Effectiveness of antidepressants

Meta-analysis of dose–effect relationships in randomised clinical trials

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Background Antidepressant drugs are usually prescribed at low doses, possibly to avoid adverse reactions. No comprehensive review has addressed the issue of dose, clinical response and tolerability in a quantitative way.

Aims To determine whether high doses of antidepressants are more effective than low doses, and how safety is affected by dose.

Method Trials comparing two or more doses of the same antidepressant were located, and all antidepressants administered were converted to the equivalent dose of imipramine. Generalised estimating equations were used to analyse percentage improvement and adverse event rate according to dose level.

Results Thirty-three studies were identified. The dose level 100–200 mg imipramine equivalents showed an average improvement of 53% by 'intention-to-treat'. Higher doses were not accompanied by increased efficacy, while lower doses showed reduction in efficacy. Adverse events significantly increased with dose.

Conclusions With a low dose of antidepressants, clinicians trade off a slightly reduced chance of improvement for a higher chance of avoiding adverse reactions.

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Antidepressant drugs are widely used in clinical practice for the treatment of depressive disorders. Several drug-utilisation studies have documented that antidepressants are prescribed at doses well below those recommended (e.g. Brugha *et al*, 1992; Munizza *et al*, 1995). Furthermore, one study documented that prescription patterns improved only moderately following targeted physician education (Katon *et al*, 1992). A possible explanation for widespread under-dosing is that depressed patients treated on an out-patient basis need to continue to work and function in the community, and cannot tolerate the adverse reactions that higher doses of antidepressants usually produce. Traditional tricyclic compounds are more frequently underdosed than the newer selective serotonin reuptake inhibitors (SSRIs), probably because of greater tolerability of the latter at therapeutic dose (Donoghue & Tylee, 1996; Craig Nelson, 1997). Recent meta-analyses comparing discontinuation rates of tricyclics and SSRIs in randomised clinical trials (RCTs) have confirmed that SSRIs have slightly lower drop-out rates for adverse reactions, while efficacy is similar (Anderson & Tomeson, 1995; Hotopf *et al*, 1997*a*; Fawcett & Barkin, 1997).

Although several RCTs with patients allocated to different doses of the same antidepressant have been performed, no comprehensive review has addressed the issue of dose, clinical response and tolerability in a quantitative way. The objective of this meta-analysis is to fill this gap, and to answer two specific questions: first, are high doses of antidepressants, both traditional and newer, more effective than low doses?; and second, how is safety affected by dose?

METHOD

All RCTs comparing two or more doses of the same antidepressant were identified from Medline, Current Contents and the Cochrane Collaboration Register of Trials. We searched for all antidepressive agents with all depressive disorders, and linked these variables with dose–response relationship and drug type. In order to retrieve all RCTs, we used an algorithm where the terms 'clinical trials', 'randomised clinical trials', 'prospective studies', 'research design' or the root word 'random' were searched for. However, most studies were identified by an assiduous scrutiny of all the references of the papers retrieved and of published reviews of literature, and also by writing to many individual authors.

Inclusion criteria for the meta-analysis were the following:

(a) RCTs comparing two different doses of the same antidepressant drug;

(b) diagnosis of depression;

(c) duration of the trial at least three weeks; and

(d) more than five patients per treatment arm.

Two outcome measures were extracted from the selected RCTs. First, the number of patients clinically improved, signified either by a reduction of more than 50% of the total score of the Hamilton Rating Scale for Depression (Hamilton, 1960), or by a moderate to marked improvement on the Clinical Global Impression Scale (Guy, 1976), or by a lack of relapse of depressive episode (where a paper reported results from more than one scale, only data from the first scale mentioned in the results sections were retained). Second, the total number of side-effects of any type.

In addition, the following variables of interest were extracted: year of publication, out-patient or in-patient setting, mean patient age, percentage of females, diagnosis, duration of treatment, drop-outs for any cause, type and dose of antidepressant drug administered, and concurrent medication or psychological treatment. Data extraction was independently performed by two reviewers, who were blind to the authors and journal title, as well as to the type of drug and dose used, in order to avoid possible bias during data extraction. Disagreements between reviewers were solved through discussion. All papers were also independently scored for methodological strength, using the check-list proposed by Jadad *et al* (1996).

