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Dose Equivalents for Second-Generation Antipsychotics: The Minimum Effective Dose Method

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Background: **Clinicians need to know the right antipsychotic dose for optimized treatment, and the concept of dose equivalence is important for many clinical and scientific purposes.** ***Methods:*** **We refined a method presented in 2003, which was based on the minimum effective doses found in fixed-dose studies. We operationalized the selection process, updated the original findings, and expanded them by systematically searching more recent literature and by including 13 second-generation antipsychotics. To qualify for the minimum effective dose, a dose had to be significantly more efficacious than placebo in the primary outcome of at least one randomized, double-blind, fixed-dose trial. In a sensitivity analysis, 2 positive trials were required. The minimum effective doses identified were subsequently used to derive olanzapine, risperidone, haloperidol, and chlorpromazine equivalents.** ***Results:*** **We reviewed 73 included studies. The minimum effective daily doses/olanzapine equivalents based on our primary approach were: aripiprazole 10 mg/1.33, asenapine 10 mg/1.33, clozapine 300 mg/40, haloperidol 4 mg/0.53, iloperidone 8 mg/1.07, lurasidone 40 mg/5.33, olanzapine 7.5 mg/1, paliperidone 3 mg/0.4, quetiapine 150 mg/20, risperidone 2 mg/0.27, sertindole 12 mg/1.60, and ziprasidone 40 mg/5.33. For amisulpride and zotepine, reliable estimates could not be derived.** ***Conclusions:*** **This method for determining antipsychotic dose equivalence entails an operationalized and evidence-based approach that can be applied to the various antipsychotic drugs. As a limitation, the results are not applicable to specific populations such as first-episode or refractory patients. We recommend that alternative methods also be updated in order to minimize further differences between the methods and risk of subsequent bias.**

Key words: dosage/equivalency/schizophrenia/antipsychotic drugs/olanzapine/risperidone/quetiapine

Introduction

Dose equivalence estimates of antipsychotics are important for many reasons. Clinicians need such information when they switch from one antipsychotic to another one or when they combine antipsychotic drugs. Trialists and meta-analysts need dose equivalence estimates for the design of fair comparisons of antipsychotic drugs,[1,2] and whenever the doses of several antipsychotics have to be converted into 1 unit. Finally, the concept is also important for cost calculations and treatment guidelines.

In a comprehensive review, Patel et al[3] listed various approaches to define dose equivalence including: the classical flexible-dose chlorpromazine equivalent method published by Davis in 1974,[4] the dose-response curve method to define near-to-maximum doses by Davis and Chen,[5] methods based on the maximum licensed doses of the various drugs,[6,7] the concept of daily defined doses (DDDs) of the World Health Organization,[8] and various (expert) consensus methods (eg, Kane et al[9], Gardner et al[10], Andreasen et al[11]). Their review made it clear that a gold standard method does not exist.

In 2003, Woods[12] introduced an approach in which he identified the minimum effective doses of the 5 second-generation antipsychotics (SGAs) available at that time based on their placebo-controlled, fixed-dose studies, and he subsequently derived chlorpromazine equivalents. Patel et al[3] found that it was the most frequently used method (714 cites found in a Web of Science search on July 25, 2013). Since the original article,[12] which made

recommendations for 5 SGAs and haloperidol based on 15 studies, several further SGAs have been developed and multiple further placebo-controlled trials have been published. In the current systematic review, we therefore (*a*) refined the method by operationalizing the decision-making process, (*b*) updated the material, and (*c*) included 8 additional SGAs.

Methods

Woods[12] identified the lowest fixed dose of each SGA that was consistently more efficacious than placebo in the primary outcome (usually the mean change of the Positive and Negative Syndrome Scale [PANSS[13]] total score or the Brief Psychiatric Rating Scale [BPRS[14]] total score from baseline in the intention-to-treat dataset). The identified doses were then used to calculate equivalence ratios. For example, if the minimum effective dose of olanzapine was 7.5 mg/d and that of asenapine was 10 mg/d, the asenapine dose that is equivalent to 1 mg/d olanzapine would be 10/7.5 = 1.33 mg/d. We made several modifications (supplementary webappendix 1 presents Wood's[12] original method):

