

Chlorpromazine Equivalent Doses for the Newer Atypical Antipsychotics

Scott W. Woods, M.D.

Background: Several clinical and research applications require an estimation of therapeutic dose equivalence across antipsychotic medications. Since the advent of the newer atypical antipsychotics, new dose equivalent estimations have been needed.

Method: The reported minimum effective dose was identified for each newer atypical antipsychotic medication and for haloperidol across all available fixed-dose placebo-controlled studies. Reported minimum effective dose equivalence ratios to haloperidol were then converted to chlorpromazine equivalents using the "2 mg of haloperidol equals 100 mg of chlorpromazine" convention.

Data Sources and Study Selection: To identify the fixed-dose studies, the following sources were searched until June 2002: MEDLINE, the bibliographies of identified reports, published meta-analyses and reviews, Cochrane reviews, Freedom of Information Act material available from the Food and Drug Administration, and abstracts from several scientific meetings from 1997 to 2002.

Results: Doses equivalent to 100 mg/day of chlorpromazine were 2 mg/day for risperidone, 5 mg/day for olanzapine, 75 mg/day for quetiapine, 60 mg/day for ziprasidone, and 7.5 mg/day for aripiprazole.

Conclusion: These equivalency estimates may be useful for clinical and research purposes. The source of the dose equivalency estimation is evidence-based and consistent across medication.

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Corresponding author and reprints: Scott W. Woods, M.D., Department of Psychiatry, Yale University School of Medicine, 34 Park St., New Haven, CT 06519 (e-mail: scott.woods@yale.edu).

Several clinical and research applications require an estimation of therapeutic dose equivalence across antipsychotic medications. Clinicians often make use of therapeutic equivalency estimates when switching from one antipsychotic to another. Many research designs also require estimates of equivalency. In studies comparing the effects of different medications, for example, on adverse events, adherence, or cost, dose equivalency estimations are needed to separate out the effects of different medications independent from the effects of different doses. Similarly, dose equivalency estimations are needed to compare dosing practices across patient groups when these groups are prescribed a variety of medications in naturalistic designs. Examples of this latter type of design are studies examining the effect of patient race or diagnosis on clinical dosing practices.

Dose equivalency tables for conventional antipsychotic medications are commonplace among psychopharmacology texts and reviews. The provenance for many of these tables may perhaps be traced to a classic publication by Davis.¹

Since the advent of the newer atypical antipsychotics, new dose equivalence estimations have been needed. Several estimations have been proposed, but they vary widely. Explicit or implied risperidone dose equivalencies of 1 mg/day,² 1.5 mg/day,³ 1 to 2 mg/day,⁴ 2 mg/day,⁵ and 2.5 mg/day⁶ per 100 mg/day of chlorpromazine have been suggested. Equivalencies for olanzapine have ranged from "2 to 3?" mg/day⁴ and 5 mg/day³ to 10 mg/day.⁶ Quetiapine equivalencies have ranged from "50 to 100?" mg/day⁴ to 100 mg/day.³ For none of these estimations has the basis or rationale been explicit. Equivalency estimations do not appear to have been published for ziprasidone or aripiprazole.

The ideal studies to estimate therapeutic dose equivalence would randomize large, representative samples of acutely ill patients with schizophrenia to multiple fixed doses of multiple medications. We are unlikely to have available such data in the near future. In the absence of such ideal data, a proxy method may be useful: equivalence ratios calculated from fixed-dose data drawn from separate drug development programs. The current report derives equivalency ratios for risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole using this proxy method.

METHOD

To calculate ratios across drug development programs, the reported minimum effective dose for each medication was identified for each medication selected. The reported minimum effective dose was commonly defined across drug development programs as the lowest dose across all available fixed-dose placebo-controlled studies that was consistently significantly superior to placebo on the principal continuous outcome measure (either the Brief Psychiatric Rating Scale [BPRS] or Positive and Negative Syndrome Scale [PANSS] total score) in the intent-to-treat analysis.

The reported minimum effective dose data were identified by reviewing all available placebo-controlled, fixed-dose and fixed-dose-range studies of risperidone, olanzapine, quetiapine, and ziprasidone. To identify these trials, the following sources were searched by the author until June 2002: MEDLINE, the bibliographies of identified reports, published meta-analyses and reviews⁷⁻¹³; 6 Cochrane Reviews¹⁴⁻²¹; and Freedom of Information Act (FOI) material available from the U.S. Food and Drug Administration (FDA). Abstracts from the 1997–2002 annual meetings of the American Psychiatric Association, the 1999 and 2001 International Congresses on Schizophrenia Research, and the 2000 and 2002 Winter Biennial Schizophrenia meetings were also hand-searched. For the fixed-dose-range studies, the average dose achieved within range was employed as the relevant dose. In March 2003, the FDA made results available on its FOI Web site for studies of the recently approved new atypical antipsychotic aripiprazole. These data were reviewed to identify a minimum effective dose for aripiprazole as well.

