Schizophrenia Bulletin vol. 41 no. 6 pp. 1397–1402, 2015
doi:10.1093/schbul/sbv037
Advance Access publication April 3, 2015

Dose Equivalents for Second-Generation Antipsychotic Drugs: The Classical Mean Dose Method

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Background: **The concept of dose equivalence is important for many purposes. The classical approach published by Davis in 1974 subsequently dominated textbooks for several decades. It was based on the assumption that the mean doses found in flexible-dose trials reflect the average optimum dose which can be used for the calculation of dose equivalence. We are the first to apply the method to second-generation antipsychotics.** ***Methods:*** **We searched for randomized, double-blind, flexible-dose trials in acutely ill patients with schizophrenia that examined 13 oral second-generation antipsychotics, haloperidol, and chlorpromazine (last search June 2014). We calculated the mean doses of each drug weighted by sample size and divided them by the weighted mean olanzapine dose to obtain olanzapine equivalents.** ***Results:*** **We included 75 studies with 16 555 participants. The doses equivalent to 1 mg/d olanzapine were: amisulpride 38.3 mg/d, aripiprazole 1.4 mg/d, asenapine 0.9 mg/d, chlorpromazine 38.9 mg/d, clozapine 30.6 mg/d, haloperidol 0.7 mg/d, quetiapine 32.3 mg/d, risperidone 0.4 mg/d, sertindole 1.1 mg/d, ziprasidone 7.9 mg/d, zotepine 13.2 mg/d. For iloperidone, lurasidone, and paliperidone no data were available.** ***Conclusions:*** **The classical mean dose method is not reliant on the limited availability of fixed-dose data at the lower end of the effective dose range, which is the major limitation of "minimum effective dose methods" and "dose-response curve methods." In contrast, the mean doses found by the current approach may have in part depended on the dose ranges chosen for the original trials. Ultimate conclusions on dose equivalence of antipsychotics will need to be based on a review of various methods.**

Key words: dose/equivalence/schizophrenia/antipsychotic drugs

Introduction

The concept of dose equivalence of antipsychotic drugs is important for many reasons. In clinical practice, such information is needed when patients are switched from one antipsychotic to another one or when antipsychotics are combined.[1–3] In research, dose equivalence estimates are needed to assure that fair doses are used when 2 antipsychotics are compared[4] in a randomized controlled trial or in a meta-analysis.[5] When several antipsychotics are used, as it is frequently the case in naturalistic studies, their doses often need to be converted into a single unit.[6] Finally, the concept is also useful for treatment guidelines.[7]

Patel et al[7] recently presented a comprehensive review of various approaches to define dose equivalence which included the minimum effective dose method originally presented by Woods[8] which has been recently updated,[9] the dose-response curve method to define near-to-maximum doses by Davis and Chen,[10] methods based on the maximum licensed doses of the various drugs,[11,12] the concept of daily-defined-doses (DDDs) of the World Health Organization,[13] and various (expert) consensus methods.[1–3] Patel et al[7] highlighted that all methods have strengths and weaknesses and that a gold standard method does not exist.

The classical method was described by Davis in 1974.[14] He identified all randomized, double-blind, flexible-dose studies on the antipsychotics available at that time and used their mean doses to calculate doses that were equivalent to chlorpromazine. This method has served as a reference for dose equivalents for several decades and it has been applied (sometimes slightly revised) in guidelines

such as that of the American Psychiatric Association.[15,16] It has, however, never been extended to second-generation antipsychotics. The present article fills this gap by systematically reviewing the randomized literature on oral second-generation antipsychotic drugs for the acute treatment of schizophrenia.

Methods

In keeping with Davis,[14] we retrieved all double-blind, flexible-dose studies on second-generation antipsychotic drugs, chlorpromazine, and haloperidol in acutely ill patients with schizophrenia. In such studies, physicians adjust the dose given to patients by their clinical response not knowing which medication was actually administered. The resulting average doses can then be considered the optimum mean doses for such patients, and they can be used to calculate dose ratios and equivalent doses of the various compounds.

