Dose-Response Meta-Analysis of Antipsychotic Drugs for Acute Schizophrenia

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Objective: The dose-response relationships of antipsychotic drugs for schizophrenia are not well defined, but such information would be important for decision making by clinicians. The authors sought to fill this gap by conducting dose-response meta-analyses.

Methods: A search of multiple electronic databases (through November 2018) was conducted for all placebo-controlled dose-finding studies for 20 second-generation antipsychotic drugs and haloperidol (oral and long-acting injectable, LAI) in people with acute schizophrenia symptoms. Dose-response curves were constructed with random-effects dose-response meta-analyses and a spline model. The outcome measure was total score reduction from baseline on the Positive and Negative Syndrome Scale or the Brief Psychiatric Rating Scale. The authors identified 95% effective doses, explored whether higher or lower doses than the currently licensed ones might be more appropriate, and derived dose equivalencies from the 95% effective doses.

Results: Sixty-eight studies met the inclusion criteria. The 95% effective doses and the doses equivalent to 1 mg of oral risperidone, respectively, were as follows: amisulpride for patients with positive symptoms, 537 mg/day and 85.8 mg; aripiprazole, 11.5 mg/day and 1.8 mg; aripiprazole LAI (lauroxil), 463 mg every 4 weeks and 264 mg; asenapine, 15.0 mg/day and 2.4 mg; brexpiprazole, 3.36 mg/day and 0.54 mg; haloperidol, 6.3 mg/day and 1.01 mg; iloperidone, 20.13 mg/day and 3.2 mg; lurasidone, 147 mg/day and 23.5 mg; olanzapine, 15.2 mg/day and 2.4 mg; olanzapine LAI, 277 mg every 2 weeks and 3.2 mg; paliperidone, 13.4 mg/day and 2.1 mg; paliperidone LAI, 120 mg every 4 weeks and 1.53 mg; quetiapine, 482 mg/day and 77 mg; risperidone, 6.3 mg/day and 1 mg; risperidone LAI, 36.6 mg every 2 weeks and 0.42 mg; sertindole, 22.5 mg/day and 3.6 mg; and ziprasidone, 186 mg/day and 30 mg. For amisulpride and olanzapine, specific data for patients with predominant negative symptoms were available. The authors have made available on their web site a spreadsheet with this method and other updated methods that can be used to estimate dose equivalencies in practice.

Conclusions: In chronic schizophrenia patients with acute exacerbations, doses higher than the identified 95% effective doses may on average not provide more efficacy. For some drugs, higher than currently licensed doses might be tested in further trials, because their dose-response curves did not plateau.

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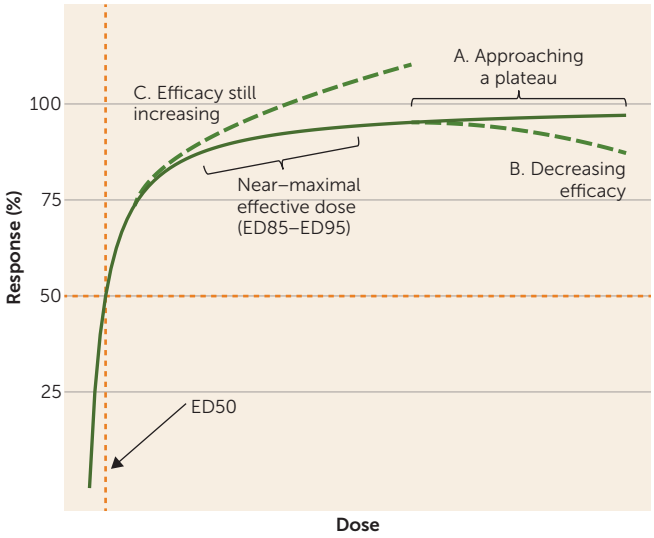
The dose-response relationships of antipsychotic drugs for the acute treatment of schizophrenia are not well understood, but further defining them would be important for many reasons. Clinicians need to know the minimum effective doses and the maximum effective doses when they prescribe antipsychotics, and guidelines attempt to provide such information.

In drug development, dose-response relationships are first derived from animal studies, but animal studies can only imperfectly predict the dose-response relationships in humans (1). In the first studies in humans, some pharmaceutical companies will thus estimate too-high doses from the animal data, and the initially tested dose range will be entirely at or above the maximally effective dose. Others may estimate too low, such that the initially tested dose range does not reach full therapeutic efficacy. Nevertheless, these early clinical studies often determine the dose ranges that are licensed, and used clinically, because subsequent studies with higher or lower doses are rarely conducted.

When therapeutic response is plotted against daily dose, many drugs have a hyperbolic dose-response curve shape (Figure 1) which becomes sigmoidal when the logarithm of the dose is used (2). Davis and Chen (3) used this concept to manually plot dose-response curves for various antipsychotic drugs to derive estimates for both near-maximum effective doses and dose equivalencies. However, since publication of their findings in 2004, multiple new drugs have been developed, new trials have been published, and mathematical functions have become available for plotting dose-response curves rather than plotting them manually.

