Dose–response relationship of recent antidepressants in the short-term treatment of depression

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Antidepressant drugs are widely recommended for the treatment of depressive disorders, and finding the "right dose for the right patient" is an important issue. Whatever antidepressant is prescribed, a proportion of adult patients with major depression fail to respond satisfactorily to adequate first-line treatment. A frequent strategy for patients with insufficient response to an initial antidepressant dose is to increase the dose. This review is about this strategy, ie, the possible benefits of prescribing higher doses of recent antidepressants. The results show that a flat dose–response curve is a class phenomenon for selective serotonin reuptake inhibitors (SSRIs), according to randomized, controlled, fixed-dose clinical trials. For the serotonin and noradrenaline reuptake inhibitors (SNRIs), the strategy of dose increase may be relevant for venlafaxine, in order to increase the number of responders. Thus, the subgroup of patients for whom high doses of SSRIs could be useful remains to be defined.

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Whatever the antidepressant drug prescribed, 30%[1] to 50%[2] of adult patients with major depression fail to respond to adequate first-line treatment, defined as a dose in the therapeutic range given for an adequate duration, ie, 4 to 6 weeks.[3] In clinical practice, when a patient responds insufficiently to an initial antidepressant dose, several options are available, such as temporizing, increasing the dose, switching to another antidepressant, or combining several drugs.[4] A survey by Fredman et al[5] of attendees at a psychopharmacology course showed that 80% or more indicated that their first choice would be to raise the selective serotonin reuptake inhibitor (SSRI) dose for a hypothetical patient with minimal response after 4 weeks, or partial response after 8 weeks, of adequate treatment, ie, fluoxetine 20 mg/day, sertraline 100 mg/day, or paroxetine 20 mg/day. For a patient with no response after 8 weeks of adequate SSRI treatment, a switch to a non-SSRI drug was the first and preferred strategy. Hirschfeld et al[4] advocated switching, combination therapy, or augmentation therapy after 4 weeks for patients who fail to respond at an adequate dosage of SSRI (ie, <25% decrease in the Hamilton Rating Scale for Depression [HAMD] or Montgomery and Åsberg Depression Rating Scale [MADRS] score). For those patients who achieve a partial response on first-line therapy (ie, 25% to 50% decrease in HAMD or MADRS score), they proposed that treatment should be continued for 6 to 8 weeks at an adequate dose before considering a change in therapeutic management.[4]

An important question is whether the frequently applied strategy of increasing the dose of antidepressant is justified. The issue is of fundamental and clinical relevance.

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Selected abbreviations and acronyms

CGI	*Clinical Global Impression*
HAMD	*Hamilton Rating Scale for Depression*
ITT	*intent-to-treat*
LOCF	*last observation carried forward*
MADRS	*Montgomery and Åsberg Depression Rating Scale*
SNRI	*serotonin and noradrenaline reuptake inhibitor*
SSRI	*selective serotonin reuptake inhibitor*

Indeed, many patients receive more than the starting dose (ie, more than one tablet of the recent antidepressant per day) during the course of treatment. Such a prescribing pattern implies the existence of a positive dose–response relationship.

Three categories of dose–response studies are found in the antidepressant literature. The first is considered to be the best method to evaluate a dose–response relationship, and consists of randomized, double-blind studies comparing two or more fixed doses of antidepressants with placebo. The second category consists of randomized, double-blind studies comparing fixed doses of antidepressants without placebo or with an active comparator. The third category includes the studies of dose augmentation when the treatment response is insufficient. Some, but not all, studies include the measurement of plasma levels of antidepressants. This approach enables study of response in terms of concentration–response relationship (these concentration–response studies are not discussed here). There are three possible shapes for the relationship between clinical efficacy and dosage: a flat dose–response curve; a curvilinear dose–response curve; and a linear dose–response curve.[6]

Materials and methods

A literature search was performed for randomized controlled double-blind studies comparing fixed doses of SSRIs or serotonin and noradrenaline reuptake inhibitors (SNRIs) with or without placebo or with an active comparator, and studies of dose augmentation in inadequate responders in the treatment of depressive disorders, published from 1980 to 2004. Studies were classified according to the antidepressant drug used (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, milnacipran, or venlafaxine), the type of the study, and the duration of the study, ie, short-term (acute phase) versus long-term (maintenance phase). Meta-analyses were also selected to obtain additional information about treatment effects.

We followed a classical method of reviewing studies, ie, it was not based on the calculation of effect size, odds ratio, or the number needed to treat. Efficacy measures were analyzed using intent-to-treat (ITT) patients with last observation carried forward (LOCF) method, and observed cases by study visit (weekly cases analysis) or at the end of the studies (completer cases analysis). Total score, change of total score, or percentage of responders on the clinical scales were considered. Visual inspection of the figures or data in the publication concerned was also used to appreciate the difference (or lack thereof) between the doses of antidepressants.

We describe here those studies that are methodologically more relevant in terms of number of patients. Studies with a small number of patients were not included in the tables. The studies generally followed a similar protocol. The HAMD 21 items,[7] 17 items,[8] or 24 items, the MADRS 10 items,[9] and the Clinical Global Impression Scale (CGI) were the most widely used reference scales. Most studies began with a single-blind placebo run-in for 1 to 2 weeks before randomization to the double-blind phase. Efficacy measures were total score on the rating scales, their change from baseline, or the response rate. Responders were generally defined as patients with a decrease in the HAMD or MADRS total score of at least 50% after at least 3 weeks of therapy (or time not given), or a score of 1 or 2 on the CGI.