Reported minimum effective doses were translated to chlorpromazine equivalents. First, haloperidol equivalent doses were estimated. This method was chosen because an estimate for the minimum effective haloperidol dose was available from a source contemporaneous with the atypical antipsychotic studies, a multiple fixed-dose trial of haloperidol and a never-marketed atypical antipsychotic.²² Haloperidol equivalencies were then converted to chlorpromazine equivalencies by applying the common “2 mg/day of haloperidol equals 100 mg/day of chlorpromazine” convention.⁴

RESULTS

For risperidone, 3 placebo-controlled studies were identified, but only 2 used fixed doses: risperidone study 0204^{23,24} and risperidone study 72.²⁵ Study 0204 employed fixed doses of 2, 6, 10, and 16 mg/day, and study 72 employed 4 and 8 mg/day. The *p* value was .051 in study 72 at the final evaluation in the intent-to-treat analysis comparing 4 mg versus placebo on the PANSS

total score. The reported minimum effective dose for risperidone was identified as 4 mg/day.

For olanzapine, 2 fixed-dose studies were identified: olanzapine study HGAP²⁶ and olanzapine study HGAD.²⁷ Study HGAP employed fixed doses of 1 and 10 mg/day. Study HGAD employed fixed-dose ranges, whose average doses achieved were 6.6, 11.6, and 16.3 mg/day. The reported minimum effective dose was identified as 10 mg/day.

For quetiapine, 4 placebo-controlled studies were identified, but only 2 used fixed doses: quetiapine study 0004²⁸ and quetiapine study 0013.²⁹ Study 0004 randomized patients to placebo or 250 mg/day. Study 0013 randomized patients to fixed doses of 75, 150, 300, 600, and 750 mg/day. The reported minimum effective dose was identified as 150 mg/day.

For ziprasidone, 4 placebo-controlled fixed-dose studies of acutely exacerbated patients were identified: ziprasidone study 106,³⁰ ziprasidone study 114,³¹ and 2 unpublished studies (ziprasidone studies 115 and 104).³² Study 106 employed fixed doses of 40 and 120 mg/day; study 114, fixed doses of 80 and 160 mg/day; study 115, fixed doses of 40, 120, and 200 mg/day; and study 104, fixed doses of 10, 40, and 80 mg/day. The 40-mg dose was not statistically superior to placebo in 2 (studies 106 and 104) of 3 studies, and the 80-mg dose was not statistically superior to placebo in 1 (study 104) of 2 studies. The 120-mg/day dose was statistically superior to placebo in both of 2 studies (studies 106 and 115) and was identified as the reported minimum effective dose.

For aripiprazole, 4 placebo-controlled fixed-dose studies of acutely exacerbated patients were identified: aripiprazole study 97201³³ and 3 unpublished studies (aripiprazole studies 94202, 97202, and 138001).³⁴ An additional small, “ascending dose” placebo-controlled study (aripiprazole study 93202) is not further considered here because dosing was not fixed. Study 97201 employed fixed doses of 15 and 30 mg/day; study 94202, fixed doses of 2, 10, and 30 mg/day; study 97202, fixed doses of 20 and 30 mg/day; and study 138001, fixed doses of 10, 15, and 20 mg/day. The 15-mg/day dose was statistically superior to placebo in both of 2 studies (studies 97201 and 138001) and was identified as the minimum effective dose. Doses lower than the minimum effective dose were not consistently statistically superior to placebo. The 2-mg/day dose was not superior to placebo in study 94202, and the 10-mg/day dose was not superior to placebo in 1 (study 94202) of 2 studies. Doses higher than the minimum effective dose were always statistically superior to placebo, with 1 partial exception. The 20-mg/day dose was superior to placebo in both of 2 studies (studies 97202 and 138001), and the 30-mg/day dose was superior to placebo in 2 studies (studies 97201 and 97202) and superior to placebo on 1 of 2 co-primary outcomes in a third study (study 94202).

Table 1. Reported Minimum Effective Fixed Doses and Chlorpromazine Dose Equivalence Ratios for Haloperidol and Newer Atypical Antipsychotics

Antipsychotic Medication	Reported Minimum Effective Fixed Dose (mg/d)	Chlorpromazine 100 mg/d Dose Equivalence (mg/d)
Haloperidol	4	2
Risperidone	4	2
Olanzapine	10	5
Quetiapine	150	75
Ziprasidone	120	60
Aripiprazole	15	7.5

For haloperidol, 1 placebo-controlled fixed-dose study was identified.²² This study employed haloperidol doses of 4, 8, and 16 mg/day. The minimum effective dose in this study was 4 mg/day. Even lower doses have not yet been studied.

Reported minimum effective doses and chlorpromazine dose equivalencies are shown in Table 1.

DISCUSSION

The principal finding of this study is that reported minimum effective doses can be identified from recent fixed-dose studies for risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, and haloperidol and that these reported minimum effective doses can be used to calculate dose equivalencies for atypical antipsychotic medications. The source of the dose equivalency estimation is evidence-based and consistent across medication. The resulting estimates are generally in the middle of the ranges of previous estimates. These equivalency estimates may be useful for clinical and research purposes.

