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

Stefan Leucht, M.D., Alessio Crippa, Ph.D., Spyridon Siafis, M.D., Maxine X. Patel, M.D., Nicola Orsini, Ph.D., John M. Davis, M.D.

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

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

See related feature: CME course (p. 361)

(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.

Am J Psychiatry 2020; 177:342-353; doi: 10.1176/appi.ajp.2019.19010034

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 nearmaximum effective doses by conducting a meta-analysis of 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 secondgeneration 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 metaanalysis following the method proposed by Crippa and

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 bellshaped 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.

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 I² statistic, where we considered I² 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=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 15 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 cral (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 for these studies 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.

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
lloperidone	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 ⁹	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

TABLE 1. Dose equivalencies for antipsychotic drugs^a

^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 (America Lateria) (https://tatuut.com/characteria) (https://tatuut.com/characte

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 doseresponse 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 $15\pm2.5 \text{ mg/day}$, the ED95 was 15.1 mg/day. The dose-response curve was still increasing at $15\pm2.5 \text{ mg/day}$, 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 nearmaximum 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 doseresponse curves, higher-than-licensed doses could be more efficacious. Only a few studies have explored whether higherthan-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 vet 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 nonresponse 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 doseresponse 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 flexibledose 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, doseresponse 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).

AUTHOR AND ARTICLE INFORMATION

Department of Psychiatry and Psychotherapy, Technical University of Munich, School of Medicine, Munich (Leucht, Siafis); Department of Psychosis Studies, Institute of Psychiatry, Psychology, and Neuroscience, King's College London (Leucht, Patel); Department of Global Public Health, Karolinska Institutet, Stockholm (Orsini); Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm (Crippa); Department of Psychiatry, University of Illinois at Chicago, and John Hopkins School of Medicine, Baltimore (Davis).

Send correspondence to Dr. Leucht (stefan.leucht@tum.de)

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.

The authors thank Samantha Roberts for her help with the literature search and Maximilian Huhn and Marc Krause for their help in selecting studies.

Dr. Leucht has received honoraria for service as a consultant or adviser and/or for lectures from Angelini, Boehringer Ingelheim, Gedeon Richter, Janssen, Johnson & Johnson, LB Pharma, LTS Lohmann, Lundbeck, MSD, Otsuka, Recordati, Sandoz, Sanofi-Aventis, Sunovion, and TEVA. Dr. Patel has received honoraria for consulting or lectures from Boehringer-Ingelheim, Janssen, Lundbeck, Otsuka, and Sunovion. The other authors report no financial relationships with commercial interests.

Received January 12, 2019; revision received August 26, 2019; accepted September 30, 2019; published online Dec. 16, 2019.

