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Research report

Dose equivalents of antidepressants: Evidence-based recommendations from randomized controlled trials

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ABSTRACT

Background: Dose equivalence of antidepressants is critically important for clinical practice and for research. There are several methods to define and calculate dose equivalence but for antidepressants, only daily defined dose and consensus methods have been applied to date. The purpose of the present study is to examine dose equivalence of antidepressants by a less arbitrary and more systematic method.
Methods: We used data from all randomized, double-blind, flexible-dose trials comparing fluoxetine or paroxetine as standard drugs with any other active antidepressants as monotherapy in the acute phase treatment of unipolar depression. We calculated the ratio of the mean doses for each study and weighted it by the total sample size to find the weighted mean ratio for each drug, which was then used to define the drug's dosage equivalent to fluoxetine 40 mg/d.
Results: We included 83 studies (14 131 participants). In the primary analysis, fluoxetine 40 mg/day was equivalent to paroxetine dosage of 34.0 mg/day, agomelatine 53.2 mg/day, amitriptyline, 122.3 mg/day, bupropion 348.5 mg/day, clomipramine 116.1 mg/day, desipramine 196.3 mg/day, dothiepin 154.8 mg/day, doxepin 140.1 mg/day, escitalopram 18.0 mg/day, fluvoxamine 143.3 mg/day, imipramine 137.2 mg/day, lofepramine 250.2 mg/day, maprotiline 118.0 mg/day, mianserin, 101.1 mg/day, mirtazapine 50.9 mg/day, moclobemide 575.2 mg/day, nefazodone 535.2 mg/day, nortriptyline 100.9 mg/day, reboxetine 11.5 mg/day, sertraline 98.5 mg/day, trazodone 401.4 mg/day, and venlafaxine 149.4 mg/day. Sensitivity analyses corroborated the results except for doxepin.
Limitations: The number of studies for some drugs was small. The current method assumes dose response relationship of antidepressants.
Conclusions: Our findings can be useful for clinicians when they switch antidepressants and for researchers when they compare various antidepressants in their research.

1. Introduction

Pharmacotherapy with antidepressants is the mainstay in the treatment of major depressive disorder. Although many types of antidepressants are currently available, evidence-based dose equivalency among them which takes relative efficacy into consideration is unknown.

Dose equivalence is critically important for clinical practice and for research. First, when clinicians change antidepressant, they need to know approximate dose equivalents to facilitate the transition. Second, dose equivalence is also relevant for pharmacoepidemiological studies for fair and accurate comparison of antidepressants to check potential over- or under-prescription. In addition, in trials comparing antidepressants, and in their meta-analyses, setting comparable dosages is necessary to facilitate the interpretation (Hansen et al., 2009).

There are several methods to define and calculate dose equivalence. Patel et al. (2013) conducted a systematic review of available methods that compare dose equivalence of antipsychotics. The representative methods include the following:

i) Original method conducted by Davis (1974). He employed data from double-blind flexible-dose trials comparing chlorpromazine

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with other antipsychotics, and then calculated the mean dose of each antipsychotic drug that was as effective as the standard comparator chlorpromazine 100 mg/day.

ii) Minimum effective dose method. The lowest dose significantly superior to placebo of equally efficacious drugs based on placebo controlled fixed dose trials was considered to be equivalent (Leucht et al., 2014; Woods, 2003).

iii) Near-effective maximum dose method. The threshold dose eliciting clinical response with the least adverse profile was considered equivalent, based on the dose-response curves from data of fixed dose randomized placebo-controlled studies (Davis and Chen, 2004).

iv) Daily defined dose (DDD) (World Health Organization, 2014). DDD is the assumed average maintenance dose per day calculated from the dosage recommendations in each drug's product information. This is the official standard of reference for WHO member states.

v) Expert consensus methods (Buckley, 2005; Gardner et al., 2010; Kane et al., 2003; Simpson et al., 2006).