Parallel-group dose comparison studies

Citalopram

The short-term studies with citalopram did not show significant differences in terms of clinical efficacy across a dose range of 20 to 60 mg/day. Even a dose of 10 mg/day was effective compared with placebo.[10] The results of the maintenance study by Montgomery et al[11] and the meta-analysis by the same authors[12] support these findings. Therefore, for the majority of patients, there is no advantage of increasing the dose of citalopram above 20 mg/day. The study by Montgomery et al[11] is particularly interesting, because, in the acute double-blind phase of one of the two initial studies *(Table I)*,[13] citalopram 20 mg/day was no more effective than placebo. However, in the long-term phase, the relapse rate was similar in the group of responders on citalopram 20 mg/day who were

randomized to placebo and in the group of those who were responders and continued in double-blind on placebo, but higher than in the group of those who were randomized to continue on citalopram 20 mg/day. These results tend to show that citalopram 20 mg/day was effective in the acute phase despite the observation that it was not significantly different from placebo.

The study by Montgomery et al[13] failed to show a benefit of citalopram 20 mg/day on the HAMD 17 items and MADRS total scores in a group of 56 evaluable patients, ie, those who remained at least 3 weeks in the study; only citalopram 40 mg/day, in a group of 49 evaluable patients, was superior to placebo and to citalopram 20 mg/day. When using change on the HAMD and MADRS total score, citalopram 20 and 40 mg/day were no different from placebo. Using the 50% reduction on the HAMD and MADRS total score, there were no differences between citalopram 20 and 40 mg/day and placebo at the end of 6 weeks. In other words, there were no more responders in the two citalopram groups than in the placebo group. All analyses were carried out on a LOCF.

In a large study by Feighner and Overo *(Table I)*,[14] citalopram 40 and 60 mg/day, but not 10 and 20 mg/day, were more effective than placebo on change on the HAMD 21 items total score on ITT-LOCF at the end of 6 weeks. However, there was no statistical analysis comparing the different doses of citalopram. The percentage of responders on the MADRS on LOCF was significantly higher in each group of citalopram dose compared with placebo; there was no statistical analysis comparing the different

Drug	No of patients in double-blind phase	Dose escalation	Total duration (weeks)	LOCF analysis	Completer cases analysis
Citalopram[13]	n=199 Evaluable patients=155	1 week	6	Placebo = 20 mg/day < 40 mg/day (total score HAMD and MADRS) Placebo = 20 mg/day = 40 mg/day (change from baseline)	NA
Citalopram[14]	n=650 ITT=650	1 week	6	Placebo = 10 mg/day = 20 mg/day < 40 mg/day = 60 mg/day (change from baseline HAMD)	NA
Escitalopram[15]	n=491 ITT=485 Completers=373	1 week	8	Placebo < 10 mg/day = 20 mg/day = 40 mg/day citalopram (change from baseline HAMD and MADRS)	Placebo < 10 mg/day = 20 mg/day = 40 mg/day citalopram (change from baseline HAMD and MADRS)
Fluoxetine[16]	n=356 ITT=345	No	6	Placebo = 60 mg/day < 20 mg/day = 40 mg/day (change from baseline HAMD)	Placebo < 20 mg/day = 40 mg/day = 60 mg/day (change from baseline HAMD)
Fluoxetine[17]	n=363 ITT=354	No	6	Placebo < 5 mg/day = 20 mg/day = 40 mg/day (change from baseline HAMD)	Placebo < 5 mg/day = 20 mg/day = 40 mg/day (change from baseline HAMD)
Fluvoxamine[18]	n=600 ITT=577	2 weeks	8	Placebo = 25 mg/day = 50 mg/day = 150 mg/day < 100 mg/day (total score HAMD13)	NA
Paroxetine[19]	n=460 ITT=454	No	6	Placebo = 10 mg/day < 20 mg/day = 30 mg/day = 40 mg/day (change from baseline HAMD)	NA
Sertraline[20]	n=369 ITT=347 Evaluable patients=289 Completers=191	No	6	Placebo < 50 mg/day =100 mg/day = 200 mg/day (change from baseline HAMD)	Placebo < 50 mg/day =100 mg/day = 200 mg/day (change from baseline HAMD)

Table I. Selective and serotonin reuptake inhibitors (SSRIs) and dose–efficacy relationship in parallel-group dose comparison studies ranked in order of increased efficacy. HAMD, Hamilton Rating Scale for Depression; MADRS, Montgomery and Åsberg Depression Rating Scale; ITT, intent-to-treat; LOCF, last observation carried forward; NA, not applicable; =, efficacy similar to; <, efficacy inferior to.

doses of citalopram between them, but visual inspection of the figures in the publication[14] suggests no such difference. Bech et al[10] reexamined this study using another psychometric approach, ie, the depression core subscales of the HAMD (HAMD6) and MADRS (MADRS6) in particular. Antidepressive and antianxiety effects could be observed after 6 weeks of therapy even at a dose of citalopram 10 mg/day, and these effects were found to be significantly superior to placebo. Both citalopram 10 and 20 mg/day had lower effect sizes (around 0.30 on the subscales and 0.20 on the scales) than 40 and 60 mg/day (around 0.54 on the subscales and 0.40 on the scales) at 6 weeks. However, the confidence intervals indicated that there were no statistically significant differences: all doses were superior to placebo, but 40 and 60 mg/day were not significantly superior to 10 or 20 mg/day.

In a small study by Bjerkenstedt et al[21] (not included in *Table I*) with 8 to 10 patients in each of 3 groups, there were no differences between citalopram 5, 25, and 50 mg/day at the end of 4 weeks on the global rating of mental health (sum of the MADRS ratings and Beck self-ratings scale for depression). Even at the lowest dose, there was a significant reduction in depressive symptoms in comparison with baseline.

The maintenance study by Montgomery et al[11] included patients of two double-blind, placebo-controlled, 6-week acute trials; one of these was published by the same authors in 1992.[13] There were no differences between citalopram 20 and 40 mg/day at the end of 24 weeks; both doses were equally effective, as measured by both relapse rates and time to relapse. The relapse rate among the 48 patients who continued to receive citalopram 20 mg/day (8%) and the 57 patients who continued to receive citalopram 40 mg/day (12%) was significantly lower than that in the 42 patients randomized to placebo (31%).

