standard, based on a preliminary examination of the data. We grouped similar doses together and compared the lower dose of the pair with this benchmark. We then conducted a meta-analysis on this group to calculated mean and 95% confidence intervals (solid diamonds) of the different dose groups compared with our benchmark. Here, all studies were included, and we find the log-linear portion of the dose-response curve at haloperidol equivalent doses of about 1 to 3 mg/d. The focus of this was to find just how low a dose was less effective than the maximal effective plateau dose. The raw data for each individual study are presented in Web Table 3. Next, we focused on the opposite question: could a very high dose differ (better, equal, or worse) from a medium dose? If this were so, how high a dose would be needed to produce a different response? Here, we used dose grouping of the higher dose of the pair (open circles), using as a reference point only those studies whose lower dose was on or higher than the near-maximal dose. Alternate groupings for sensitivity analysis are presented on our supplement (Web Figs. 12 and 13, and Web Table 3). As a further test, we did a meta-regression. We also calculated the slope of near-maximal and plateau dose range as continuous data with the low dose of each individual study being entered (rather than dose grouping). The slope of the log-dose versus response relationship is equal to zero and is not significantly different from zero. When the doses are under 3.3 mg/d, the differences from maximal dose are massive and highly significant. Above this, all studies show all doses to have about equal efficacy. We examined this by several different methods, and all methods agree. We feel that the burden of proof for those who argue that high doses are less effective is to produce evidence that this is the case. We could not find such evidence.

increase in dose, the increase in response becomes less and less. Basic science experiments can be conducted at the median effective dose (ED_{50}), where most psychotropic drugs only partially alleviate the disease and where psychiatrists should titrate the dose toward the greatest effect possible without producing unnecessary side effects. There is an uncertainty principle inherent in clinical dose-response curves, due to this diminishing increment of response, and a consequent lack of statistical power to detect small differences in efficacy and to measure them accurately.

Part A: The Concept of Dose Equivalence: Discussion and Critique

Problem of Slow Onset of Action and of Indistinct End Point

An antipsychotic medication rarely restores patients to complete normality but rather reduces schizophrenic or psychotic symptoms. The residual symptoms vary from patient to patient. There is no firm benchmark that signals when a patient has reached maximal improvement. Patients show gradual improvement over several weeks of treatment.^{22,23} Often, the clinician increases the dose and/or adds other augmenting drugs, although there has not been time for that dose to produce its maximum efficacy. Because most patients do not recover completely, clinicians tend to increase the dose in the hope of achieving a better response. Both factors result in a net effect of overshooting and therefore cause an overestimate of the near-maximal ED. Consequently, flexible-dose studies have provided inaccurate evidence for establishing optimal dosages (see Web: *Further discussion of indistinct end point and assumption that all antipsychotics are equally efficacious*).

Critique of Dose Equivalence

Most antipsychotic drugs have been studied at high doses, far along the plateau portion (such as point E on Fig. 1A) of the dose-response curve, but some drugs have been studied near the log-linear portion. As an illustration, assume that 400 mg of chlorpromazine is the near-maximal ED and suppose the manufacturer of high-potency drug X promoted high doses [perhaps 40 mg/d ($ED_{99.999}$; Fig. 1B)]. If both drugs showed similar clinical outcome or efficacy, one could falsely conclude that the 40-mg dose of the high-potency drug X is the equivalent of 400 mg of chlorpromazine (a dose equivalence of 1:10). If, in fact, 4 mg is the near-maximal ED of drug X (ie, the ED_{95}), such a dose would also be equivalent to chlorpromazine (a dose ratio of 1:100). The dose ratio of the 2 drugs (ie, how many milligrams of one are equivalent to the milligrams of the other) would be grossly inaccurate. The Schizophrenia Patient Outcomes Research Team guidelines provide an example in

its dose equivalency table for fluphenazine decanoate and haloperidol decanoate.¹⁰ This table assumes that the dose-response relationship is strictly linear-linear with no plateau. The implicit concept of this and all guidelines is to make a linear interpolation (a simple proportion), which ignores the fact that the dose-response curve plateaus.

Insofar as an SGA may be more efficacious than an FGA, the term equivalent dose is ambiguous, because it has 2 contradictory definitions. Specifically, first, the fully ED of chlorpromazine is about 400 mg and of haloperidol is about 5 to 10 mg. If the SGA was more effective than FGA, then which dose is the equivalent dose to this? Is it that SGA dose which is equal in efficacy to the FGA dose, which is 2 mg risperidone? Second, the equivalent dose can be taken to mean the near-maximal ED range of both SGA and FGA (ie, the ED_{95} of risperidone is 4 mg/d and the ED_{95} of chlorpromazine is 400 mg/d). Here, these doses are not equally efficacious, but they are at the drugs' ED_{95} . In other words, when drugs have unequal efficacy, then the equivalent dose could be the ED_{95} of both or the low dose of the more effective drugs, which matches the fully ED of the other.

Part B: Dose-Response Meta-analysis

We have defined the region where the log-linear dose-response transitions to a diminishing region, the "near-maximal ED range" or the " ED_{85} to ED_{95} ," a shorthand for the lowest dose range that is sufficient to produce an almost full clinical response. Because exceedingly high doses will cause unnecessary side effects, it is important to use the lowest fully ED to minimize side effects. This transition region is not a distinct inflection point (see Web: *Concept of near-maximal effective dose*). As the dose-response curve approaches a plateau asymptotically, the efficacy difference between this dose and a much higher dose decreases, and hence, a very large sample size would be needed to measure a significant difference.

The aims of the study are as follows:

1. We identified all randomized, double-blind studies of FGA and SGA drugs, plotted their dose-response curves, and estimated the ED_{50} and the near-maximal ED range (ED_{85} to ED_{95}) for each drug.
2. We next estimated the dose equivalencies based on ED_{50} calculated in (1).
3. We performed a meta-analysis to evaluate whether medium and high doses differ in efficacy. Many clinicians use high doses (or combine similar antipsychotics which functionally produce a high dose). Others postulate a therapeutic window where a high dose may produce a worse response. Geddes et al⁵ stated that doses above 12 mg/d of haloperidol equivalent produce less efficacy than 6- to 12-mg/d doses. Geddes et al use this to argue that the observed benefit of clozapine and other SGA

drugs is really an artifact of overly high doses of FGA used as comparison drugs in trials.

4. One purpose of this review is to present a quantitative summary of the principal studies so that the reader can visually inspect the data and make informed decisions. The raw data are visually depicted in graphs, which can be atheoretically inspected.

METHODS

Selection and Study Characteristics

We used all random-assignment (to at least 2 different doses), double-blind, controlled, clinical trials of schizophrenia or schizoaffective patients of FGAs and of 9 SGAs (amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, remoxipride, risperidone, sertindole, and ziprasidone) with no restriction on publication date, language (we translated to English), or sample size (N). This approach has the protection of randomization, in contrast to meta-regression, which is a correlational technique. We performed sensitivity analyses to explore the possibility of other biases (see Web: *Studies not included*).

