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ORIGINAL PAPER

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Is dose escalation of antidepressants a rational strategy after a medium-dose treatment has failed?

A systematic review

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Abstract *Background* Maximizing the dose of antidepressants is widely recommended in cases of non-response to medium-dose treatment. However, scientific evidence supporting high-dose treatment is scarce. Systematic studies comparing dose escalation with alternative strategies for refractory depression (i. e. augmentation or change of compound) are lacking. The aim of this publication is to review available direct and indirect evidence concerning dose increase of antidepressants after a medium-dose trial has failed. *Method* We performed a systematic literature search of Medline (1966–2003) and reviewed studies and publication references for available evidence. *Data sources and study selection* Studies of the following types were included: 1) dose increase studies in treatment refractory patients, 2) comparative dose studies, 3) therapeutic drug monitoring studies. *Results* Available data suggest differential efficacy of various pharmacological classes at more than medium-dosage. Direct evidence shows no increase of efficacy with high-dose selective serotonin reuptake inhibitor (SSRI) treatment; however, indirect evidence suggests enhanced therapeutic efficacy with high-dose tricyclic antidepressants. Few clinical data show ultra-high-dose treatment with the irreversible monoamine-oxidase-(MAO-) inhibitor tranylcypromine to be effective for refractory depression. Data concerning other selective compounds are insufficient to allow any definitive conclusion on the benefit of high-dose treatment. *Conclusions* Based on available data high-dose antidepressant treatment of patients refractory to medium-dose treatment is recommended for tricyclic compounds but not for SSRI. Some data suggest beneficial efficacy of ultra-high doses of the irreversible MAO-I tranylcypromine. Research on other substance groups is limited and inconclusive. Prospective studies comparing dose escalation with alternative strategies for treatment of non-responding patients are needed.

Key words antidepressants · dose escalation · treatment-refractory depression · non-response · review

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Introduction

Non-response to antidepressant pharmacotherapy is a common problem in the treatment of depression [30]. Thirty percent of patients treated for major depression do not respond to the first antidepressive trial; another 30 % respond but display residual symptoms [6, 13, 43, 72, 75]. In the event of non-response to medium-dose treatment, maximizing the dose of the antidepressant medication is one recommended strategy [2, 7, 13]. This recommendation appears to be widely implemented in daily clinical routines. In a study conducted by Fredman and coworkers, 80 % of study therapists selected dose escalation when response to SSRI antidepressant treatment was unsatisfactory [33]. The efficacy of maximizing drug doses, however, is subject to debate [22].

Interestingly, several studies examining antidepressant plasma levels demonstrate that a considerable portion of patients who are treated with adequate doses do not reach therapeutic plasma levels for drugs for which a therapeutic window in blood concentration has been established [38, 102]. Simpson found that half of a patient sample treated with 200 mg imipramine per day was below therapeutic serum levels [102]. Laux found

insufficient plasma levels in 6 of 8 non-responders with adequate drug doses [54]. Approximately 5 % to 10 % of patients are thought to have subtherapeutic TCA plasma levels, even when given maximal dosages (e. g. 300 mg imipramine per day) and despite full compliance [105]. Application of recommended antidepressant doses has been repeatedly suggested as subtherapeutic due to differences in metabolizer status [38, 41, 42, 84, 102, 104].

Additional information about dose maximization that may be helpful for clinical practice and research, in particular, can be obtained from comparative dose studies and from therapeutic drug monitoring (TDM) studies of patients who are not selected for refractoriness. For this review, we included comparative dose studies, as well as drug monitoring studies, of populations not selected with regard to refractoriness, although they only represent indirect evidence for the question at hand.

In order to draw conclusions for clinical practice and research, the primary aim of this study is to review available evidence supporting the implementation of high-dose antidepressant therapy of treatment refractory patients.