In a meta-analysis of 9 placebo-controlled studies by Montgomery et al,[12] 2 fixed-dose studies (474 patients) and 7 flexible-dose studies were included for a total of 949 patients, 586 of whom received citalopram and 363 placebo. Only patients who were treated for at least 4 weeks were included in the meta-analyses. For change in HAMD total score, available data showed that citalopram 20 mg/day (n=61) and 40 mg/day (n=74), but not 60 mg/day (n=38), were superior to placebo (n=154); the two lowest dosages were similarly effective on visual inspection of the figures in the publication.[12] For change in the MADRS total score, available data showed that citalopram 20 mg/day (n=123) and 40 mg/day (n=136) were superior to placebo (n=140); the two citalopram dosages were similarly effective on visual inspection of the figures in the publication.[12] The authors concluded the similarity of efficacy—or flat dose–response curve—of citalopram 20, 40, and 60 mg/day doses.

Escitalopram

The only fixed-dose–response study with escitalopram indicates that 10 mg/day was equally as effective as 20 mg/day *(Table I)*.[15] Patients with more severe depression might respond better with doses of escitalopram above 10 mg/day.[22]

In the study by Burke et al,[15] escitalopram 10 and 20 mg/day and the racemic form citalopram 40 mg/day were more effective than placebo on change on the HAMD 24 items and MADRS total score at the end of 8 weeks. There was no statistical analysis between the two doses of escitalopram, but visual inspection of the figures in the publication[15] does not suggest such a difference. Differences in response rate between each of the escitalopram dosage groups (50% and 51.2% for 10 and 20 mg/day, respectively) and the racemic form citalopram group (45.6%) were not significant, but the response rates were significantly greater for each group of active substance compared with the 27.7% response on placebo, with LOCF analysis in the MADRS. According to Bech et al,[22] who reexamine this study using another psychometric approach,[10] when all included patients were analyzed, no dose–response relationship was seen. However, in the 212 severely depressed patients (MADRS total score ≥30), a positive dose–response relationship for escitalopram was seen on MADRS and the two subscales (HAMD6, MADRS6) after 6 and 8 weeks of therapy. At the end of 8 weeks, the effects sizes, analyzed on ITT-LOCF, were around 0.34 on the subscales and 0.32 on MADRS for escitalopram 10 mg/day, around 0.73 on the subscales and 0.71 on MADRS for escitalopram 20 mg/day, and around 0.46 on the subscales and 0.37 on MADRS for racemic form of citalopram 40 mg/day. Only escitalopram 20 mg/day and the racemic form of citalopram 40 mg/day were superior to placebo. However, the confidence intervals indicated that the differences were not significant.

Fluoxetine

The studies with fluoxetine did not show significant differences in terms of clinical efficacy across a dose range

of 20 to 60 mg/day. Even a dose of 5 mg/day was effective compared with placebo *(Table I)*.[17] Therefore, for the majority of patients, there is no advantage of increasing the dose of fluoxetine above 20 mg/day. It might even be the case that the higher dose of 60 mg/day is less effective in major depressive disorder.[23]

In the first study by Wernicke et al *(Table I)*,[20] doses of fluoxetine 20 and 40 mg/day, but not 60 mg/day, were more effective than placebo on change on the HAMD total score on ITT-LOCF at the end of 6 weeks. Fluoxetine 20 and 40 mg/day were statistically superior to 60 mg/day. No statistical comparison was performed between fluoxetine 20 and 40 mg/day, but visual inspection of the data in the publication[16] suggests that there was no such difference. The higher number of discontinuations in the 60-mg/day group, in particular because of side effects, might have skewed the results, with only 45% patients who completed in the higher dosage group compared with 62% and 60% in the 20- and 40-mg/day groups, respectively. The weekly analysis with patients who remained in the study showed more efficacy for the three doses of fluoxetine compared with placebo on change on the HAMD total score at the end of 6 weeks. No statistical comparison was published between the active treatment groups but visual inspection of the figures in the publication[16] does not suggest such differences. The response rates in patients treated for at least 3 weeks were 52.8%, 60.6%, and 48.4% on fluoxetine 20, 40, and 60 mg/day, respectively, and significantly different for each group of active substance from the 27.3% response on placebo on the HAMD.

In a second study by Wernicke et al[17] in a different patient population *(Table I)*, fluoxetine 5, 20, and 40 mg/day were more effective than placebo on change on the HAMD total score on ITT-LOCF at the end of 6 weeks. No statistical comparison was made between fluoxetine 5, 20, and 40 mg/day, but visual inspection of the data in the publication[17] suggest that there was no difference. The weekly analysis with patients who remained in the study showed more efficacy for the 3 doses of fluoxetine compared with placebo on change on the HAMD total score at the end of 6 weeks. No statistical comparison was shown between the active treatment groups but visual inspection of the figures in the publication[17] did not suggest any differences. The response rates in patients treated for at least 3 weeks were 54.4%, 64.3%, and 64.7% on 5, 20, and 40 mg/day, respectively, which were significantly different for each group with active treatment from the 32.7% response on placebo on the HAMD.

Beasley et al[23] pooled the data from the two studies by Wernicke et al.[16,17] They found that the efficacy of fluoxetine 60 mg/day did not differ from placebo, and that there were no significant differences among the doses of 5, 20, and 40 mg/day on change on the HAMD total score on ITT-LOCF. Response rate (49.4% for 5 mg/day and 54% for 20 mg/day) and remission rate defined as HAMD total score decreased to 10 or less after at least 3 weeks (40.2% for 5 mg/day and 43.5% for 20 mg/day) showed a similar pattern. The authors concluded that fluoxetine 5 mg/day might be a threshold dose for therapeutic efficacy.

