A Decision Analysis Approach to Neuroleptic Dosing: Insights From a Mathematical Model

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Background: Although several published studies suggest that little benefit accrues from raising doses of conventional antipsychotic drugs above 500–800 chlorpromazine equivalents per day (CPZeq/day), institutionalized patients with schizophrenia often receive larger doses. Decision analysis could alter this practice by helping clinicians select doses through use of quantitative models that incorporate the consequences of each dose, the likelihood of those consequences, and explicit risk/benefit weightings.

Method: This study uses representative published data to develop equations and graphs that describe dose-associated likelihoods of treatment response, side effects, and balances between benefits and incidence of side effects.

Results: Response rates fit a sigmoid curve that flattens at 500 CPZeq/day; a hyperbolic curve describing side effects reaches a plateau at much higher doses. Combining these curves shows that higher drug doses yield ever diminishing returns, because as the dose increases, the number of side effects per benefited patient also increases. A table and graphs show clinicians how to use these results to critique their current practices and make explicit risk/benefit judgments about dosages.

Conclusion: Mathematical expressions for dose-related side effect and response rates are potentially useful tools for evaluating low-, intermediate-, or high-dosage neuroleptic treatment regimens.

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Despite the arrival of several new medications in the U.S. psychopharmacologic armamentarium, standard or conventional antipsychotic drugs (i.e., medications whose antipsychotic potency is directly correlated with dopamine D_2 blockade[1]) continue to play an important role in current treatment of schizophrenia.[2,3] Published reports suggest that daily neuroleptic dosages of 500–800 chlorpromazine equivalents (CPZeq/day) yield near maximum antipsychotic efficacy, that lower doses (300–500 CPZeq/day) are often optimal, and that long-term dosing above 375 CPZeq/day increases adverse reactions.[2,4] However, schizophrenic patients frequently receive much higher doses of antipsychotic medications.[2,5–9] This practice sometimes reflects nontherapeutic motivations (e.g., financial pressures,[9] fear of being blamed for relapse,[10] or desire to appease nursing staff[8]), but many psychiatrists also believe that large doses assure that all potential responders have received an adequate trial of neuroleptic medication.[10,11] Moreover, high neuroleptic doses have been used to define treatment resistance[12] and to evaluate antipsychotic efficacy.[13,14] Large doses also have been recommended for treatment of violent patients.[15]

Psychiatrists' neuroleptic dosage choices thus involve considerable guesswork, or what cognitive psychologists term "judgments under uncertainty."[16] As a technique for avoiding idiosyncratic and potentially suboptimal treatment choices, medical decision theory asks practitioners to select treatments by using mathematical models that quantify consequences and likelihoods.[17]

This article presents a decision-analytic approach to the selection of antipsychotic drug dosages. The next section explains the construction of mathematical models describing the relationships between antipsychotic dosages, likelihood of response, and likelihood of serious side effects. Subsequent sections explore the kind of information that these models contain, including some practical insights about the benefits and pitfalls associated with neuroleptic dose choices.

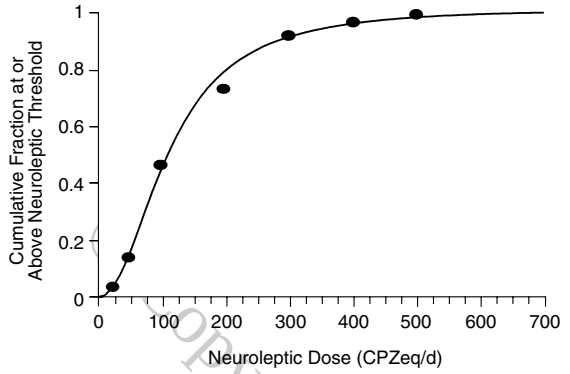
METHOD

Model Treatment Assumptions

Model construction often requires reasonable but simplifying assumptions about the treatment context. For purposes of this article, let us assume that

1. a psychotic patient with schizophrenia will undergo initial treatment with the conventional antipsychotic Drug Z;
2. any acute side effects (e.g., extrapyramidal symptoms and dystonias appearing during the initial days of treatment) can be addressed and managed

Figure 1. Sigmoid Curve Fitted to Cumulative Fraction of Patients Reaching Neuroleptic Threshold*



*Based on data from McEvoy et al.[11] Abbreviation: CPZeq/d = chlorpromazine equivalents per day.

safely[18,19] and therefore will not affect decisions about management;

3. the patient, if Drug Z responsive, will receive the same dose for prophylaxis against recurrence of psychosis over the next 6 months.