1. We primarily calculated olanzapine equivalents, because the minimum effective haloperidol dose is less well understood (see "Results" section). For ease of reference, we also present haloperidol and risperidone equivalents. In keeping with Woods,[12] we did not investigate the minimum effective chlorpromazine dose, as the chlorpromazine literature is composed entirely of small, old trials,[15] which differ in methodological rigor from more recent SGA trials. However, chlorpromazine equivalents were estimated based on the original finding by Davis that 1.6 mg haloperidol corresponds to 100 mg chlorpromazine.[4] Woods assumed that 2 mg haloperidol corresponds to 100 mg chlorpromazine,[12] which was based on an APA (American Psychiatric Association) guideline statement[16] and not empirical evidence.
2. Woods[12] did not operationalize the criterion "consistently superior" and sometimes only one trial was available (so that "consistency" could not be verified). Our primary criterion was that a dose was statistically significantly superior to placebo for the primary outcome in one double-blind randomized controlled trial (RCT). To explore the possibility that minimum effective doses had been missed due to insufficient power, we meta-analyzed the results of lower doses when available. Standardized mean differences (effect size [ES]) expressed as Hedges's *g* were calculated together with their 95% CIs based on a fixed-effects model (the use of a random effects model did not change any result). Due to various problems in trial methodology in recent years, such as increasing placebo response[17,18] and high dropout rates,[19] it is currently difficult to demonstrate statistical superiority. These developments lead to an increasing number of failed trials (studies in which neither the new drug nor the active comparator was more effective than placebo), so that even well-established compounds such as haloperidol[20] or olanzapine[21] sometimes do not show separation from placebo or that a lower dose was significantly more efficacious than placebo, whereas higher or intermediate doses were not effective.[22,23] In this environment, we feel it is unlikely that superiority to placebo is just a chance finding.
   In order to examine what happens if a more conservative approach is considered, we conducted a sensitivity analysis, which required that a dose was efficacious in a second RCT. In essence, this is in keeping with a rule for the registration of a compound by the Food and Drug Administration (FDA). If a dose was supported by only one trial, the next higher dose that was efficacious in another trial qualified for the secondary criterion.
3. In contrast to Woods,[12] we also included RCTs, which used a dose of the same drug that was presumed to be ineffective by the original authors (eg, olanzapine 1 mg/d).
4. We included fixed-dose studies and trials that were defined as "fixed-dose range" studies by their authors (eg, iloperidone 4–8 vs 10–16 mg/d vs placebo or olanzapine 5 ± 2.5 vs 10 ± 2.5 mg/d vs placebo). For the latter, we conservatively assumed that the upper limit of the dose range was efficacious (Woods[12] used the midpoint of the range).

We examined the following SGAs and haloperidol in adult patients with schizophrenia or schizoaffective disorder: amisulpride, aripiprazole, asenapine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, sertindole, ziprasidone, and zotepine. We excluded studies in special populations such as adolescents, elderly, first-episode patients, stable patients (mainly relapse-prevention studies), patients with predominant negative symptoms, or patients with treatment resistance (except for clozapine, which is licensed for treatment resistance), as these populations might require different doses. As a result, the findings will not be applicable to these populations.

Our literature search was mainly based on the exhaustive searches for 4 systematic reviews on SGAs by our group.[2,24–26] They included the register of the Cochrane Schizophrenia Group (which is compiled by regular systematic searches in more than 15 databases, clinical trial registers, hand searches, and conference proceedings,[27] available up to August 2009) and MEDLINE/PubMed, Embase, Cochrane Central, and clinicaltrials.gov (last search: September 2012). We updated the latter searches in June 2013 (for search terms, see supplementary webappendix 2). We also searched the medical reviews that pharmaceutical companies must submit to the FDA, Cochrane reviews comparing SGAs and haloperidol vs placebo,[28–30] and Cochrane reviews on

optimum SGA doses.[31,32] Finally, we sent the draft results section of each antipsychotic to its manufacturer with a request for additional unpublished trials and the possibility for comments. Most manufacturers replied (see "Acknowledgments" section), which increased our confidence that no study was missed. All data were extracted by S.L. and independently verified by M.S. The analyses were conducted with Excel 2010 and Comprehensive Meta-analysis Version 2.[33]

Results

Supplementary webappendix 3 shows the PRISMA (Preferred Reporting Items for Systematic Reviews) diagram of the search. A description of the 73 included studies is provided in supplementary webappendix 4. The vast majority of the studies lasted 6 weeks (n = 45) or 8 weeks (n = 14), with a range between 3 and 48 weeks and a mean/median of 6.9/6.0 weeks. Table 1 illustrates which doses separated from placebo and the findings are summarized below. Where we describe a dose as being efficacious, this dose was statistically significantly superior to placebo (or a presumed ineffective dose) in the intention-to-treat analyses of the primary outcome based on the original authors' tests. Table 2 presents minimum effective doses and dose equivalencies.

Amisulpride

The single dose-finding study in acute schizophrenia compared amisulpride 400, 800, and 1200 mg/d with a dose of 100 mg/d,[34] which the original authors had presumed to be subtherapeutic. It showed a bell-shaped dose-response curve, where 400 and 800 mg/d were associated with the largest reduction in symptoms, however 400 mg/d was significantly more efficacious than 100 mg/d only in an unadjusted test. Amisulpride 100 mg/d was not actually an ineffective dose as it produced a mean 18.4 BPRS total score reduction from baseline (approximately equivalent to 28 points PANSS total score reduction[105]). It is therefore impossible to derive a minimum effective dose based on our method (see tables 1 and 2).