We applied a quantitative methodology to determine near-maximum effective doses by conducting a meta-analysis of

FIGURE 1. Schematic dose-response curve[a]



[a] In this schematic dose-response curve, response to treatment is plotted against the dose administered. The shape is often hyperbolic (2), meaning that the curve typically asymptotes and approaches a plateau (scenario A). The near-maximal dose range is roughly the 85%–95% effective doses (ED85–ED95). The ED50 is the dose where 50% of the maximum efficacy is obtained. The dotted lines present both a scenario (B) of a bell-shaped curve where high doses lead to decreasing efficacy and a scenario (C) where the plateau has not been reached yet. In preclinical research, the log of the dose is often used, which typically makes the curve's shape sigmoidal (2). We did not use this approach because it is less suitable for identifying the ED95 and because the resulting curves are more difficult to interpret.

dose-response studies (4). We explored whether, for some drugs, higher than currently licensed doses should be tested in further trials. Finally, we used the near-maximum effective doses to obtain dose equivalence estimates.

METHODS

Inclusion Criteria

We included all fixed-dose studies that compared at least two doses of the following drugs with placebo in adult patients with acute exacerbations of schizophrenia or schizoaffective disorder: amisulpride, aripiprazole (oral and long-acting injectable [LAI]), asenapine, brexpiprazole, cariprazine, clozapine, haloperidol (oral), iloperidone, lurasidone, olanzapine (oral and LAI), paliperidone (oral and LAI), quetiapine (immediate release and extended release), risperidone (oral and LAI), sertindole, ziprasidone, and zotepine. We planned separate analyses for four patient subgroups: first-episode patients, patients with predominant negative symptoms, elderly patients, and patients with treatment-resistant illness. We excluded maintenance studies for patients with stable presentations a priori, as lower doses than those used for acute treatment may be sufficient for relapse prevention (5). Studies that used a subtherapeutic dose comparator of the same drug, rather than placebo, were added in a sensitivity analysis, given that such subtherapeutic doses are often not entirely ineffective (6).

Search Strategy

Our literature search was based on the searches used for three recent studies on antipsychotic dose equivalencies (the minimum effective dose method and the classical mean dose method [7–10]). For those reviews, we undertook exhaustive searches including multiple electronic databases, medical reviews submitted to the U.S. Food and Drug Administration, reference lists of other meta-analyses of second-generation antipsychotic drugs (11–14), Cochrane reviews comparing second-generation antipsychotics and haloperidol against placebo (15–17), and Cochrane reviews on optimum second-generation antipsychotic doses (18, 19), and we sent requests to the manufacturers of the second-generation antipsychotics (now including brexpiprazole and cariprazine). There were no language restrictions except for studies from China, for which quality concerns have been raised (20). We updated the electronic searches in multiple databases on November 11, 2017, and ran a final PubMed search on November 27, 2018. (Search terms are presented in Table S1 in the online supplement.) Two reviewers examined reports independently. Risk of bias was assessed with the Cochrane risk-of-bias tool (21). All data were extracted (by S.L.) and compared with independent extractions (by S.S.) or with extractions for previous meta-analyses by our group.

Meta-Analytic Method

Statistical model. We conducted a dose-response meta-analysis following the method proposed by Crippa and Orsini (4). The outcome measure was the intent-to-treat score change from baseline on the Positive and Negative Syndrome Scale (PANSS) (22) or the Brief Psychiatric Rating Scale (BPRS) (23), except for studies in patients with predominant negative symptoms, where the PANSS negative subscale or the Scale for the Assessment of Negative Symptoms (24) was used. The effect size was the standardized mean difference (Cohen's d). A two-stage approach was applied for data synthesis. In the first stage, a flexible dose-response model was estimated within each study, using regression splines. Splines represent a family of smooth functions that can describe a wide range of curves (25). The curves consist of piecewise polynomials over consecutive intervals defined by k knots that can facilitate curve fitting, because many nonlinear curves can be examined by estimating only a small number of coefficients. We characterized the dose-response relation using three knots located at the 25th, 50th, and 75th percentiles. Splines have an advantage over conventional nonlinear models such as the Emax model in that, in contrast to the latter, it does not require either a specific shape or parallel shapes of the dose-response curve. In a second step, the parameters describing the study-specific curves were combined using a multivariate random-effects model (4).

Estimation of 50% and 95% effective doses. We used the resulting dose-response curves to estimate the 95% effective dose (ED95) and 50% effective dose (ED50), as is customary

in dose-response analysis (1, 4), for each drug. The ED50 here is the mean dose that produces 50% of the maximum reduction of the patients' symptoms, as measured by the PANSS or BPRS, compared with placebo, and the ED95 is the mean dose that produces 95% of the maximum reduction (Figure 1).

Estimation of dose equivalence. We used the ED95s of each compound to calculate risperidone, olanzapine, and haloperidol dose equivalence ratios. For example, if the ED95 of risperidone was 6.26 mg/day and that of aripiprazole 11.5 mg/day, the aripiprazole dose that is equivalent to 1 mg/day risperidone would be 11.5/6.3=1.84 mg/day.

We performed four sensitivity analyses, in which 1) we included studies that used a subtherapeutic-dose comparator of the same drug rather than placebo; 2) we excluded studies that were conducted exclusively in patients with schizoaffective disorder; 3) we analyzed immediate-release and extended-release quetiapine separately; and 4) we excluded "failed" studies in which neither a single dose of the drug under investigation nor, if available, an established comparator drug was more efficacious than placebo.