The study by Fabre and Putman[24] (not included in *Table I*) included patients with different degrees of depression. In the 38 patients with mild illness (HAMD of 14 to 19), with 20 who completed the study, there was no significant improvement at any of the fluoxetine dose level of 20, 40, or 60 mg/day compared with placebo at the end of 6 weeks. In the 46 patients with moderate-to-severe depression (HAMD of ≥20), with 27 who completed the study, change in the HAMD total score was not significantly different between active treatment groups, but was significantly different for the placebo group compared with all fluoxetine dose groups, except for the 40-mg/day group.

Dunlop et al[25] have studied 372 patients with mild depression (HAMD of 15 to 19) (not included in *Table I*). Fluoxetine 20, 40, and 60 mg/day each produced an improvement that was no different from placebo on change in the HAMD total score in 355 ITT patients with LOCF at the end of 6 weeks. The results with completer cases analysis, ie, 214 patients who finished the study, on change in the HAMD total score were similar to those of the ITT-LOCF analysis. The response rates in HAMD total score for 260 patients treated at least 3 weeks were 53%, 51%, and 59% on fluoxetine 20, 40, and 60 mg/day, respectively, and were significantly different from the 36% response on placebo only for fluoxetine 60 mg/day. Persistent improvement and delayed persistent improvement were significantly more frequent in each active treatment group than in the placebo group on the CGI scale, according to a pattern analysis that permitted to evaluate true drug response to antidepressants, characterized both by 2 weeks or greater delay in onset of initial improvement and nonfluctuating persistence of it once achieved[26,27]; there were no differences between the three fluoxetine groups on visual inspection of the figures in the publication.[25]

Fluvoxamine

The only fixed-dose–response study of fluvoxamine has two characteristics *(Table I)*.[18] First, it included a low dose of 25 mg/day fluvoxamine. Second, in the primary efficacy assessment, the authors excluded 8 items from the HAMD 21 items, such as insomnia, agitation, psychic and somatic anxiety, gastrointestinal symptoms, and general somatic symptoms, which are common to depression and SSRI side effects. This exclusion is unusual because all SSRIs have these clinical manifestations as potential side effects (other studies did not delete these items). A gradual escalation was performed over 2 weeks and the authors considered only the final 6 weeks at fixed dose in the evaluation of efficacy. When the HAMD 21 items total score was used, no significant treatment effects, compared with placebo, were noted at the end of the study.

In this fixed-dose study on a large sample,[18] only fluvoxamine 100 mg/day showed a significant therapeutic benefit over placebo at end-point analysis (on LOCF) on modified HAMD 13 items final score at the end of 6 weeks at fixed dose. Significant differences were not seen between fluvoxamine 25, 50, or 150 mg/day or placebo. On the HAMD 13 items responder analysis, the differences were significant for fluvoxamine 100 and 150 mg/day compared with placebo, but not between these two dosages on visual inspection of the figures in the publication[18] on completer cases analysis.

Paroxetine

In the publication by Dunner and Dunbar *(Table I)*,[19] there is a short description of a study involving 460 patients. The paroxetine 10 mg/day dose was no more effective than placebo, even on the HAMD depressed mood item. The authors reported also on a pooled analysis from a worldwide database, involving 1091 patients who remained on a fixed dose of paroxetine or placebo for at least 4 weeks, which showed no differences in terms of clinical efficacy across a dose range of 20 to 40 mg/day paroxetine. Therefore, for the majority of patients, there is no advantage in increasing the dose of paroxetine above 20 mg/day.

In this study,[19] there were no differences between paroxetine 10 mg/day and placebo on change on the HAMD total score at the end of 6 weeks. Significant differences were seen between other doses of paroxetine of 20, 30, and 40 mg/day and placebo. There were no differences between the three higher dosages of paroxetine on visual inspection of the figures of the publication.[19]

Sertraline

The SSRI sertraline did not show significant differences in terms of clinical efficacy across a dose range of 50 to 200 mg/day, according to a major study by Fabre and Putman *(Table I)*.[20] Therefore, for the majority of patients, there is no advantage to increase the dose of sertraline above 50 mg/day.

In the study by Fabre and Putman,[20] sertraline 50 mg/day, but not 100 and 200 mg/day, was more effective than placebo at end-point analysis on change on the HAMD 17 items total score on ITT-LOCF at 6 weeks. There was no statistical analysis performed between the different doses, but inspection of the data in the publication[20] suggests no differences. Evaluable patients, defined as those who had taken study medication at least up to the 11th day of the double-blind phase, with efficacy assessment performed on or after this date. With this population of 289 evaluable patients, all doses of sertraline were statistically superior to placebo on change on the HAMD total score with LOCF at the end of 6 weeks. There was no statistical analysis of the different doses, but inspection of the data in the publication[20] suggests no differences; on the CGI, the percentage of responders was 58.5%, 62.7%, 58.9%, and 42.1% in the sertraline 50, 100, 200 mg/day and placebo groups, respectively. Inspection of the data in the publication[20] for the 191 patients who completed the study suggests no difference between the three doses of sertraline on change on the MADRS total score. Moreover, efficacy was similar in patients with moderate depression (HAMD score at baseline: 17 to 24) and with severe depression (HAMD score at baseline: 25 or more). A small part of this study with 30 patients had been released 6 years earlier in a short publication,[28] with the same conclusions.

In a very small study in 17 patients at the start of the study and 8 at the end, Guy et al[29] could not demonstrate the efficacy of sertraline 50 and 100 mg/day over placebo on the HAMD 17 items at the end of 4 weeks. No symptomatic improvement was noted for sertraline 200 or 400 mg/day. Lower dosages were better tolerated than higher dosages.

Milnacipran

Three fixed-dose studies[30-32] and one dose-ranging study[33] were identified for milnacipran *(Table II)*. The studies showed flat dose–response relationship between 100 and 300 mg/day; milnacipran 50 mg/day was less effective than higher doses and even than placebo.