Each method has its strengths and limitations, and no gold standard method exists. In the case of antidepressants, to the best of our knowledge, dose equivalence is provided only as DDD and by the consensus methods (Inagaki and Inada, 2006; Inagaki et al., 1999). DDD is often defined as a compromise among available information from various countries and does not provide any information about efficacy of each drug (World Health Organization, 2014). Ali (1998) and Fava and Davidson (1996) studies showed a table of equivalent dose of antidepressants, but no further detail about how they calculated and obtained these values were provided.

The minimum effective dose method is limited by availability of placebo-controlled dose-finding studies and, when such is available, by their design if the trial had set the true minimum effective dose and if the trial was powered enough to detect such difference. Near-effective maximum dose design, while theoretically attractive, is even more severely affected by availability of appropriate studies in which we can draw dose-response curves. In the current study we therefore aimed to examine antidepressant dose equivalence applying the original method by Davis (1974). This method used data from double-blind flexible-dose studies, in which physicians adjust dosages to optimize the clinical response without knowing the prescription. It may be assumed that the resulting average doses represent the optimum mean doses for each drug so this can be used to estimate the clinically equivalent doses between drugs.

2. Materials and methods

As standard drugs, we chose fluoxetine and paroxetine, which are the first and second most often trialed drugs in the recent years (Cipriani et al., 2009). Both are representative selective serotonin reuptake inhibitors (SSRI) with similar side effect profiles and recommended dose ranges. The current study is an updated derivative work from our two recent Cochrane reviews for fluoxetine (Magni et al., 2013) and paroxetine (Purgato et al., 2014). We merged the results for fluoxetine and paroxetine by converting paroxetine mean dosage of each study into fluoxetine mean dosage by the calculation below. The validity of the decision to merge the two datasets was examined in a sensitivity analysis.

2.1. Types of studies

We retrieved all randomized, double-blind, flexible-dose trials comparing fluoxetine or paroxetine with any other active antidepressants as monotherapy in the acute phase treatment of unipolar depression.

2.2. Types of participants

The reviews included participants 18 years or older, of both sexes, with a primary diagnosis of unipolar major depression according to standardized criteria, DSM-III, DSM-III-R, DSM-IV (American Psychiatric Association, 2000), ICD-10 (World Health Organization, 1992), Feighner criteria (Feighner et al., 1972) or Research Diagnostic Criteria (Spitzer et al., 1978). Studies using ICD- 9 were excluded because it only lists disease names but do not have diagnostic criteria.

We excluded studies that focused on children and adolescents only, or on elderly patients (mean age $>=$65 years), because their indicated dosages and/or efficacy may be different from the case of adults.

We included participants with some subtypes of depression, such as chronic, with catatonic features, with melancholic features, with atypical features, with postpartum onset, and with a seasonal pattern. We included studies in which up to 20% of participants presented with depressive episodes in bipolar affective disorder and participants with a concurrent secondary diagnosis of another psychiatric disorder. We excluded participants with a concurrent primary diagnosis of another psychiatric disorder and participants with a serious concomitant medical illness.

2.3. Interventions

The standard intervention drugs in this study were fluoxetine or paroxetine as flexible dose monotherapy. We concentrated on the acute phase treatment, defined as 4–16 weeks of treatment, with the preferred endpoint at 8 weeks. When 8-week data were not available, we used outcomes closest to 8 weeks within the 4–16-week range. We excluded trials in which fluoxetine or paroxetine was compared only to placebo or another class of psychopharmacological agents such as anxiolytics, anticonvulsants, antipsychotics or mood stabilizers, and trials in which fluoxetine or paroxetine was used as an augmentation strategy.