Table 1. Results of Placebo-Controlled, Fixed-Dose (Fixed-Dose Range) Studies

	Dose Groups in mg/d									
Amisulpride	100	400	800	1200						
Puech et al[34]		–[a]	+	–						
Aripiprazole	2	5	10	15	20	30				
Cutler et al[35]	–	–	+							
McEvoy et al[36]			+	+	+					
Kane et al[37]				+		+				
RGH-MD-04[38]			+							
Potkin et al[39]					+	+				
Study 94202[20] (F)	–		–			–				
Study 93202[40]						–				
Asenapine	0.4	0.8	1.6	3.2	4.8	10	20			
Study 041-002[41]	–	–	–							
Study 041-013[42]				–	–					
Kane et al[43]						+	+[b]			
Potkin et al[44]						+				
Hera 041-021[45]						–	–			
Clozapine[c]	100	300	600							
Simpson et al[46]		+	+							
Haloperidol	4	4.5	6	8	10	12	15	15 ± 5	16	20
Zimbroff et al[47]	+			+					+	
Vichaiya et al[48]		+								
Garry et al[49]			–							
Simpson et al[50]			–							
Kane et al[43]				+						
Barbato et al[51]					–					
Meltzer et al[52]					+					
Kane et al[37]					+					
Study 049[53]					–					
Garcia et al[54]					+					
Study 94202[20]					–					
Arvanitis et al[55]						+				
Potkin et al[56]							+			
Study 115[57]							+			
Beasley et al[58]								+		
Zborowski et al[59]									+	

Table 1. Continued

	Dose Groups in mg/d									
Study 93202[40]										+
Marder et al[60]										+
Chouinard et al[61]										–
Klieser et al[62]										–
Iloperidone	4	4–8	8	10–16	12	12–16	20–24	24		
Study ILPB202[63]	–		–							
Potkin et al (Study 1)[56]	–		–		+					
Potkin et al (Study 2)[56]		+		+						
Potkin et al (Study 3)[56]						–	+			
Cutler et al[64]								+		
Lurasidone	20	40	80	120	160					
Study 049[53] (F)	–	–	–							
Ogasa et al[65]		+		+						
Meltzer et al[66]		+		+						
Nasrallah et al[22]		–	+	–						
Nakamura et al[67]			+							
Loebel et al[68]			+		+					
Study D1001002[69]		[d]	[d]							
Olanzapine	1	5 ± 2.5	10	10 ± 2.5	15	15 ± 2.55				
Beasley et al[70]	–		+							
Beasley et al[58]		–		+		+				
Beasley et al[71] (F)		–[e]		–[e]		–[e]				
Kane et al[72]			+[f]							
Marder et al[73]			+[f]							
Davidson et al[74]			+[f]							
Hirayasu et al[75]			+[f]							
Meltzer et al[66]					+					
Barbato et al[51]					+					
Corrigan et al[76]					+					
Patil et al[77]					+					
AstraZeneca[78]					+					
Schmidt et al[79]					+					
Hera 041-021[45]					+					
Kinon et al[21]					–					
Paliperidone	1.5	3	6	9	12	15				
Coppola et al[80]	–		–							
Canuso et al[81]			–[g]		+[g]					
Davidson et al[74]		+		+		+				
Kane et al[72]			+	+	+					
Marder et al[73]			+		+					
Hirayasu et al[75]			+							
Canuso et al[82]					+[h]					
Quetiapine	75	150	<250	250	300	400	450	600	750	800
Immediate release (IR)										
Arvanitis et al[55]	–	+			+			+	+	
Small et al[83]			–[i]							
Fabre et al[84]				+						
Lindenmayer et al[23]					–			–		
Kahn et al[85]						+				
King et al[86]							+[j]			
11915A[87]								+		
11916A[88]								+		
Loebel et al[68]								+		
Canuso et al[82]										–[k]
Potkin et al[89]								–[l]		–[l]
Cutler et al[90]										–
Extended release (XR)										
Kahn et al[85]						+		+		+
Lindenmayer et al[23]					–			+		–
Cutler et al[90]						–		–		–

Table 1. Continued

	Dose Groups in mg/d						
Risperidone	2	4	6	8	10	12	16
Study 0204[60,61,91]	+[m]		+[m]		+[m]		+[m]
RIS-USA-72[92]		+		+			
Peuskens et al[93]		+[n]		+[n]		−[n]	+[n]
Bose et al[94]		+					
Potkin et al[89]			+[o]				
Potkin et al[39]			+				
Barbato et al[51]			+				
Casey et al[95]			+				
Study 041-002[41]			+				
Potkin et al[44]			−				
Potkin et al[56]				+[p]			
Study D1001002[69]		[q]					
Sertindole	8	12	16	20	24		
Zimbroff et al[47]		+		+	+		
Van Kammen et al[96]	−	−		+			
Zborowski et al[59]				+	+		
Hale et al[97]			+[r]	−[r]	+[r]		
Ziprasidone	10	40	80	120	160	200	
Daniel et al[98]			+		+		
Goff et al[99] (F)	−	−			−[s]		
Keck et al[100]		−		+			
Study 104[101]	−	−	−				
Study 115[57]		+		+		+	
Cutler et al[64]					+		
Zotepine	75	150	300				
Cooper et al[102]			+[t]				
Cooper et al[103]			+[t]				
Knoll[104]	[u]	[u]	[u]				