In a study by Ansseau et al,[30] milnacipran was prescribed at a dose of 50 or 100 mg/day, with a third group receiving amitriptyline 150 mg/day. At the end of 4 weeks at fixed doses, milnacipran 100 mg/day was as effective as amitriptyline 150 mg/day on change in mean scores on the HAMD 24 items and MADRS with time, in the 109 patients who were treated for the whole period (completer cases). The authors concluded that milnacipran 100 mg/day was more effective than 50 mg/day, but statistical analysis was not in favor of this conclusion.

In a dose-ranging study by Ansseau et al,[33] the dose–response at fixed doses could only be evaluated for the first 2 weeks. On visual inspection of the figures in the publication,[33] there were no differences between milnacipran 200 and 300 mg/day and fluvoxamine 200 mg/day on change in mean scores on the HAMD 24 items and MADRS with time.

Lecrubier et al[31] described a study with three dosages of milnacipran 50, 100, and 200 mg/day. At the end of 8 weeks, in a total of 412 patients, milnacipran 100 mg/day, but not 50 or 200 mg/day, was more effective than placebo on change on the HAMD 17 items total score; milnacipran 100 and 200 mg/day, but not 50 mg/day, was superior to placebo on change in MADRS total score. There was no statistical analysis between the three doses of milnacipran, but inspection of data in the publication[31] suggests that milnacipran 100 and 200 mg/day were superior to 50 mg/day, and that there was no difference between them. The percentage of responders, for a total of 412 patients, were 48%, 65%, and 53% in milnacipran 50-, 100-, and 200-mg/day groups, respectively, compared with 44% in placebo group on the HAMD; the difference was only significant between milnacipran 100 mg/day and placebo.

In the study by Guelfi et al,[32] milnacipran was prescribed at doses of 100 and 200 mg/day, with a third group receiving fluoxetine 20 mg/day. At the end of 12 weeks, there were no differences between the three groups on change on the HAMD 17 items and MADRS total scores on ITT-LOCF. Per protocol analysis, ie, 237 patients who

Reference	No patients in double-blind phase	Dose escalation (weeks)	Total duration	Control group	LOCF analysis	Completer cases analysis
Ansseau et al,[30] 1989	n=144 Included in analysis=131 Completers=109	5 days	4-7	Amitriptyline 150 mg/day	50 mg/day < 100 mg/day = 150 mg/day	50 mg/day < 100 mg/day = 150 mg/day (change over time HAMD and MADRS)
Ansseau et al,[33] 1991	n=127 Included in analysis=120	No	4	Fluvoxamine 200 mg/day	7 dropouts in first 2 weeks	200 mg/day = 300 mg/day = 200 mg/day first 2 weeks (change over time HAMD and MADRS)
Lecrubier et al,[31] 1996	n=527 Included in analysis=412	NA	8	Placebo	NA	Placebo = 50 mg/day < 100 mg/day = 200 mg/day (change from baseline HAMD and MADRS)
Guelfi et al,[32] 1998	n=300 ITT=289	No	12	Fluoxetine 20 mg/day	100 mg/day = 200 mg/day = 20 mg/day (change from baseline HAMD and MADRS)	NA

Table II. Milnacipran and dose–efficacy relationship in parallel-group dose comparison studies ranked in order of increased efficacy. HAMD, Hamilton Rating Scale for Depression; MADRS, Montgomery and Åsberg Depression Rating Scale; ITT, intent-to-treat; LOCF, last observation carried forward; NA, not applicable; =, efficacy similar to; <, efficacy inferior to.

completed at least a 14-day treatment period, showed no differences between the three groups on change on the HAMD and MADRS total scores at the end of 12 weeks. The responders rate were 62%, 54%, and 51% on HAMD, and 64%, 55%, and 49% on MADRS in milnacipran 100 and 200 mg/day, and fluoxetine 20 mg/day groups, respectively on ITT-LOCF; the difference was only significant between milnacipran 100 mg/day and fluoxetine 20 mg/day on the MADRS.

Venlafaxine

In the venlafaxine studies, doses varied between 25 and 375 mg/day *(Table III)*. A positive dose–response curve was only demonstrated with trend analysis. However, the difference between the higher dose range and placebo was not pronounced.[34] Better efficacy could be obtained with a dose of venlafaxine above 75 mg/day in terms of remission rate.[36] In a review concerning all aspects of antidepressant use, Preskorn[2] mentioned an ascending then descending dose–response curve for venlafaxine in an evaluation comparing 7 dose levels between 25 and 375 mg/day with placebo, coming from fixed- and flexible-dose studies. However, the major difference in terms of mean HAMD score change, ie, 2 points, was between a group of patients receiving 175 mg/day and another receiving 182 mg/day, hardly a different dose! This suggests a calculation artifact rather than a pharmacological dose–response curve.[2] For the majority of patients, a dose of venlafaxine 75 mg/day should be adequate.

In a study by Mendels et al,[34] venlafaxine was prescribed at fixed dose of 25 mg/day for the low-dose group and at fixed interval dose of 50 to 75 mg/day and 150 to 200 mg/day for 2 other groups, with a fourth group receiving placebo. At the end of 6 weeks, there was a high placebo response and only trend analysis on ITT-LOCF was statistically significant and showed that efficacy improved with increasing doses of venlafaxine according to change in the HAMD 21 items and MADRS. The results for completer cases analysis were not interpretable. Kelsey et al[37] analyzed other aspects of the above study[34] and found a significant difference in response rate between the high-dose group and the placebo group on the basis of the HAMD and MADRS total scores; none of these data were described numerically in the article.