Methods

A systematic literature search of Medline (1966–2003) was completed using the key words *depression*, *treatment resistance*, *treatment refractory*, *antidepressant*, *high-dose treatment*, *dose-response relationship*, *plasma level*, and *therapeutic drug monitoring*. In addition, all references of the papers retrieved by the Medline search were reviewed for relevant articles and abstracts. Publications in English, German and French were included.

Studies were grouped in the following way: (1) high-dose treatment of treatment refractory depressed patients, (2) comparative dose studies, and (3) studies concerning therapeutic drug-monitoring of antidepressants. Publications in these groups were further subgrouped according to class of antidepressant examined (tri-/tetracyclics, SSRIs, MAO-I, other selective compounds), and according to the applied design.

Studies were categorized according to their level of evidence. Randomized double-blind controlled studies investigating the effect of dose escalation in selected non-responders are regarded as of strongest evidence. Open-label studies of selected treatment resistant patients obviously deliver only moderate evidence for the efficacy of dose increase in these patients. Comparative dose-studies of a general depressed patient sample are informative for understanding the general dose-effect relationship of a certain compound but offer only indirect (i. e. moderate) evidence for the effect of dose escalation in non-responders. Finally, studies of the correlation between antidepressant plasma-level and treatment response do not offer more than indirect evidence for the effect of dose increase in non-responders since plasma levels are to a high degree dependent on individual metabolization. They do, however, show a clear correlation to treatment response in tricyclic antidepressants. We therefore regard TDM studies as being of moderate evidence in tricyclics and of low evidence in SSRIs.

Results

Nine studies directly addressing the question at hand were found. Seven of these studies are randomized controlled double-blind studies [17, 24, 29, 31, 57, 97, 99] and two studies are small-sized open trials [28, 61]. Of the 9 studies, 8 were conducted using SSRIs (fluoxetine, sertraline, paroxetine) and one was conducted using maprotiline [17]. A total of 1174 treatment-resistant patients were included (1159 from randomized controlled trials). Two additional studies examined the effectiveness of ultra-high-dose treatment with tranylcypromine in patients not previously treated with the substance [4, 5] (Table 1).

As expected, we found a large number of drug monitoring studies, particularly for the heterocyclic antidepressants, and comparative dose studies of the different compounds.

High-dose treatment in treatment-refractory patients with major depression

Heterocyclic antidepressants

The only study of the older substance groups with treatment-resistant patients was conducted using the tetracyclic compound *maprotiline* [17]. In a randomized controlled double-blind study, a dose increase of maprotiline to 150 mg/d after a previous 3-week medium-dose treatment did not have a superior effect compared to continuation of the initial dose (100 mg/d).

Selective serotonin reuptake inhibitors (SSRIs)

There are several non-responder studies that evaluate SSRI dose-escalation in patients who are refractory to previous medium-dose treatment. Schweizer and coworkers conducted a randomized double-blind study of 77 patients who were refractory to a 3-week treatment with 20 mg/d *fluoxetine* [97]. Non-responding patients were randomly assigned to receive either high-dose therapy with 60 mg/d fluoxetine or to continue the previous dose for a period of 5 weeks. High-dose treatment did not show any superior efficacy in this study. A multicenter study with identical design also failed to show any difference in rate of overall clinical response between the 20 mg and the 60 mg dose, although most outcome measures indicated high-dose treatment was slightly superior (though non-significant) [24]. The high-dose group had a significantly higher drop-out rate because of adverse events. The low-dose group had a significantly higher rate of dropouts due to lack of efficacy.