Note: (+) = statistically significantly better than placebo/very low dose in the primary outcome. (−) = not statistically significantly better than placebo/very low dose in the primary outcome. The light grey background illustrates the minimum effective dose based upon our main (primary) criterion (at least 1 trial with a statistically significant difference compared to placebo/low dose). The dark grey background illustrates the minimum effective dose based upon our more conservative secondary criterion (at least 2 positive studies). If a dose met both criteria, only the dark grey background was used. F = failed study, ie, a study in which neither the new drug nor the active comparator was more effective than placebo. A study is only marked as failed in the row for the new drug, not in the row for the active comparator.

[a]Only significantly better than 100 mg/d in an uncontrolled test.
[b]Significantly better in the mixed model for repeated measurements analysis, not in the last-observation-carried-forward analysis.
[c]As only one study was available, a minimum effective dose could not be defined based on our secondary criterion.
[d]The results of this study comparing lurasidone 40 and 80 mg/d with placebo were not obtained.
[e]Low-dose olanzapine (1 mg/d) as a comparator, not placebo.
[f]The highly significant statistical tests of these 4 paliperidone studies, which used olanzapine 10 mg/d only for "assay sensitivity," were made post hoc tests by us.
[g]12 mg/d could be reduced to 9 and 6 mg/d and to 3 mg/d.
[h]The initial target dose 9 mg/d could be increased to 12 mg/d. The 2-week monotherapy phase of the study was used for the evaluation.
[i]Quetiapine was more efficacious than placebo at doses higher than 250 mg/d (average 360 mg/d).
[j]Low-dose quetiapine 50 mg/d as a control, not placebo.
[k]The initial target dose 600 mg/d could be increased to 800 mg/d. The 2-week monotherapy phase of the study was used.
[l]Participants with ≤70 kg bodyweight received 400 mg/d, which could be increased to 600 mg/d, and those with >70 kg received 600 mg/d, which could be increased to 800 mg/d. The 2-week monotherapy phase results are presented.
[m]The US American and Canadian parts of the same study have been published separately.
[n]Low-dose 1 mg/d risperidone as a comparator, not placebo.
[o]Participants with ≤70 kg bodyweight received 4 mg/d and those with >70 kg received 6 mg/d. The 2-week monotherapy phase results are presented.
[p]The fixed-dose range was 6–8 mg/d.
[q]The risperidone dose of this unpublished study was 4 mg/d.
[r]Low-dose sertindole 8 mg/d as the comparator, not placebo.
[s]The comparator was ziprasidone 4 mg/d, not placebo. Ziprasidone 160 mg/d and haloperidol were only efficacious in the Clinical Global Impression scale, not in the Brief Psychiatric Rating Scale (BPRS).
[t]The dose could be reduced to 150 mg/d.
[u]75, 150, and 300 mg/d were compared with placebo, the results were not obtained.

Table 2. Minimum Effective Doses of Second-Generation Antipsychotic Drugs and Dose Equivalents

Drug	Minimum Effective Dose	OLA 1 mg Equivalent	RIS 1 mg Equivalent	HAL 1 mg Equivalent	CPZ 100 mg Equivalent
Amisulpride	–	–	–	–	–
Aripiprazole	10	1.33 (1)	5 (2.5)	2.5 (2.2)	4 (3.6)
Asenapine	10	1.33 (1)	5 (2.5)	2.5 (2.2)	4 (3.6)
Clozapine	300?	40 (30)	150 (75)	75 (67)	120 (107)
Haloperidol	4 (4.5)	0.53 (0.45)	2 (1.13)	1	1.6
Iloperidone	8[a] (12)	1.07[a] (1.2)	4[a] (3)	2[a] (2.7)	3.2[a] (4.3)
Lurasidone	40	5,33 (4)	20 (10)	10 (8.9)	16 (14.2)
Olanzapine	7.5 (10)	1	3.75 (2.5)	1.88 (2.2)	3 (3.6)
Paliperidone	3 (6)	0.4 (0.6)	1.5 (1.5)	0.75 (1.3)	1.2 (2.1)
Quetiapine	150 (250)	20 (25)	75 (62.5)	37.5 (55.6)	60 (88.9)
Risperidone	2 (4)	0.27 (0.4)	1	0.5 (0.9)	0.8 (1.4)
Sertindole	12 (16)	1.60 (1.6)	6 (4)	3 (3.6)	4.8 (5.7)
Ziprasidone	40 (80)	5.33 (8)	20 (20)	10 (17.8)	16 (28.4)
Zotepine	–	–	–	–	–