In the study by Khan et al,[35] venlafaxine was prescribed at fixed doses of 75, 150, and 200 mg/day. At the end of 12 weeks, among the 353 or 346 ITT patients (the authors are imprecise on this issue), each dose of venlafaxine was significantly superior to placebo on the HAMD 21 items total score with LOCF. For the MADRS total score, the authors reported that each dose of venlafaxine was also significantly superior to placebo (data not shown in the publication). No statistical analysis was performed between each group of active treatment, but visual inspection of the data in the publication[35] on the HAMD

Reference	No patients in double-blind phase	Dose escalation (weeks)	Total duration (weeks)	LOCF analysis	Completer cases analysis
Mendels et al,[34] 1993	n=312 ITT=302 Completers: 232	1	6	Placebo < 25 mg/day < 50-75 mg/day < 150-200 mg/day (change from baseline HAMD and MADRS on trend analysis)	Not interpretable
Khan et al,[35] 1998	n=403 ITT=353 or 346 Completers=NA	1	12	Placebo < 75 mg/day = 150 mg/day = 200 mg/day (total score HAMD)	Placebo < 75 mg/day = 150 mg/day = 200 mg/day
Rudolph et al,[36] 1998	n=358 ITT=323 Completers= 194 or 173	1	6	Placebo < 75 mg/day = 150-225 mg/day = 300-375 mg/day (total score HAMD) Placebo < 75 mg/day < 300-375 mg/day =150-225 mg/day (change from baseline MADRS)	Placebo < 75 mg/day = 150-225 mg/day = 300-375 mg/day (total score HAMD)

Table III. Venlafaxine and dose–efficacy relationship* in parallel-group dose comparison studies ranked in order of increased efficacy. HAMD, Hamilton Rating Scale for Depression; MADRS, Montgomery and Åsberg Depression Rating Scale; ITT, intent-to-treat; LOCF, last observation carried forward; NA, not applicable; =, efficacy similar to; <, efficacy inferior to.

total score with ITT-LOCF suggests no differences. Observed cases analysis, defined as analyses of observed patients at each time point, gave similar results.[35] The percentage of responders on the CGI was better for each venlafaxine group, but no difference was found between the three doses on visual inspection of the figures in the publication[35] at the end of 12 weeks with ITT-LOCF. The authors stated that there were no significant differences in the incidence of side effects between the different dosage groups of venlafaxine.[35] Among the treatment-emergent study events that led to discontinuation from the study, there was no positive dose–response for somnolence, dizziness, asthenia, and insomnia, while there was for nausea with 17% of patients on higher dose and 8% on the lower dose of venlafaxine reporting nausea, versus 1% (a low value) in those on placebo.

In the study by Rudolph et al,[36] venlafaxine was prescribed at fixed dose of 75 mg/day for the low-dose group and at fixed interval dosage of 150 to 225 mg/day and 300 to 375 mg/day for other 2 groups, with a fourth group receiving placebo. At the end of 6 weeks, significant differences were seen between each group of active substance and placebo on the HAMD 21 items total score with ITT-LOCF. There were no differences between each group of active treatment. At the end of 6 weeks, each group of active treatment was superior to placebo, and venlafaxine 300 to 375 mg/day was superior to venlafaxine 75 mg/day, on change on the MADRS total score on ITT-LOCF.

Among the 194 or 173 patients (the authors are imprecise on this issue) who completed the study (completer cases), each group of active treatment was better than placebo on the HAMD total score. There were no significant differences between each group of active treatment. Among the completer cases, the percentage of those who achieved a score of 8 or less on HAMD total score was 19% on placebo, and 25%, 48%, and 54% on venlafaxine 75 mg/day, 150 to 225 mg/day, and 300 to 375 mg/day, respectively, at the end of 6 weeks. There was no positive dose–response for anorexia, dizziness, headache, and insomnia, while there was one for nausea present in 58% of patients on higher dose of venlafaxine versus 14% in those on placebo. Part of this study has been reported previously.[38,39]

Reboxetine

In most protocols, there was a gradual escalation from 2 to 10 mg/day. For example, reboxetine 8 to 10 mg/day was compared with imipramine 150 to 200 mg/day.[40] Thus, despite availability of several short clinical trials, we cannot comment on the dose–response relationship for reboxetine. Duloxetine is not discussed here, but no positive dose–response relationship has been found for 40 to 120 mg/day.

Dose augmentation studies in nonresponders

The three studies of dose augmentation in nonresponders or inadequate responders were double-blind, randomized, controlled trials with a fixed-dose design, and were all conducted in outpatients *(Table II)*. The definition of nonresponders was identical in two of the studies,[41,42] but different in the third.[43] Another difference was the initial period of the studies, where antidepressants were prescribed for 3 weeks each, but in an open, single-blind, or double-blind manner. Finally, for the two studies with fluoxetine, a dose augmentation was made well before the steady state was achieved, in particular for norfluoxetine, owing to the very long half-life of this active metabolite.

Fluoxetine

The study by Dornseif et al[41] was performed more than 15 years ago. It is of great importance because it demonstrated that there is no advantage of tripling the dose of fluoxetine to 60 mg/day in outpatients who fail to initially respond to 20 mg/day for 3 weeks; during the next 5 weeks, patients in both groups responded to the same extent and at the same rate. The response rates to fluoxetine 20 and 60 mg/day were 40.5% and 44.7%, respectively. The remission rates (HAMD 21 items ≤7) were 33.3% and 36.2%, respectively, at the end of 8 weeks.

The values of plasma levels from this study were reported by Beasley et al.[23] At the end of 8 weeks, there was no relationship with the percentage change in the HAMD total score, in either the 20-mg/day or the 60-mg/day group.

Another dose-augmentation study was performed by Schweizer et al[42] using a similar design to that of Dornseif et al.[41] There was no advantage in tripling the dose of fluoxetine to 60 mg/day in patients who had failed to respond initially to 20 mg/day for 3 weeks. At the end of 8 weeks, 49% and 50% of patients had responded to fluoxetine 20 and 60 mg/day, respectively.