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Statistical analysis

Outcome variables

The following outcome variables were computed for each study arm:

(a) percentage improvement=number of patients clinically improved/total number of patients randomised;

(b) adverse event rate=[(total number of adverse drug reactions+total number of withdrawals) / total number of patients randomised]/(number of weeks of treatment).

The total number of patients randomised was not always readily available from the publications, owing to the tradition in this setting of reporting results on patients actually completing treatment. In this meta-analysis, the percentage improvement and the adverse event rate were computed on the basis of the total number of patients randomised (where an intention to treat existed), which had to be reconstructed on the basis of the reported number of withdrawals or exclusions. The working definition of adverse event rate used in this report was chosen so as to reflect not only pure adverse reactions to antidepressant drugs but also all other situations leading to total or partial failure of the treatment (e.g. withdrawals due to lack of efficacy or patient refusal), in order to quantify the total burden of negative events per week of treatment. Again, this is in contrast with the common practice of ignoring dropouts when evaluating treatment results.

Antidepressant dose

In order to compare the different drugs involved in the studies, and considering that all antidepressant drugs act on the same clinical manifestations of depression, we decided to standardise the recommended therapeutic doses with respect to the recommended dose of imipramine (150 mg/day), the first antidepressant introduced into clinical practice. This generated for each drug an equivalence factor by which the doses investigated in each trial were multiplied. For instance, the therapeutic dose for phenelzine is 45 mg, and the conversion factor is 150/45=3.33; a prescribed dose of 90 mg/day of phenelzine has been converted to an imipramine equivalent dose of $90 \times 3.33 = 299.7$ mg/day. Average therapeutic doses and corresponding conversion factors are given in Table 1.

Modelling

Generalised estimating equations (Diggel *et al*, 1994) were used to model the outcome variables of interest, allowing for the grouping factor (random effect) represented by each study considered. A constant correlation among arms from the same study was assumed. Tests for normality showed that percentage improvement was sufficiently well behaved not to require transformations, while adverse event rate was transformed to its square root in order to stabilise the variance.

The variables used as independent factors were the following: antidepressant daily dose level (placebo, less than 100 mg, 100–200 mg, 201–250 mg, more than 250 mg), antidepressant class (tricyclics, SSRIs, monoamine oxidase inhibitors (MAOIs), atypical antidepressants), Jadad *et al* (1996) quality score (ranging from 1 to 5; the higher the score the better the quality of the study), proportion of females, and sample size of the study (fewer than 50, 51–100, more than 100 patients). All these variables were converted to appropriate binary indicators. When analysing percentage improvement, duration of treatment was also considered, as a continuous variable.

By default, the fixed effect for drug level was considered in the models for both outcome variables, using the dose level of 100–200 mg (the generally acknowledged therapeutic range) as a reference. Coefficients of the model for the various drug levels therefore estimate differences of effect with respect to this dose level. Forward selection was used to add to this minimal model other significant terms ($P<0.05$). The model coefficients were then used to estimate the average percentage improvement and average adverse event rate for the five dose levels considered; their corresponding 95% confidence intervals (CIs) were computed using the estimated variance–covariance matrix of the coefficients. For adverse event rate, estimated effects are based on the square of the linear combinations of the coefficients; similarly, the calculation of 95% CIs was made on the square root scale, and the values obtained were then back-transformed to the linear scale by taking their square.

Table 1 Average daily dose and conversion factor to imipramine for antidepressants considered in the study

Class of antidepressant	Dose range (mg/day)	Average daily therapeutic dose (mg)	Conversion factor to imipramine
Tricyclics			
Imipramine	100–200	150	–
Clomipramine	100–200	150	1
Tetracyclics			
Maprotiline	100–150	125	1.2
SSRIs			
Fluoxetine	20–40	30	5
Citalopram	30–60	45	3.33
Fluvoxamine	100–200	150	1
Minalcipram	100–200	150	1
Sertraline	100–150	125	1.2
Paroxetine	20–40	30	5
Venlafaxine	75–225	150	1
MAOIs			
Isocarboxazid	10–30	20	7.5
Phenelzine	30–60	45	3.33
Moclobemide	150–300[1]	225	0.66
Atypical antidepressants			
Bupropion	200–300	250	0.6
Nefazodone	300–600	450	0.33
Minaprine	200	200	0.75
Rolipram	2.25	2.25	66.6

SSRI, selective serotonin reuptake inhibitor; MAOI, monoamine oxidase inhibitor.
1. Benkert *et al* (1996).