Search Strategy

The following databases were searched for relevant articles: Medline (January 1966 to December 2002), International Pharmaceutical Abstracts (1970 to December 2002), CINAHL (1982 to December 2002), PsychINFO (1887 to December 2002), and the Cochrane Database of Systematic Reviews (issue 3, 2002). We also searched reference lists in relevant journal articles. Both the Quality of Reporting of Meta-Analyses (QUOROM) statement²⁴ and the empirical study by McAuley et al²⁵ indicate that exclusion of unpublished studies produces a systematic positive bias, so we included Food and Drug Administration website data obtained through the Freedom of Information Act, poster presentations, unpublished data from Cochrane reviews, such as those from Waraich et al²⁶ and Kennedy et al,²⁷ conference abstracts, and manuscripts submitted for publication.

Principal Outcome

As our principal outcome variable, we used the Positive and Negative Syndrome Scale (PANSS).²⁸ When the PANSS was not available, the Brief Psychiatric Rating Scale²⁹ was used, or, when neither was available, the Clinical Global Rating was used. Change scores that were adjusted for baseline (analysis of covariance) were preferred; when not available, the raw change scores (baseline minus end-point score) were used; when both were unavailable, the unadjusted end-point score was used. Time to relapse and number of relapses were used for maintenance studies. Effect sizes were computed from the outcome variable by dividing the improvement score of the high dose minus that of

the lower dose by their pooled standard deviation. There are basically 2 types of treatment trials for antipsychotics: (1) treatment to improve symptoms of patients in an acute episode or (2) treatment to elicit a better response in non-responder maintenance or prophylactic treatment of at least partially recovered patients to prevent a relapse.

Data Extraction

Data extraction of the means, Ns, and SD data of all studies were independently carried out by 2 reviewers. The last-observation-carried-forward method and intent-to-treat sample were used for the meta-analysis.

Validity Assessment

We performed sensitivity analyses and explored the effects of different dosages, different grouping by dose, study quality, design, completeness, outcome variable type, and publication type.

Quantitative Data Synthesis

Meta-analyses were executed using Comprehensive Meta-Analysis (1.0.25)³⁰ and MetaWin.³¹ We used fixed-effects models, except when significant heterogeneity dictated the use of random-effects models, to evaluate hypotheses such as the therapeutic window hypothesis and to calculate error bars around points on dose-response curves. (Significant heterogeneity implies that effect sizes between studies differ more than expected by chance.) (See Web for results on both models.)

Construction of Dose-Response Curve

We constructed dose-response curves from fixed-dose, double-blind studies with random assignment to different doses. Placebo-controlled studies were useful, because if a given dose is not better than placebo, it is likely that this dose is near-placebo efficacy. Most dose-response data for FGAs include only 2 doses and no placebo. We initially determined that when the dose-response curve begins to plateau, this relatively flat portion provides a benchmark on which to compare other doses. Knowing this, we determined the location of specific doses on the dose-response curve as follows. If dose C is better than dose B (Fig. 1A), it is on the linear portion. If dose C is equal to dose D in efficacy, it is on the plateau. For the analysis of FGAs, we use an iterative successive approximation method. We began by comparing a very, very low dose range with a high-dose benchmark and then successively compared a very low dose, a low dose, and a medium dose, respectively, with this high-dose benchmark (see chlorpromazine Fig. 1B, results for a working example). We can plot the dose-response curve as a decrease (ie, a negative number) in effect size units under the efficacy produced by maximal EDs (see Web: *Concept of near-maximal effective dose*). Because intramuscular (IM) haloperidol is approximately twice as bioavailable as oral administration,

we multiplied IM doses by 2 in our dose-equivalence meta-analysis.³²

Construction of Haloperidol Dose Equivalent and Test of Therapeutic Window Hypothesis

Based on our dose-response analysis, we have calculated new dose-equivalence tables at ED₅₀ or ED₈₅ to ED₉₅. Using these newly constructed ED₅₀, we constructed pooled dose-response curves for FGAs using haloperidol equivalent doses. We also tested whether very high doses are more, equally, or less effective than medium doses (the latter is the therapeutic window or Geddes et al hypothesis).

RESULTS

Dose-Response of FGAs

Chlorpromazine

The plot of controlled studies of 75, 150, or 300 mg/d chlorpromazine suggests that these doses are on the log-linear portion of the dose-response curve, and estimates that the ED₅₀ for chlorpromazine is approximately 150 mg/d (Fig. 1B).³³⁻³⁵ There were 4 studies with medium doses between 300 and 388 mg/d, which were compared with a higher benchmark (500 mg/d or greater). We found the pooled difference of these 4 studies (300³⁴⁻³⁶ to 388 mg³⁷) to be -0.27 [(-0.45, -0.09), *P* = 0.004] effect size units lower than the plateau portion. The negative effect sign indicates that the dose of interest is less efficacious than plateau. Controlled dose-response studies in the range of 450 to 600 mg/d showed that these doses were equivalent to the plateau dose range [effect size = 0.00 (-0.29, 0.29)], that is, the near-maximal ED range (Table 2).³⁸⁻⁴⁰ The randomized, double-blind, fixed-dose studies of chlorpromazine versus placebo support these findings. Specifically, we found that chlorpromazine failed to be more effective than placebo at 300 mg/d or less (Table 1).²² At 300 to 400 mg/d chlor-

promazine, equivocal evidence for efficacy was found,²² but chlorpromazine doses of 500 mg or greater were consistently found to be more effective than placebo.²²

High-Potency FGA Dose-Response Curve

Haloperidol

We established that the haloperidol dose range of 1 to 3.2 mg/d was clearly less effective than the plateau doses [effect size, -0.57 (-0.95, -0.20,)] (the “-” sign indicates that dose of interest is less effective than plateau doses) on the log-linear portion of the dose-response curve (Fig. 1C).⁴¹⁻⁴³ We next examined the dose range of 3.3 to 4.0 mg/d and found no difference between this dose range and the plateau doses [effect size, -0.14 (-0.35, 0.07)],⁴⁴⁻⁴⁷ thus establishing that 3.3 to 4.0 mg/d haloperidol is in the near-maximal ED range and near the plateau portion of the haloperidol dose-response curve. Haloperidol dose ranges of >4.0 to 8.0 mg/d showed similar results [effect size, -0.27 (-0.57, 0.03)].^{42,48-51} Note that this nonsignificant effect size is larger (more negative) than the effect size observed in the 3.3- to 4.0-mg/d range (Fig. 1C), possibly because 1 of the 4 studies⁴⁵ in the 3.3 to 4.0 group included many first-admission patients who responded to a lower dose. The other 3 studies are typical multiepisode patients. The dose-response curve plateaus at >8.0 to 12 mg/d [effect size, 0.05 (-0.21, 0.31), or over 12 mg/d is essentially zero].^{42,46,52-55} As the linear portion transitions to the plateau portion, we expect the transition to be gradual. (Note the statistical uncertainty inherent in measuring small differences) (see Web: *Power considerations in the construction of dose-response curves and Adjustment of near-maximal ED for dose-response curve of haloperidol*). Due to this uncertainty, we do not feel that any dose should be considered as the threshold dose for full response, but rather that the region of the dose-response curve that is near the near-maximal efficacy is roughly 3.3 to 10 mg/d. As there are very few

TABLE 1. Clinical Effectiveness of Chlorpromazine Compared With Placebo in Controlled Studies by Dose of Chlorpromazine*

Chlorpromazine Dose Range (mg/d)	No. Studies		
	Chlorpromazine More Effective Than Placebo	Chlorpromazine Slightly More Effective Than Placebo	Chlorpromazine Equal to Placebo
≤300	10	6	9
>300-400	4	3	1
>400-500	4	0	1
>500-800	14	0	0
>800	9	0	0
Total	41	9	11

Adapted from Table 2 of Ref. 22.