Note: We present the minimum effective doses and the doses in milligrams that are equivalent to 1 mg/d olanzapine (OLA), 1 mg/d risperidone (RIS), 1 mg/d haloperidol (HAL), and 100 mg/d chlorpromazine (CPZ). Numbers in parentheses are the results of the sensitivity analysis (2 positive trials). The results of the sensitivity analysis are only shown if they deviated from the primary analysis. (−): means that no recommendation could be made. (?): the result is very questionable because it is based on a single small study comparing clozapine 300 mg/d with 100 mg/d, but not with placebo.
[a]Excluding patients with schizoaffective disorder, the minimum effective iloperidone dose based on the primary criterion is 12 mg/d; the resulting equivalence doses (mg/d) are: olanzapine 1.6, risperidone 6, haloperidol 3, and chlorpromazine 4.8.

Aripiprazole

Seven fixed-dose, placebo-controlled studies[20,35–40] examined aripiprazole doses between 2 and 30 mg/d. The dose of 2 mg/d was ineffective in 2 studies.[20,35] In a single trial, 5 mg/d was more efficacious than placebo only at a few visits, but not at endpoint (primary outcome).[35] Meta-analyses of the single 5 mg/d dose[35] and the two 2 mg/d doses[20,35] (n = 379, ES: 0.18, 95% CI: −0.03 to 0.39, P = .10) or of the 2 mg/d dose groups[20,35] (n = 285, ES: 0.13, 95% CI: −0.10 to 0.36, P = .28) were also not significant. A dose of 10 mg/d was more efficacious than placebo in 3 trials[35,36,38] and is the minimum effective dose based on the primary criterion and the sensitivity analysis. This is different from the earlier recommendation by Woods[12] (15 mg/d) for whom 2 recent studies[35,38] were not yet available (see tables 1 and 2). Higher doses consistently separated from placebo, as well, except for 2 unpublished studies.[20,40] Study 94202 failed as no aripiprazole dose and also not the active comparator haloperidol (10 mg/d) was found to be effective.[20] Study 93202 was negative, because although the active comparator haloperidol (20 mg/d) showed efficacy for the primary outcome, aripiprazole (30 mg/d) separated from placebo only in secondary outcomes.[40]

Asenapine

Five placebo-controlled, fixed-dose trials[41–45] examined asenapine doses between 0.4 and 20 mg/d. In 2 initial studies, doses up to 4.8 mg/d were not found to be efficacious,[41,42] although there was a trend when the 4.8 and 3.2 mg/d doses[42] were meta-analytically combined (n = 182, ES: 0.29, CI: −0.02 to 0.59, P = .06). An ongoing study is therefore re-examining 5 mg/d.[107] A dose of 10 mg/d is currently the minimum effective dose based on both criteria, because it separated from placebo in 2[43,44] out of 3 studies.[43–45] There is one additional negative study, in which asenapine with a dose of neither 10 nor 20 mg/d was efficacious, while the active comparator olanzapine 15 mg/d was effective,[45] and another ongoing study is re-examining 10 and 20 mg/d doses.[108]

Clozapine

Placebo-controlled, dose-finding studies on clozapine were not available. As clozapine is restricted only for use in patients with treatment resistance, we included a small study in this patient group, which found that clozapine 600 and 300 mg/d were better than 100 mg/d.[46] Arguably, 300 mg/d is the minimum effective dose based on our primary criterion. The sensitivity analysis could not be conducted, because only one study was available.

Haloperidol

Haloperidol has been frequently used as an additional active comparator in placebo-controlled trials of SGAs, usually at fixed doses that are nowadays considered to be relatively high such as 8 mg/d,[43] 10 mg/d,[20,37,51–54] 12 mg/d,[55] 15 mg/d,[56,57,99] 15 ± 5 mg/d,[58] 16 mg/d,[59] and 20 mg/d.[40,60–62] These doses were generally statistically significantly more efficacious than placebo apart from a few studies, which failed as no treatment was better than placebo[20,51,53,62,99]; 20

mg/d were also not efficacious in Klieser and Lehmann[62] and in Chouinard et al.[61] However, the evaluation of the low end of the dose range for haloperidol is suboptimal. In a seven-arm sertindole study, 4, 8, and 16 mg/d haloperidol were all more efficacious than placebo.[47] This finding is corroborated by a study from 1971 in which haloperidol doses up to 4.5 mg/d were superior to placebo,[48] while 2 other small (52 and 24 participants, respectively), old studies found only a trend for superiority of haloperidol up to 6 mg/d compared with placebo.[49,50]

Thus, 4 mg/d is the minimum effective haloperidol dose according to our primary criterion, while 4.5 mg/d fulfills that of the sensitivity analysis.