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RESULTS

A total of 49 papers were retrieved through the search as described above. A total of 17 papers were excluded from the analysis: 11 papers because efficacy data could not be extracted (Blashki *et al*, 1971; Barnes & Guarino, 1980; Branconnier *et al*, 1983; Halaris *et al*, 1983; Bjerkenstedt *et al*, 1985; Fabre & Putman, 1987; Hebenstreit *et al*, 1989; D'Amico *et al*, 1990; Khan *et al*, 1991; Dunner & Dunbar, 1992; Montgomery *et al*, 1992), two papers where a therapeutic dose was not defined (Wilcox *et al*, 1996; Schiwy *et al*, 1989), and four papers because original data were already published (Altamura *et al*, 1988; Wernicke *et al*, 1989; Dunlop *et al*, 1990; Beasley *et al*, 1992). Hence, 32 RCTs comparing two different doses of antidepressants were included in the analysis. In addition, one study (Benkert *et al*, 1997, see Appendix) that compared two doses of two different antidepressant drugs was considered as two separate studies, bringing to 33 the total number of studies analysed. The 33 studies included had a total of 78 arms of active treatment and 16 placebo arms. All the studies considered in the meta-analysis are listed in the Appendix. Adverse events could be extracted from only 22 studies, corresponding to 64 treatment arms.

The studies considered were published between 1975 and 1997, approximately half of them before 1990. Twenty-four studies lasted 4–6 weeks, five lasted 7–156 weeks, and two studies lasted three weeks only. Studies involving only out-patients made up 61% of the total, 24% involved in-patients only, and both in-patients and out-patients featured in 6% (in 9% of the studies the setting was not specified). In almost 70% of the cases the studies were collaborative. Out of the 33 studies, 25 treated severely depressed patients, diagnosed as having major affective disorder, major depression, endogenous depression or bipolar affective disorder. Two studies had a non-specific diagnosis (e.g. depressed mood), and six studies considered both major and minor depression. Thirty studies applied specific diagnostic classifications of depression, using the *Diagnostic and Statistical Manual of Mental Disorders*, versions II, III or III–R (American Psychiatric Association, 1976, 1980, 1987) (20 studies), the Research Diagnostic Criteria (Spitzer *et al*, 1978) (seven studies), and the *International Classification of Diseases*, 9th revision (ICD–9) (one study) (World Health Organization, 1978).

The classes of antidepressant drug employed are shown in Table 2. Four papers studied tricyclic or tetracyclic antidepressants (considered together in this paper), 16 studied SSRIs, five studied MAOIs, and eight studied atypical antidepressants. Patient exclusion criteria were those commonly used in clinical trials of antidepressants, namely age greater than 65 or 70 years (12 studies), suicidal risk (14 studies), alcoholism (13 studies), drug abuse (14 studies), pregnancy or lactation (14 studies), severe somatic disorders (20 studies) and the presence of concurrent psychiatric disorders (21 studies). Studies involving SSRIs tended to exclude patients with greater age and with severe somatic disorders more frequently than studies involving tricyclics (60% versus none for both exclusion criteria).

A total of 5844 patients were randomly allocated to 78 treatment arms, and 998 patients to 16 placebo arms. The sample sizes of the studies ranged from 17 to 953, with a median of 88. The demographic characteristics of the random samples were described in 27 studies. Patients' ages ranged from 18 to 89 years, and average age ranged from 35 to 54 years. The proportion of female patients in the studies reviewed ranged from 41% to 100%, with a median of 66%. The Jadad quality score was 1 for one study, 2 for eleven studies, 3 for fifteen studies, and 4 for six studies (Jadad *et al*, 1996).

For each study, the imipramine equivalent dose per arm was computed according to the rule stated above, and then recoded into four categories: less than 100 mg, 100–200 mg, 201–250 mg and more than 250 mg. The first category corresponds to doses usually considered below the therapeutic range for imipramine, the second category to doses within the therapeutic range, and the third and fourth categories to doses higher and much higher than the therapeutic range, respectively. The mean imipramine equivalent dose in the first category was 66 mg, in the second 153 mg, in the third 224 mg, and in the fourth 312 mg. Table 3 details the number of study arms per dose category according to antidepressant drug class. Finally, the placebo arm was considered as dose zero in the analysis.