*Global judgment of authors based on review of individual studies (“more effective,” clearly, significantly better; “slightly more effective,” equivocal, nonsignificant trends; and “equal,” clearly nonsignificant).

TABLE 2. The ED₅₀ and Near-maximal Effective Dose for FGAs and SGAs

Drug	ED ₅₀	Near-maximal Effective Dose
FGAs		
Chlorpromazine	150 mg/d	400–450 mg/d
Haloperidol	0.5–2 mg/d	3.5–10 mg/d
Haloperidol decanoate	25 mg/mo	100–200 mg/mo
Trifluoperazine	—	10–15 mg/d
Thiothixene	—	<10 mg/d
Fluphenazine	—	<6.9 mg/d
Fluphenazine decanoate/enanthate	—	25 mg/2 wk
SGAs		
Olanzapine	9 mg/d	>16 mg/d
Olanzapine IM	>6 mg/d	>10 mg/injection
Risperidone	2 mg/d	4 mg/d
Risperidone depot	15 mg/mo	50 mg/mo
Amisulpride	50 mg/d	200 mg/d
Aripiprazole	<1.5 mg/d	10 mg/d
Quetiapine	80–215 mg/d	150–600 mg/d
Remoxipride	60 mg/d	120–240 mg/d
Sertindole	10 mg/d	12–20 mg/d
Clozapine	—	>400 mg/d
Ziprasidone, acute	63 mg/d	120–160 mg/d
Ziprasidone, maintenance	40 mg/d	80–160 mg/d

small sample studies in the 0.5- to 3-mg/d dose range, we can only approximate the ED₅₀ dose range of 0.5–2 mg/d haloperidol (Table 2).

Other High-Potency Typical

- 1. Trifluoperazine:** A large sample, well-controlled study of trifluoperazine found that 15 mg/d was as effective as a high dose (a small 10-mg/d study yielded similar results), suggesting that this dose range is on the plateau portion of the dose-response curve [effect size, 0.01 (–0.23, 0.26)].^{56,57}
- 2. Thiothixene:** One small study of thiothixene suggests that 10 mg of thiothixene is on (or near) the plateau portion of the dose-response curve.⁵⁸
- 3. Fluphenazine:** Four small studies probed the near-maximal ED range of acute oral fluphenazine with a dose range of 5.0 to 7.5 mg/d,^{59–63} with one study administering 10 mg/d.⁶⁴ Many flexible-dose studies found 6- to 10-mg/d range to be equal to medium and to high dose of other FGAs.^{65–70} (For further discussion, see Web: *Adjustment of near-maximal effective dose for dose-response curve of haloperidol, fluphenazine, thiothixene, and trifluoperazine*).

Haloperidol and Fluphenazine Decanoate Maintenance Dose-Response Curves

In a single study using haloperidol decanoate, monthly doses of 25, 50, 100, and 200 mg were observed to be on the log-linear portion of the dose-response curve (Fig. 2J).⁴⁸ A number of low-dose fluphenazine decanoate studies^{71–77} found more relapses in those low-dosage groups in which doses substantially less than half of the usual dose of 25 mg/2 weeks were used.

Pooled Dose-Response Curve

We calculated a pooled dose-response curve using our new method based on double-blind randomized studies, which is almost completely free of the flexible-dose bias. We present in Figure 1D the dose-response curve for pooled FGAs in haloperidol equivalents. Haloperidol equivalent doses of 0.1 to approximately 2.8 mg/d are on the linear portion of the dose-response curve, and plateau occurs at the near-maximal ED range of about 3.3 to 8.0 mg/d or 8.0 to 12.0 mg/d. High doses (>12.0 mg/d) are clearly on the plateau portion of the dose-response curve. We estimate the near-maximal ED range to be 3.3 to 10 mg haloperidol equivalents. Sensitivity analyses based on several alternate assumptions found identical results (see Web: *Sensitivity analysis*).

Are High Doses More Effective, Equally Effective, or Less Effective (Therapeutic Window) Than the Medium Dose?

Many clinicians use high doses. The therapeutic window hypothesis suggests that an exceedingly high dose of an FGA produces a less efficacious response point. Indeed, Geddes et al⁵ suggest that the most effective haloperidol dose is 6 to 12 mg/d, and higher doses are substantially less effective. A straightforward test of this hypothesis is to examine all randomized, blinded dose comparisons of this dose range [≥ 6 mg/d (median, 10.7 mg/d) or 6 to 12 mg/d] against all higher doses [>12 mg/d (median dose 64 mg/d)] (see Tables 3 and 4 which give the limits and median dose in both dose groups). Forty-two such studies (N = 1821 patients)^{42,46–48,51–56,58–62,78–101} showed no significant difference between medium-dose (median, 10.7 mg/d) versus high-dose (median, 40 mg/d) groups [effect size = –0.06 (–0.15, 0.04); Table 3]. The “–” sign indicates that the medium dose is less effective (nonsignificantly) than the high dose, the opposite of the Geddes et al’s or therapeutic window hypothesis. Doses are under experimental control in that patients were randomized to medium versus high doses. Because it is clearly possible that this definition of high dose may be slightly off (ie, the Geddes et al cutoff point may not have been the optimal dose), we examined a variety of different definitions of medium and/or high dose in our