2.4. Comparators

Comparator drugs included conventional antidepressive agents as follows:

1. Tricyclics (TCAs); Amitriptyline, Clomipramine, Desipramine, Dothiepin/Dosulepin, Doxepin, Imipramine, Lofepramine, Trimipramine, Nomifensine, and Nortriptyline
2. Heterocyclics; Maprotiline, and Mianserin
3. SSRIs; Citalopram, Escitalopram, Fluvoxamine, Paroxetine, and Sertraline
4. SNRIs; Duloxetine, Milnacipran, and Venlafaxine
5. MAOIs or newer ADs; Agomelatine, Mirtazapine, Moclobemide, Phenelzine, and Reboxetine
6. Other conventional antidepressive drugs; Amineptine, Amisulpride, Bupropion, Pramipexole, Nefazodone, Tianepine, and Trazodone

No restrictions on dose, frequency or intensity were applied in the first round of the study selection. From this source dataset, we selected all double-blind, flexible-dose studies, and we included studies whose flexible dose range were within or included either the lower or the upper limit of the target dose range of each drug, set a priori as follows:

Fluoxetine 10–80 mg/day, Paroxetine 12.5–75 mg/day, Agomelatine 25–50 mg/day, Amisulpride 50–300 mg/day, Amitrip-

tyline 75–300 mg/day, Bupropion 150–450 mg/day, Citalopram 20–40 mg/day, Clomipramine 25–250 mg/day, Desipramine 100–300 mg/day, Doxepin 25–300 mg/day, Duloxetine 40–120 mg/day, Escitalopram 10–20 mg/day, Fluvoxamine 50–300 mg/day, Imipramine 75–300 mg/day, Lofepramine 140–210 mg/day, Maprotiline 25–225 mg/day, Milnacipran 12.5–200 mg/day, Mirtazapine 15–45 mg/day, Moclobemide 150–600 mg/day, Nefazodone 200–600 mg/day, Nortriptyline 75–150 mg/day, Phenelzine 45–90 mg/day, Pramipexole 0.375–4.5 mg/day, Reboxetine 8–12 mg/day, Sertraline 50–200 mg/day, Trazodone 150–400 mg/day, Trimipramine 75–300 mg/day, and Venlafaxine 75–375 mg/day.

These target ranges were mainly defined by U.S. Food and Drug Administration (FDA)-approved labelings. However we made some adjustments to these ranges to reflect clinical practice patterns that might not have been considered in the FDA-reviewed studies according to Gartlehner et al. (2011). In case dosing range had multiple patterns by products, we adopted the widest range. For the drugs for which we could not find out dose ranges in FDA-approved labels or Gartlehner et al. (2011), we used databases of UK Medicines and Healthcare Products Regulatory Agency (MHRA) and the European Medicines Agency (EMA). For amineptine, dothiepin/dosulepin, mianserin, nomifensine and tianepine we could not find a standard dose range, and we therefore accepted any dose range.

2.5. Search methods

Searches of the Cochrane Depression, Anxiety and Neurosis Group (CCDAN) registers were conducted up to May 2012. CCDAN's trial registers are collated from routine weekly generic searches of MEDLINE (1950-), EMBASE (1974-) and PsycINFO (1967-), quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL) and additional databases. Reports of trials are also sourced from international trials registers of the World Health Organization's trials portal (ICTRP), ClinicalTrials.gov, drug company home pages, the hand-searching of key journals, conference proceedings and other (non-Cochrane) systematic reviews and meta-analyses. Details of CCDAN's generic search strategies can be found on the Group's website (http://ccdan.cochrane.org/specialised-register). (Cf. Magni et al. (2013) and Purgato et al. (2014) for more details). We updated our search using MEDLINE and CENTRAL in January 2015.

2.6. Data extraction and management

At least two independent review authors extracted data from the included studies and also assessed their quality in accordance with the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2011). When inadequate details of methodological characteristics of trials were provided, the authors were contacted in order to obtain further information.

We extracted the following data from the flexible dose arms in the included studies:

1) Number of participants in each arm.
2) Mean daily dosage actually prescribed and its SD.

We graded each study's potential source of bias as high, low or unclear in the following domains (Higgins et al., 2011; Wood et al., 2008):

1) Allocation concealment
2) Blinding

Any disagreement was resolved by discussion of the two raters and, where necessary, in consultation with a third author.

2.7. Statistical analysis

We conducted the analyses if, for each antidepressant drug, there was at least one trial comparing it against either of our standard drugs, fluoxetine or paroxetine.