None of the independent variables considered (antidepressant class, Jadad quality score, proportion of females, sample size of the study, and duration of treatment) turned out to be significant, and none was therefore retained in the final regression models derived for the two outcome measures of interest; hence, only terms relating to dose level were kept in the final model (Table 4).

Table 2 Number of studies of each drug class

Class of antidepressant	Number of studies
Tricyclics	
Imipramine	2
Clomipramine	1
Tetracyclics	
Maprotiline	2
SSRIs	
Fluoxetine	5
Citalopram	2
Fluvoxamine	1
Minalcipram	2
Sertraline	3
Paroxetine	1
Venlafaxine	1
MAOIs	
Isocarboxazid	1
Phenelzine	2
Moclobemide	2
Atypical antidepressants	
Bupropion	1
Nefazodone	2
Minaprine	3
Rolipram	2

SSRI, selective serotonin reuptake inhibitor; MAOI, monoamine oxidase inhibitor.

A graphical representation of estimated percentage improvement and adverse event rate is displayed in Fig. 1. Overall, about half of the patients randomised to active treatment were considered improved at the end of the trials. The dose level 100–200 mg of imipramine equivalents – taken as reference category – showed an average improvement of 53%. Higher doses were not accompanied by increased efficacy compared with the therapeutic range: doses of 201–250 mg showed an average improvement of 46%, and doses over 250 mg of 48%. Doses of less than 100 mg showed an average improvement of 46%, a significant but small reduction in efficacy – 7% compared with the reference category. The placebo arms showed an average improvement of 35%, significantly lower than the reference category and the <100 mg dose level. Regarding the adverse event rate, doses <100 mg showed a significant reduction with respect to the level 100–200 mg, while doses greater than 250 mg showed a significant increase with respect to the same reference

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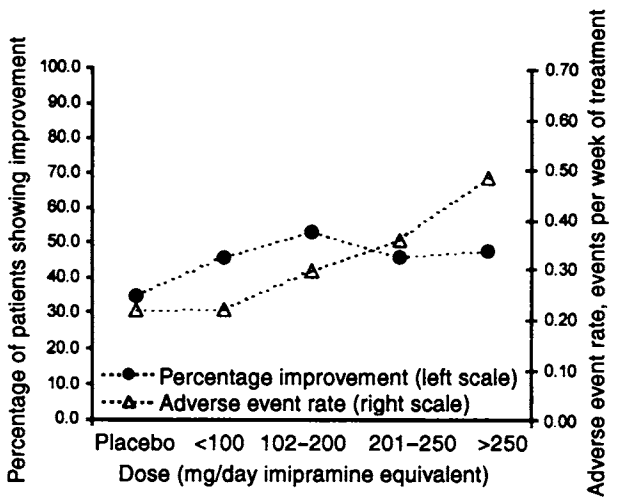

Fig. 1 Estimated percentage improvement and adverse event rate from the final regression models.

range. The placebo arms showed an average adverse event rate of 0.22, similar to the <100 mg dose level but significantly lower than the reference category's adverse event rate.

Finally, in order to mimic the statistical analysis usually performed in clinical trials with antidepressants, we ran an additional regression (not reported in Table 4) having as dependent variable the percentage improvement in patients who completed treatment. The estimated average improvement in treatment completers was 69% for the therapeutic range, 60% (significantly different from the reference category, $P<0.003$) for doses less than 100 mg, 67% (not significantly different from the reference category, $P=0.726$) for doses 201–250 mg, and 76% (not significantly different from the reference category, $P=0.172$) for doses greater than 250 mg. The average percentage of withdrawals per arm was 25% in the first dose category, 22% in the second, 28% in the third and 35% in the fourth.