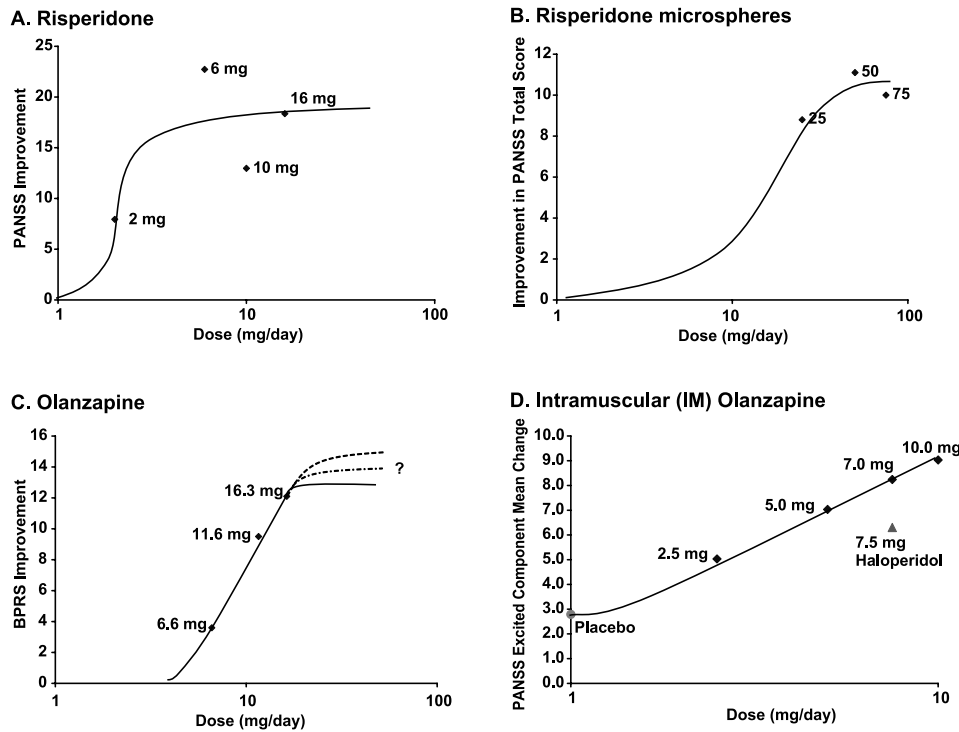


FIGURE 2. A, Risperidone dose-response curve. The dose-response curve is based on the combined US and Canadian registrational study of risperidone where patients were randomly assigned to placebo, 2, 6, 10, and 16 mg/d risperidone. The 2-mg dose produced half the improvement as the average improvement of the plateau phase, as measured by the average improvement of 6, 10, and 16 mg combined. In this and all graphs, the symbols indicate raw data points and the reader should focus on this. B, Risperidone microspheres. We present the dose-response curve from the large registrational study of depot risperidone microspheres. C, Olanzapine dose-response curve. A roughly log-linear dose-response relationship is observed. Note the similarity of the dose-response curve in the 6-week oral study studies to the 1-day study. An additional study compared placebo, 1-mg, and 10-mg doses; and the efficacy of the 1-mg dose is very close to that of placebo and does not show efficacy. D, IM olanzapine dose-response curve. Note that the dose-response curve for IM olanzapine at a few hours after injection is similar to the dose-response curve after 6 weeks of oral treatment. The outcome variable is on the impulsivity-hostility factor. This consists of the following PANSS items: poor impulse control, hostility, uncooperativeness, excitement, and tension; all symptoms that are observable are not dependent on a lucid patient's ability to provide a coherent description of hallucinations or delusions. IM olanzapine peaks in plasma at around 30 minutes, but the clinical effect increases over time, until about 90 minutes when it begins to plateau. The 90-minute observation period probably represents the peak therapeutic effect of the injection and therefore the most valid end point in our opinion. A roughly linear dose-response relationship is observed, although differences between doses close to each other are not statistically significant. [(C); Web: *Acute 2- to 24-hour dose-response curve for olanzapine and ziprasidone—single dose intramuscular emergency treatment*].^{109,110} E, Aripiprazole dose-response curve. Most doses of aripiprazole seem to be on the plateau portion of the dose-response curve, and 2 mg/d was close to the plateau. If the 2-mg dose was actually on the plateau, then the linear portion of aripiprazole may be undefined, and it is possible that all the investigational studies missed the log-linear portion. F, Amisulpride dose-response curve. Although the efficacy of 100 mg/d of amisulpride is slightly less than the higher doses, it still produces a substantial rate of improvement in response. Because amisulpride causes dose-related extrapyramidal symptoms, although considerably less than typicals, it is clinically important to appreciate its dose-response curve. G, Dose-response curve of quetiapine. There are 2 controlled clinical trials of different doses of quetiapine, a fixed-dose study¹⁴² of 75, 150, 300, 600, and 750 mg/d and a flexible-dose–ranging study,¹⁴³ where the mean dose of the low-dose group was 209 mg and that of the high-dose group was 360 mg. Note that the most ED of quetiapine in the fixed-dose study was 150 mg/d, which was very similar to the 360-mg dose. At higher doses, the drug was slightly less efficacious particularly at a dose of 750 mg/d. H, Ziprasidone dose-response curve. Several studies of ziprasidone were conducted versus placebo for acute treatment trials. In addition, one large maintenance study was conducted. The dose-response curves are similar but not identical and roughly parallel. These data suggest that a slightly (about 25 mg/d) lower dose may be needed as maintenance medication. I, Sertindole dose-response curve. Note that 8 mg of sertindole was slightly less efficacious than placebo as shown by the point plotted below the zero improvement score. The 12-mg dose was almost as effective as the 20- and 24-mg dose. J, Haloperidol decanoate dose-response curve. The dose-response curve for haloperidol decanoate nicely follows the dose-response curve and appears to begin to flatten out at 200-mg dose.