Fitting a dose-response curve with all drugs pooled. We converted all dose arms into risperidone equivalents and fitted a dose-response curve across drugs. We tested with linear splines up to the dose at which the dose-response curve still showed a significantly increasing slope. The significance threshold was set at $p<0.1$, given the low power of this test (4). Risperidone dose equivalents derived from the minimum effective dose method (7, 8, 26) were used in a sensitivity analysis.

Heterogeneity and publication bias. Heterogeneity was assessed with a chi-square test of heterogeneity ($p<0.1$) and the I^2 statistic, where we considered I^2 values >50% to suggest considerable heterogeneity (27). The possibility of small-trial or publication bias could not be formally tested because the number of studies available for each compound was too small (at least 10 studies are needed [21]). All statistical analyses were conducted with the dosresmeta package in R (28).

RESULTS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the search and a description of the 68 included studies are provided in Figure S1 and Table S2 in the online supplement (number of studies: amisulpride, N=3; aripiprazole, N=5; aripiprazole LAI (lauroxil), N=1; asenapine, N=6; brexpiprazole, N=4; cariprazine, N=4; clozapine, N=1; haloperidol, N=1; iloperidone, N=4; lurasidone, N=7; olanzapine, N=4; olanzapine LAI, N=1; paliperidone, N=5; paliperidone LAI, N=4; quetiapine, N=4; risperidone, N=4; risperidone LAI, N=1; sertindole, N=4; and ziprasidone, N=5 (one study provided data for two drugs). For the predefined analyses of specific patient subgroups, data were available only for patients with predominant negative symptoms, and there was a single clozapine study in patients with treatment-resistant illness. Study duration ranged from 4 to 26 weeks, with a median of 6 weeks; the single 26-week study evaluated patients with predominant negative symptoms (29). (For risk of bias assessment, see Figure S2 in the online supplement.) The dose-response curves are presented in Figure 2. Table 1 presents ED95s, ED50s, and the risperidone, olanzapine, and haloperidol equivalencies derived from these doses.

Amisulpride for Patients With Predominant Negative Symptoms

Two types of amisulpride studies were available. For the first type, two studies (30, 31) on low-dose amisulpride (50–300 mg/day) for patients with predominant negative symptoms suggested that the ED95 was reached at approximately 70 mg/day in this population. There was no significant heterogeneity ($Q=0.7$, $p=0.69$, $I^2=0\%$). Visual inspection of the dose-response curve does not suggest that higher doses would be more efficacious (Figure 2A).

Amisulpride for Patients With Positive Symptoms

The single dose-finding study with acute exacerbations of positive symptoms compared amisulpride at 400 mg/day, 800 mg/day, and 1200 mg/day with 100 mg/day (32). Because the low-dose arm is considered to be subtherapeutic as a comparator, this study was eligible only for the sensitivity analysis. However, because these are the only amisulpride data available, we included the findings in Figure 2 with the main results (Figure 2T). Amisulpride showed a bell-shaped dose-response curve in which the ED95 was achieved at 537 mg/day.

Oral aripiprazole. Five fixed-dose placebo-controlled studies (33–37) examined aripiprazole doses between 2 mg/day and 30 mg/day. Homogeneous results showed that the ED95 was achieved at around 12 mg/day (see Table 1). The curve was slightly bell-shaped, with no indication that higher doses would be associated with more efficacy (Figure 2B).