In a very small open-label study, Fava and coworkers examined the clinical effect of raising the dose of fluoxetine to 60–80 mg/d for 15 patients who had not responded to a previous 8- to 12-week treatment with 20 mg fluoxetine per day [28]. All patients improved significantly after dose increase. Tolerability of high-dose treatment was fair. In 1994, Fava and co-workers conducted a randomized double-blind study on the same subject [29]. Forty-one patients resistant to a previous 8-week treatment with 20 mg/d of fluoxetine were randomly assigned to receive a dose increase to 40–60 mg/d

(depending on tolerability), treatment augmentation with 25–50 mg/d of the tricyclic desipramine, or treatment augmentation with 300–600 mg/d of lithium carbonate. Dose increase of fluoxetine proved to be the most effective strategy in patients who partially responded to the previous treatment phase, whereas lithium augmentation proved superior in non-responders. However, in a recently published study by the same authors that involved a larger sample (n = 101), there was no significant difference in response rates across the three treatment groups, neither in the total sample nor in the subgroup analyses of non- and partial responders [31]. The main shortcomings of both double-blind studies are the relatively low doses of lithium and desipramine (mean lithium level was 0.21 mmol/l), the small sample of patients in each of the three treatment branches, and the different levels of response. Another study that compared medium-dose treatment to SSRI dose escalation in non-responders is the large double-blind multi-center trial conducted by Benkert and coworkers, as previously mentioned [17]. Eighty-six non-responders to a 3-week trial of medium-dose *paroxetine* (20 mg/d) were randomized to receive dose escalation to 40 mg/d or continue medium-dose treatment. High dose treatment was not found to be superior; however, there was a non-significant trend supporting efficacy of high-dose paroxetine for patients with severe major depression. One significant shortcoming of this design is the rather mild dose increase to 40 mg/d paroxetine, which is regarded by many clinicians as still within a medium-dose range. In patients who were refractory to an open 3-week sertraline treatment trial (50 mg/d), Schweizer and coworkers compared dose continuation with dose increase to 150 mg/d in a randomized double-blind study [99]. There was no significant difference in any outcome measure between the two groups after week 8. In a recently published randomized controlled double-blind study of 295 patients who had previously failed to respond to a 6 week open trial of medium-dose sertraline (4 weeks 50 mg/d + 2 weeks 100 mg/d) Licht & Qvitzau showed a significantly lower response rate (56 %) to high-dose treatment with sertraline (200 mg/d) compared to treatment continuation with 100 mg/d (70 %) or addition of 30 mg/d of mianserine (67 %) [58].

Monoamine-oxidase inhibitors

Regarding the irreversible monoamine-oxidase inhibitor (MAO-I), *tranylcypromine*, a few open-label studies suggest an increase of therapeutic efficacy when raising the dose up to 100–200 mg/d. In an original study conducted by Amsterdam & Berwish, seven highly refractory patients were given a dose increase to 90–170 mg/d (mean: 112 mg ± 16 mg) [4]. Four of the patients achieved full remission and one patient remitted partially. Treatment length ranged from two weeks to four months. Interestingly, mild side effects, mainly hypotonia, diminished at the maximum dose range. Tyramine-induced reactions were not observed at all. Amsterdam confirmed his own findings in a later publication after expanding his sample to 14 subjects [5]. With a mean dose of 128 mg/d (± 27 mg/d), 50 % of patients showed full remission and 21 % showed partial remission. Sympatholytic side-effects occurred frequently (71 %), but mainly at moderate doses. In both of Amsterdam's studies, however, the previous unsuccessful treatments had not been performed with tranylcypromine, so these trials cannot be regarded as dose-increase studies in the strict sense. The effectiveness of ultra-high doses of tranylcypromine in treatment-refractory patients has also been supported in several case reports [46, 76, 90, 98].

Other antidepressants

A recent small-scale open study of 5 patients resistant to different previous treatments found that 4 of 5 patients responded (ΔHAMD ≥ 50 %) to ultra-high-dose treatment with venlafaxine (450–600 mg/d) [61]. Tolerability was also reported to be good. The small sample size and long study period of six months, increasing probability of spontaneous remissions, are major shortcomings of this study.