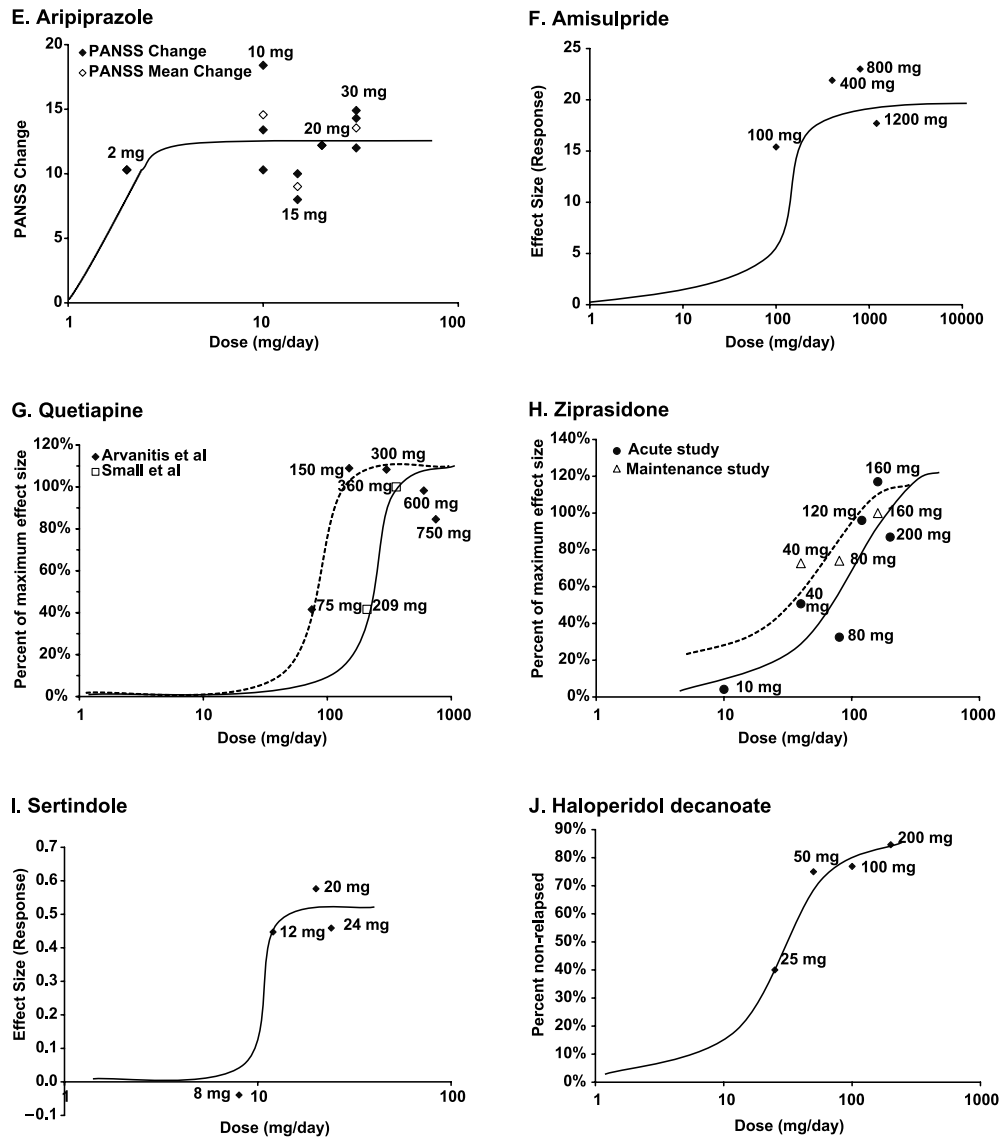


FIGURE 2. (Continued)

sensitivity analysis. We tested several other cutoff points (>3.3, ≥6, 6 to 12, etc.) summarized in Table 3. Using our definition of near-maximal ED, we found similar results, small nonsignificant differences, which were opposite in direction from that postulated by Geddes et al.⁵ In high doses (>12 mg/d) versus much higher doses (median, 64 mg/d), the dose-response curve was essentially flat [effect size, 0.00 (−0.14, 0.15)].

The Threshold Dose or Therapeutic Window in Treatment-Resistant Patients or Other Populations

Treatment-resistant patients may be resistant for pharmacokinetic or for pharmacodynamic reasons and might

possibly respond to a higher dose of FGA. It is possible that patients in a severe acute exacerbation may require a higher dose. Since we have data from various populations of patients including over 2500 patients (in 55 studies that compared a medium vs. high dose), we can test whether certain subpopulations such as treatment-resistant patients may respond to a higher dose. It is possible that the upper end of the therapeutic window (decreases response with too overly doses) occurs only with very high doses such as over 30 or 50 mg/d haloperidol or moderately high doses over 20 or 25 mg/d. (There may be a wide therapeutic window or a narrow therapeutic window.) (Fig. 1D; Web Table 3 and Web Figs. 12 and 13). We examined studies on treatment-resistant patients. We also explored the effects of whether the

TABLE 3. Sensitivity Analysis: Are High Doses More Effective Than the Near-maximal Effective Dose?

Dose Limits*	Medium Dose (mg/d)	High-dose (mg/d)	No. Studies	Effect Size	95% CI	P
	Median	Median				
>3.3	11.1	35.7	53	-0.07	(-0.15, 0.01)	0.092
≥6.0 [†]	10.7	40.0	42	-0.06	(-0.15, 0.04)	0.224
6.0–12.0 [†]	8.4	53.5	22	-0.10	(-0.23, 0.02)	0.104
>8.0	15.0	48.0	31	-0.06	(-0.18, 0.05)	0.297
>8.0–12.0	10.0	40.0	11	-0.17	(-0.36, 0.02)	0.081
>12.0	20.0	63.7	20	0.00	(-0.14, 0.15)	0.974

All comparisons used fixed-effect models, since tests for heterogeneity showed no significant heterogeneity.

*These values represent the dose limits of the medium-dose group.

[†]Based on Geddes et al's definition of optimal dose.

study was designed as a high-dose or as a dose-response study. High dose produced virtually the exact same efficacy as medium dose no matter what definition of high dose was used (ie, >20, >25, >30, or >50 mg/haloperidol equivalents) (see Fig. 1D; Web Figs. 12 and 13, Web Table 3). The dose response appears to be the same for the first few days as for later points in time for the acute psychotic patients (Table 4). In short, we tested whether a variety of population or design variables affected the results, for both single drugs (haloperidol), or by using our original (or other) dose equivalen-

cies. The finding was unchanged (see Table 4 and also Web Table 4: *Sensitivity analysis: are higher doses more, equally, or less efficacious than medium doses?*). The results were virtually identical in all groups, with no significant differences. Although the studies were conducted in a variety of patient populations, the findings on dose were very homogenous (see Table 3). We tested the hypothesis that patients may require a higher dose on the first day of treatment, as well as the alternate hypothesis that patients would become tolerant to antipsychotics and require a higher

TABLE 4. Does High-dose Treatment Produce Better Results in Selected Populations?

	Effect Size*	95% CI	t test	P	Test for Heterogeneity		
					Q Value [†]	df	P
Designed as high-dose treatment	-0.05	(-0.19, 0.10)	1.56	0.12	23.82	16	0.09
Other	-0.01	(-0.10, 0.09)	1.49	0.14	38.09	37	0.42
Overall [‡]	—	—	—	—	0.22	1	0.64
Treatment of resistant patients	-0.03	(-0.18, 0.13)	1.17	0.24	20.51	15	0.15
Other	-0.01	(-0.10, 0.08)	1.58	0.11	32.68	38	0.71
Overall [‡]	—	—	—	—	0.04	1	0.84
Dose-response studies	0.04	(-0.13, 0.20)	0.35	0.72	11.53	11	0.40
Other	-0.03	(-0.12, 0.06)	2.04	0.04	41.25	42	0.50
Overall [‡]	—	—	—	—	0.45	1	0.50
Treatment of symptomatic episode	-0.02	(-0.18, 0.14)	1.04	0.30	11.75	15	0.70
Other	-0.01	(-0.10, 0.08)	1.66	0.10	41.47	38	0.32
Overall [‡]	—	—	—	—	0.01	1	0.93
Treatment of chronic patients	-0.04	(-0.18, 0.10)	1.48	0.14	25.06	19	0.16
Other	0.00	(-0.10, 0.09)	1.41	0.16	32.29	34	0.55
Overall [‡]	—	—	—	—	0.13	1	0.71
Plasma level studies	-0.01	(-0.18, 0.16)	0.88	0.38	9.54	9	0.39
Other	-0.01	(-0.10, 0.08)	1.74	0.08	43.70	44	0.48
Overall [‡]	—	—	—	—	0.00	1	0.98

*Effect size measures improvement over plateau. The *t* statistic evaluates whether the subgroup is different from all other groups.

[†]The *Q* statistics evaluates whether all studies show that same effect within each population.

[‡]Overall *Q* statistics evaluates whether the 2 subgroups agree with each other (within-groups test).

dose in subsequent weeks by comparing dose-response studies of 1 to 2 days with dose response of the typical 3- to 8-week study. We found no difference. If tolerance occurred, a high ED₅₀ would have been observed in the 3- to 8-week study (Web: Tables 3 and 4, Figs. 12 and 13).

Dose-Response of SGAs

Figure 2 presents dose-response curves for all SGAs.