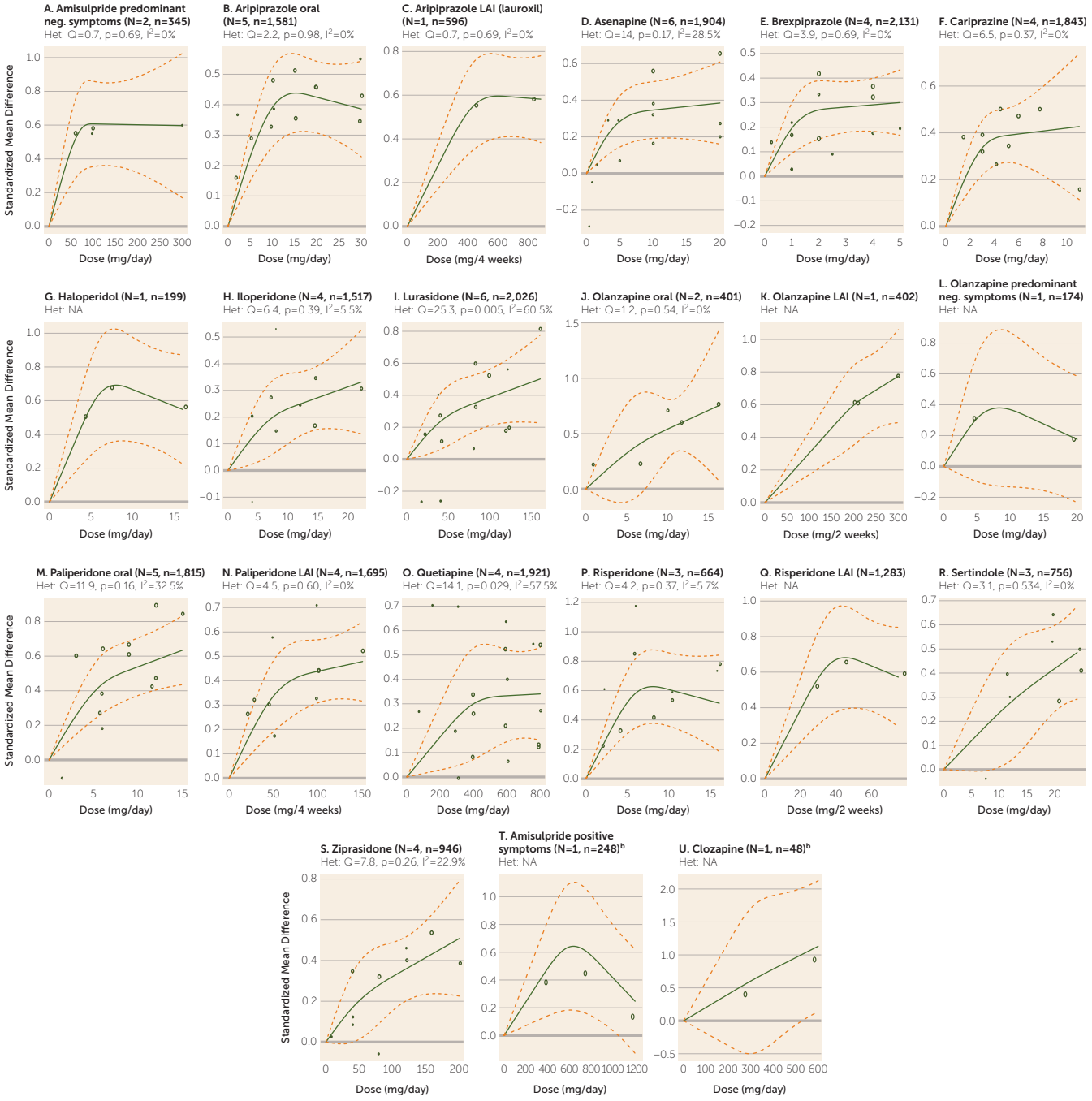
Aripiprazole LAI (lauroxil). One study of aripiprazole lauroxil (38) compared 441 mg every 4 weeks and 882 mg every 4 weeks with placebo. The ED95 was 463 mg every 4 weeks, and the curve plateaued (Figure 2C).

Asenapine. According to six rather homogeneous studies examining asenapine doses between 0.4 mg/day and 20 mg/day (39–44), the ED95 was reached at 11 mg/day and the dose-response curve plateaued (Figure 2D).

Brexpiprazole. According to data from four homogeneous studies (45–48), the ED95 was reached at 3.4 mg/day and the dose-response curve plateaued (Figure 2E).

Cariprazine. Based on data from four homogeneous studies (49–52) with doses between 1.5 and 12 mg/day, the ED95 was 7.6 mg/day and the dose-response curve plateaued (Figure 2F).

FIGURE 2. Dose-response curves of individual antipsychotic drugs[a]



[a] Het=heterogeneity; LAI=long-acting injectable; N=number of studies; n=number of subjects; NA=not assessible because there was only one study. The dots and circles indicate the effect sizes for the individual doses, and the size of the dots and circles indicates sample size. The dotted lines are 95% confidence intervals. We used knots at the 25th, 50th, and 75th percentiles to anchor the curves. The following studies were used in the analysis: amisulpride in patients with predominant negative symptoms (30, 31); aripiprazole oral (33–37); aripiprazole LAI (lauroxil) (38); asenapine (39–44); brexpiprazole (45–48); cariprazine (49–52); haloperidol (54); iloperidone (55, 56); lurasidone (57–62); olanzapine oral (63, 64); olanzapine, patients with predominant negative symptoms (65); olanzapine LAI (66); paliperidone oral (67–71); paliperidone LAI (72–75); quetiapine (76–79); risperidone oral (80–82); risperidone LAI (83); sertindole (54, 84, 85); ziprasidone (87–90); amisulpride, patients with positive symptoms (32); and clozapine (53).

[b] In these studies, the comparator was low-dose amisulpride (100 mg/day) and low-dose clozapine (100 mg/day), respectively. Although the results belong to the sensitivity analysis including low-dose comparators instead of placebo, we present them here because they are the only available results for these drugs.

Clozapine. A small study with data for 48 patients with treatment-resistant illness met the criteria for the sensitivity analysis with subtherapeutic doses as a comparators. Because it was the only clozapine study, we included it in Figure 2 (Figure 2U). Doses of 300 mg/day and 600 mg/day were better than 100 mg/day (53), and the ED95 was 567 mg/day.