No fixed-dose studies are available for clozapine, so the current method could not be applied to clozapine. A dose of 50 mg/day of clozapine has been proposed as equivalent to chlorpromazine 100 mg/day.⁴

A strength of the study is the comprehensive search strategy used to identify relevant studies. Although most of the relevant studies have been published, 1 key study, risperidone study 72,²⁵ was identified only in abstract form, and full data were found via the FDA FOI search. Similarly, risperidone study 0204 was considered by the FDA to have been 1 study, although results for the Canadian²³ and American²⁴ sites were reported separately.

An important limitation of the proposed method is its reliance on only placebo-controlled fixed-dose studies to establish the reported minimum effective dose on which the equivalencies were based. Somewhat lower doses, intermediate between doses studied in the clinical trials that were ineffective and the minimum dose effective among those studied, could well be effective in clinical practice. However, since such doses have not been studied using methods that are consistent across medications,

they cannot be used in an evidence-based system to establish dose equivalencies.

Highlighting this limitation, the equivalencies suggested here rely on a single placebo-controlled multiple fixed-dose study of haloperidol²² with conversion from haloperidol equivalencies to chlorpromazine equivalencies. However, other data suggest that the current estimates may not be far off the mark. The current data suggest that the minimum effective dose of haloperidol is approximately 4 mg/day and that the minimum effective dose of chlorpromazine is approximately 200 mg/day. Most of the older placebo-controlled haloperidol²⁰ and chlorpromazine²¹ research identified by Cochrane Reviews agree fairly well with the current estimates. A crossover study of haloperidol 4.5 mg versus placebo in 29 patients showed a significant advantage for haloperidol over placebo.³⁵ A study of 3 to 4.5 mg/day of haloperidol in 25 patients per group showed larger global improvements in the haloperidol patients compared with placebo patients that did not appear, however, to be statistically significant.³⁶ The largest placebo-controlled chlorpromazine study comparing 208 schizophrenic patients receiving a fixed dose of 300 mg/day with 212 patients receiving placebo appears to have shown that 300 mg/day produced global improvement rates significantly higher than placebo.³⁷ Two other small studies found that schizophrenic patients receiving 150 mg/day improved to a significantly greater degree on the BPRS than patients receiving placebo.^{38,39} However, a recent study of 53 schizophrenic patients allocated to fixed doses of either 300 or 600 mg/day of chlorpromazine⁴⁰ found that improvement on the BPRS in the 2 chlorpromazine groups combined was not significantly superior to improvement in the similarly sized placebo group.

Similarly, the risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole data also derive from only a few studies. The minimum effective doses identified were evaluated in only 1 or 2 studies per medication. Confidence in the reported minimum effective dose estimates is increased somewhat by data showing that doses lower than the reported minimum effective doses (risperidone 2 mg/day, olanzapine 1 mg/day and approximately 6.6 mg/day, quetiapine 75 mg/day, ziprasidone 40 and 80 mg/day, and aripiprazole 2 and 10 mg/day) did not separate from placebo in 9 of 11 comparisons. However, intermediate doses such as risperidone 3 mg/day or olanzapine 8 mg/day have not been studied.

Another limitation of this proposed method is that equivalency at one point in the dose range does not necessarily imply the same equivalency at higher doses. An equivalency calculation based on dose-response curves using all the data from all doses could be attempted, but this approach would require making an assumption that the order of the dose response relation (e.g., linear, quadratic) be the same across medications.

As an alternative to the proposed fixed-dose method, it would be possible to duplicate the flexible-dose method used in the classic paper by Davis¹ cited earlier. This analysis gathered flexible-dose, active-controlled trials of conventional antipsychotics and derived equivalency ratios from the average doses achieved. The rationale provided by Davis was that prescribers in flexible-dose studies generally titrate doses to optimal response. An advantage of attempting to use the flexible-dose method to derive equivalency estimates for newer atypical antipsychotics is that data for some medications would be somewhat less sparse. Moreover, more flexible-dose comparisons among atypical antipsychotics are likely to be added to the literature over time. The opportunity to enrich the evidence base underlying the equivalencies lends an additional advantage to this method.

The flexible-dose method, however, may provide a more biased estimate of therapeutic equivalence. Relative doses achieved in flexible-dose trials, as pointed out by Davis, are influenced not only by efficacy but also by the relative milligram strength selected for the blinded trial medications. It is possible that the relative milligram strength selected for the blinded trial medications could even outweigh efficacy considerations in determining doses achieved. This potential bias may be particularly influential when maximum or minimum dose limits are specified by the protocol. Another difficulty with the flexible-dosing comparison method is that it will be necessary to adjust for any differences between medications in efficacy. A further complication is that many of the flexible-dose active-controlled studies have no placebo group, and studies with only active controls raise questions about whether efficacy can be conclusively asserted and therefore also raise questions about comparative efficacy. Future research should adapt the flexible-dosing method to studies of the newer atypical antipsychotics and compare the resulting dose equivalencies with the estimates reported here based on fixed-dose studies.

The data for aripiprazole, a drug approved by the FDA after manuscript submission, were added after acceptance and additional review.

Drug names: aripiprazole (Abilify), chlorpromazine (Thorazine and others), clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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