REFERENCES

- Pinheiro JC, Bretz F, Branson M: Analysis of dose-response studies: modeling approaches, in Dose Finding in Drug Development. Edited by Ting N. New York, Springer, 2016, pp 146–171
- 2. Kenakin T: The mass action equation in pharmacology. Br J Clin Pharmacol 2016; 81:41–51
- 3. Davis JM, Chen N: Dose response and dose equivalence of antipsychotics. J Clin Psychopharmacol 2004; 24:192–208
- 4. Crippa A, Orsini N: Dose-response meta-analysis of differences in means. BMC Med Res Methodol 2016; 16:91
- Uchida H, Suzuki T, Takeuchi H, et al: Low dose vs standard dose of antipsychotics for relapse prevention in schizophrenia: metaanalysis. Schizophr Bull 2011; 37:788–799
- Beasley CM Jr, Hamilton SH, Crawford AM, et al: Olanzapine versus haloperidol: acute phase results of the international doubleblind olanzapine trial. Eur Neuropsychopharmacol 1997; 7:125–137
- Leucht S, Samara M, Heres S, et al: Dose equivalents for secondgeneration antipsychotics: the minimum effective dose method. Schizophr Bull 2014; 40:314–326
- 8. Rothe PH, Heres S, Leucht S: Dose equivalents for second generation long-acting injectable antipsychotics: the minimum effective dose method. Schizophr Res 2018; 193:23–28
- 9. Leucht S, Samara M, Heres S, et al: Dose equivalents for antipsychotic drugs: the DDD method. Schizophr Bull 2016; 42(suppl 1):S90–S94
- Leucht S, Samara M, Heres S, et al: Dose equivalents for secondgeneration antipsychotic drugs: the classical mean dose method. Schizophr Bull 2015; 41:1397–1402
- Leucht S, Arbter D, Engel RR, et al: How effective are secondgeneration antipsychotic drugs? A meta-analysis of placebocontrolled trials. Mol Psychiatry 2009; 14:429–447
- Leucht S, Komossa K, Rummel-Kluge C, et al: A meta-analysis of head-to-head comparisons of second-generation antipsychotics in the treatment of schizophrenia. Am J Psychiatry 2009; 166:152–163
- Leucht S, Corves C, Arbter D, et al: Second-generation versus firstgeneration antipsychotic drugs for schizophrenia: a meta-analysis. Lancet 2009; 373:31–41
- 14. Leucht S, Cipriani A, Spineli L, et al: Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet 2013; 382:951–962
- 15. Belgamwar RB, El-Sayeh HG: Aripiprazole versus placebo for schizophrenia. Cochrane Database Syst Rev 2011; (8):CD006622
- 16. Rattehalli RD, Zhao S, Li BG, et al: Risperidone versus placebo for schizophrenia. Cochrane Database Syst Rev 2016; 12:CD006918

- 17. Adams CE, Bergman H, Irving CB, et al: Haloperidol versus placebo for schizophrenia. Cochrane Database Syst Rev 2013; (11):CD003082
- Li C, Xia J, Wang J: Risperidone dose for schizophrenia. Cochrane Database Syst Rev 2009; (4):CD007474
- Donnelly L, Rathbone J, Adams CE: Haloperidol dose for the acute phase of schizophrenia. Cochrane Database Syst Rev 2013; (8): CD001951
- Woodhead M: 80% of China's clinical trial data are fraudulent, investigation finds. BMJ 2016; 355:i5396
- 21. Higgins JPT, Green S: Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. Chichester, UK, Wiley and Sons, 2011 [updated March 2011]
- 22. Kay SR, Fiszbein A, Opler LA: The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull 1987; 13:261–276
- 23. Overall JE, Gorham DR: The Brief Psychiatric Rating Scale. Psychol Rep 1962; 10:790–812
- Andreasen NC: The Scale for the Assessment of Negative Symptoms (SANS): conceptual and theoretical foundations. Br J Psychiatry Suppl 1989; 155(7):49–58
- Durrleman S, Simon R: Flexible regression models with cubic splines. Stat Med 1989; 8:551–561
- 26. Woods SW: Chlorpromazine equivalent doses for the newer atypical antipsychotics. J Clin Psychiatry 2003; 64:663–667
- Higgins JPT, Thompson SG, Deeks JJ, et al: Measuring inconsistency in meta-analyses. BMJ 2003; 327:557–560
- Crippa A, Orisini N: Multivariate dose-response meta-analysis: the dosresmeta R package. Journal of Statistical Software, Code Snippets 2016; 72:1–15
- 29. Lecrubier Y, Bouhassira M, Olivier V, et al: Olanzapine versus amisulpride and placebo in the treatment of negative symptoms and deficit states of chronic schizophrenia. Eur Neuropsychopharmacol 1999; 9:S288
- Danion JM, Rein W, Fleurot O, et al: Improvement of schizophrenic patients with primary negative symptoms treated with amisulpride. Am J Psychiatry 1999; 156:610–616
- Boyer P, Lecrubier Y, Puech AJ, et al: Treatment of negative symptoms in schizophrenia with amisulpride. Br J Psychiatry 1995; 166:68–72
- 32. Puech A, Fleurot O, Rein W, et al: Amisulpride, and atypical antipsychotic, in the treatment of acute episodes of schizophrenia: a dose-ranging study vs haloperidol. Acta Psychiatr Scand 1998; 98: 65–72
- 33. Cutler AJ, Marcus RN, Hardy SA, et al: The efficacy and safety of lower doses of aripiprazole for the treatment of patients with acute exacerbation of schizophrenia. CNS Spectr 2006; 11:691–702
- 34. Kane JM, Carson WH, Saha AR, et al: Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. J Clin Psychiatry 2002; 63: 763–771
- 35. McEvoy JP, Daniel DG, Carson WH Jr, et al: A randomized, double-blind, placebo-controlled study of the efficacy and safety of aripiprazole 10, 15, or 20 mg/day for the treatment of patients with acute exacerbations of schizophrenia. J Psychiatr Res 2007; 41:895–905
- 36. Potkin SG, Saha AR, Kujawa MJ, et al: Aripiprazole, an antipsychotic with a novel mechanism of action, and risperidone vs placebo in patients with schizophrenia and schizoaffective disorder. Arch Gen Psychiatry 2003; 60:681–690
- US Food and Drug Administration, Center for Drug Evaluation and Research: Application Number 21-436: Medical Review(s) (94202 S) (https://www.accessdata.fda.gov/drugsatfda_docs/ nda/2002/21-436_Abilify_medr_P1.pdf)
- Meltzer HY, Risinger R, Nasrallah HA, et al: A randomized, doubleblind, placebo-controlled trial of aripiprazole lauroxil in acute exacerbation of schizophrenia. J Clin Psychiatry 2015; 76:1085– 1090