Iloperidone

There were 5 placebo-controlled fixed-dose (or fixed-dose range) studies, which examined iloperidone doses between 4 and 24 mg/d. Two 4 mg/d doses[56,63] and their meta-analysis were ineffective (n = 293, ES: 0.12, CI: −0.11 to 0.35, P = .30). A dose of 8 mg/d was also ineffective in 2 trials,[56,63] and yet the fixed-dose range of 4–8 mg/d was efficacious in another study.[56] The upper limit of this dose range, 8 mg/d, therefore, qualifies for the minimum effective dose according to our primary criterion. A dose of 12 mg/d separated from placebo in a further study[56] and is thus the minimum effective dose based on the sensitivity analysis. Higher doses were efficacious, as well, except for the fixed-dose range of 12–16 mg/d in Study 3005 (Potkin Study 3).[56]

We note that if patients with schizoaffective disorder are excluded (as nowadays required by the FDA[63]), the minimum effective dose would be 12 mg/d for our primary criterion: In Study 3004,[56,63] neither 4–8 nor 12–16 mg/day was efficacious, in Study 3000 (Potkin Study 1) 12 mg/day remained effiacious, while in the Study 3 of Potkin et al.,[56,63] both 12–16 and 20–24 mg/d were effective.

Lurasidone

There were 7 fixed-dose, placebo-controlled studies, which examined lurasidone doses between 20 and 160 mg/d.[22,53,65–69] The dose of 20 mg/d was not efficacious in a single study, which failed as neither any lurasidone dose (20, 40, and 80 mg/d) nor haloperidol 10 mg/d was significantly superior to placebo.[53] The dose of 40 mg/d was efficacious in 2[65,66] out of 4[22,53,65,66] trials (one of which was a failed study[53]) and is therefore the minimum effective dose. Higher doses were usually efficacious, except for 80 mg/d in the failed study[53] and 120 mg/d in a study reported by Nasrallah et al.[22] Data from study NCT00711269/D1001002[69] (40 and 80 mg/d) are not available. A study that re-examines 20 mg/d is expected to complete in September 2014.[109]

Olanzapine

We identified 15 relevant studies, which examined olanzapine doses between 1 and 15 ± 2.5 mg/d.[21,45,51,58,66,70–79] One olanzapine 1 mg/d[70] dose group and 2 fixed-dose range groups of 5 ± 2.5 mg/d did not separate neither from placebo[58] nor from the presumed ineffective dose of 1 mg/d olanzapine.[71] However, their meta-analysis was significant (n = 393, ES: 0.20, CI: 0.005–0.40, P = .04). Therefore, 7.5 mg/d (the upper range of 5 ± 2.5 mg/d) is the minimum effective dose. Higher olanzapine doses (10, 10 ± 2.5, 15, and 15 ± 2.5 mg/d) were more efficacious than placebo in 13[45,51,58,66,70,74,75,76–79] out of 15 studies. The exceptions were the recent study on a glutamatergic compound[21] and the failed study by Beasley et al 1997[71] in which only the highest olanzapine dose (15 ± 2.5 mg/d) was more efficacious than 1 mg/d, but only in secondary outcomes. The authors commented that olanzapine 1 mg/d was not completely ineffective.[71] A dose of 10 mg/d olanzapine is the minimum effective dose based on the sensitivity analysis.

Paliperidone

Seven studies were included, which compared paliperidone doses between 1.5 and 15 mg/d[72–75,80–82] with placebo. Paliperidone 1.5 mg/d was not effective in the single study that examined this dose,[80] whereas 3 mg/d in a single study[74] was efficacious and thus is the minimum effective dose based upon the primary criterion.[74] The 6 mg/d dose did separate from placebo in 3[72,73,75] out of 5 studies[72,73,75,80,81] and thus meets the criterion of the sensitivity analysis. Doses higher than 6 mg/d were consistently more efficacious than placebo.[72–74,81,82]

Quetiapine

We included 12 studies on quetiapine immediate release[23,55,68,82–90] and 3 on extended release,[23,85,90] which examined doses between 75 and 800 mg/d. While 75 mg/d was ineffective,[55] 150 mg/d separated from placebo in the single study examining it[55] and is the minimum effective dose based upon the primary criterion. The dose of 250 mg/d qualifies for the criterion of the sensitivity analysis (Fabre et al[84]). Overall determining dose response for quetiapine is not straightforward as higher doses did not separate from placebo in several studies, including quetiapine 800 mg/d arms[23,90] (see table 1).