DISCUSSION

Antidepressant dose plays a definite role in the pharmacological treatment of depression – a delicate balance is sought between the achievement of symptom relief and the avoidance of adverse reactions leading to treatment discontinuation. However, there are surprisingly few RCTs addressing the dose–response issue. A possible explanation suggested by Gram (1990) is that the attention of the scientific community has been captured for many years by the relationship between plasma concentration and clinical effect, thus leaving dose in the background. In addition, fixed-dose clinical trials are difficult to design and expensive to conduct (Benkert *et al*, 1996). For newer antidepressants, the interest in dose–response studies has been more pronounced, partly because of the requirements from regulatory bodies to provide such data. Accordingly, only ten RCTs with patient allocation to different doses of tricyclics and MAOIs, the first classes introduced in clinical practice, were available for this meta-analysis, while we retrieved more studies on the dose-efficacy of SSRIs and atypical antidepressants.

Some authors have argued that current recommended doses are based on little empirical evidence (Greenberg & Fisher, 1989). Under-treatment has been considered a frequent cause of therapeutic failure, although many clinicians question whether general practitioners are really wrong to prescribe at lower doses (Kendrick, 1996 and subsequent letters; Martin *et al*, 1997). The lack of agreement on the dose-efficacy and dose-safety of antidepressants prompted the present meta-analysis, which tries to answer these questions in a quantitative way, deriving data from published RCTs.

Table 3 Treatment arms categorised by drug class and dose

Antidepressant class	Dose (mg/day imipramine equivalent)				
	0	<100	100–200	201–250	>250
Arms used for analysis of improvement					
Placebo	16				
Tricyclics/tetracyclics		5	3	1	1
SSRIs		12	19	3	4
MAOIs		2	5	1	2
Atypical antidepressants		7	9	3	1
Arms used for analysis of adverse events					
Placebo	11				
Tricyclics/tetracyclics		4	0	0	0
SSRIs		11	14	3	3
MAOIs		0	1	1	2
Atypical antidepressants		5	7	2	0

SSRI, selective serotonin reuptake inhibitor; MAOI, monoamine oxidase ihhibitor.

Efficacy and intention to treat

The meta-analysis showed two unexpected findings relating to the efficacy of antidepressants. First, the clinical efficacy estimated according to the intention to treat did not exceed 50% of the original samples. The remaining patients either dropped out for whatever reason or did not show any improvement. This estimate is considerably lower than the estimate provided by the authors of the original studies, who almost invariably did not apply an intention-to-treat analysis. In an attempt to replicate the analyses provided by the original studies, we limited the evaluation of efficacy to treatment completers, obtaining an estimate of the improvement rate considerably higher than when using intention-to-treat analysis – higher by amounts ranging from 13% for the lowest dose to 26% for the highest dose, largely attributable to an increasing number of withdrawals as the dose increases. This false impression of greater improvement at higher doses probably contributed to the widespread belief that antidepressants are effective in two-thirds of subjects (Fawcett & Barkin, 1997). A thorough review of the methodological adequacy of RCTs with antidepressants conducted by Hotopf *et al*

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Table 4 Coefficients from the final regression models

Dose (mg/day imipramine equivalent)	Model coefficient	s.e. of coefficient	*P*-value of coefficient	Estimated effect[1]	95% CI for estimated effect[2]
Patients showing improvement (%)					
Placebo	−0.185	0.032	<0.001	34.8	25.4–44.3
<100	−0.073	0.028	0.010	46.0	36.9–55.1
100–200	0.533	0.027	<0.001	53.3	48.0–58.5
201–250	−0.070	0.045	0.117	46.3	34.9–57.7
>250	−0.049	0.044	0.266	48.3	37.0–59.7
Adverse event rate (events/week)					
Placebo	−0.077	0.028	0.006	0.22	0.13–0.33
100	−0.076	0.024	0.002	0.22	0.13–0.33
100–200	0.543	0.043	<0.001	0.30	0.21–0.39
201–250	0.055	0.038	0.147	0.36	0.23–0.52
>250	0.152	0.042	<0.001	0.48	0.32–0.67

1. The dose range 100–200 mg was the reference category in the model (i.e. constant term, since no other factor entered the final model) so coefficients express differences in effect with respect to this category.
2. For adverse event rate, model coefficients are on a square root scale, while estimated effects and corresponding 95% CIs are on a linear scale; see 'Statistical analysis' sub-section.

(1997*b*) confirmed that failure to use intention-to-treat analysis was among the most common methodological shortcomings of RCTs with antidepressants.