Risperidone

The best dose-response data for risperidone are found in the North American clinical trial,¹⁰²⁻¹⁰⁴ because this study has a placebo group for comparison. Here, dose of 2 mg/d risperidone is 50% less efficacious than the average of all higher doses (6, 10, and 16 mg/d) and 60% less efficacious than the 6-mg/d dose, the most ED (Fig. 2A). The higher doses (10 and 16 mg/d) are not statistically different from the 6-mg/d dose, and, in the 2 other randomized dose-response trials, there is little difference in efficacy between 4, 8, 12, and 16 mg/d¹⁰⁵ or between 4 and 8 mg/d.¹⁰⁶ In the former study, 4 mg/d is slightly better than 8 mg/d, and, in the latter, 8 mg/d is slightly better than 4 mg/d, suggesting to us that the dose-response curve is plateauing at about 4 mg/d (Web: Figs. 9 and 10). In the first quarter of 1997, the mean dose used in the New York state system for inpatients was 7.1 mg/d.¹⁰⁷ This decreased to 4.9 mg/d in the third quarter of 2001. The efforts made to market risperidone at a lower dose range of 4 to 6 mg/d by risperidone's sponsor may have contributed in part to this change in dosing pattern. A mean dose also would include doses of elderly patients or others for whom a lower dose is clearly indicated, and a mean dose of all patients would be less than that of adult schizophrenic patients. The optimal dose of 4 to 6 mg/d risperidone was known, since approximately 1992 to 1993 when the first initial presentations of the North American, the Canadian Clinical Trial and the International Clinical Trial began to be presented followed by their publication in 1993 to 1995. It is apparent that in New York State Hospitals, physicians were prescribing higher doses than what should be prescribed, based on these clinical data, with a mean dose of 7 mg/d. There must have been a fair number of patients with risperidone doses above 8 mg/d, suggesting that some state hospital clinicians might have had the clinical intuition that a high dose was useful.

Because risperidone causes dose-related extrapyramidal symptoms, it is important to use the minimal dose that would produce full efficacy and minimize extrapyramidal symptoms. We estimate that the near-maximal ED of risperidone is 4 mg/d, and the ED₅₀ is 2 mg/d (see Web: *Agreement of dose-response curves for SGAs*). The randomized study of depot risperidone microspheres found the near-maximal ED to be approximately 50 mg/mo [with both

the lower dose (25 mg/mo) and the higher dose (75 mg/mo), producing less improvement] (Fig. 2B).¹⁰⁸

Olanzapine

The best data on the olanzapine dose-response come from the United States double-blind, randomized registrational trial, because there is a placebo group for perspective.¹⁰⁹ Patients were randomized to the dose range of 5 mg/d \pm 2.5 mg, 10 mg/d \pm 2.5 mg, and 15 mg/d \pm 2.5 mg olanzapine.^{109,110} The response of all 3 doses is on the log-linear portion (Fig. 2C). Low olanzapine doses (mean, 6 mg/d) constituted about 33% of the approximately 16-mg/d (or more) dose. The curve did not reach the beginning of the plateau phase. When we pooled the raw data from this and other dose-ranging studies which did not have a placebo group,¹¹⁰ the dose-response curve appeared exactly linear over these dose ranges (plots shown elsewhere).¹¹¹ In a randomized double-blind study,¹¹² treatment of acute agitation in 148 patients (three-fourths schizophrenics and the remainder manic) for 4 days with olanzapine up to 40 mg/d, average doses between 25 and 29 mg, compared with 10 mg olanzapine, showed that the higher dose of olanzapine produced a more rapid and better reduction in the PANSS impulsive/hostility factor ($P = 0.006$), despite the fact that the 10-mg group received almost 20 times higher doses of supplemental lorazepam on a PRN basis.

We suggest that the near-maximal ED for olanzapine may be more than 16 mg/d (uncertainty represented by curves with a question mark in Fig. 2C). Citrome and Volavka¹⁰⁷ conducted an important study comparing olanzapine, clozapine, risperidone, and haloperidol. During the first period, patients received fixed doses, but, during the second 6-week period, they received variable doses. The maximal ED of olanzapine was 40 mg/d. Olanzapine produced improvement in phase 2 trials but was not observed with the other drugs.^{50,107} Citrome and Volavka¹⁰⁷ reviewed the clinical nonblinded trials of olanzapine at doses higher than 20 mg/d, providing suggestive evidence that these doses are useful.

Single-dose IM Olanzapine

In one study, patients with schizophrenia were randomly assigned to receive blinded IM doses of olanzapine as follows: placebo, 2.5, 5.0, 7.5, and 10.0 mg/d olanzapine; or 7.5 mg/d haloperidol, with approximately 45 patients in each group.^{113,114} (This is comparable to 5 to 20 mg/d total daily dose of oral olanzapine.) This dose-response curve provides a guide for the emergency treatment of patients with IM olanzapine (Fig. 2D). It is also interesting to compare the dose-response curve in the acutely exacerbated patients in the emergency 1-day, or 4-hour treatment with the dose response of typical schizophrenic patients in a 6- to 8-week study. The

dose-response curves appear roughly similar. The outcome variable used is the Excited Component of the PANSS,¹¹⁵ which we call the impulsivity-hostility factor.^{104,111}

Aripiprazole

The dose-response curve of aripiprazole indicates that the dose producing full efficacy plateaus below 10 mg/d (Fig. 2E). However, the 2-mg/d dose is almost as effective as the 10- to 30-mg/d dose range. We speculate that the ED₅₀ for aripiprazole would be approximately 1 mg/d, based on the observation that 2 mg/d is well above the half-maximal improvement score.¹¹⁶⁻¹²²

Amisulpride, Remoxipride, and Sertindole

A fixed-dose, blinded amisulpride trial found that the 100-mg/d dose was slightly less efficacious than higher doses.¹²³ The favorable result found with 400 mg/d amisulpride suggests that the near-maximal ED is below this dose. We interpolated an ED₅₀ of approximately 50 mg/d amisulpride (Fig. 2F). The dose-response curve for remoxipride shows that the near-maximal ED range is 120 to 240 mg/d (Web: Fig. 11; Table 2).^{124,125} The 8-mg/d dose of sertindole is clearly suboptimal, as it is less effective than the 12- or 20-mg dose (Fig. 2I).^{47,126,127} The 12-mg/d dose of sertindole is slightly less efficacious than the higher dose but not significantly so.

Clozapine

With toxic drugs such as clozapine, clinicians concerned about side effects can sometimes undershoot the dose and accept a less than optimal improvement. The only clozapine dose-response study was a small study that found that 600 mg daily was somewhat superior to 300 mg/d, which in turn was superior to 100 mg/d, and that some patients clinically needed 900 mg/d.¹²⁸ VanderZwaag et al¹²⁹ randomly assigned patients to 3 targeted plasma-level ranges, mean clozapine plasma level 91, 251, and 396 mg/d, or mean average dose of 165, 373, and 511 mg/d. The medium and high plasma-level group showed greater improvement (and about equal improvement) than the low plasma-level group. Four controlled plasma-level studies,¹³⁰⁻¹³³ 3 with 400 mg/d clozapine and 1 with 600 mg (therapeutic monitors) found favorable responses more often in patients with high plasma levels, and poor response in those with lower plasma levels, suggesting that many patients require doses above 400 mg/d (see Web: *Clozapine*). When the dose was increased in a randomized, double-blind subgroup, most of the poor responders responded.^{131,133} Plasma-level studies (where dose is uncontrolled) are difficult to interpret, as the clinician will adjust the dose upward in nonresponders. This is likely to result in nonresponders having high plasma levels. This said, if nonresponders have low plasma levels, it

is likely these patients were underdosed, and these studies do find patients with low plasma levels in nonresponders.¹³⁴⁻¹³⁷ Evidence from these studies strongly suggest that the near-maximal ED of clozapine is substantially above approximately 400 mg/d for some patients.