- 39. US Food and Drug Administration, Center for Drug Evaluation and Research: Application Number 22-117: Medical Review(s) (041-021 SH): A multicenter, randomized, double-blind, fixed-dose, 6-week trial of the efficacy and safety of asenapine compared with placebo using olanzapine positive control in subjects with an acute exacerbation of schizophrenia. (https://www.accessdata.fda.gov/drugsatfda_docs/ nda/2009/022117s000_MedR_P1.pdf)
- 40. Kane JM, Cohen M, Zhao J, et al: Efficacy and safety of asenapine in a placebo- and haloperidol-controlled trial in patients with acute exacerbation of schizophrenia. J Clin Psychopharmacol 2010; 30: 106–115
- US Food and Drug Administration, Center for Drug Evaluation and Research: Application Number 22-117: Medical Review(s) (041-002 S). Center for drug evaluation and research. Application number 22-117. Medical review(s). (https://www.accessdata.fda.gov/drugsatfda_docs/ nda/2009/022117s000_MedR_P1.pdf)
- US Food and Drug Administration, Center for Drug Evaluation and Research: Application Number 22-117: Medical Review(s) (041-013 S). (https://www.accessdata.fda.gov/drugsatfda_docs/nda/ 2009/022117s000_MedR_P1.pdf)
- 43. Kinoshita T, Bai YM, Kim JH, et al: Efficacy and safety of asenapine in Asian patients with an acute exacerbation of schizophrenia: a multicentre, randomized, double-blind, 6-week, placebo-controlled study. Psychopharmacology (Berl) 2016; 233:2663–2674
- 44. Landbloom R, Mackle M, Wu X, et al: Asenapine for the treatment of adults with an acute exacerbation of schizophrenia: results from a randomized, double-blind, fixed-dose, placebo-controlled trial with olanzapine as an active control. CNS Spectr 2017; 22:333–341
- 45. Kane JM, Skuban A, Ouyang J, et al: A multicenter, randomized, double-blind, controlled phase 3 trial of fixed-dose brexpiprazole for the treatment of adults with acute schizophrenia. Schizophr Res 2015; 164:127–135
- 46. Correll CU, Skuban A, Ouyang J, et al: Efficacy and safety of brexpiprazole for the treatment of acute schizophrenia: a 6-week randomized, double-blind, placebo-controlled trial. Am J Psychiatry 2015; 172:870–880
- Ishigooka J, Iwashita S, Tadori Y: Efficacy and safety of brexpiprazole for the treatment of acute schizophrenia in Japan: A 6-week, randomized, double-blind, placebo-controlled study. Psychiatry Clin Neurosci 2018; 72:692–700
- Correll CU, Skuban A, Hobart M, et al: Efficacy of brexpiprazole in patients with acute schizophrenia: review of three randomized, double-blind, placebo-controlled studies. Schizophr Res 2016; 174: 82–92
- 49. Durgam S, Starace A, Li D, et al: An evaluation of the safety and efficacy of cariprazine in patients with acute exacerbation of schizophrenia: a phase II randomized clinical trial. Schizophr Res 2014; 152:450–457
- 50. Durgam S, Cutler AJ, Lu K, et al: Cariprazine in acute exacerbation of schizophrenia: a fixed-dose, phase 3, randomized, double-blind, placebo- and active-controlled trial. J Clin Psychiatry 2015; 76: e1574–e1582
- Kane JM, Zukin S, Wang Y, et al: Efficacy and safety of cariprazine in acute exacerbation of schizophrenia: results from an international phase III clinical trial. J Clin Psychopharmacol 2015; 35:367–373
- 52. Durgam S, Litman RE, Papadakis K, et al: Cariprazine in the treatment of schizophrenia: a proof-of-concept trial. Int Clin Psychopharmacol 2016; 31:61–68
- Simpson GM, Josiassen RC, Stanilla JK, et al: Double-blind study of clozapine dose response in chronic schizophrenia. Am J Psychiatry 1999; 156:1744–1750
- Zimbroff DL, Kane JM, Tamminga CA, et al: Controlled, doseresponse study of sertindole and haloperidol in the treatment of schizophrenia. Am J Psychiatry 1997; 154:782–791
- 55. Potkin SG, Litman RE, Torres R, et al: Efficacy of iloperidone in the treatment of schizophrenia: initial phase 3 studies. J Clin Psychopharmacol 2008; 28(suppl 1):S4–S11