Efficacy and dose

The second unexpected finding relating to efficacy was a rather flat dose–response curve. Doses beyond the therapeutic range failed to bring higher rates of response; doses below the therapeutic range were significantly less effective, but only by approximately 7%. Dose zero, the placebo arm, showed an average improvement of 35%, in line with the findings of several studies in the field of depression (Greenberg & Fisher, 1989). Most of the studies we considered used an inert placebo. If active placebo had been used, the improvement rate might have been higher, as shown by a recent meta-analysis of trials comparing antidepressants with active placebos (Moncrieff *et al*, 1998).

The improvement rates were not influenced by percentage of females, sample size, duration of treatment or quality score of the studies. It is worth noting, however, that the Jadad *et al* (1996) quality score in our meta-analysis did not show enough variation among studies, possibly because it is not sensitive enough for a meta-analysis of randomised trials: one point of a maximum total score of 5 is assigned by default since all studies are randomised; another point went to most trials because they were described as double-blind. Finally, drug class did not show any association with outcome – estimates of improvement (and adverse event rate) across the dose levels were not affected by the class of drugs used.

The adverse event rate computed for each study where adverse reactions were reported tried to provide an overall indicator of both pharmacological toxicity and other events which had a negative impact on treatment, such as failure to complete it for any reason. The incidence of adverse events in the studies analysed was probably not linear, but very few studies reported their timing. We therefore assumed a linear incidence across the weeks of treatment, thus underestimating their real incidence – or, at least, certainly not overestimating it. Adverse events increased significantly with higher doses, while at doses below the therapeutic level (<100 mg imipramine equivalents) their occurrence was minimised. These findings may have implications for clinical practice that we will discuss below.

Limitations

The present meta-analysis has several limitations, which will be examined in turn. First, the small number of RCTs with subject allocation to different doses prevented a separate analysis by drug class, and obliged us to convert all drugs to imipramine equivalents. This conversion is based on well-established therapeutic doses and dose ranges provided in the literature, but it certainly implied some choices that not everybody may agree with. In addition, the studies selected involved different settings, choice of subjects, availability of other kinds of treatments, etc. Although the majority of studies treated major depression, six studies dealt with both minor and major depression, and two did not specify the type of depression. We decided to keep them in the analysis because they mirror clinical practice, where antidepressant drugs are often prescribed to patients with milder forms of the disorder.

Clinical implications

Antidepressants are often prescribed in clinical practice at low doses, below 100 mg imipramine equivalent. The present meta-analysis indicates that at that dose level the rate of improvement is only moderately lower than at the therapeutic range, and adverse events occur significantly less frequently. Accordingly, prescribing a low dose of antidepressants seems to be a reasonable choice – a slightly reduced chance of improvement is traded off against a higher chance of avoiding adverse reactions, and so continuing treatment. In a drug utilisation study conducted in community mental health centres of the Piedmont region in Italy, the authors found that antidepressant drugs, and especially tricyclics, were often underdosed (Munizza *et al*, 1995). Psychiatrists participating in that study explained that the issue of treatment tolerability, and the concern that subjects might drop out of treatment, were the main reasons behind this therapeutic choice.

Improving treatment of major depression is an ongoing challenge. The development of new classes of antidepressant drug has certainly increased the therapeutic options for both patients and physicians, but the efficacy rates have not changed appreciably (Fawcett & Barkin, 1997). The ideal antidepressant, combining higher efficacy and perfect tolerability, is still to be developed, and the cost of bringing it to market would exceed $250 million (Preskorn, 1994). So far, very little research has been conducted on cheaper and perhaps more effective interventions aimed at retaining depressed patients on treatment, by managing adverse reactions and improving the therapeutic relationship between patient and physician. If such strategies could be devised and implemented, perhaps the proportion showing improvement could really rise to two-

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thirds of all treated patients, a target still far away in clinical practice.

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APPENDIX – STUDIES INCLUDED IN THE META-ANALYSIS

Tricyclics

Imipramine

Frank, E., Kupfer, D. J., Perel, J. M., *et al* (1993) Comparison of full-dose versus half-dose pharmacotherapy in the maintenance treatment of recurrent depression. *Journal of Affective Disorders*, **27**, 139–145.