The selected medication dosage, therefore, should reflect the likelihood of response to a short but adequate medication trial (perhaps 6 weeks[20]) and the likelihood of serious side effects during *maintenance* administration.

Neuroleptic Dose-Response Relationships

If Drug Z is a high-potency neuroleptic, the neuroleptic threshold dosing procedure[11] provides a simple but elegant way to find a patient's lowest effective dose of medication. The neuroleptic threshold dose is the minimum amount of neuroleptic that causes a detectible increase in rigidity. To find it, one initiates treatment by using a low dose of a high-potency neuroleptic (e.g., haloperidol 2 mg/day), and examines the patient every 2 days as the dose is adjusted upward or downward. McEvoy and colleagues[11] found that the neuroleptic threshold dose provided "virtually all the therapeutic benefit available to neuroleptic-responsive patients"(p744); higher doses only increased side effects. In McEvoy and colleagues' study, patients reached the neuroleptic threshold at mean ± SD doses of 185 ± 115 CPZeq/day, a finding that agrees with other investigators' reports concerning median effective neuroleptic doses,[2,4] median side-effect-producing doses,[18,21,22] and receptor occupancy.[23,24]

For some antipsychotic drugs and clinical situations, however, the neuroleptic threshold dosing technique is impracticable. If Drug Z is not a high-potency neuroleptic, its effects on rigidity may be comparable to coadministering a high-potency drug and an antiparkinsonian agent, which might obscure or raise the apparent neuroleptic threshold above the actual remission-producing dose. The initially small (100 CPZeq/day) doses used in neuroleptic threshold titration may be less effective than larger doses during the first hours to days of treatment.[4] Also, in many treatment settings, clinicians cannot examine patients every other day during the first 2 weeks of drug therapy.

However, clinicians can take advantage of neuroleptic threshold dosing principles even if they cannot use the neuroleptic threshold dosing approach itself. McEvoy and colleagues' report[11] gives clinicians a way of estimating the chance that a given dose will induce a clinical response if the patient is Drug Z responsive. In Figure 1, the fraction of McEvoy and colleagues' patients who reached or exceeded neuroleptic threshold ("cumulative fraction at or above neuroleptic threshold") is plotted as a function of neuroleptic dosage. In doing so, one obtains points that can be fitted to a sigmoid curve[25] commonly used to express dose-response relationships:

$$y_1 = 1 - \frac{1}{1 + \left[\frac{x}{a}\right]^b} = \frac{x^b}{a^b + x^b} \qquad [1]$$

where y_1 is the cumulative neuroleptic threshold fraction, x is the dose of neuroleptic in CPZeq/day, and a and b are data-specific constants. Equation 1 has several noteworthy properties that distinguish it from other proposed curves for describing dose-response relationships (e.g., logistic regression equations[26]): it passes through zero, implying that a "dose" of no medication should lie above no one's neuroleptic threshold; it asymptotically approaches unity, consistent with the expectation that high enough doses will eventually produce increased rigidity in almost everyone; and it parsimoniously uses only two adjustable parameters. The estimates $\hat{a} = 114.5$ and $\hat{b} = 2.200$ used to fit the curve in Figure 1 were obtained using weighted, iterative, nonlinear regression carried out with BMDP Statistical Software (Berkeley, Calif., 1990).

Describing the Response Rate

Figure 1 and Equation 1 show that high enough doses will cause almost all patients to reach neuroleptic threshold. Achieving neuroleptic threshold is not a guarantee of clinical response, however, because not all treated patients respond to a given drug. We must keep this in mind as we attempt to use the information in Equation 1 to calculate the dose-dependent response rate. We should also keep in mindthat placebo-controlled studies of standard antipsychotic drugs consistently show improvement in a fraction of schizophrenic patients who do not receive active medication.[27,28] This suggests that the overall response rate R for treated patients equals $P + M$, where P represents the placebo response rate and M represents the fraction of patients who improved only because of medication.