Ziprasidone

The dose-response relationship of ziprasidone is noteworthy because dose-response curve data are available for treating exacerbating patients and for maintenance purposes. The best data on ziprasidone efficacy for acutely ill exacerbated patients are unpublished data found on the Food and Drug Administration website.¹³⁸ Initially, ziprasidone was used at an overly low dose. Multiple registrational studies helped to elucidate the therapeutic dose. We calculated the dose-response curve against placebo using these data. No data exist showing that ziprasidone has full efficacy above placebo until a dose of 120 to 160 mg/d is achieved. The 80 mg/d dose groups in the two studies¹³⁸ have somewhat disparate findings, and pooled data do not show full efficacy (Fig. 2H). The large long-term maintenance study¹³⁹ found that the dose-response curve for maintenance treatment (Fig. 2H, open triangles, dashed line) was shifted to the left of the dose-response curve of the acute study (Figure 2H, solid circles, solid line), an effect more prominent with relapse rate as end point but also present with respect to PANSS change score outcome. The near-maximal ED range is estimated to be approximately 120 to 160 mg/d for treating acute schizophrenia and 80 to 120 mg/d for maintenance treatment.

Single-dose Studies of Ziprasidone

Two randomized double-blinded, 24-hour studies of exacerbated patients receiving IM ziprasidone were conducted in which 2 mg/d versus 10 mg/d in 117 patients and 2 mg/d versus 20 mg/d in 79 patients were evaluated.^{114,138,140,141} Assessment was performed a few hours after initial injection. Although the 20-mg/d dose of ziprasidone exhibited a trend toward a greater reduction on the PANSS than the 2-mg/d dose, the difference was not statistically significant ($P = 0.12$),¹⁴¹ and the 10-mg/d dose was similar to the 2-mg/d dose.¹⁴⁰ Some authors incorrectly give the impression that the ziprasidone IM at the 20-mg/d dose confers an antipsychotic effect. It does have a sedative effect. In neither study was a significant effect demonstrated on the PANSS at 24 hours (the flexible dose portion of the study; see Web: *Acute 2- to 24-hour dose-response curve for olanzapine and ziprasidone—single dose intramuscular emergency treatment*). These studies appeared to have missed the linear or plateau portion of the dose-response curve completely (see Web: *Missing the near-maximal effective dose*).

Quetiapine

A fixed-dose, randomized blinded trial¹⁴² found that 75-mg/d dose of quetiapine produced an improvement of 2.24 PANSS points (Fig. 2G, solid diamond). The next highest dose, 150 mg/d, produced a decrease of 8.67 PANSS points, which is the greatest improvement observed of all doses in this study (ie, 75, 150, 300, 450, and 750 mg/d). Higher doses, particularly 750 mg/d, were slightly less effective (6.33 PANSS points). In another double-blind study,¹⁴³ patients were assigned to 2 flexible-dose range doses of quetiapine (and placebo) with an overlap between the 2 dosage groups; that is, the LOCF average dose of 360 mg (range, 50 to 566 mg; average dose of completers, 488 mg) was compared with the average dose of 209 mg (range, 50 to 267 mg; average dose of completers, 248 mg). The high-dose group produced an improvement of 8.7 Brief Psychiatric Rating Scale points, the low dose produced improvement of 4.2 points, and placebo produced a 1-point improvement (Fig. 2G, open square; Table 2). Dropout for treatment failures were 25/96 for high dose, 34/96 for low dose, and 42/96 for placebo. The results are modestly different (see Web: *Agreement of dose-response curves for SGAs*). Some have speculated that higher doses of quetiapine produce better outcome. The Arvanitis et al¹⁴³ data at 750 mg/d contradicts this; however, it is possible that the initial studies completely missed the full dose-response curve. The fact that individuals do clinically improve at higher doses in open studies does not prove that the higher dose was responsible, as such improvement might reflect the passage of time, augmenting drugs, or other confounding factors. The sponsor for quetiapine has 2 studies of dose response, one nearing completion and the other just beginning, so more information will be available in the future. Clinicians need to watch for this because this new information may alter the estimate of near-maximal ED.

DISCUSSION

Incorrect doses will lead to either insufficient improvement or excessive side effects. We constructed dose-response curves for FGAs and SGAs based on groups randomized to different doses, a method which places the dose under experimental control with the protection of blinding and random-assignment against both known and unknown biases. Our data suggest that current guidelines to FGA and SGA uses are, in part, incorrect. As guidelines contradict each other, they all cannot be correct. Although we present dose-response curves for FGAs and SGAs, we feel the reader should focus on the empirical data points. In practice, clinicians tend to use higher doses of FGAs than are really needed. Baldessarini et al¹⁴⁴ did a survey in the Boston area and found that approximately 50% of patients were prescribed a haloperidol dose above 28 mg/d, which greatly

exceeds our near-maximal effective haloperidol dose range of 3.5 to 10.0 mg/d. Even today, high doses of FGAs are used in the United States^{145,146} and in the United Kingdom, where 50% of inpatients are on more than one antipsychotic and 40% of those receiving haloperidol are on doses over 15 mg/d.¹⁴⁷ Because patients recover gradually from the schizophrenic episode over the course of 4 to 6 weeks, dose escalation may estimate a falsely high dose, due to the effect of passage of time. We find no evidence that supports the use of high doses of FGAs. The opposite may be true for clozapine. We review 4 different methodologies of controlled studies and also studies where dose was uncontrolled. We interpret dose in targeted, fixed plasma-level studies differently than fixed-dose studies, because, in the former, no patient would receive plasma levels lower than the target, whereas, with fixed-dose studies, many patients have low plasma levels with 400 mg/d and some have low levels even with 600 mg/d.¹⁴⁸ While the medium clozapine dose was slightly lower, but not that much lower, than the studies by Potkin et al,¹³³ Perry et al,¹³² or Fabrazzo et al,¹⁴⁴ the fact that random reassignment to a higher dose in several of these studies produced more responders than a control group who continued on the same dose indicates that at least some patients require doses roughly above the initial dose of 384 to 484 mg, depending on the study. Some European clinicians conduct frequent plasma level monitoring and achieve good response with mean doses of 300 mg; however, as a consequence, this monitoring targets high dose to those who need them. Plasma level is influenced (about 25% variation) by dose schedule (thrice a day, twice a day, or every day) and time of blood draw. VanderZwaag et al¹²⁹ provide a helpful discussion. Although there is a need for more dose, targeted plasma levels, and random reassignment studies, we suggest dose of clozapine used may be too low throughout the world for some patients but too high for others. There are wide differences in clozapine metabolism, so we recommend monitoring serum levels to ensure adequate plasma levels and to guard against excessive plasma levels.