- 56. US Food and Drug Administration, Center for Drug Evaluation and Research: Application Number 22-192: Medical Review: Drug Approval Package, Fanapt (iloperidone) tablets. (https:// www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022192s000_ MedR_P1.pdf)
- 57. Loebel A, Cucchiaro J, Sarma K, et al: Efficacy and safety of lurasidone 80 mg/day and 160 mg/day in the treatment of schizophrenia: a randomized, double-blind, placebo- and activecontrolled trial. Schizophr Res 2013; 145:101–109
- Loebel A, Silva R, Goldman R, et al: Lurasidone dose escalation in early nonresponding patients with schizophrenia: a randomized, placebo-controlled study. J Clin Psychiatry 2016; 77:1672–1680
- 59. Meltzer HY, Cucchiaro J, Silva R, et al: Lurasidone in the treatment of schizophrenia: a randomized, double-blind, placeboand olanzapine-controlled study. Am J Psychiatry 2011; 168: 957–967
- Nasrallah HA, Silva R, Phillips D, et al: Lurasidone for the treatment of acutely psychotic patients with schizophrenia: a 6-week, randomized, placebo-controlled study. J Psychiatr Res 2013; 47: 670–677
- 61. Ogasa M, Kimura T, Nakamura M, et al: Lurasidone in the treatment of schizophrenia: a 6-week, placebo-controlled study. Psychopharmacology (Berl) 2013; 225:519–530
- 62. US Food and Drug Administration, Center for Drug Evaluation and Research: Application Number 200603: Medical Review(s) (049 S): A 6-week, double-blind, randomized, fixed dose, parallel-group study of the efficacy and safety of three dose levels of SM-13496 (lurasidone) compared to placebo and haloperidol in patients with schizophrenia who are experiencing an acute exacerbation of symptoms (https://www.accessdata.fda.gov/drugsatfda_docs/nda/ 2010/2006030rig1s000MedR.pdf)
- 63. Beasley CM Jr, Sanger T, Satterlee W, et al: Olanzapine versus placebo: results of a double-blind, fixed-dose olanzapine trial. Psychopharmacology (Berl) 1996; 124:159–167
- 64. Beasley CM Jr, Tollefson G, Tran P, et al: Olanzapine versus placebo and haloperidol: acute phase results of the North American doubleblind olanzapine trial. Neuropsychopharmacology 1996; 14:111–123
- 65. Lecrubier Y, Quintin P, Bouhassira M, et al: The treatment of negative symptoms and deficit states of chronic schizophrenia: olanzapine compared to amisulpride and placebo in a 6-month double-blind controlled clinical trial. Acta Psychiatr Scand 2006; 114:319–327
- 66. Lauriello J, Lambert T, Andersen S, et al: An 8-week, double-blind, randomized, placebo-controlled study of olanzapine long-acting injection in acutely ill patients with schizophrenia. J Clin Psychiatry 2008; 69:790–799
- 67. Kane J, Canas S, Kramer M, et al: Treatment of schizophrenia with paliperidone extended-release tablets: a 6-week placebo-controlled trial. Schizophr Res 2007; 90:147–161
- Davidson M, Emsley R, Kramer M, et al: Corrigendum to "Efficacy, safety, and early response of paliperidone extended-release tablets (paliperidone ER): results of a 6-week, randomized, placebocontrolled study" [Schizophrenia Research 93 (1–3) (2007) 117–130]. Schizophr Res 2007; 96:273–274
- 69. Canuso CM, Lindenmayer JP, Kosik-Gonzalez C, et al: A randomized, double-blind, placebo-controlled study of 2 dose ranges of paliperidone extended-release in the treatment of subjects with schizoaffective disorder. J Clin Psychiatry 2010; 71:587–598
- 70. Canuso CM, Schooler N, Carothers J, et al: Paliperidone extendedrelease in schizoaffective disorder: a randomized, controlled study comparing a flexible dose with placebo in patients treated with and without antidepressants and/or mood stabilizers. J Clin Psychopharmacol 2010; 30:487–495
- 71. Coppola D, Melkote R, Lannie C, et al: Efficacy and safety of paliperidone extended release 1.5 mg/day: a double-blind, placebo- and active-controlled study in the treatment of patients with schizophrenia. Psychopharmacol Bull 2011; 44:54–72