We therefore write the following equation to describe the dose-dependent response rate for Drug Z:

$$y_2 = P + M\,[x^b / (a^b + x^b)] \qquad [2]$$

Equation 2 tells us that at a dose of zero, a randomly selected patient has a chance P (the placebo response rate) of responding. The chance of responding rises as the dose of Drug Z is increased and asymptotically approaches $P + M$ as the dose reaches high levels.

In McEvoy and colleagues' study,[11] 67 of the 95 subjects followed for 5 weeks ultimately responded to haloperidol treatment. This 70.5% response rate is similar to ones obtained after 18 to 45 days in studies reviewed by Baldessarini and associates[4] and is almost identical to the 70% response rate obtained by Davis and colleagues'[28] pooling of the major early placebo-controlled antipsychotic medication studies. Davis and colleagues also found that the placebo response rate in these studies was 25%,[28] a value very close to that obtained in the recent North American study[29] on the efficacy of risperidone. Later numerical calculations in this article therefore use the estimates $\hat{P} = 0.25$ and $\hat{M} = 0.45$.

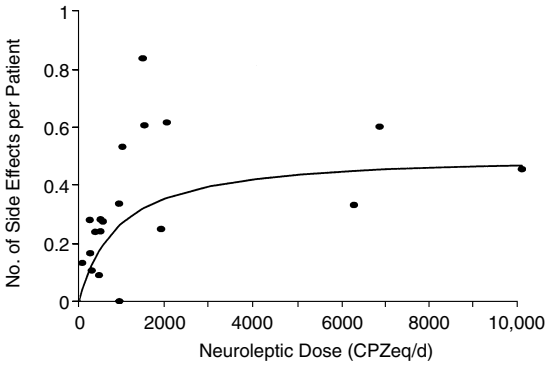
Modeling Likelihood of Serious Side Effects

Dosage decisions should reflect the likelihood of serious, disabling reactions as well as antipsychotic efficacy. For many chronically ill schizophrenic patients, outpatient care offers limited opportunity for close follow-up. Fears about causing relapses make clinicians reluctant to reduce antipsychotic doses,[10] especially during the first several months after an acute episode of illness. Consequently, patients typically receive their predischarge medication dosage as maintenance treatment,[4] even if lower doses might suffice.[30] Therefore, although the neuroleptic dose needed in acute-phase treatment is often higher than that needed during maintenance treatment, the decision model in this article assumes that choosing a particular dose of medication during the acute phase of treatment will result in continued exposure of treatment-responsive patients to that dose—and its associated side effects—for at least 6 months.

In their meta-analytic review of maintenance antipsychotic therapy for adults with psychotic disorders, Bollini and colleagues[2] found that the treatment benefits were maximized at doses of about 375 CPZeq/day. In the 10 reports of side effects that they analyzed, however, the likelihood of adverse reactions continued to rise when doses rose above that level. The total numbers of severe neurologic sequelae (acute dystonia, akathisia, tardive dyskinesia, and seizures) reported by Bollini and colleagues are plotted as numbers of side effects per patient in Figure 2. These points can be fitted to the hyperbolic binding curve function

$$y_3 = Ax/(B + x) \qquad [3]$$

Figure 2. Hyperbolic Curve Fitted to Rates of Neurologic Side Effects*



*Based on data from Bollini et al.,[2] Table 3.

where y_3 is the number of side effects per patient, x is the neuroleptic dose in CPZeq/day, and A and B are empirically derived constants. Although many types of curves could be fitted to Bollini and colleagues' data, a binding curve is a relatively simple form that incorporates the reasonable assumption that neurologic side effects will be roughly proportional to D_2 receptor occupancy.[31] The estimates $\hat{A} = 0.5132$ and $\hat{B} = 917.7$ were obtained from Bollini and colleagues' Table 3 data (with the megadose 39,000 CPZeq/day not used) using BMDP Software's robust (Huber's $k = 2$), weighted, nonlinear regression procedure. The weighted mean length of neuroleptic exposure for the 886 patients whose side effect rates appear in Figure 2 was 26.96 weeks. It should be noted that many of the studies reviewed by Bollini and colleagues predate the advent of DSM-III, and therefore refer to patients with a variety of psychoses.