Risperidone

Twelve relevant studies compared risperidone doses between 2 and 16 mg/d with placebo[39,41,44,51,56,60,61,69,89,92,94,95] or presumed ineffective risperidone 1 mg/d.[93] The dose of 2 mg/d was not more efficacious than placebo in the separately published US part[60] of the pivotal study 0204, but it was in the Canadian part[61] and overall (see FDA report[91]). Consequently, 2 mg/d qualifies as the primary minimum effective dose. Risperidone 4 mg/d met the criterion of the sensitivity analysis. It was more efficacious than risperidone 1 mg/d (a presumed ineffective dose)

in a large international study[93] and it was more efficacious than placebo in a recent trial on cariprazine.[94] In RIS-USA-72,[92] it separated from placebo in the study's primary outcome (the number of participants with at least 20% PANSS total score reduction), the superiority in the mean PANSS total score change was only of borderline statistical significance (P = .051). The results of a 4 mg/d risperidone group of a lurasidone study have not been published (Study NCT00711269/D1001002[69]). Risperidone doses of 6 mg/d or higher were consistently more efficacious than placebo in all other studies,[39,41,51,56,89,95] except for 6 mg/d in one asenapine trial,[44] and 12 mg/d did not separate from risperidone 1 mg/d in the large international study.[93]

Sertindole

Three placebo-controlled studies[47,59,96] and 1 with low-dose sertindole (8 mg/d) as a comparator[97] examined doses between 8 and 24 mg/d. The dose of 8 mg/d was not efficacious in the single study comparing it with placebo[96] and was therefore used as a "presumed ineffective" dose instead of placebo in another study in which it was confirmed as being less efficacious than 16 and 24 mg/d.[97] The dose of 12 mg/d was more efficacious than placebo in 1[47] out of 2 studies[47,96] and is therefore the minimum effective dose fulfilling the primary criterion. The dose of 16 mg/d meets the criterion of the sensitivity analysis.[97] Higher doses of 20 mg/d[47,59,96] and 24 mg/d[47,59,97] were efficacious in 3 trials each.

Ziprasidone

We included 6 studies, which compared ziprasidone doses between 10 and 200 mg/d,[57,64,98–101] with placebo or ziprasidone 4 mg/d.[99] 10 mg/d was not efficacious in 2 trials,[99,101] and their meta-analysis was also not significant (n = 127, ES: 0.01, CI: −0.34 to 0.35, P = .96). A dose of 40 mg/d separated from placebo in 1 study[57] and is therefore the minimum effective dose according to the primary criterion, which is corroborated by a maintenance study, although it was excluded because it was conducted in patients with a stable presentation.[110] A dose of 80 mg/d separated from placebo in 1[98] out of 2 studies[98,101] and therefore—taken together with the positive study on 40 mg/d[57]—meets the criterion of the sensitivity analysis. Higher doses were consistently efficacious in studies that examined them,[57,64,98,100] except 1 failed study[99] in which only 160 mg/d and haloperidol 15 mg/d separated from the presumed ineffective dose of 4 mg/d ziprasidone, but only for secondary outcomes.

Zotepine

Data on the only dose-finding study that compared zotepine 75, 150, and 300 mg/d with placebo could not be obtained.[104] The only other 2 placebo-controlled trials[102,103] employed fixed doses of 300 mg/d and yet these could be reduced to 150 mg/d. The majority of patients stayed on 300 mg/d in 1 trial, but the proportion doing so in the other trial has not been reported.[103] In theory, 300 mg/d would be the minimum effective dose, but this finding is very doubtful.

Discussion

We refined, updated, and expanded the frequently used dose equivalence method first presented by Woods in 2003[12] by including 8 other SGAs and by expanding the database from 15[12] to now 73 RCTs. Some minimum effective doses had to be changed, whereas others were corroborated by new supporting evidence.