- Nasrallah HA, Gopal S, Gassmann-Mayer C, et al: A controlled, evidence-based trial of paliperidone palmitate, a long-acting injectable antipsychotic, in schizophrenia. Neuropsychopharmacology 2010; 35:2072–2082
- 73. Pandina GJ, Lindenmayer JP, Lull J, et al: A randomized, placebocontrolled study to assess the efficacy and safety of 3 doses of paliperidone palmitate in adults with acutely exacerbated schizophrenia. J Clin Psychopharmacol 2010; 30:235–244
- 74. Gopal S, Hough DW, Xu H, et al: Efficacy and safety of paliperidone palmitate in adult patients with acutely symptomatic schizophrenia: a randomized, double-blind, placebo-controlled, dose-response study. Int Clin Psychopharmacol 2010; 25:247–256
- 75. Kramer M, Litman R, Hough D, Lane R, Lim P, Liu Y, Eerdekens M. Paliperidone palmitate, a potential long-acting treatment for patients with schizophrenia: results of a randomized, double-blind, placebo-controlled efficacy and safety study. Int J Neuropsychopharmacol 2010; 13:635–647
- 76. Arvanitis LA, Miller BG: Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo: the Seroquel Trial 13 Study Group. Biol Psychiatry 1997; 42:233–246
- 77. Kahn RS, Schulz SC, Palazov VD, et al: Efficacy and tolerability of once-daily extended release quetiapine fumarate in acute schizophrenia: a randomized, double-blind, placebo-controlled study. J Clin Psychiatry 2007; 68:832–842
- Cutler AJ, Tran-Johnson T, Kalali A, et al: A failed 6-week, randomized, double-blind, placebo-controlled study of once-daily extended release quetiapine fumarate in patients with acute schizophrenia: lessons learned. Psychopharmacol Bull 2010; 43: 37–69
- Lindenmayer JP, Brown D, Liu S, et al: The efficacy and tolerability of once-daily extended release quetiapine fumarate in hospitalized patients with acute schizophrenia: a 6-week randomized, doubleblind, placebo-controlled study. Psychopharmacol Bull 2008; 41: 11–35
- Marder SR, Meibach RC: Risperidone in the treatment of schizophrenia. Am J Psychiatry 1994; 151:825–835
- Chouinard G, Jones B, Remington G, et al: A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. J Clin Psychopharmacol 1993; 13:25–40
- US Food and Drug Administration, Center for Drug Evaluation and Research: Approval Package, Application Number 20588/S002 and 20272/S007 (https://www.accessdata.fda.gov/drugsatfda_ docs/nda/97/20588.pdf)
- Kane JM, Eerdekens M, Lindenmayer JP, et al: Long-acting injectable risperidone: efficacy and safety of the first long-acting atypical antipsychotic. Am J Psychiatry 2003; 160:1125–1132
- 84. van Kammen DP, McEvoy JP, Targum SD, et al: A randomized, controlled, dose-ranging trial of sertindole in patients with schizophrenia. Psychopharmacology (Berl) 1996; 124:168–175
- Zborowski J, Schmitz P, Staser J, et al: Efficacy and safety of sertindole in a trial of schizophrenic patients. Biol Psychiatry 1995; 37: 661–662
- 86. Hale A, Azorin JM, Kasper S, et al: Sertindole improves both the positive and negative symptoms of schizophrenia: results of a phase III trial. Int J Psychiatry Clin Pract 2000; 4:55–62
- Daniel DG, Zimbroff DL, Potkin SG, et al: Ziprasidone 80 mg/day and 160 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 6-week placebo-controlled trial. Neuropsychopharmacology 1999; 20:491–505
- 88. Keck P Jr, Buffenstein A, Ferguson J, et al: Ziprasidone 40 and 120 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 4-week placebo-controlled trial. Psychopharmacology (Berl) 1998; 140:173–184
- 89. US Food and Drug Administration, Center for Drug Evaluation and Research: Approval Package for Application Number 20-825