An equation describing maintenance treatment side effects must reflect my model's assumption that patients who are Drug Z nonresponders will receive no maintenance treatment with Drug Z. One can develop the appropriate equation by taking the product of the dose-dependent response rate, y_2, and the dose-dependent side effect rate, y_3, and writing the following expression to obtain the number of side effects per patient treated at dosage x:

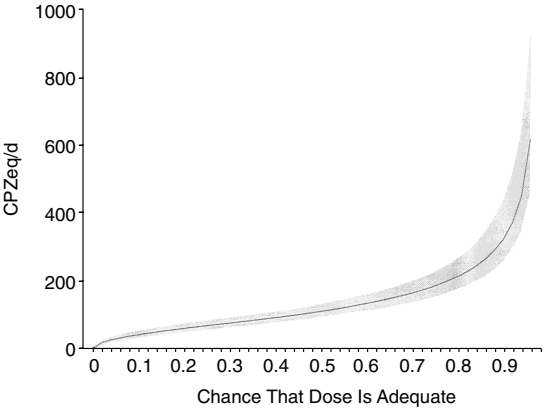
$$y_4 = \{P + M\,[x^b / (a^b + x^b)]\}\,[Ax / (B + x)] \qquad [4]$$

Estimating Precision

Equation 1 is a central *estimate* of the likelihood that a given daily dose is adequate to produce a response if the patient is a Drug Z responder. In clinical practice, however, we often need to know how much medication we must administer to achieve a level of certainty that the dose was adequate, and the precision of this estimate. We can use the data from McEvoy and colleagues[11] to address these issues if we assume that their data come from a representative, random sample of patients with schizophre-

nia. If we reverse the axes in Figure 1, we can replot Equation 1 with confidence intervals for the dose associated with each cumulative neuroleptic threshold rate (see Figure 3). Because the confidence intervals are not distributed symmetrically about the central estimate of the dose, the 90% confidence intervals shown in Figure 3 were calculated with a computer program designed especially for this interval-estimation task. The program generated 2000 bootstrap samples from McEvoy and colleagues' data, calculated estimates of a and b for each bootstrap sample, and used these ($\hat{a}$, $\hat{b}$) pairs to calculate confidence intervals for values of y_1 = {0.02, 0.04, 0.06, …, 0.98} with the "BC_a" resampling procedure.[32]

Figure 3. Ninety Percent Confidence Intervals for Adequate Treatment Dose



Balancing Benefits With Side Effects

The real price of raising neuroleptic doses is, as we have seen, an increased risk of serious neurologic side effects. There would be no problem (other than small excess financial costs) with administering higher-than-necessary neuroleptic doses if doing so did not appreciably increase serious side effects. Figure 2 shows that beyond 5000 CPZeq/day, large dose increases cause small increases in likelihood of side effects. However, at doses below 1000 CPZeq/day—that is, at doses that yield antipsychotic responses for more than 98% of patients—the side effect rate climbs steadily.

To balance potential benefits and risks, one should select the dose at which the potential benefit from an incremental dose increase equals the incremental risks from side effects.[33] The incremental benefits and risks of raising doses are linear functions of the *slopes* of the response and side effect curves. Therefore, the *net gain* from a dosage increment is the weighted difference between the first derivatives of Equations 2 and 4:

$$\text{net gain} = y_5 = \frac{dy_2}{dx} - Q\frac{dy_4}{dx} \qquad [5]$$

To understand the meaning of the weighting factor Q, note that for a given value of Q, the dose x where net gain is zero ($y_5 = 0$) is the dose at which the incremental benefits from increasing doses exactly offset the increase in adverse neurologic reactions. The value of x at which $y_5 = 0$ thus is the optimum dose, because increasing doses beyond this point results in a net *loss* when benefits and side effects are weighed against each other.