In the primary analysis we included all relevant studies and calculated, for each drug, the weighted ratio of mean doses from direct comparisons. First the ratio of the mean doses for each study was calculated, and then it was weighted by the total sample size to find the weighted mean ratio. We converted paroxetine mean doses of each study into fluoxetine mean dose studies by using the weighted ratio of mean doses from trials directly comparing fluoxetine and paroxetine, i.e. by multiplying the mean doses of paroxetine of each trial by this weighted mean ratio, and then combined the paroxetine trials with the fluoxetine trials. Then the overall weighted mean ratio of each drug were recalculated to define the drug's dosage equivalent to fluoxetine 40 mg/d.

If a certain antidepressant was compared both to fluoxetine and paroxetine in the same trial, in order to avoid double counting in the synthesis of fluoxetine and paroxetine datasets, we divided the number of participants in the comparator drug arm in half.

We conducted the following four sensitivity analyses to examine the robustness of our primary analysis.

1. We conducted a meta-analysis of the ratio of means (RoM) between a target drug and fluoxetine or paroxetine, when there were two or more trials reporting both the mean and SD for their flexible dose arms (Friedrich et al., 2008, 2012). We used the fixed effect model, as we assume that all the comparisons should be measuring the same underlying, true ratio of means. The results were then recalculated to define the drug's dosage equivalent to fluoxetine 40 mg/d and its 95% confidence interval (CI). We also calculated I-squared to examine heterogeneity of the ratios across trials.
2. We did the same analysis as the primary but by using only the fluoxetine dataset. As we used both fluoxetine and paroxetine combined dataset in our primary analysis and the validity of the method combining the two datasets was not certain, this sensitivity analysis examined how the results might be different when based on the fluoxetine dataset only without additional paroxetine results.
3. Although in the included studies both the standard and comparator drug have been titrated to be optimally effective thanks to the flexible-dose design, it does not necessarily assure that they are equally efficacious. We therefore ran a third sensitivity analysis by adjusting the ratio of the means in the primary analysis by the relative risk (RR) for response for that particular comparison. The mean of these adjusted ratios, weighted by sample size, were then recalculated to define the drug's dosage equivalent to fluoxetine 40 mg/d.
4. Dose range set for each drug in each study might affect the result of ratio of mean dose in each study. Therefore, we excluded outlying studies in which the comparator dose range did not include the value calculated from our primary analysis. Then we conducted this fourth sensitivity analysis using the same calculation as our primary analysis.

Finally, we followed and adapted the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system (Balshem et al., 2011), and rated the quality of evidence of our findings, i.e., confidence we can place in the equivalence estimates, from the following three points of view in three grades of high, moderate or low. The grading of high was downgraded if there were significant risks of bias in the included studies (study limitations), if 95%CI were wide from a clinical point of view and/or if there were only a few contributing studies (imprecision), or if I-squared in the

ROM meta-analysis was above 50% and/or if results differed substantively in sensitivity analyses (inconsistency).

3. Results

3.1. Included studies

We found 144 flexible dose trials meeting the inclusion criteria. Of these, mean doses could be extracted from 83 studies (14 131 participants), contributing 61 comparisons for fluoxetine and 24 comparisons for paroxetine. One 3-arm study comparing fluoxetine, paroxetine and sertraline was included. We treated this study as three 2-arm (i.e. fluoxetine vs. paroxetine, fluoxetine vs. sertraline, paroxetine vs. sertraline) studies and divided the sample size of sertraline arm in half where appropriate in order to avoid double-counting the same subjects in the evidence synthesis. Of the 167 arms included, dose ranges set for 153 arms (91.6%) were completely within the range defined above for the selection of studies, and those for 14 (8.4%) overlapped with, but either the upper limit was above or the lower limit was below, these ranges (2 for amitriptyline, 7 for imipramine, 1 for mirtazapine, 1 for nortriptyline, 2 for trazodone, and 1 for venlafaxine). We could extract SD of mean dose in 51 studies. Fig. 1 shows the PRISMA flowchart of study selection and Webappendix 1 shows the characteristics of the included studies. We found no study of amineptine, amisulpride, citalopram, milnacipran, nomifensine, phenelzine, pramipexole, tianeptine, or trimipramine.