We calculated olanzapine equivalents because for olanzapine most flexible dose studies with broad dose ranges were available so that it was the most appropriate comparator drug. We examined the following second-generation antipsychotics, chlorpromazine, and haloperidol in adult patients with schizophrenia or schizoaffective disorder: amisulpride, aripiprazole, asenapine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, sertindole, ziprasidone, 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, as these populations might require different doses. Fixed-dose studies were also excluded, as our method required studies which allowed investigators to titrate the dose.

The literature search was mainly based on the update of the exhaustive searches for 4 systematic reviews on second-generation antipsychotics by our group.[17–20] We searched Medline, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), PsycInfo, BIOSIS, Clinicaltrials.gov, and the WHO clinical trial Web site (up to June 2013), and once again in PubMed in June 2014 (for search terms, see supplementary appendix 1). We also searched the medical reviews that pharmaceutical companies must submit to the FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm). Study selection and data extraction were made independently by at least 2 reviewers (M.S., S.L., or reviewers from our previous publications).

We conducted 3 analyses:

1. *Weighted means*: In order to derive olanzapine equivalents, the sample size weighted mean dose of each compound was divided by the weighted mean olanzapine dose. This was our primary analysis as it included data from all flexible-dose studies. It assumes that the different studies were sufficiently similar such that if all the drugs had been used in one very large study, the same mean doses would have been found.
2. *Direct ratios*: The ratios of mean doses in all individual studies were calculated and then the sample size weighted ratios were averaged which allows for some variability in methods of the single studies to be reduced. This analysis could only use studies in which a drug was directly compared with our chosen comparator drug olanzapine.
3. *Direct and indirect ratios*: In addition to direct ratios as outlined above, indirect ratios were also included to allow for more data to be used. For example, if we wished to convert amisulpride into olanzapine equivalents, not only studies comparing amisulpride with olanzapine could be used (direct method) but also studies that compared amisulpride with another drug after expressing the latter drug in olanzapine equivalents (indirect method). This approach introduces indirectness in the estimates.

All 3 analyses included only those studies which allowed for prescribing of the lower and the upper doses as determined by each drug's target dose range.[2] The rationale was that if not even target doses could be prescribed within the trials, then these trials were not appropriate to identify the optimum dose. For example, the mean ziprasidone dose in a study with a predefined dose range of 20–60 mg/d would necessarily be too low and distort the analysis. The target dose ranges were taken from the International Consensus Study of Antipsychotic Dosing[2]: amisulpride 400–800 mg/d, aripiprazole 15–30 mg/d, chlorpromazine 300–600 mg/d, clozapine 200–500 mg/d, haloperidol 5–10 mg/d, olanzapine 10–20 mg/d, paliperidone 6–9 mg/d, risperidone 4–6 mg/d, sertindole 12–20 mg/d, ziprasidone 120–160 mg/d, zotepine 100–300 mg/d. For quetiapine, the target dose ranges was defined by us as 400–750 mg/d (rather than the suggested 800 mg/d in Gardner et al[2] which would have excluded all quetiapine immediate release studies). The 3 most recent antipsychotics were not included in Gardner et al[2] and so we defined that their target dose ranges as: asenapine 10–20 mg/d, lurasidone 40–120 mg/d, and iloperidone 12–24 mg/d.[21] In subsequent sensitivity analyses, we included all randomized, double-blind, flexible-dose studies even if the target dose ranges were not prescribed.

Finally, we used the olanzapine equivalent dose of chlorpromazine found by our method 1 ("weighted means") and, together with the chlorpromazine equivalent doses found for further first-generation antipsychotics by Davis 1974, to subsequently provide olanzapine equivalent estimates for these first-generation antipsychotics. These estimates are even more "indirect" because they were derived from different analyses but, in the absence of other data, they may still be useful. Examples

for the calculation of olanzapine equivalents according to each method are provided in supplementary appendix 2.