When $y_5 = 0$, we can rearrange Equation 4 to express Q as a function of the derivatives, that is, as the ratio of the incremental increase in response rate to the incremental increase in serious adverse neurologic reactions. This tells us that Q, in essence, expresses a view about how the added antipsychotic efficacy associated with incremental dosage increases should be balanced against the increased incidence of side effects. The value of Q represents the decision-maker's opinion about the lowest acceptable ratio of benefited patients to side effects. If, for example, a decision-maker feels that the value of successfully treating two additional patients exactly offsets the harm caused to one patient who suffers serious neurologic side effects, then $Q = 2$. Higher values of Q would suggest more risk avoidance and smaller neuroleptic doses; lower values of Q would imply greater tolerance of side effects and larger doses. Finally, because each dose x is associated with a certain value of Q (i.e., the value where $y_5 = 0$), a clinician who chooses to administer a certain dose of antipsychotic can be regarded as having made an implicit choice about where side effects offset gains in the response rate, and this point can be translated into a ratio of benefited patients to adverse reactions.

RESULTS

Estimating Response and Side Effect Rates

Equations 1–5 are simple but powerful tools for evaluating dose choices. Perhaps their most straightforward application involves estimating the fraction of patients who will benefit from a given dose of medication. We can show this by considering a population of 1000 psychotic schizophrenic patients. If each receives a dose of just 200 CPZeq/day, we would estimate from Equation 1 that 773 will be at or above their neuroleptic threshold. These 773 patients also will have received a dose adequate to produce a response if they are drug responsive. From Equation 2, we estimate that 598 patients will respond to that dose. If they receive the same dose for maintenance therapy, we can expect (from Equation 4) that the side effect rate will be 0.055, implying that about 55 serious neurologic side effects will occur.

Doubling the dose to 400 CPZeq/day will treat 940 patients at or above neuroleptic threshold and 673 will respond—13% more than responded at 200 CPZeq/day.

Table 1. Risk/Benefit Ratios, Response Rates, and Side Effect Rates at Neuroleptic Doses

Dose (CPZeq/d)	Q[a]	Fraction of All Treated Patients Who Respond	Number of Side Effects per Responding Patient
200	2.84	0.598	0.091
300	1.28	0.652	0.126
400	0.68	0.673	0.156
600	0.27	0.689	0.203
800	0.15	0.694	0.239
1000	0.09	0.696	0.268

[a]Q = number of additional benefited patients that justifies causing one additional serious side effect.

Under our treatment model's assumptions, all 673 will receive maintenance therapy at 400 CPZeq/day, and 105 serious neurologic side effects will occur—91% more than at the 200-CPZeq/day dose. Doubling the dose again (to 800 CPZeq/day) adds just 46 more patients to the adequately treated category and creates only 21 more responders. However, during maintenance treatment at 800 CPZeq/day, the expected number of side effects will increase to 166, 58% above the expected number of side effects at the 400-CPZeq/day dose.

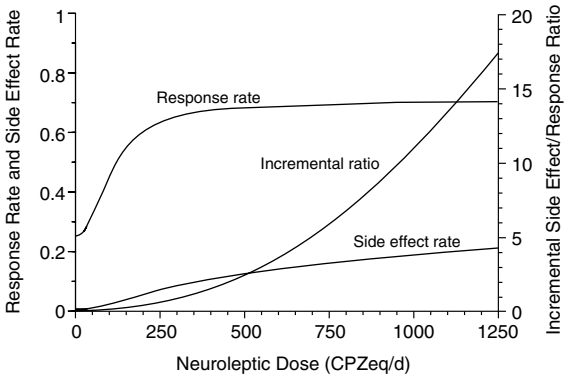
The Price of Certainty

Figure 3 shows that the upper limit of the 90% confidence interval of the 80%-adequate dose is approximately 260 CPZeq/day. Recall that by definition, there is a 95% chance that the true value falls below the upper limit of a 90% confidence interval. We can, therefore, be 95% sure that by administering a 260-CPZeq/day dose, 80% of patients will have received enough antipsychotic medication to derive whatever benefit the drug can give them. Similarly, we can be 95% sure that about 400 CPZeq/day will adequately treat 9 of 10 patients, and a dose of 600 CPZeq/day—a dose well below that which many patients take over extended periods—has a 95% chance of being sufficient for 95% of patients. A few patients who do not respond to 600 CPZeq/day might respond to higher doses. But, Figure 3 shows that if we insist on determining who these patients are, we will run into problems. Above 600 CPZeq/day, the confidence intervals widen rapidly, and antipsychotic doses must be substantially increased for each additional fraction of patients whose dose is adequate.