Comparative dose studies

Heterocyclic antidepressants

We found a total of 32 comparative dose studies on all substance groups. In an early open-label study of 29 patients with depressive disorder receiving *nortriptyline* or placebo, a significant increase in cumulative response rate was observed in non-responders after raising the dose from 30 mg/d to 75 mg/d. Further dose increase to 150 mg/d did not show a marked effect due to the small sample size [73]. Watt and coworkers observed a significantly higher percentage of patients achieving recovery after four weeks of taking 300 mg/d of *imipramine* versus 150 mg/d [113]. Simpson and coworkers showed superior efficacy of high-dose imipramine treatment at 300 mg/d over 2–4 weeks compared to 150 mg/d in several (mainly sleep-related) rating items, but also found an equal number of non-responders in both treatment groups [101]. Wilson and coworkers conducted an ECT-imipramine-placebo comparative study on a small number of female patients [116]. Imipramine was administered at 150 mg/d (n = 6) in a first sample and at 240 mg/d (n = 10) in a second sample. The response to imipramine rose with the higher dose and was then compared to electroconvulsive therapy (ECT) administered on the second study sample. Several later reviews confirmed that 150 mg/d (or less) of imipramine is subtherapeutic for moderately to severely depressed patients [8, 39, 42, 84, 92], which suggests maximization of

Table 1 Non-responder studies: high-dose treatment studies in treatment-resistant patients

Author (year)	Drug(s)	Dosage (I = group 1, II = group 2, etc.)	No. of participants, study design, trial length	Results
Fava et al. (2002)	Fluoxetine	I: 40–60 mg Flu II: 20 mg Flu + 25–50 mg Des III: 20 mg Flu + 300–600 mg Li	N = 101, RCT, DB, 4 weeks	No significant overall differences between groups, nor among partial responders and non-responders
Licht & Qvitzau (2002)	Sertraline	I: 100 mg II: 200 mg III: 100 mg + 30 mg Mia	N = 295, RCT, DB, 5 weeks	Dose increase to 200 mg resulted in a lower response rate than dose continuation or addition of Mia
Mbaya (2002)	Venlafaxine	450–600 mg	N = 5, open label uncontrolled, 24 weeks	≥ 50 % decrease in HAMD score in 4 of 5 patients
Schweizer et al. (2001)	Sertraline	I: 50 mg II: 150 mg	N = 37, RCT, DB, 5 weeks	No difference between treatment groups
Benkert et al. (1997)	Maprotiline Paroxetine	Ia: 150 mg IIa: 100 mg Ib: 40 mg IIb: 20 mg	N = 174,RCT, DB, MC 3 weeks	Neither significant differences between 20 mg and 40 mg group in the case of paroxetine, nor between 100 mg and 150 mg group in the case of maprotiline
Fava et al. (1994)	Fluoxetine	I: 40–60 mg Flu II: 20 mg Flu + 25–50 mg Des. III: 20 mg Flu + 300–600 mg Li	N = 41, RCT, DB 4 weeks	20 mg Flu + Li was most effective among non-responders. Among partial responders as well as in the overall sample 50–60 mg Flu proved to be the best treatment
Fava et al. (1992)	Fluoxetine	60–80 mg	N = 15, open label uncontrolled, 4 weeks	Significant improvement of all patients on 60–80 mg (as opposed to 20 mg before)
Amsterdam (1991)	Tranylcypromine	90–180 mg (M = 128 ± 27 mg)	N = 14, open label uncontrolled, ≥ 3 weeks	Significant improvement. Previous treatment not with Trp
Schweizer et al. (1990)	Fluoxetine	I: 20 mg II: 60 mg	N = 77, RCT, DB, 5 weeks	No significant differences between 20 mg and 60 mg group
Amsterdam & Berwish (1989)	Tranylcypromine	90–170 mg (M = 112 ± 16 mg)	N = 7, open label uncontrolled, 2 weeks to 4 months	Significant improvement. Previous treatment not with Trp.
Dornseif et al. (1989)	Fluoxetine	I: 20 mg II: 60 mg	N = 572, RCT, DB, 5 weeks	No significant differences between 20 mg and 60 mg group

DB double blind; *Des* desipramine; *Flu* fluoxetine; *M* mean; *MC* multicentric; *Mia* mianserine; *RCT* randomized controlled trial; *Trp* tranylcypromine

the tricyclic dose may be beneficial for patients who do not sufficiently respond to a lower dose.