Results

Supplementary appendix 3 shows the PRISMA diagram of the search. Seventy-five studies with 16 555 participants were included. Supplementary appendix 4 presents a description of important characteristics of these studies. Most studies were conducted by pharmaceutical companies for registration purposes. The median study duration was 7 weeks (range 4–78 wk). The participants' mean duration of illness (in those studies that presented this characteristic) was 12.3 (SD = 6.0) years, the mean age 36.8 (SD = 5.7) years, demonstrating relatively chronic populations as is commonly seen in antipsychotic drug trials.

Table 1 presents the equivalence doses based on the 3 analyses of all drugs compared with olanzapine 1 mg/d, and the number of participants on which the estimates are based. No eligible flexible-dose, double-blind trials in acutely ill patients with schizophrenia on iloperidone, lurasidone, and paliperidone were found because no flexible-dose studies comprising the target dose ranges[2] were available (although iloperidone doses could be calculated in the sensitivity analysis). For most drugs, the estimates based on the 3 approaches were comparable with each other and also comparable with those of the "minimum effective dose method" published elsewhere[9] and presented together with 2 methods based on expert consensus[2,3] in Table 1 to facilitate comparison. Supplementary appendix 5 presents the results of the sensitivity analysis (all studies) which, however, showed only very minor discrepancies from the main analyses. Table 2 shows the olanzapine equivalent estimates for additional first-generation antipsychotics that were included in Davis.[14]

Discussion

In 1974, John Davis[14] presented a method for the calculation of dose equivalents of first-generation antipsychotics which has been used by schizophrenia guidelines and textbooks for decades. In this article, we expanded this classical method to second-generation antipsychotic drugs. We think that the report will be a useful tool for clinicians and researchers as it represents a rational and evidence-based approach to the definition of dose equivalence of antipsychotics.

Various authors agree that very large randomized controlled trials which compare multiple fixed doses of multiple drugs would be needed, ideally, to define dose equivalencies. However, given the high number of antipsychotics, it is unlikely that these will ever be available.[2,7,8,22] A recent review therefore concluded that a "gold standard" method does not exist[7] and, as with all other approaches, the one first presented by Davis[14] has limitations.

It is the most important limitation of the method that the mean doses obtained from the clinical trials may depend on the predefined dose ranges within which the investigators can titrate the doses. An example that has been debated in this context is the Clinical Antipsychotic Trials of Intervention Effectiveness study[23] where doctors could titrate the following drugs within the following ranges and 4 different doses: olanzapine 7.5, 15, 22.5, or 30 mg/d; quetiapine 200, 400, 600, 800 mg/d; risperidone 1.5, 3, 4.5, 6 mg/d; ziprasidone 40, 80, 120, 160 mg/d; perphenazine 8, 16, 24, 32 mg/d. It turned out that the patients had received mean doses of all drugs somewhat below the third dose step (olanzapine 20.1 mg/d, quetiapine 543.4 mg/d, risperidone 3.9 mg/d, ziprasidone 112.8 mg/d, perphenazine 20.8 mg/d). The choice of all dose ranges was based in a fair way on the recommendations of the manufacturers of the drugs. But the mean risperidone appears to be somewhat low and the mean olanzapine dose appears to be somewhat high, suggesting that the predefined dose ranges might have played a role. Another example is haloperidol for which with a few exceptions the lower dose ranges in the studies started only at 4 mg/d or 5 mg/d, although it is possible that for many patients lower doses are sufficient. For example, McEvoy et al[24] showed that doses titrated according to the neuroleptic threshold method (on the average 3.7 mg/d) were as efficacious as 2–10 times higher doses. In contrast, the upper haloperidol dose limit in the studies was often 20 mg/d which is nowadays considered a relatively high dose. This finding may explain why a relatively high haloperidol dose (0.74 mg/d) was equivalent to 1 mg/d olanzapine (see Table 1). Ideally, the investigators should be completely flexible in adjusting the doses in the trials (eg, regarding haloperidol: lower limit 1 mg/d, no upper limit, use of 1 mg haloperidol tablets to titrate the dose), but this is never the case. We addressed the problem in part by including only those randomized controlled trials that had included the target dose ranges as suggested by an international expert consensus,[2] because if not even target doses could be prescribed within the trials, then these trials were not appropriate to identify the optimum dose (see above). Moreover, we also conducted sensitivity analyses which considered all studies, including those where the full target ranges were not covered. Only minor differences were seen which are probably unlikely to have any significant clinical consequences (see supplementary appendix 5).