TABLE 1. Dose equivalencies for antipsychotic drugs[a]

Antipsychotic	ED50 (mg/day)	ED95 (mg/day)	Risperidone, 1 mg eq[b]	Olanzapine, 1 mg eq[b]	Haloperidol, 1 mg eq[b]	Minimum Effective Dose (mg/day)[c]	Consensus: Target/Median Maximum Dose (mg/day)[d]	SPC: Target/ Maximum Dose (mg/day)[e]
Amisulpride, predominant negative symptoms	31.53	72.37	n.e.	11.19	n.e.	n.a.	n.a.	50–300
Amisulpride, predominant positive symptoms	264.26	536.94	85.77	35.39	84.82	n.a.	400–800/1000	400–800/1200
Aripiprazole	4.77	11.50	1.84	0.76	1.82	10	15–30/30	10–15/30
Aripiprazole LAI (lauroxil)	217.19[f]	462.63[f]	2.64	1.09	2.61	441[f]	n.a.	441–882/882[f]
Asenapine	2.82	14.97	2.39	0.99	2.36	10	n.a.	10/20
Brexpiprazole	0.73	3.36	0.54	0.22	0.53	2	n.a.	2–4/4
Cariprazine	1.65	7.63	1.22	0.50	1.21	1.5	n.a.	1.5–6/6
Haloperidol	2.96	6.33	1.01	0.42	1.00	4	5–10/20	FDA: 1–15/100 EMA: 2–10/20
Iloperidone	5.75	20.13	3.22	1.33	3.18	8	n.a.	12–24/24
Lurasidone	43.88	147.03	23.49	9.69	23.23	40	n.a.	40–160/160
Olanzapine, predominant positive symptoms	5.99	15.17	2.42	1.00	2.40	7.5	10–20/30	10–20/20
Olanzapine LAI	127.03[g]	277.18[g]	3.16	1.31	3.13	210[g]	n.a.	150–300[g]
Olanzapine, predominant negative symptoms	2.88	6.47	n.e.	0.09	n.e.	n.a.	n.a.	n.a.
Paliperidone	3.86	13.35	2.13	0.88	2.11	3	6–9/12	3–12/12
Paliperidone LAI	32.43[f]	119.97[f]	1.53	0.63	1.52	25[f]	n.a.	39–234/234[f]
Quetiapine	207.41	482.08	77.01	31.78	76.16	150	400–800/1000	IR: 150–750/ 750; XR: 400 –800/800
Risperidone	2.82	6.26	1.00	0.41	0.99	2	4–6/8.5	4–8/16
Risperidone LAI	17.57[g]	36.56[g]	0.42	0.17	0.41	25[g]	25–50/50[g]	25/50[g]
Sertindole	10.33	22.53	3.60	1.49	3.56	12	12–20/22	10–20/24
Ziprasidone	68.47	186.39	29.77	12.29	29.45	40	120–160/200	40–160/200

[a] Clozapine was not presented in the table, because the data were based on a single small trial (N=48) that was not placebo controlled. ED50=50% effective dose; ED95=95% effective dose; EMA=European Medicines Agency; eq=equivalent; ES=effect size (standardized mean differences calculated as Cohen's d); FDA=U.S. Food and Drug Administration; IR=immediate release; LAI=long-acting injectable; n.a.=not available; n.e.=not estimable because the failed study was the only included study; SPC=summary of product characteristics; XR=extended release.

[b] The doses of long-acting injectable antipsychotics were converted to a daily dose by dividing the ED95 by the injection interval in days, except for paliperidone LAI, for which we used the conversion factor presented by Gopal et al. (118).

[c] Minimum effective doses were derived from the reviews of Leucht et al. 2014 (7) and Rothe et al. 2018 (8), amended with data on the newer antipsychotics, brexpiprazole (46, 48) and cariprazine (49).

[d] Recommended target and median maximum doses are from the international consensus study of Gardner et al. 2010 (94), based on a case vignette with a "moderately symptomatic adult man with DSM-IV schizophrenia with ≥2 years of antipsychotic treatment and not considered treatment refractory" (94).

[e] Recommended target and maximum doses for adults with an acute episode or predominant negative symptoms (without considering dose adjustments in special populations, e.g., elderly patients, comorbidities, concomitant drugs) derived from the summary of product characteristics from the FDA (retrieved from https://dailymed.nlm.nih.gov/dailymed/), except for amisulpride and sertindole (retrieved on the same day from the UK's Medicines and Healthcare Products Regulatory Agency at http://www.mhra.gov.uk/spc-pil/). Information about the use of haloperidol in Europe was also drawn from the European Medicines Agency (https://www.ema.europa.eu/en/medicines/human/referrals/haldol-associated-names).

[f] Every 4 weeks.

[g] Every 2 weeks.

The dose-response curve continues increasing beyond 600 mg/day, although cautious interpretation is advised because there were only two data points and because the sample size was small.

Haloperidol. The single haloperidol dose-finding study (54) compared 4 mg/day, 8 mg/day, and 16 mg/day and showed a bell-shaped dose-response curve. The ED95 was achieved at 6.3 mg/day (Figure 2G).

Iloperidone. Four placebo-controlled dose-finding studies (three were summarized in one publication [55, 56]) examined iloperidone doses between 4 mg/day and 24 mg/day. According to homogeneous results, the ED95 was 20.1 mg/day.

The dose-response curve had a relatively narrow range, with even the most efficacious examined doses leading to no higher effect sizes than approximately 0.3. The dose-response curve does not appear to have reached a plateau (Figure 2H).

Lurasidone. Six dose-finding studies examined lurasidone doses between 20 mg/day and 160 mg/day (57–62). (Data from study NCT00711269/D1001002 were not available.) The ED95 was achieved at 147 mg/day. The results were significantly heterogeneous (I^2=61%), and the dose-response curve suggests that higher doses could be more efficacious than the highest dose tested so far (160 mg/day) (Figure 2I).