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Clomipramine

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Tetracyclics

Maprotiline

Rouillon F., Phillips, R., Serrurier, D., *et al* (1989) Recurrence of unipolar depression and efficacy of maprotiline. *Encéphale*, **15**, 527–534.

Maprotiline and paroxetine

Benkert, O., Szegedi, A., Wetzel, H., *et al* (1997) Dose escalation vs. continued doses of paroxetine and maprotiline: a prospective study in depressed out-patients with inadequate treatment response. *Acta Psychiatrica Scandinavica*, **95**, 288–296.

Selective serotonin reuptake inhibitors

Fluoxetine

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Citalopram

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Fluvoxamine

Walczak, D. D., Apter, J. T., Halikas, J. A., et al (1996) The oral dose–effect relationship for fluvoxamine: a fixed-dose comparison against placebo in depressed outpatients. *Annals of Clinical Psychiatry*, **8**, 139–151.

Minalcipram

Ansseau, M., von Frenckell, R., Gerard, M. A., et al (1991) Interest of a loading dose of minalcipram in endogenous depressive inpatients. Comparison with the standard regimen and with fluvoxamine. *European Neuropsychopharmacology*, **1**, 113–121.

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Sertraline

Amin, M., Lehmann, H. & Mirmiran, J. (1989) A double-blind, placebo-controlled dose-finding study with sertraline. *Psychopharmacology Bulletin*, **25**, 164–167.

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Venlafaxine

Mendels, J., Johnston, R., Mattes, J., et al (1993) Efficacy and safety of b.i.d. doses of venlafaxine in a dose–response study. *Psychopharmacology Bulletin*, **29**, 169–174.

MAOIs

Isocarboxazid

Davidson, J., Miller, R., Turnbull, C. D., et al (1984) An evaluation of two doses of isocarboxazid in depression. *Journal of Affective Disorders*, **6**, 201–207.

Phenelzine

Ravaris, C. L., Nies, A., Robinson, D. S., et al (1976) A multiple-dose, controlled study of phenelzine in depression–anxiety states. *Archives of General Psychiatry*, **33**, 347–350.

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Moclobemide

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Atypical antidepressant drugs

Bupropion

Kane, J. M., Cole, K., Sarantakos, S., et al (1983) Safety and efficacy of bupropion in elderly patients: preliminary observations. *Journal of Clinical Psychiatry*, **44**, 134–136.

Nefazodone

Mendels, J., Reimherr, F., Marcus, R. N., et al (1995) A double-blind, placebo-controlled trial of two dose ranges of nefazodone in the treatment of depressed outpatients. *Journal of Clinical Psychiatry*, **56** (suppl. 6), 30–36.

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Minaprine

Wheatley, D. (1989) Minaprine: an anticholinergic-free antidepressant? Results of a controlled trial of mianserin. *British Journal of Psychiatry*, **155**, 106–107.

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Montgomery, S. A., Baldwin, D. S., Priest, R. G., et al (1991) Minaprine and dose response in depression. An investigation of two fixed doses of minaprine compared with imipramine. *Pharmacopsychiatry*, **24**, 168–174.

Rolipram

Bennie, E. H., Cghakravarti, S. K., Jarman, C. M., et al (1998) A double-blind dose-finding study of rolipram in patients with major depressive disorder. *Human Psychopharmacology*, **3**, 275–280.

Fleischhaker, W. W., Hinterhuber, H., Bauer, H., et al (1992) A multicenter double-blind study of three different doses of the new cAMP-phosphodiesterase inhibitor rolipram in patients with major depressive disorder. *Neuropsychobiology*, **26**, 59–64.

CLINICAL IMPLICATIONS

- In randomised clinical trials (RCTs) comparing different doses, effectiveness of antidepressant treatment does not exceed an improvement rate of 50% of randomised patients.
- Doses below 100 mg/day imipramine equivalents are marginally less effective than the therapeutic range (100–200 mg/day), but produce significantly fewer adverse events.
- Doses higher than the therapeutic range are as effective as the therapeutic dose but more toxic.

LIMITATIONS

- The limited number of RCTs with patient allocation to different doses prevented a separate analysis by drug class.
- All antidepressants had to be converted to imipramine equivalents.
- The studies selected involved different settings and types of patients.

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