As another limitation Davis's method[14] assumes linear relationships between the doses of different drugs and that all antipsychotics are equally efficacious but this is also true for other dose comparison methods. Thus, for example, doubling the risperidone dose is considered the same as doubling the quetiapine dose. However, the dose-response curves of the individual drugs are usually sigmoidal,[10] ie, beyond a certain threshold higher doses only lead to more side effects but not more efficacy. Davis and

Table 1. Primary Analysis (Studies Which Included the Target Dose Ranges)

Dose Equivalent to Olanzapine 1 mg/d								
Drug	*n*	Weighted Means (*SD*)	Direct Ratios (*SD*)	Direct and Indirect Ratios (*SD*)	Minimum Effective Dose Method[9]	Consensus-Based Method by Andreasen et al[3]	Consensus-Based Method by Gardner et al[2]	
Amisulpride	390	38.33 (8.76)	38.17 (1.61)	31.41 (7.01)	n.a.	n.a.	34.48	
Aripiprazole	1013	1.41 (0.3)	1.33 (0.2)	1.26 (0.25)	1.33	1.34	1.49	
Asenapine	913	0.89 (n.a.)	0.99 (n.a.)	0.99 (n.a.)	1.33	n.a.	n.a.	
Clozapine	88	30.62 (18.64)	n.a.	39.96 (n.a.)	40	22.8	20	
Chlorpromazine	451	38.88 (16.9)	n.a.	28.77 (8.38)	n.a.	21.31	30.3	
Haloperidol	1953	0.74 (0.22)	0.89 (0.02)	0.76 (0.25)	0.53	0.39		0.5
Iloperidone	n.a.	n.a.	n.a.	n.a.	1.07	n.a.	n.a.	
Lurasidone	n.a.	n.a.	n.a.	n.a.	5.33	n.a.	n.a.	
Olanzapine	4341	1.0	1.0	1.0	1.0	1.0	1.0	
Paliperidone	n.a.	n.a.	n.a.	n.a.	0.4	n.a.	0.45	
Quetiapine	1261	32.27 (7.4)	27.64 (2.04)	31.84 (6.97)	20	29.97	37.04	
Risperidone	1623	0.38 (0.12)	0.27 (0.1)	0.27 (0.1)	0.27	0.28	0.3	
Sertindole	314	1.08 (0.2)	1.06 (n.a.)	0.94 (0.29)	1.6	n.a.	1.0	
Ziprasidone	1071	7.92 (1.56)	6.48 (0.97)	6.67 (1.12)	5.33	10.48	8.0	
Zotepine	60	13.24 (n.a.)	n.a.	16.35 (n.a.)	n.a.	n.a.	14.93	

Note: *n*, number of participants in the primary main analysis (weighted means); n.a., not available.