Paroxetine

The study by Benkert et al[43] used the same protocol as Dornseif et al[41] and Schweizer et al,[42] and evaluated two antidepressants, paroxetine and maprotiline. This study

could not demonstrate an advantage of doubling the dose of paroxetine to 40 mg/day in patients who had failed to respond initially to 20 mg/day for 3 weeks. In another group of 273 patients (not included in *Table IV*), no advantage of increasing the dosage of maprotiline to 150 mg/day in patients who had failed to respond initially to 100 mg/day for 3 weeks could be demonstrated. No significant benefits of dose escalation were found.

The study by Benkert et al[43] enabled the evaluation of the role of initial severity of depression in both groups of patients treated with paroxetine or maprotiline. When a separate analysis was made for minor and major depression at baseline, no significant differences were seen in terms of efficacy between these clinically defined categories and the doses of the two antidepressants.

Discussion

Increasing the dose of antidepressants seems to be the preferred strategy of doctors when depressed patients have an insufficient response after 4 to 8 weeks of adequate treatment.[5] However, there are surprisingly few randomized controlled trials addressing the issue of whether a higher proportion of patients respond when higher doses are given.

Our review of eight clinical trials at fixed doses that have evaluated the dose–response relationship of SSRIs in the treatment of major depressive disorders suggests that the dose–response curve is flat *(Table I)*. Moreover, three augmentation studies could not demonstrate an advantage of doubling the dose of paroxetine, or tripling the dose of fluoxetine, in patients who had failed to respond initially to 20 mg/day for 3 weeks *(Table IV)*. There was a heterogeneity of the results in that some studies did not show a significant difference between the active substance and placebo[13,18] or between the highest dosage and placebo.[16] In other studies, doses below the lowest recommended ones were as effective as higher doses and superior to placebo, for example, 5 mg/day fluoxetine.[17]

The lack of positive dose–response relationship with SSRIs was observed in these eight trials, which were all performed with protocols of the type that is mandatory for the registration of a new antidepressant. The main objective of these clinical trials was to establish efficacy, while protocols on dose–response relationship are not mandatory, despite the fact that some information on this issue is mentioned in the prescription guidelines and patient information leaflet.

Baker et al[44] have a different opinion regarding the dose–response curve of SSRIs. They adequately underlined that most dose–response studies expressed a composite result mixing a dose–response for beneficial effects and another one for side effects. With their approach, ie, excluding dropouts, they found a small increase in efficacy with higher doses of SSRIs. By grouping the fixed-doses studies of Wernicke et al[16,17] and Fabre and Putman,[20] the slope of improvement, as evaluated from response rates, was statistically significant on meta-analysis, ie, 3.1% improvement for each 100 mg/day SSRIs equivalents; this slope was not statistically significant for the individual studies. Thus, Baker et al[44] concluded that "study designs better tailored to address the relevant clinical question would test hypotheses more appropriately than previous studies." Despite the fact that we did not use the technique of meta-analysis in our review, we propose that the risk of type 2 error concerning a positive dose–response relationship with SSRIs is small.

There are several methodological points to discuss in

Drug	No patients in first period	First period (weeks)	No patients at augmentation	Total duration (weeks)	LOCF analysis	Completer cases analysis
Fluoxetine[41]	572	3 Single-blind	n=371 Completers=278	8	20 mg/day = 60 mg/day (change from baseline HAMD)	20 mg/day = 60 mg/day (change from baseline HAMD)
Fluoxetine[42]	108	3 Open	n=77 Completers=NA	8	20 mg/day = 60 mg/day (total score HAMD)	20 mg/day = 60 mg/day (total score HAMD)
Paroxetine[43]	271	3 Double-blind	n=86 Completers=NA	6	20 mg/day = 40 mg/day (total score and change from baseline HAMD and MADRS)	20 mg/day = 40 mg/day (total score and change from baseline HAMD and MADRS)

Table IV. Selective serontonin reuptake inhibitors (SSRIs) and dose–efficacy relationship in dose-augmentation studies in nonresponders ranked in order of increased efficacy. HAMD, Hamilton Rating Scale for Depression; MADRS, Montgomery and Åsberg Depression Rating Scale; ITT, intent-to-treat; LOCF, last observation carried forward; NA, not applicable; =, efficacy similar to; <, efficacy inferior to.

view of the above findings. One concerns the difference between ITT and completer cases analyses. The clinical efficacy of antidepressants estimated according to ITT sample does not favor active treatment. Indeed, completer cases analysis often leads to a higher rate of improvement than ITT analysis. This might be attributed to an increased number of dropouts as the dose of antidepressant is increased, as shown by Bollini et al,[45] who considered all classes of antidepressants. From a regulatory point of view, the ITT analysis is important to protect the patients from a false, favorable evaluation of beneficial effects of drugs. Therefore, with ITT sample evaluation, one could expect a flat dose–response curve. However, completer cases analyses were generally not different from ITT analyses in these SSRI trials. This means that higher doses of SSRIs are really no more effective than lower doses.

A second methodological point is the proposal that SNRIs might have a clinical superiority over SSRIs because of the simultaneous inhibition of noradrenaline (NA) and serotonin (5-HT) reuptake (ie, a "dual" mechanism). For venlafaxine, 5-HT and NA reuptake inhibition were demonstrated to be sequentially engaged according to the dose.[46] The four clinical trials at fixed doses that have evaluated the dose–response relationship of milnacipran in the treatment of major depression suggests that the dose–response curve is flat *(Table II)*. There were no placebo groups in three of these studies, and the results are not sufficiently informative in this context.[47] The three clinical trials at fixed doses that have evaluated the dose–response relationship of venlafaxine in the treatment of major depressive disorders showed equivocal results. A significant positive trend was demonstrated with increasing dose of venlafaxine,[34] even if some differences between groups with low and high doses were not significant. A higher remission rate might be achieved with doses higher than 75 mg/day.[36]

A third methodological point concerns the quality of the trials. Most of the trials that we reviewed did not satisfy for the Consolidated Standards of Reporting Trials (CONSORT) statement,[48] insisting on the definition of ITT and the reporting of a flow diagram. This applies even though the studies were published after this document appeared for the first time.[49] ITT patients were generally defined as all patients who took at least one dose of medication in a double-blind condition and had at least one postbaseline efficacy assessment either during drug therapy or within 3 days of the last dose. These criteria do not correspond to the definition of ITT patients, ie, number of patients included in each intervention group at the inclusion in the double-blind phase and considered in the primary data analysis. In a proportion of studies, the flow diagram, when given, did not provide good enough information on the number of patients who entered each phase of the trial.