Risks and Benefits

Earlier, we saw that a neuroleptic "dosage policy" could be represented by Q, a variable that summarizes views about risk/benefit balancing. We can translate a daily dose into a value of Q by assuming that a decision-maker has selected that dose as the point at which incremental increases in benefits offset incremental increases in side effects. Table 1 lists values of Q, response rates, and side effect rates for selected neuroleptic doses.

Figure 4. Response Rate, Side Effect Rate, and Incremental Ratio of Side Effect to Response for a Range of Neuroleptic Doses



The table suggests that administering 200 CPZeq/day represents a *primum non nocere* position: three patients must benefit if one is to have serious side effects. A dose of 800 CPZeq/day represents the opposite view: psychosis is so serious that relieving it in one patient is worth placing seven patients at risk.

The ratio of side effects to responses associated with incremental dose increases is depicted graphically in Figure 4. Here, the inverse of Q, the incremental ratio of side effects to response rate (measured along the right ordinate) is juxtaposed with the response and side effect rates.

DISCUSSION

The preceding analysis shows how tradeoffs between risks and benefits can be conveniently depicted to help clinicians make informed, individualized decisions about neuroleptic dosages. Equations that describe dose-related response and side effect rates are the keys to this process: they give clinicians more nuanced and thorough information than is provided by tabulations of optimal dose ranges, mean or median effective doses, or dose-associated likelihoods of responses or side effects.

The Equations' *forms* alone provide useful information about antipsychotic medications. For example, the finding that cumulative likelihood of reaching neuroleptic threshold follows an asymptotic sigmoid curve tells us that doses below a certain level will have minimal effects for most patients and that doses beyond a certain level will yield rapidly diminishing returns.

Equations 1–5 also allow display of response and side effect data in an easily apprehended graphic form. The figures in this article are only examples of those that could be generated to answer particular clinical questions. The risk/benefit balancing issues examined in this article appear to apply to venlafaxine dosages in depression,[34] imipramine levels in panic disorder,[35] and fluphenazine

levels in schizophrenia.[36] Equations describing medication effects are easily manipulated tools: they summarize a great deal of information, and sophisticated decision-makers can use them to address a host of psychopharmacologic problems.

This article has emphasized a quantitative attitude toward clinical decision making and has shown how a common clinical problem can be interpreted and described mathematically. In the process, selected data have been analyzed by using reasonable—but potentially fallible—assumptions. Here lie many potential pitfalls that should dissuade clinicians from uncritical applications of findings in this article. Despite more than 40 years of experience with neuroleptic drugs, our understanding of relationships among dosage, blood levels, receptor occupancy, response rate, and side effects is still being debated.[37,38] The table and figures in this article are based on equations derived from only two of the psychiatric literature's many reports on neuroleptic doses and side effects. The equations incorporate data concerning a subset of side effects from maintenance treatment and refer to only one of many contexts where clinicians use neuroleptics.

The calculations in this article are based on reasonable but narrow assumptions about a treatment approach. Violations of these assumptions would reduce the applicability of the calculations. For example, a practice of attempting to reduce maintenance neuroleptic dosage shortly after stabilization would decrease the side effect rate and would increase values of *Q* in Table 1. Continuing to treat patients whose response is negligible (a not uncommon practice) would increase the side effect rate and decrease *Q*. Consideration of side effects that accrete after 6 months would also decrease *Q*.

Despite these limitations, there are several ways in which calculations in this article are directly relevant to practicing psychiatrists. First, the calculations force us to face facts: raising neuroleptic doses increases both the chance that patients will respond and the chance that they will suffer serious side effects. Although this seems obvious, the persistence of high-dosage antipsychotic therapy suggests that this point is lost amid the pressures and ingrained habits that influence clinicians' behavior. Problems caused by psychotic, disruptive, and/or aggressive patients may assume an immediacy that overwhelms concerns about long-term side effects and realistic consideration of the limited benefits of high-dose neuroleptics.[8] Marginally competent, long-term inpatients—persons who derive only modest benefits from antipsychotic medication and who may have limited ability to complain about less-than-optimal treatment—may be especially likely to experience prolonged, high-dose neuroleptic exposure.[39] Although neuroleptic dosages should reflect awareness of the long-range consequences of taking potentially toxic drugs, this ideal often goes unrealized. This paper displays a mode of thinking about dose choice, risks, and benefits that is underrepresented in the psychiatric literature and that is far different from the global-thinking style that most clinicians ordinarily employ.[40]