Authors agree that ideally large RCTs, which compare multiple fixed doses of multiple drugs, would be needed but, given the high number of antipsychotics, it is unlikely that these will ever be available.[3,10,12] The key strength of the method presented by Woods[12] is that an operationalized, evidence-based criterion can be applied to each antipsychotic. A critical limitation is the question how well the minimum effective doses of each drug could be identified by the dose-finding trials. Most mean ESs of the minimum effective doses were in a small range and thus, by and large, comparable: asenapine 10 mg/d, n = 561, ES: 0.31, CI: 0.14–0.47; iloperidone 8 mg/d, n = 585, ES: 0.24, CI: 0.08–0.40; lurasidone 40 mg/d, n = 705, ES: 0.13, CI: −0.02 to 0.28 (excluding 1 failed study,[53] the result was significant, n = 569, ES: 0.23, CI: 0.06–0.39); olanzapine 7.5 mg/d, ES: 0.20, CI: 0.005–0.40; risperidone 2 mg/d, ES: 0.32, CI: 0.02–0.62; sertindole 12 mg/d, ES: 0.36, CI: 0.09–0.62; ziprasidone 40 mg/d, ES: 0.21, CI: 0.01–0.40 (an ES for clozapine could not be calculated). The mean ESs of haloperidol 4 mg/d (n = 139, ES: 0.49, CI: 0.16–0.83), paliperidone 3 mg/d (n = 243, ES: 0.60, CI: 0.34–0.86, but 1.5 mg/d was not effective and even tended to be less efficacious than placebo[80]), and possibly also aripiprazole 10 mg/d (n = 497, ES: 0.40, CI: 0.22–0.58) were medium sized, so that future studies might reveal that lower doses are effective, as well. Finally, the minimum effective dose of quetiapine (150 mg/d) appears low, but its ES was high (n = 99, ES: 0.70, CI: 0.29–1.10), and it was numerically higher than all other quetiapine doses including 750 mg/d in the pivotal quetiapine study.[55] Several negative results for high doses of quetiapine (see table 1) suggest that the dose-response relationship for this antipsychotic is difficult to understand. But the quetiapine example also shows that including ES in the judgment is problematic, because placebo response[17,111] and dropout rates[19,112] have increased over the decades, and they have been made responsible for small ESs in recent studies in which even well-established drugs such as haloperidol or olanzapine do not separate from placebo.[20,21] Consequently, it is difficult to compare ESs from different periods. Moreover, these in part relatively high ESs also

demonstrate that the application of the "FDA two studies rule," as used in the sensitivity analysis, is particularly subject to the small number of trials available, because the doses identified were often higher.

Other limitations are that we excluded studies in specific populations, which may require different doses. RCTs suggest that 2–3 mg/d haloperidol is effective in first-episode patients.[113,114] Five placebo-controlled, fixed-dose amisulpride studies suggest that 50 mg/d is the minimum effective dose for patients with predominant negative symptoms.[115–119] Moreover, most included trials are registrational studies with limited follow-up and generalizability, and the approach does not take side-effects into account, which in practice need to be balanced with efficacy. Statistical significance depends in part on the sample size. Theoretically, very high sample sizes could enable even very low doses to show some efficacy over placebo. We included a few "fixed-dose range" studies. However, if we had excluded them all, only the minimum effective dose for iloperidone would need to be increased to 12 mg/d.

The relative value of the minimum effective dose method should also be considered in light of the limitations of other methods to define dose equivalence (see also Patel et al[3] for a detailed review). All methods (including Woods[12]) assume linearity, but the dose relationships between drugs could also be different (eg, quadratic), and the dose-response curves are usually sigmoidal.[5] Even when consensus methods were used, experts simply assumed linearity.[11] Further, as consensus methods[9–11] also depend on the knowledge of experts, we wonder whether the extent of their knowledge is likely to fully include all relevant RCTs as this review included 73 RCTs, some of which were unpublished.

The original method proposed by Davis[4] estimated chlorpromazine equivalents by calculating the ratio of the mean doses of each antipsychotic and the mean chlorpromazine dose used in flexible-dose trials. This method is not limited by the robustness of the evidence base from which the minimum effective dose is identified, and a larger evidence base may be available. Its major limitation is that drugs can usually only be given in predefined doses ranges which, in extreme cases, may not even include the optimum dose. Moreover, Davis assumed that all first-generation antipsychotics are equally efficacious, but small efficacy differences between SGAs may exist.[2,26]

Davis and Chen[5] constructed dose-response curves from dose-finding studies for each antipsychotic to identify near-to-maximum effective doses (ED95) and median effective doses (ED50). This approach is extensively used in preclinical research and, while this might seem appropriate, it is again hampered by the paucity of available data and inconsistencies of different dose-finding studies of the same drug.

Cochrane meta-analyses on the doses of a few antipsychotics exist.[31,32,120] This is the most comprehensive method, but their aim was not to identify dose equivalence. Rather various efficacy and tolerability outcomes were examined to identify the optimum doses of each drug.

DDDs are the "assumed, average, maintenance doses" of drugs for their main indication in adults.[3,8] They have been developed by the World Health Organization as a technical metric to measure drug utilization rather than to define dose equivalence. Finally, "maximum licensed methods"[6,7] express doses as a percentage of the maximum licensed dose of a drug. For example, the maximum chlorpromazine dose according to the British National Formulary[121] is 1000 mg/d, corresponding to 100%. Obviously, whether this method can be used for dose equivalence depends on the premise that the maximum licensed doses are really the maximally efficacious doses. For example, the summary of product characteristics for risperidone indicates that the effective dose range is from 4 to 16 mg/d, although studies have shown that doses higher than 6–8 mg/d are associated only with more side-effects but not with more efficacy.[60,61,93]

We conclude that, as with all other methods to define dose equivalence, our update and refinement of the minimum effective dose method has strengths and limitations, but that it will be useful in many situations. We recommend that alternative methods also be updated in order to minimize further differences between the methods and risk of subsequent bias.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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