In a randomized controlled multi-center trial of 122 outpatients treated by general practitioners with low doses of *clomipramine* (30 mg/d versus 75 mg/d), no correlation between dose and response was seen [44]. In a randomized, double-blind study comparing five fixed doses of clomipramine (25, 50, 75, 125, and 200 mg/d) over a period of 6 weeks a significant, yet moderate dose-response relationship was observed in the completer analysis, whereas endpoint evaluation and last observation carried forward (LOCF) analysis failed to show a positive dose-response correlation [23]. Dropouts due to adverse events rose with increasing doses, whereas dropouts attributable to symptom worsening or lack of effect declined with increasing doses.

Similarly, no correlation between dose and clinical effect was seen in a large randomized, controlled, double-blind multi-center study that compared 75 mg/d and 150 mg/d of *imipramine*, *amitriptyline* and *maprotiline* after a 4-week medication trial [118]. An early randomized comparative dose study of *maprotiline* (150 mg versus 225 mg/day) in a small sample of 20 patients showed no significant dose dependency of response [117].

For *trazodone*, a dose-response relationship is not well-established. Considerable evidence for the efficacy of this drug for treatment of severe depressive states was derived from early studies when trazodone was prescribed in relatively high doses (up to 600 mg/d). Concerns about dose-dependent side effects have reduced the recommended dose range to 200–450 mg/d [105].

Selective serotonin reuptake inhibitors (SSRIs)

The available dose-finding studies of fluoxetine show best clinical results with the minimal effective dose. Administration of high doses of different compounds does not show any clinical advantage but is associated with increased adverse events [15]. Wernicke and coworkers showed equal effectiveness of lower fixed doses of fluoxetine (20 mg/d in the first study, 5 mg/d in the second study) and a high rate of adverse events in high doses [114, 115]. However, the 5 mg dose showed a slightly in-

Table 2 Comparative dose studies of heterocyclic antidepressants in patients not resistant to treatment

Author (year)	Drug(s)	Dosage (I = group 1, II = group 2, etc.)	No. of participants, study design, trial length	Results
Danish University Antidepressant Group (DUAG) (1999)	Clomipramine	I: 25 mg II: 50 mg III: 75 mg IV: 125 mg V: 200 mg	N = 151, RCT, MC, DB, 6 weeks	Significant, but modest correlation between dose and clinical improvement in completer analysis
WHO (1986)	Imipramine Maprotiline Amitriptyline	For *each* drug: I: 75 mg II: 150 mg	N = 370, RCT, MC, 4 weeks	No significant differences in efficacy between 75 mg and 150 mg groups
Simpson et al. (1976)	Imipramine	I: 150 mg II: 300 mg	N = 51, RCT, DB, 2–4 weeks	Significantly greater improvement of 300 mg group
Woggon et al. (1976)	Maprotiline	I: 150 mg II: 225 mg	N = 20, RCT, DB, 4 weeks	No significant differences between 150 mg and 225 mg group. Tendency toward better results at 225 mg
Gringras et al. (1975)	Clomipramine	I: 30 mg II: 75 mg	N = 122, RCT DB, 4 weeks	No significant differences in efficacy between 30 mg and 70 mg group
Watt et al. (1972)	Imipramine	I: 150 mg II: 300 mg	N = 58, open-label study, 4 weeks	Significantly higher rate of recovery with 300 mg/d (50 %) than with 150 mg/d (21 %)
Nodine et al. (1965)	Nortriptyline	I: 30 → 75 → 150 mg II: PCB	N = 60, RCT, DB. Dose increase in case of non-response after 14 d	Response rate increased with increasing drug dose between 30 and 75 mg/d. No marked effect with 150 mg/d due to small sample size
Wilson et al. (1962)	Imipramine	I: 150 mg (vs ECT) II: 240 mg (vs. ECT)	N = 16 (I: 6 + II: 10) Semi-randomized, comparing imipramine 150 mg (I) and imipramine 240 mg (II) vs. ECT	Improvement rate with 150 mg imipramine significantly less than ECT. Improvement rate with 240 mg imipramine equal to ECT