Oral olanzapine for patients with positive symptoms. In two homogeneous studies (63, 64) examining doses between 1 mg/day and 15±2.5 mg/day, the ED95 was 15.1 mg/day. The dose-response curve was still increasing at 15±2.5 mg/day, suggesting that higher doses could be more efficacious (Figure 2J).

Oral olanzapine for patients with predominant negative symptoms. A single study in 174 patients with predominant negative symptoms compared olanzapine at 5 mg/day and 20 mg/day with placebo (65). The ED95 was 6.5 mg/day (Figure 2K). The dose-response curve was bell-shaped.

Olanzapine LAI. A single study (66) compared 210 mg every 2 weeks, 405 mg every 4 weeks, and 300 mg every 2 weeks with placebo. We converted 405 mg every 4 weeks to 203 mg every 2 weeks for comparability. The ED95 was 277 mg every 2 weeks. At 300 mg every 2 weeks, the dose-response curve was not plateauing yet. But because of the similar results of 203 mg and 210 mg every 2 weeks, this result was based on only two doses (Figure 2L).

Oral paliperidone. In five studies that examined doses between 1.5 mg/day and 15 mg/day (67–71), the ED95 was 13.4 mg/day. The dose-response curve suggests that at 15 mg/day a plateau possibly had not been reached yet (Figure 2M).

Paliperidone LAI. According to data from four studies in acute patients (N=1,695) (72–75) with doses between 25 and 150 mg every 4 weeks, the ED95 was 120 mg every 4 weeks. The dose-response curve seemed to be slightly rising at 150 mg every 4 weeks (Figure 2N).

Quetiapine. We included four studies of quetiapine (76–79) with doses between 75 mg/day and 800 mg/day. The ED95 was 482 mg/day, and the dose-response curve showed a plateau (Figure 2O). There was considerable heterogeneity (I^2=58%). Indeed, when immediate-release and extended-release quetiapine were analyzed separately in a sensitivity analysis, the immediate-release formulation had a clearly lower ED95 (297 mg/day) than the extended-release formulation (739 mg/day) (see Table 1; see also Figure S3 in the online supplement). However, the lowest extended-release dose examined was 300 mg/day, meaning that the effects of lower extended-release doses are not known.

Oral risperidone. Three dose-finding studies compared risperidone doses between 2 mg/day and 16 mg/day with placebo (80–82). Homogeneous results showed a bell-shaped dose-response. The 95% effective dose was 6.3 mg/day (Figure 2P).

Risperidone LAI. In one study in 283 acute patients (83) comparing 25 mg every 2 weeks, 37.5 mg every 2 weeks, and 75 mg every 2 weeks with placebo, the ED95 was 37 mg every 2 weeks. The dose-response curve was bell-shaped (Figure 2Q).

Sertindole. Three studies compared sertindole doses between 8 mg/day and 24 mg/day with placebo (54, 84, 85). The ED95 was 22.5 mg/day, and the dose-response curve still appeared to be rising at 24 mg/day (Figure 2R), but we note that this rise disappeared in the sensitivity analysis that included a study with subtherapeutically dosed sertindole as the comparator (86) (see Figure S3 in the online supplement).

Ziprasidone. Four studies analyzed doses between 10 mg/day and 200 mg/day (87–90). Homogeneous results suggested a 95% effective dose of 186 mg/day and the dose-response curve was still increasing at 200 mg/day (Figure 2S).

Zotepine. We were unable to obtain data from the only dose-finding study we identified (91).

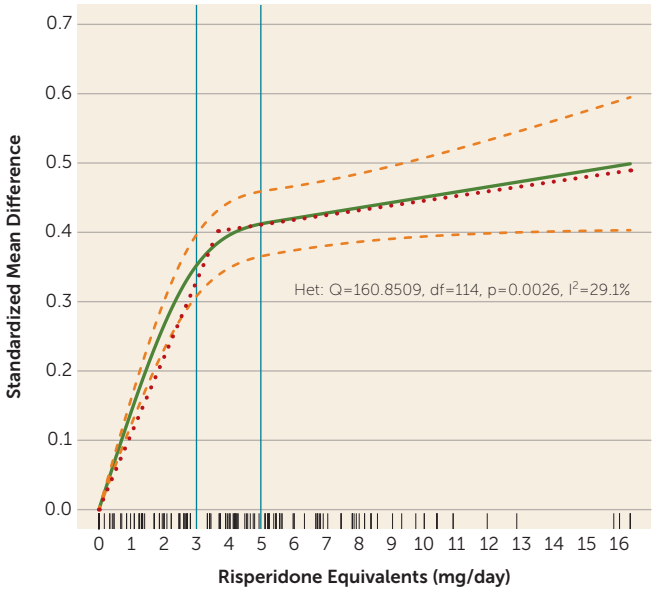
Sensitivity Analyses

One study using olanzapine 1 mg/day (6), one using risperidone 1 mg/day (92), one using sertindole 8 mg/day (86), and one using ziprasidone 4 mg/day (93) were added to the sensitivity analysis of subtherapeutic doses rather than placebo as comparators. The results on amisulpride, clozapine, and sertindole were reported above. The remaining studies (6, 92, 93) did not change the results much (see Table 1 and Figure S3 in the online supplement). The most notable change after excluding failed studies (37, 48, 56, 62, 65, 71, 78, 89) was that the ED95 of lurasidone decreased from 147 mg/day to 109 mg/day. Excluding studies that were conducted exclusively in patients with schizoaffective disorder (relevant only for paliperidone [70, 71]) did not have a major impact on the results (see Table 1 and Figure S3 in the online supplement).