3.2. Primary analysis

In the primary analysis, mean dosage of fluoxetine 40 mg/day was equivalent to paroxetine dosage of 34.0 mg/day. Table 1 shows the equivalent dosages of each drug compared to fluoxetine 40 mg/day in the primary analysis combining both the fluoxetine and paroxetine datasets.

3.3. Sensitivity analyses

Table 1 tabulates the results from the four a priori sensitivity analyses.

Sensitivity analysis 1 using RoM meta-analysis provide not only equivalent dosages but also their 95%CI along with measure of heterogeneity. Low to moderate heterogeneity was suggested for agomelatine, desipramine, maprotiline, nefazodone, and sertraline.

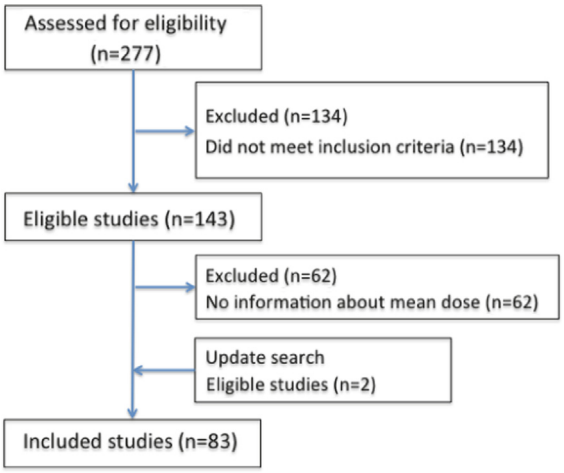

Fig. 1. PRISMA flow chart of study selection.

In sensitivity analysis 3, RR for response of each individual RCT was not significant except for one study and the pooled RR for each drug was not significant except for sertraline (1.11, 95%CI: 1.03 to 1.20, Webappendix 1). The results, adjusted for these significant differences in efficacy, were concordant with the primary analysis results.

Overall the results from the four sensitivity analyses were largely concordant with those from the primary analysis. Doxepin was the only drug for which differences greater than 20% in two or more sensitivity analyses were noted (140.1 mg in the primary analysis but 93.2 mg in Sensitivity analysis 1, 181.3 mg in Sensitivity analysis 3 and 196.3 mg in Sensitivity analysis 4).

3.4. Quality of evidence supporting dose equivalency

Quality of evidence supporting dose equivalency for each drug is also shown in Table 1. High quality of evidence supported dose equivalency for agomelatine, amitriptyline, desipramine, imipramine, maprotiline, moclobemide, nefazodone, paroxetine, sertraline and venlafaxine. The supporting evidence was judged moderate for bupropion, clomipramine, dothiepine, doxepin, fluvoxamine, mirtazapine, reboxetine and trazodone.

4. Discussion

This is the first study to examine dose equivalence of antidepressants based on randomized evidence. We carried out a systematic and comprehensive search for all flexible-dose randomized trials comparing either fluoxetine or paroxetine, the two most extensively studied antidepressants in the literature, against another active antidepressant and integrated their results by calculating the mean ratio of the achieved doses, weighted by numbers of included patients, which was then recalculated back to be equivalent to 40 mg/day of fluoxetine. The results of this primary analysis were largely corroborated by four sensitivity analyses, except for doxepin. The quality of supporting evidence was rated as high or moderate for most of the examined antidepressants, except for escitalopram, lofepramine, mianserin and nortriptyline.

There have been a few attempts at finding dose equivalency of antidepressants. In comparison with Ali (1998) proposal, our results tended to find considerably lower dosages to be equivalent to fluoxetine 40 mg/day except for noritriptyline. In comparison with Fava and Davidson (1996) study, mean dose of fluvoxamine, nefazodone, noritriptyline, paroxetine and sertraline were comparatively close to our results, but similar to Ali's table, other drugs dosages were much higher than our results. It must be pointed out that these authors did not provide sufficient details about how they calculated the equivalency and it appears that their methods were mostly unsystematic and opinion-based.