RCT randomized controlled trial; *DB* double-blind; *MC* multicentric; *PCB* placebo; *ECT* electroconvulsive therapy

ferior response rate [115]. Likewise, no correlation between clinical efficacy and plasma levels of fluoxetine and its metabolite, norfluoxetine, could be shown. The flat dose-response curve for *paroxetine* (doses between 20 and 40 mg/d) is confirmed by the manufacturer's analysis of a multi-center fixed-dose comparative study of 460 patients for over 6 weeks (at 10 mg, 20 mg, 30 mg, 40 mg per day) and two pooled analyses of a worldwide database involving 2135 and 1091 patients [26]. There is, however, some evidence from flexible-dose studies that in severely depressed melancholic patients a daily dose higher than 20 mg is required [25, 47]. For *sertraline*, equal efficacy was shown for 50 mg, 100 mg and 200 mg per day but increasing drop-out rates were shown at higher doses [3, 27, 106]. Regarding total HAMD scores, however, Amin and coworkers found the 200 mg/d-dose group to be significantly superior compared to placebo [3]. One study reported a curvilinear relationship with the maximum antidepressive effect at 100 mg/d, compared to lower response rates at 50 and 200 mg/d [87]. The limitation of the latter study is, however, the very small sample size (6–11 patients per treatment group) and the lack of a parallel group design. The different response rates are therefore not clearly related to the different drug doses and are possibly more strongly related to the time treated. A lower response rate from high-dose treatment (200 and 400 mg/d) compared to low-dose treatment (50 and 100 mg/d) was reported by Guy and coworkers in a very small sample study (n = 17) [45]. This study also showed a lack of difference between the placebo and lower dose treatment groups. For *citalopram*, a flat dose-response curve was repeatedly shown in comparative fixed-dose studies [18, 67, 68]. However, a minimal effective dose was set at 40 mg/d in one study [66] and at 20 mg/d in a meta-analysis by the same author that included 949 patients [67]. It has been reported that high doses of citalopram are more effective in patients with severe depression [68]. In a multi-center, randomized, double-blind placebo-controlled study of *fluvoxamine* that involved 600 outpatients, a positive dose-dependent efficacy was shown with increasing clinical improvement between 25 and 100 mg/d, and decreasing efficacy at 150 mg/d [112].

Monoamine-oxidase inhibitors (MAO-I)

For the MAO-I *phenelzine*, Ravaris and coworkers showed a daily dose of 60 mg to be superior to 30 mg, which again was no better than the placebo [86]. A later double-blind randomized trial was performed with 60 depressive patients comparing daily doses of 45 and 90 mg/d. The study revealed significantly greater improvement in the high-dose treatment group [108]. No reports on ultra-high dose treatment with phenelzine in non-responders were found.