Chen[10] have demonstrated these sigmoidal dose-response relationships for several antipsychotic drugs. Thus, the assumption that doubling the risperidone dose is the same as doubling the quetiapine dose is only valid on the linear part of the dose-response curves before these reach a plateau.[10] In a related vein, Andreasen et al[3] had to statistically adjust their dose-response results with a "power model" because the relationships for some drugs such as ziprasidone could not be entirely explained by linear regression. Finally, recent meta-analyses suggested small efficacy differences between second-generation antipsychotics.[20]

As with any review, the quality of evidence varied and here, the number of studies and participants available for the different antipsychotics differed greatly. For example, the data from several thousands of patients were available for olanzapine, whereas only a few studies contributed data based on far fewer patients on zotepine or clozapine (88 and 60 patients, respectively). Thus, our clozapine results are not robust, which may be a reason why they were different from the statements in expert consensus documents,[2,3] and why the results of the 3 methods we used occasionally differed. Our primary analysis, the "weighted mean dose," had the advantage that it included data from all flexible-dose studies. While the "direct ratios" analysis had the advantage that – by first calculating dose ratios for the single studies – to a certain extent methodological heterogeneity of the studies could be taken into account, only comparisons with olanzapine could be used. Thus, the "direct and indirect ratio" analysis was also considered but this necessarily added indirectness and was not as straightforward.

The strengths of this classical dose comparison method are to some extent also the shortcomings of other methods. A major strength is that, compared with other methods, for a number of drugs more data were available. For example, the frequently applied method by Woods[8] (which has been recently updated[9]) largely depends on how well the minimum effective doses of the various drugs have been identified. As pharmaceutical companies usually conduct only 1 or 2 dose-finding studies, these results are usually based on very limited and partly conflicting data. Whether the minimum effective doses can be identified depends in part on how large the sample sizes were and is also more limited by a current difficulty to find statistically significant differences compared with placebo due to increasing placebo response and other factors.[25] Nevertheless, Table 1 shows that many results were comparable with the Woods method and also with the 2 expert consensus-based methods.

The method by Davis and Chen[10] to construct dose-response curves from dose-finding studies for each antipsychotic to identify near-to-maximum effective doses (ED95) and median effective doses (ED50) is similarly hampered by the paucity of available data and inconsistencies of different dose-finding studies of the same drug. Expert consensus methods are not really evidence based[1–3] and they are possibly more appropriate to provide target/optimum dose ranges rather than dose equivalencies. The same holds true for a few Cochrane reviews which attempt to find out optimum doses of antipsychotics by meta-analyses of their efficacy and side-effects, but they are not designed to find dose equivalencies.[26] Finally, the DDD concept of the World Health Organization has been

Table 2. Olanzapine Equivalents for Additional Old First-Generation Antipsychotics That Were Included in the Original Publication by Davis[14]

	Dose Equivalent to 100 mg Chlorpromazine[a]	Dose Equivalent to 1 mg Olanzapine[b]
Acetophenazine	23.5	9.1
Butaperazine	8.9	3.5
Carphenazine	24.3	9.4
Chlorpromazine	100	38.9
Chlorprothixene	43.9	17.1
Fluphenazine	1.2	0.5
Haloperidol	1.6	0.6
Mesoridazine	55.3	21.5
Perphenazine	8.9	3.5
Piperacetazine	10.5	4.1
Prochlorperazine	14.3	5.6
Thioridazine	95.3	37.1
Thiothixene	5.2	2.0
Trifluoperazine	2.8	1.1
Triflupromazine	28.4	11.0

Note: [a]This column presents the doses that are equivalent to 100 mg/d chlorpromazine according to the publication by Davis.[14] [b]These are olanzapine equivalents derived from our estimate of the equivalence ratio between olanzapine and chlorpromazine: 1 mg olanzapine = 38.9 mg chlorpromazine or 100 mg chlorpromazine = 2.572 mg olanzapine.

developed as a technical metric to measure drug utilization rather than to define dose equivalence,[7,13] although it is sometimes used in meta-analyses as well.