Our study followed the method originally used for antipsychotics by Davis (1974), who employed data from double-blind flexible-dose randomized trials of chlorpromazine and calculated the mean dose of each antipsychotic drug that was as effective as the standard comparator chlorpromazine 100 mg/day. Davis's results have been used by guidelines and textbooks for decades. Recently the same method was applied to atypical antipsychotics (Stefan Leucht et al., 2015). As discussed in the Introduction, there are other proposed methods to calculate dose equivalence and no single method may be considered the gold standard in all circumstances (Patel et al., 2013). Given the clinical and methodological importance of defining dose equivalency, further efforts to examine this issue for antidepressants are warranted. The results from our study and from other methods need be taken into consideration together in discussing dose equivalency of antidepressants in the future.

The present study is not without limitations. First, the number of included studies and participants were relatively small for some

Table 1
Dose equivalent to 40 mg fluoxetine.

	Praimary analysis[a]			Sensitivity analysis 1[b]					Sensitivity analysis 2[c]			Sensitivity analysis 3[d]			Sensitivity analysis 4[e]			Quality of evidence
	Number of included studies (N.s.)	Number of participants (N.p.)	Weighted mean dose (/flu40 mg)	N.s.	N.p.	Ratio of means [95%CI]	Recalculated mean dose (/flu40 mg) [95%CI]	I^2 (%)	N.s.	N.p.	Weighted mean dose (/flu40 mg)	N.s.	N.p.	Weighted mean dose (/flu40 mg)	N.s.	N.p.	Weighted mean dose (/flu40 mg)	
Agomelatine	2	1143	53.2	2	1143	1.33 [1.29, 1.38]	53.2 [51.6, 55.2]	0	2	1143	53.2	2	1143	51.0	2	1143	53.2	high
Amineptine	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Amisulpiride	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Amitriptyline	8	653	122.3	4	278	3.27 [3.06, 3.49]	130.8 [122.4, 139.6]	85	6	356	99.6	6	552	137.0	5	306	106.4	high
Bupropion	2	201	348.5	2	201	9.10 [8.19, 10.12]	364.0 [327.6, 404.8]	89	1	123	402.1	1	123	346.2	2	201	348.5	moderate
Citalopram	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Clomipramine	2	1073	116.1	1	1019	n.a.	n.a.	n.a.	1	54	102.1	1	1019	119.3	2	1073	116.1	moderate
Desipramine	2	104	196.3	2	104	4.91 [4.29, 5.62]	196.4 [171.6, 224.8]	0	2	104	196.3	1	58	187.4	2	104	196.3	high
Dothiepin	2	119	154.8	2	119	3.30 [3.06, 3.55]	132.0 [122.4, 142]	99	2	119	154.8	1	60	158.0	1	60	231.7	moderate
Doxepin	3	166	140.1	2	91	2.33 [2.02, 2.68]	93.2 [80.8, 107.2]	98	3	166	140.1	2	115	181.3	2	115	196.3	moderate
Duloxetine	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Escitalopram	1	325	18.0	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	1	325	19.0	1	325	18.0	low
Fluvoxamine	3	280	143.3	3	280	3.98 [3.66, 4.33]	159.2 [146.4, 173.2]	96	1	100	119.2	1	120	232.6	2	220	159.6	moderate
Imipramine	12	1725	137.2	8	1043	2.99 [2.88, 3.10]	119.6 [115.2, 124.0]	90	7	923	121.5	8	1003	129.1	11	1665	139.5	high
Lofepramine	1	122	250.2	1	122	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	1	122	297.7	1	122	250.2	low
Maprotiline	2	117	118.0	2	117	2.87 [2.69, 3.06]	114.8 [107.6, 122.4]	0	1	46	125.0	1	71	124.0	2	117	118.0	high
Mianserin	1	65	101.1	n.a.	n.a.	n.a.	n.a.	n.a.	1	65	101.1	n.a.	n.a.	n.a.	1	65	101.1	low
Milnacipran	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Mirtazapine	4	737	50.9	1	197	n.a.	n.a.	n.a.	2	265	54.6	4	737	44.1	4	737	50.9	moderate
Moclobemide	6	679	575.2	5	470	14.91 [14.16, 15.70]	596.4 [566.4, 628.0]	90	6	679	575.2	6	679	535.5	6	679	575.2	high
Nefazodone	6	532	535.2	2	165	13.52 [12.51, 14.61]	540.8 [500.4, 584.4]	0	4	286	563.9	4	445	560.9	5	458	516.5	high
Nomifensine	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Nortriptyline	1	205	100.9	n.a.	n.a.	n.a.	n.a.	n.a.	1	205	100.9	1	205	105.8	1	205	100.9	low
Paroxetine	4	581	34.0	3	378	0.77 [0.73, 0.81]	30.8 [29.2, 32.4]	69	4	581	34.0	4	581	33.0	4	581	34.0	high
Phenelzine	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Pramipexole	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Reboxetine	3	941	11.5	1	168	n.a.	n.a.	n.a.	2	421	15.4	3	941	12.3	n.a.	n.a.	n.a.	moderate
Sertraline	8	1676	98.5	6	1326	2.53 [2.43, 2.64]	101.2 [97.2, 105.6]	39	6	1227	95.5	7	1568	88.6	8	1676	98.5	high
Tianeptine	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Trazodone	3	191	401.4	1	40	n.a.	n.a.	n.a.	2	83	325.1	3	191	421.9	1	43	386.9	moderate
Trimipramine	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Venlafaxine	9	2684	149.4	5	1927	4.24 [4.12, 4.36]	169.6 [164.8, 174,4]	94	7	2468	150.1	7	2468	141.5	9	2684	149.4	high
SUM	83	14131		51	9000				60	9300		63	12338		70	12391		