Real progress has been made regarding available knowledge of the dose-response curves of SGAs, since the Food and Drug Administration now requires at least one dose-ranging study on reasonable sample sizes. We think dose-ranging studies often have the doses too close to each other, particularly at the high doses where they should be spaced progressively further apart. Citrome and Volavka's¹⁰⁷ excellent narrative review of SGAs discusses individual studies included in our dose-response plots. Unfortunately, these findings are often not translated into guidelines or practice. Citrome and Volavka¹⁰⁷ provide interesting data that the mean risperidone dose in 1997 in the New York State system was 7.1 mg/d. It was known that the best dose of risperidone was about 4 to 6 mg/d in the early 1990s. The

dose of olanzapine in New York State is increasing, and Citrome and Volavka find that 26% of patients received greater than 20 mg/d by 2001¹⁰⁷ in clinical practice, which reflects the dose-response curve suggested in this paper. Studies that compare an SGA with another SGA should use EDs. This is not always done [eg, several studies compared low-dose clozapine (eg, 200 mg) with adequate dose of the sponsor's SGAs].

Does a High-dose Help or Hurt Some Patients? (The Therapeutic Window Hypothesis)

We found no evidence that high doses produced a better (or worse) response than medium doses, a consistent finding maintained over many definitions of "medium or high." Geddes et al⁵ assume that exceedingly high doses (above 12 mg/d haloperidol equivalent) of FGAs produce a worse response than moderate doses (6 to 12 mg/d). Geddes et al's data⁵ find that clozapine and some other SGAs are more effective than FGAs, but they dismissed this as an artifact based on this assumption. Using their definitions, we find trends, although not statistically significant, which are in direct opposition, falsifying Geddes et al's explanation. We also performed sensitivity analysis with slight modification of dose cutoff points, which did not change the conclusions at all (see Web: *Sensitivity analysis: are higher doses more, equally, or less efficacious than medium doses?*). Given that we had 55 studies and over 2500 patients, if we had been more or less effective than medium dose, we would have expected to find more studies reporting significant results. Only 2 studies^{53,79} showed a significant difference favoring a high dose, and this is counterbalanced by several studies clearly favoring a lower dose, although not significantly.

Treatment-Resistant Patients

Is there a subpopulation where high doses may be helpful? We found no evidence for this. There was no pattern for high dose to be more effective in any of the subgroups examined. It is also possible that massive doses may be required. Our examination of various definitions of high dose failed to find any dose that altered response.

Acute Emergency Treatment

The dose range at 3.3- to 4-mg/d seemed to be closer to plateau than the 4- to 8-mg/d and the 8- to 12-mg/d dose equivalencies. There is only one dose-response study of first-episode patients,⁴⁵ which did find evidence that first-episode patients may respond to a lower dose and this might explain this blip. Note that there were 2 other studies, both of which used typical exacerbated patients in an episode: one, a typical drug company registrational study,⁴⁷ and the other, a study sponsored by the National Institute

of Mental Health on severely ill state hospital patients.⁴⁴ We found roughly the same dose-response curve for FGAs in acute trials lasting a few days or in 2 trials of olanzapine (a 2-day trial and a 4-day trial), as was also found in the longer 4- to 8-week trial. This suggests that tolerance does not occur (ie, the dose-response curve for partial response in the first few days is similar to that for the full 4- to 8-week trials).

Maintenance Medications

While many guidelines state that much lower doses are required for maintenance treatment to prevent relapses, we found almost no evidence relevant to this. One large maintenance study of oral antipsychotic drugs found that a 60% dose reduction from acute dose range (around 400 mg of chlorpromazine units) produces a substantially greater relapse rate.¹⁴⁹ One ziprasidone study hints that maintained patients may require a slightly lower dose.¹³⁹ These studies are not necessarily contradictory, because one is a 60% reduction and the other is a more modest 25% reduction. The comparisons of depot dose to oral dose are complicated due to the lack of a precise method of equating IM versus oral drug formulations. While the possibility remains that there may be a difference in the acute and maintenance doses, there is no body of evidence supporting progressive maintenance-dose reductions. The studies have not been conducted. Meta-analysis is the messenger indicating this gap in our knowledge. If these dose reduction recommendations were wrong, the consequence of following them would be unnecessary relapse (see Web: *Sensitivity analysis—can a lower dose be used in maintenance treatment?*).

Problems with Dose Equivalence

One problem with conversion from dose equivalencies is that an error in either the source or targeted drug equivalent dose (eg, 4 mg/d drug X is equivalent to 100 mg/d drug Y) would translate to an error in the result. Moreover, errors in one could be amplified by an error in the other. It is better to have the estimated near-maximal EDs listed in a reference table. With knowledge of the dose the patient is on and the near-maximal ED of both, the clinician can make a common-sense adjustment (see Web: *Assumption that all psychotics are equally efficacious*).

Individual Difference and Limitation of Our Data

The range for individual patients may be wider than our estimated dose range for pharmacokinetic or pharmacodynamic reasons. Perhaps, a haloperidol daily dose of 2 mg may be fully effective for one patient but 12 or 20 mg/d for another patient. If we know the amount of variability, we could adjust the dose within this range. Dose-response studies only indicate the mean dose response and do not

identify a subgroup that may respond to a higher dose or to a lower dose. Unfortunately, we have no data to know how wide this is. The studies use the random and reassignment strategies pioneered by Volavka et al^{44,93-95,100} to address this question. The results from these studies do not depart in any significant way from all other designs (see Table 4). These studies focus on patients who do not respond to the first dose (here targeted to a plasma level). It would be important to know if nonresponders would respond to a higher or, for that matter, a lower dose, but these data are unfortunately absent and continue to be absent for SGA drugs, an important gap in our knowledge.

A plot of response versus plasma level in many of these studies^{44,93,94,150,151} found that those patients with the lowest plasma level tended to have poor response, and the breakpoint from the log-linear to plateau seems to be similar to the dose-response curve reported in this paper.

It is also possible that patients in an acute exacerbated episode may require higher doses than patients in a mild exacerbation. One limitation of the controlled trials is that these are only conducted with patients able to give informed consent. We have little information on patients who are too psychotic to give informed consent. We were able to approximate the dose-response curve for several FGAs. We cannot state with precision what the near-maximal ED is for most typical antipsychotics. We do not know the individual variability between patients. This and the inherent uncertainty due to the loss of power in measuring efficacy near the plateau portion indicate that our approximations are just that. We feel that clinicians need to consider clinical experience with their patients, as well as this evidence from controlled trials viewed in the perspective of common sense. We are in favor of empirically varying dose by trial and error in an individual patient (and are opposed to rigidly defined dosage guidelines). We do not list the recommended doses from guidelines we consider incorrect, as this would be unnecessarily argumentative. While more studies are needed, the clinician needs to choose doses for their contemporaneous patients. Most of the dose-response studies that will be done have been conducted. Our best conclusion is the graphic display of the raw data in the figures, but our interpretation is listed in Table 2.

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