These multiple issues show that dose equivalency is a complex concept and that no single method is superior to the other ones in all circumstances. An update of Davis's method was also urgently needed because, if one approach does not provide (reliable) estimates for on antipsychotic, another approach might be chosen. For example, it was not possible to provide equivalent doses for amisulpride, chlorpromazine, or zotepine by the updated minimum effective dose method by Woods[8,9] and for the current method no data on iloperidone (except in the sensitivity analysis), lurasidone, and paliperidone were available. Future studies should also provide dose equivalencies for short-acting intramuscular formulations and long-acting injectables, and they should address specific populations such as patients with predominant negative symptoms, treatment-resistant patients, stable patients, first-episode patients, and patients early in the course of treatment. We excluded studies in these populations from the current analysis because relatively few such studies exist and these studies are not evenly distributed between the antipsychotics. For example, most of the 13 studies included in a recent meta-analysis on second- versus first-generation antipsychotics in first-episode patients with schizophrenia were on olanzapine, risperidone, and haloperidol, while for several other second-generation antipsychotics not a single randomized controlled trial was available.[27] As first-episode patients generally need lower doses, the inclusion of the few available studies would have distorted the results. Whether the equivalence doses found can still be used for specific patients is another question. It is possible that the doses are equivalently lower (or higher, eg, for treatment-resistant patients) across all drugs for specific populations. In that case our dose equivalencies could also be applied to specific groups, but in the absence of data it appears safer to recommend them mainly for chronic patients as they are typical for antipsychotic drug trials in schizophrenia.

We conclude that as all available methods have limitations, ultimate decisions on dose equivalence will have to be based on a review of various approaches.

Supplementary Material

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

Acknowledgment

We thank Sunovion Pharmaceuticals for replying to our request regarding lurasidone. In the last 3 years, S.L. has received honoraria for lectures from Abbvie, AstraZeneca, Bristol-Myers Squibb, ICON, Eli Lilly, Janssen, Johnson & Johnson, Roche, Sanofi-Aventis, Lundbeck, and Pfizer; for consulting/advisory boards from Roche, Eli Lilly, Medavante, Bristol-Myers Squibb, Alkermes, Janssen, Johnson & Johnson, and Lundbeck. Eli Lilly has provided medication for a study with S.L. as primary investigator. S.H. has received honoraria from Janssen-Cilag, Eli Lilly, Sanofi-Aventis, Lundbeck, and Johnson & Johnson; he has accepted travel or hospitality payment from Janssen-Cilag, Sanofi-Aventis, Johnson & Johnson, Pfizer, Bristol-Myers Squibb, AstraZeneca, Lundbeck, Novartis, and Eli Lilly; he has participated in clinical trials sponsored or supported by Eli Lilly, Janssen-Cilag, Johnson & Johnson, Bristol-Myers Squibb, AstraZeneca, Otsuka, Lundbeck, Novartis, Servier, Pierre Fabre, Pfizer, Organon, Roche, and Merck; and he has participated in advisory activities and boards for Janssen, Johnson & Johnson, Eli Lilly, Lundbeck, Otsuka, and Roche. M.X.P. holds a Clinician Scientist Award supported by the National Institute for Health Research and has also received consultancy fees, lecturing honoraria, and/or research funding from Janssen, Lilly, Endo, Lundbeck, Otsuka, and Wyeth. M.X.P. has previously worked on clinical drug trials for Janssen and Amgen and is currently working on a clinical study supported by Lundbeck. T.F. has received lecture fees from Eli Lilly, Meiji, Mochida, Merck Sharp & Dohme (MSD), Otsuka, Pfizer, and Tanabe-Mitsubishi and consultancy fees from Sekisui and Takeda Science Foundation. He has received royalties from Igaku-Shoin, Seiwa-Shoten, and Nihon Bunka Kagaku-sha publishers. He has received grant or research support from the

Japanese Ministry of Education, Science, and Technology, the Japanese Ministry of Health, Labor and Welfare, the Japan Foundation for Neuroscience and Mental Health, Tanabe-Mitsubishi, and Mochida. He is a diplomate of the Academy of Cognitive Therapy. A.C. was expert witness for Accord Healthcare for a patent issue about quetiapine extended release. J.G. is a National Institute for Health Research (NIHR) Senior Investigator. M.S. and J.M.D. have no conflict of interest to declare.

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