n.a. = not available.

[a] Included all eligible studies.
[b] Included studies which reported mean and S.D. Meta-analysis of the ratio of means was conducted.
[c] Fluoxetine trials only.
[d] As in primary analysis but adjusted by relative risk of response of each study.
[e] Excluded outlying studies in which the comparator's flexible dose range did not include the dosage calculated from the primary analysis.

drugs. Unfortunately many of the identified flexible-dose studies using fluoxetine and paroxetine did not report the mean doses achieved in the flexible dose arms. In addition, even when they did report the mean dose, they failed to report its SD, so that we were unable to include some of the identified studies in the calculation of RoM. Second, Davis's method assumes that antidepressants have a dose response. For antidepressants, the dose response relationships have been suggested but not clearly demonstrated (Hansen et al., 2009). Davis's method is therefore of more hypothesis-generating than hypothesis-confirming nature. Third, since the efficacy of each drug may not be completely equal (Cipriani et al., 2009), the method to consider intervention mean dose as equivalent to comparator mean dose might not be accurate. Fourth, dose range of each drug in each study varied somewhat. However, when we conducted sensitivity analyses 3 and 4 to examine the influence of differences in treatment efficacy and range of dosage, we found no large differences between the primary and sensitivity analyses except for doxepin. Doxepin was the only drug to show inconsistent results, probably because of the small number and inconsistency of the included studies.

In summary, our findings can be useful for clinicians when patients need to switch one antidepressant to another or add another antidepressant by providing a target dose range to aim at. In clinical practices, the clinicians should further take many more factors into consideration, including age, sex, body weight, complications and preferences of the patients on the one hand, and possible adverse effects and costs on the other. For researchers our findings would provide guidance for deciding dose ranges for fair and accurate comparison of antidepressants. It is advised that future flexible dose studies report their achieved mean dose with SD, so that more data can be analyzed by Davis's method. In addition, other methods to estimate dose equivalency in antidepressants are warranted.

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Conflict of interest

YH, MP, LRM, NT, AC, and CB have no conflict of interest to declare.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2015.03.021.

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