Second, the calculations have potential heuristic value. The previous sections contain a conceptual framework that systematically appraises risks and benefits and that translates presently available knowledge about response rates and side effects into mathematical formulae. This article's contextual and quantitative assumptions impose clear limits on the applicability of its numerical findings. However, readers can see how this article's conceptual framework could apply to other treatment contexts, even though such application would require changing the numerical values used here. For example, one could revise Equation 1 to reflect adverse reactions to multiyear drug exposure, gender-related differences in dosage or clinical response,[41] or findings that drug-naive patients reach their neuroleptic threshold at lower doses than previously exposed patients.[11]

Third, if the assumptions underlying the choices of curve forms are reasonable, then the contours of the curves shown in the figures say something specific about what happens when neuroleptic doses are raised. Both the response rate and side effect curves plateau (i.e., asymptotically approach an upper limit) once doses rise beyond a certain point, but the response rate plateau begins well before the plateau for the side effect curve. Here, then, is a graphic explanation for the oft repeated finding[2,4] that raising dosages above 500 CPZeq/day benefits only a few additional patients but significantly increases the chance of serious side effects.

Fourth, equations and figures in this article are based on systematically obtained data derived from well-conducted studies. They therefore are, at the very least, reasonable initial estimates of the efficacy and dose-associated risks of conventional antipsychotic drugs for schizophrenic patients taken as a whole. The side effect curve summarizes results for 886 subjects from 10 carefully selected studies.[2] The total response rate in McEvoy and colleagues' study[11] was similar to results reported elsewhere for patients followed for comparable time periods.[4] Equation 1 closely fits McEvoy and colleagues' data, gives precise estimates of response rates (see Figure 3), and confirms previously published reports showing that few patients respond to doses below 100 CPZeq/day, that increasing numbers respond as doses are raised to 200–500 CPZeq/day, and that almost all treatment-responsive patients will respond to doses of 500–800 CPZeq/day.[4,11,20]

Fifth, this article shows how statistics about outcomes for groups of patients can improve treatment decisions about individual patients. Clinicians rarely use rigorous decision-making techniques. They rarely ask themselves

how sure they want to be about giving patients an adequate trial of medication. They rarely ask themselves (let alone those who take antipsychotic medication) how many patients should "pay" (through dose-related side effects) for the chance to give a single patient enough medication to respond. However, clinicians can use quantitative data to consider drug dosages from what might be termed a "policy" standpoint and to look at what their practices imply over time for the groups of patients that they treat. For example, if the data and curve-fits used to generate Figure 4 are valid and generalizable, then clinicians who regularly treat patients with 10 to 15 mg/day of haloperidol (500–750 CPZeq/day) are implicitly deciding that to benefit one additional patient, it is acceptable to cause one to four serious side effects during the first 6 months of maintenance therapy. Knowing this, clinicians can ask themselves whether they indeed feel this way and, if not, adjust their future practice accordingly.

Finally, the considerations that underlie calculations in this article can help physicians readjust their clinical practices and decision making in an era when "novel" antipsychotic drugs offer treatment options that are more effective and/or have fewer side effects. Until recently, American psychiatrists had comparatively little to offer schizophrenic patients besides treatment with neuroleptics and may have felt justified in exposing initially nonresponsive patients to high dosages because the available alternatives (e.g., electroconvulsive therapy, propranolol, or lithium[20]) were only modestly effective. In the 1980s, psychiatrists might have felt that resolving one patient's psychosis justified exposing 10 (or more) patients to potentially severe side effects. Risk/benefit calculations in the 1990s should be influenced, however, by the proven efficacy of clozapine in treatment-resistant patients[12] and by the arrival of new, well-tolerated[14,42]—if not first-line[43]—pharmacologic options in schizophrenia.

Drug names: fluphenazine (Prolixin and others), haloperidol (Haldol and others), imipramine (Tofranil and others), propranolol (Inderal and others), venlafaxine (Effexor).

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