Regarding the reversible MAO-I *moclobemide*, a randomized double-blind study comparing 150 mg/d and

Table 3 Comparative dose studies of selective serotonin reuptake inhibitors (SSRI) patients not resistant to treatment

Author (year)	Drug(s)	Dosage (I = group 1, II = group 2, etc.)	No. of participants, study design, trial length	Results
Walczak et al. (1996)	Fluvoxamine	I: 25 mg II: 50 mg III: 100 mg IV: 150 mg	N = 600, RCT PCB controlled, DB, MC 7–8 weeks	Positive dose-response relationship between 25 and 100 mg/d. Decrease of efficacy at 150 mg/d
Fabre et al. (1995)	Sertraline	I: 50 mg II: 100 mg III: 200 mg	N = 369, RCT, DB, MC 6 weeks	No significant differences between 50 mg, 100 mg, and 200 mg group
Montgomery (1995)	Citalopram	I: 10 mg II: 20 mg (1994) III: 40 mg (1992) IV: 60 mg	N = 650, RCT, PCB controlled, DB, MC	Unpublished data No significant differences between dosages, although lower doses were less effective in some analyses of the data
Dunner et Dunbar (1992)	Paroxetine	I: 10 mg II: 20 mg III: 30 mg IV: 40 mg	N = 460, RCT, PCB controlled, DB, MC, 6 weeks	20 mg proved to be the optimal dose. The authors do not exclude that higher doses would have been more effective if they had been reached via gradual titration
	Paroxetine	10–50 mg	N = 2135, retrospective analysis of world wide database, ≥ 4 weeks	No significant differences in efficacy over the dose range from 10 to 50 mg
Montgomery et al. (1992)	Citalopram	I: 20 mg II: 40 mg	N = 199, RCT, PCB controlled DB	Significantly greater improvement of 40 mg group
Beasley et al. (1990)	Fluoxetine	5/20/40/60 mg	Reanalysis of Wernicke et al. (1987, 1988; see below)	5 mg, 20 mg, and 40 mg superior to 60 mg dosage
Amin et al. (1989)	Sertraline	I: 50 mg II: 100 mg III: 200 mg	N = 30, RCT, PCB controlled, DB, MC	No difference between different dosages regarding HAMD-Item Depressed Mood. Statistical difference regarding total HAMD score only between placebo and 200 mg dosis but not between placebo and lower dosage groups
Reimherr et al. (1988)	Sertraline	I: 50 mg II: 100 mg III: 200 mg	N = 6–11 per treatment group, RCT, DB, 8 weeks (study compared sertraline with amitriptyline in different doses)	100 mg more effective than 50 mg and 200 mg. No parallel group design
Wernicke et al. (1988)	Fluoxetine	I: 5 mg II: 20 mg III: 40 mg	N = 354, RCT, PCB controlled, DB, 6 weeks	No significant differences between 20 mg and 40 mg group (both dosages more effective than 5 mg)
Wernicke et al. (1987)	Fluoxetine	I: 20 mg II: 40 mg III: 60 mg	N = 356, RCT, PCB controlled, DB, MC, 4 weeks	Best efficacy at 40 mg. Good efficacy and lowest drop-out rate at 20 mg
Guy et al. (1986)	Sertraline	I: 50 mg II: 100 mg III: 200 mg IV: 400 mg	N = 17, RCT, DB, MC, 4 weeks	Lower response rate of pooled 200 and 400 mg dose groups compared to pooled 50 and 100 mg dose groups. No difference between lower dose groups and PCB
Bjerkenstedt et al. (1985)	Citalopram	I: 5 mg II: 25 mg III: 50 mg	N = 26, RCT, DB, 4 weeks	No clear difference between groups. Drug level measurement suggests an MED at 15 mg

RCT randomized controlled trial; *DB* double-blind; *PCB* placebo; *MC* multicentric; *MED* minimal effective dose

300 mg/d did not show any significant difference in overall clinical response [55]. Another randomized double-blind trial comparing 300 mg/d and 450 mg/d of moclobemide did not show any difference in response between treatment groups [36]. Similarly, a double-blind comparative study of three different doses of moclobemide (300 mg, 450 mg, 600 mg per day) did not show any difference in therapeutic efficacy nor any correlation between the degree of MAO inhibition and clinical response [85]. However a pooled data analysis showed doses higher than 450 mg/d to be more effective in severely depressed patients [9].