(104 S): Medical Review(s) (https://www.accessdata.fda.gov/ drugsatfda_docs/nda/2001/20-825_Geodan_medr_P1.pdf)

- 90. US Food and Drug Administration, Center for Drug Evaluation and Research: Approval Package for Application Number 20-825: Medical review (https://www.accessdata.fda.gov/drugsatfda_ docs/nda/2001/20-825_Geodan_medr_P1.pdf)
- 91. Pharmaceuticals K: A multicentre, double-blind, placebo-controlled, parallel-group, dose-ranging study to evaluate the efficacy, safety and tolerability of zotepine 75, 150, and 300 mg daily doses in the treatment of acute schizophrenia. Study Reference No BPI 1201
- Peuskens J: Risperidone in the treatment of patients with chronic schizophrenia: a multi-national, multi-centre, double-blind, parallel-group study versus haloperidol. Br J Psychiatry 1995; 166:712–726
- Goff DC, Posever T, Herz L, et al: An exploratory haloperidolcontrolled dose-finding study of ziprasidone in hospitalized patients with schizophrenia or schizoaffective disorder. J Clin Psychopharmacol 1998; 18:296–304
- Gardner DM, Murphy AL, O'Donnell H, et al: International consensus study of antipsychotic dosing. Am J Psychiatry 2010; 167: 686–693
- 95. Van Putten T, Marder SR, Mintz J: A controlled dose comparison of haloperidol in newly admitted schizophrenic patients. Arch Gen Psychiatry 1990; 47:754–758
- 96. Rifkin A, Doddi S, Karajgi B, et al: Dosage of haloperidol for schizophrenia. Arch Gen Psychiatry 1991; 48:166–170
- 97. McEvoy JP, Hogarty GE, Steingard S: Optimal dose of neuroleptic in acute schizophrenia: a controlled study of the neuroleptic threshold and higher haloperidol dose. Arch Gen Psychiatry 1991; 48:739–745
- Geddes J, Freemantle N, Harrison P, et al: Atypical antipsychotics in the treatment of schizophrenia: systematic overview and metaregression analysis. BMJ 2000; 321:1371–1376
- 99. Kinon BJ, Volavka J, Stauffer V, et al: Standard and higher dose of olanzapine in patients with schizophrenia or schizoaffective disorder: a randomized, double-blind, fixed-dose study. J Clin Psychopharmacol 2008; 28:392–400
- 100. Saha AR, Ali MW, Ingenito GG, et al: Safety and tolerability of aripiprazole at doses higher than 30 mg. Int J Neuropsychopharmacol 2002; 5(supp. 1):S185
- 101. Citrome L: A review of aripiprazole in the treatment of patients with schizophrenia or bipolar I disorder. Neuropsychiatr Dis Treat 2006; 2:427–443
- 102. Lindenmayer JP, Citrome L, Khan A, et al: A randomized, doubleblind, parallel-group, fixed-dose, clinical trial of quetiapine at 600 versus 1200 mg/d for patients with treatment-resistant schizophrenia or schizoaffective disorder. J Clin Psychopharmacol 2011; 31:160–168
- 103. Honer WG, MacEwan GW, Gendron A, et al: A randomized, doubleblind, placebo-controlled study of the safety and tolerability of highdose quetiapine in patients with persistent symptoms of schizophrenia or schizoaffective disorder. J Clin Psychiatry 2012; 73:13–20
- 104. Goff DC, McEvoy JP, Citrome L, et al: High-dose oral ziprasidone versus conventional dosing in schizophrenia patients with residual symptoms: the ZEBRAS study. J Clin Psychopharmacol 2013; 33: 485–490
- 105. Davidson M, Emsley R, Kramer M, et al: Efficacy, safety and early response of paliperidone extended-release tablets (paliperidone ER): results of a 6-week, randomized, placebo-controlled study. Schizophr Res 2007; 93:117–130
- 106. Leucht S, Leucht C, Huhn M, et al: Sixty years of placebo-controlled antipsychotic drug trials in acute schizophrenia: systematic review, Bayesian meta-analysis, and meta-regression of efficacy predictors. Am J Psychiatry 2017; 174:927–942
- Spertus J, Horvitz-Lennon M, Abing H, et al: Risk of weight gain for specific antipsychotic drugs: a meta-analysis. NPJ Schizophr 2018; 4:12