Dose Equivalencies

Table 1 presents the doses equivalent to risperidone 1 mg/day, olanzapine 1 mg/day, and haloperidol 1 mg/day derived from the ED95s. An Excel spreadsheet for dose conversions, which also presents estimates based on the minimum effective dose method (updated with the newer drugs brexpiprazole and cariprazine [7, 8]), the mean dose method (10), the daily

FIGURE 3. Dose-response curve across antipsychotic drugs, with doses converted to risperidone equivalents[a]



[a] Het=heterogeneity. The estimated dose-response curve is represented by solid black line and its 95% confidence intervals by dotted black lines. The red dotted line represents the linear spline at 3.7 mg/day risperidone equivalents, above which the slope did not show a significant increase (p>0.1). The rug plot above the x-axis represents the individual study arms converted to risperidone equivalents.

defined doses (DDD) method (9), and an expert consensus method (94), can be downloaded from our web site (http://www.cfdm.de/media/doc/Antipsychotic%20dose%20conversion%20calculator.xls).

Dose-Response Curve With All Drugs Pooled

The dose-response curve of all study arms converted to risperidone equivalents is presented in Figure 3. The ED95 was 13.06 mg/day. However, the curve appeared to flatten between 3 and 5 mg/day, and the slope showed no significant increase above 3.66 mg/day (p=0.1). Deriving risperidone equivalents from the minimum effective dose method (7, 8, 26) yielded a similar dose-response curve (see Figure S3 in the online supplement).

DISCUSSION

We used dose-response meta-analysis to identify the near-maximum effective doses of 20 antipsychotics to explore whether the licensed doses for some drugs may be higher or lower than the maximum effective doses and whether it may be worthwhile examining higher doses for some drugs. We also derived dose equivalencies, which are presented with results of other methods in an Excel spreadsheet, available at our web site, that maybe used in practice.

This dose-response analysis provides information that is important for clinicians. For example, risperidone 2 mg/day was associated with an effect size of approximately 0.25, while 6 mg/day led to an effect size of 0.6, more than twice as high. The method is based on empirical data rather than the licensed dose ranges, which are influenced by the initial estimates from animal studies and as a result can be too high or too low. But these early studies influence the choice of licensed doses. Indeed, for some drugs, the upper limits of licensed doses were higher than the maximum effective doses. The clearest examples are drugs with bell-shaped dose-response curves. For example, the maximum licensed doses of aripiprazole (30 mg/day) and risperidone (16 mg/day) far exceeded the ED95s for these drugs (11.5 mg/day and 6.3 mg/day, respectively). With the limitation that only one dose-finding trial was available for haloperidol, for the average patient doses greater than approximately 6.5 mg/day also may not provide more efficacy. This may also be true for risperidone LAI in doses above 40 mg every 2 weeks. The results for haloperidol are supported by a Cochrane review (19), and no clear efficacy differences were found between lower and higher doses in several studies conducted in the 1980s that could not be included in our analysis because they were not placebo controlled (Van Putten et al. [95] [5, 10, and 20 mg/day], Rifkin et al. [96] [10, 30, and 80 mg/day], and McEvoy et al. [97] ["neuroleptic threshold doses," average 3.4 mg/day, compared with doses 2–10 times higher, average 11.6 mg/day]). For antipsychotics with bell-shaped curves, a likely reason for the curve shape is that although efficacy plateaus beyond a certain dose, the frequency of extrapyramidal side effects continues to increase. These extrapyramidal side effects may mimic negative symptoms, which may contribute to higher PANSS scores. Extrapyramidal symptoms can also lead to earlier and higher rates of discontinuation, such that the antipsychotic has less time to act on symptoms (98).

In contrast, for the drugs with clearly increasing dose-response curves, higher-than-licensed doses could be more efficacious. Only a few studies have explored whether higher-than-licensed doses may be more efficacious. In one study, olanzapine at 40 mg/day was more efficacious than at lower doses (10 mg/day and 20 mg/day), corresponding with our increasing dose-response curve, but only in a severely ill subgroup (99). One safety study compared aripiprazole 30, 45, 60, 75, and 90 mg/day in patients with stable symptoms and found no differences in efficacy (100, 101). Two studies revealed no superiority for quetiapine at 1200 mg/day compared with 600 mg/day (102) or 800 mg/day (103). In another study, Goff et al. (104) found no difference between ziprasidone 320 mg/day and 160 mg/day in patients who did not respond to 160 mg/day. In our analysis, a plateau was not yet attained for paliperidone at a dose of 12 mg/day, which is the maximum licensed dose. A dose of 15 mg/day has not been licensed, possibly because it produced more side effects than lower doses (105).