The studies used a variety of inclusion and diagnostic criteria. The majority of studies with SSRIs and SNRIs included only outpatients, but sometimes inpatients, outpatients, and daypatients were included.[13] Minimum inclusion scores on the scales were variable, which means that initial severity of depression was not the same. Severity of depression may influence the relationship between SSRI or SNRI dose and clinical response. The number of previous episodes and the number of patients who had not received antidepressants before or who had failed to respond to one or several trials could also influence the results.[50,51] This lack of homogeneity may have obscured a significant relationship. One possibility would be that a better efficacy with higher doses of SSRIs exists only for severe depression and/or for different types of depression.

In studies with flexible dosage, an apparent lack of response early in treatment triggers an increase in dose, sometimes up to the maximum tolerated dose, and the response seen later is then attributed to the higher dose rather than being identified as a possible delayed response to a lower dose. Therefore, the efficacy is tested at rather high doses, which, in the case of SSRIs particularly, may not be necessary. This method encourages the clinicians to use the maximum tolerated dose rather than the minimal effective dose.

In studies with fixed-dose design, higher doses are started abruptly, most often without gradual escalation, or with a short titration time, unlike in clinical practice. Thus, early discontinuation could be expected because there may be more side effects in the higher dosage group. For those dropouts, the possibility of good subsequent response cannot be excluded. This can lead to a discrepancy between the results for the ITT and completer cases analyses. In addition, the clinical response to antidepressants is not observed immediately. In some patients, more than 3 weeks are required before an improvement in symptoms becomes obvious, while side effects appear soon after starting treatment.

A final point is that, in clinical trials, patients represent a carefully selected cohort in order to ensure comparable baseline populations. In clinical practice, patients often

have affective disorders with more comorbid conditions and are likely to receive more complex drug regimens. Determination of response is highly individual and does not necessarily correspond to that performed under controlled clinical trial conditions.

Clinical implications

The studies that have evaluated the dose–response relationship of SSRIs and SNRIs have been equivocal, with considerable difficulties in establishing a clear optimal dose or dose range in the treatment of major depression. Clinicians who increase the dose of an SSRI in an early nonresponder or partial responder, ie, before at least 3 weeks at fixed dose, and then see improvement may conclude that the subsequent response proved that the patient needed a higher dose. However, it may be that the patient simply needed a longer time on the drug to achieve the response. This issue was confirmed by three prospective studies on dose augmentation.[41-43] This casts doubt on the customary practice of increasing dosage when there is nonresponse early in treatment, according to dose-adjusted trial designs reported between 1980 and 2004.

The majority of depressed patients should be treated with a low dosage of SSRIs and SNRI, generally corresponding to one tablet per day. Increasing the dose may perhaps be beneficial for some patients with depression, in particular those with severe depression. An antidepressant for which this strategy may be relevant, in order to increase the number of responders, is venlafaxine. Although this has not been often studied, if higher dosages are required, they will be better tolerated if achieved through dose titration. ❑

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Relación dosis-respuesta de nuevos antidepresivos en el tratamiento a corto plazo de la depresión

Los fármacos antidepresivos están ampliamente recomendados para el tratamiento de los trastornos depresivos y un tema importante es el encontrar la "dosis adecuada para el paciente apropiado." Independientemente del antidepresivo prescrito, un porcentaje de pacientes adultos con depresión mayor no responden satisfactoriamente a un adecuado tratamiento de primera línea. Una estrategia frecuente para pacientes con una respuesta insuficiente a una dosis inicial de antidepresivos es aumentar la dosis. Esta revisión se refiere a esta estrategia; es decir, los posibles beneficios de prescribir dosis más altas de los nuevos antidepresivos. De acuerdo con ensayos clínicos randomizados, controlados y con dosis fijas los resultados demuestran que una curva dosis-respuesta aplanada es un fenómeno importante para los inhibidores selectivos de la recaptación de serotonina (ISRS). Para los inhibidores de la recaptación de serotonina y noradrenalina (IRSN) la estrategia del aumento de dosis puede ser relevante para la venlafaxina, en cuanto a aumentar el número de respondedores. De este modo, el subgrupo de pacientes para los cuales las altas dosis de ISRS podrían ser útiles aun está por definirse.

Relation dose-réponse des antidépresseurs récents dans le traitement à court terme de la dépression

Les antidépresseurs sont largement recommandés dans le traitement des troubles dépressifs et trouver la « bonne dose pour le bon patient » est un défi. Quel que soit l'antidépresseur prescrit, un certain nombre de patients adultes présentant une dépression majeure ne répondent pas de façon satisfaisante à un traitement initial. Une stratégie fréquente pour les patients avec une réponse insuffisante à un premier antidépresseur consiste à augmenter la dose. Cette revue concerne cette stratégie, c'est-à-dire les possibles bénéfices d'une prescription de doses plus élevées pour les antidépresseurs récents. Les résultats montrent qu'une courbe dose-réponse plate est un phénomène de classe pour les inhibiteurs sélectifs du recaptage de la sérotonine (ISRS), selon les études randomisées et contrôlées, à doses fixes. Pour les antidépresseurs inhibiteurs du recaptage de la sérotonine et de la noradrénaline (IRSN), la stratégie d'augmenter la dose peut être pertinente pour la venlafaxine, dans le but d'accroître le nombre de répondeurs. Ainsi, le sous-groupe de patients pour lesquels des doses élevées d'ISRS pourraient s'avérer utiles reste à être défini.

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