- De Hert M, Detraux J, van Winkel R, et al: Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. Nat Rev Endocrinol 2011; 8:114–126
- Davis JM: Dose equivalence of the antipsychotic drugs. J Psychiatr Res 1974; 11:65–69
- Andreasen NC, Pressler M, Nopoulos P, et al: Antipsychotic dose equivalents and dose-years: a standardized method for comparing exposure to different drugs. Biol Psychiatry 2010; 67:255–262
- 111. Huhn M, Nikolakopoulou A, Schneider-Thoma J, et al: Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. Lancet 2019; 394:939–951
- 112. Agid O, Siu CO, Potkin SG, et al: Meta-regression analysis of placebo response in antipsychotic trials, 1970–2010. Am J Psychiatry 2013; 170:1335–1344
- 113. Leucht S, Winter-van Rossum I, Heres S, et al: The optimization of treatment and management of schizophrenia in Europe (OPTiMiSE) trial: rationale for its methodology and a review of the effectiveness of switching antipsychotics. Schizophr Bull 2015; 41:549–558

- 114. Kahn RS, Winter van Rossum I, Leucht S, et al: Amisulpride and olanzapine followed by open-label treatment with clozapine in firstepisode schizophrenia and schizophreniform disorder (OPTi-MiSE): a three-phase switching study. Lancet Psychiatry 2018; 5: 797–807
- 115. Siskind D, McCartney L, Goldschlager R, et al: Clozapine v first- and second-generation antipsychotics in treatment-refractory schizophrenia: systematic review and meta-analysis. Br J Psychiatry 2016; 209:385–392
- 116. Samara MT, Klupp E, Helfer B, et al: Increasing antipsychotic dose for non response in schizophrenia. Cochrane Database Syst Rev 2018; 5:CD011883
- 117. Hiemke C, Bergemann N, Clement HW, et al: Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology: Update 2017. Pharmacopsychiatry 2018; 51:9–62
- Gopal S, Gassmann-Mayer C, Palumbo J, et al: Practical guidance for dosing and switching paliperidone palmitate treatment in patients with schizophrenia. Curr Med Res Opin 2010; 26: 377–387