Indeed, toxicity findings, for example from animal studies, can limit attempts to trial higher doses. We did not examine side effects because given the enormous problem of non-response in schizophrenia (106), we believe that knowledge of the near-maximum efficacious doses is important

irrespective of side effects. That being said, the importance of the multiple side effects of antipsychotics (extrapyramidal side effects, weight gain, increase in prolactin levels, QTc prolongation, etc.) in clinical decision making cannot be sufficiently emphasized. For example, the increasing dose-response efficacy curve of olanzapine must be counterbalanced by the dose-related weight gain associated with the drug (107). Metabolic side effects are an important factor for physical comorbidities and likely excess mortality (108). Clinicians therefore must be alert to side effects such as weight gain produced by antipsychotics such as olanzapine and quetiapine, and whenever possible they should use low doses.

The single purpose of plotting the dose-response curve combining all drugs was to explore the concept that overall antipsychotic dose-response shows a hyperbolic pattern with a plateau. The estimated ED95 of 13.06 mg/day risperidone equivalents was high. As shown in Figure 3, data were available for only a few very high doses, which may have artificially led to a slightly increasing slope at the right end of the curve. Moreover, the curve clearly started to flatten between 3–5 mg/day risperidone equivalents, with relatively little efficacy gain achieved by higher doses. Nevertheless, our purpose in this analysis was of a theoretical rather than a clinical nature.

Dose-response meta-analysis avoids several limitations of other dose equivalence methods. The minimum effective dose method is based on the lowest dose of each antipsychotic that was statistically significantly more efficacious than placebo (7, 8, 26). Whether a dose is significantly better than placebo, however, depends in part on sample size. Indeed, some minimum effective doses found in previous publications (7, 8, 26) were almost fully efficacious (e.g., aripiprazole 10 mg/day) in contrast to some others (e.g., risperidone 2 mg/day). Thus, doses on different parts of the dose-response curves were compared, which distorts the relationships. The classical mean dose method estimates chlorpromazine equivalents by calculating the ratio of the mean doses of each antipsychotic in flexible-dose trials (10, 109). But flexible-dose studies usually have predefined dosing ranges, which may not even include the optimum dose (13, 14). Neither expert consensus methods (94, 110) nor the daily defined dose (DDD) method (9) are rigorously evidence-based.

While the approach we used overcomes these problems, it does have limitations. We could only use the aggregated data for a few doses for each drug, and our judgments of the shapes of the curves were based on visual inspection. The 95% confidence intervals of the spline curves were often wide, which reflects substantial uncertainty and variability. While the studies of some drugs included large numbers of patients (e.g., more than 1,000), few patient data were available for other drugs. The most extreme example is clozapine (one randomized controlled trial with 48 patients); its curve is clearly of low validity, and it was presented only for the sake of completeness. The results are based on the available doses, but in cases of increasing dose-response curves, the ED95 might actually be higher. The dose-response relationships in specific populations, such as first-episode patients, elderly patients (who need lower doses), and patients with treatment-resistant illness, are likely to be different. The method used here assumes equal efficacy of antipsychotic drugs. A network meta-analysis suggested efficacy differences between some drugs, although we considered them to be small (111). In contrast, the method should not be affected by the increase in placebo response and the resulting decrease in effect sizes over recent decades (106, 112). As long as we were able to identify the near-maximum (95%) effective dose of each compound, how large their superiority is compared with placebo is not important. As for all other methods, dose-response meta-analysis assumes linear relationships, but this is not necessarily the case across all examined doses. For example, according to our analysis, 20 mg/day olanzapine corresponds to 8.25 mg/day risperidone, but as risperidone's dose-response curve is bell-shaped, it would not make clinical sense to switch a patient to 8.25 mg/day. Therefore, clinicians should not simply apply our conversion calculator but should also consider the individual dose-response curves presented in Figure 2.

Our analysis does not provide evidence regarding the effectiveness of switching antipsychotics. A narrative review of 10 inconclusive trials (113) and a recent first-episode study (114) did not find evidence to support switching for nonresponse. According to these data, switching might be most appropriate when problematic side effects are present, except in cases of treatment resistance, where clozapine is a superior drug (115). Similarly, our analysis in average patients, most of whom will respond to moderate doses, was not designed to identify those who benefit only from higher does. A Cochrane review of 10 relatively small trials did not yield evidence that might support increasing the dose for nonresponse (116), except for one trial in which patients who had not improved on lurasidone at 80 mg/day within 2 weeks then benefited from an increase to 160 mg/day (57).

The method presented here does not allow us to derive reliable lower dose limits. For the lower dose limits listed in Table 1, we used the doses from the summaries of product characteristics, from an international consensus study, and from the minimum effective dose method. We also recommend comparison with other methods (http://www.cfdm.de/media/doc/Antipsychotic%20dose%20conversion%20calculator.xls).

We stress that our results provide some guidance based on "average" patients with chronic illness. Individual dosing decisions should be guided by the properties of each drug (e.g., pharmacodynamic and pharmacokinetic properties, side effects), patient characteristics (e.g., age, illness stage, severity, physical comorbidities, and previously known individual effective doses), and concomitant treatments that could, by interaction, influence drug plasma levels (117).

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An Excel spreadsheet for dose conversions based on various methods is available at the authors' web site: http://www.cfdm.de/media/doc/Antipsychotic%20dose%20conversion%20calculator.xls.

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