Other antidepressants

For the newer antidepressive compounds (except for SSRIs) available dose finding studies offer only indirect evidence regarding the therapeutic efficacy of dose increases in treatment resistant patients. In a study of 60

Table 4 Comparative dose studies of monoamine-oxidase inhibitors (MAO-I) in patients not resistant to treatment

Author (year)	Drug(s)	Dosage (I = group 1, II = group 2, etc.)	No. of participants, study design, trial length	Results
Radat et al. (1996)	Moclobemide	I: 300 mg II: 450 mg III: 600 mg	N = 47, RCT, DB, 6 weeks	No significant differences between groups
Gagiano et al. (1995)	Moclobemide	I: 150 mg II: 300 mg III: 450 mg	N = 270, RCT, DB, MC 6 weeks	No significant differences between groups apart from a slightly greater improvement of anxiety/agitation in the 150 mg group
Lensch et al. (1987)	Moclobemide	I: 150 mg II. 300 mg	N = 23, RCT, DB, 4 weeks	No difference in overall clinical response
Tyrer et al. (1980)	Phenelzine	I: 45 mg II: 90 mg	N = 60, RCT, DB, 4 weeks	Significantly greater improvement of 90 mg group
Ravaris et al. (1976)	Phenelzine	I: 30 mg II: 60 mg	N = 62, RCT, PCB controlled, DB, 6 weeks	Significantly greater improvement of 60 mg group

RCT randomized controlled trial; *DB* double-blind; *PCB* placebo; *MC* multicentric

unipolar depressed patients, *venlafaxine* showed a non-significant tendency towards superior efficacy at 375 mg/d after six weeks of treatment, compared to 225 mg/d, 75 mg/d, and placebo [98]. This difference between the high and the low dose as well as the positive dose-response relationship finally became significant in a later publication of the same study group on a sample of 358 patients [93]. Two other placebo-controlled trials, one with 312 patients receiving 25, 50–75 or 150–200 mg/d [63] and another with 384 patients receiving 75, 150 or 200 mg/d [100], confirmed the positive dose-response relationship of venlafaxine in these dose-ranges.

For *nefazodone*, which was recently withdrawn from the market, data of a phase-two [63] and a phase-three trial [32] suggest superior efficacy of a high dose range (100–600 mg/d) compared to a low dose range (50–300 mg/d). A study with a flexible fixed-dose design suggests that an effective dose-response relationship ranges from 300 mg/d up to 500 mg/d [81]. For *mirtazapine* and *reboxetine*, no studies comparing fixed doses in either refractory or non-refractory patients were found. For *bupropion*, one randomized double-blind study of elderly patients was found that compared 150 mg/d with 300–450 mg/d [48]. No difference between high- and low-dose groups was found in this study. Correspondingly, drug monitoring studies of bupropion describe a curvilinear concentration-response relationship for the parent compound as well as for the metabolites [40, 78]. Due to the unclear relationship between the parent compound and its metabolites, dose adjustments based on bupropion serum concentrations are not recommended [80, 81].

TDM studies

TDM studies deliver only indirect evidence regarding the effect of dose escalation in non-responders, since a linear relationship between oral dose, plasma level and clinical response cannot be assumed due to individual differences in drug metabolism [14]. However, 28 drug monitoring studies and several review articles are included in this analysis.

Heterocyclic antidepressants

Studies considering the correlation between plasma levels of heterocyclic antidepressants and clinical efficacy show high plasma levels to be superior. For the tricyclics amitriptyline, nortriptyline, desipramine and imipramine, the likelihood of a therapeutic response is markedly improved when the dosage is optimized according to the plasma levels [77]. A linear, sigmoidal or curvilinear relationship between plasma level and clinical response, as well as strong differences in inter-individual plasma levels of *imipramine* and its active metabolite desipramine with identical oral doses, was shown in several larger studies [37, 38, 77, 88]. However, the positive correlation was not confirmed by two other studies [11, 102]. For *nortriptyline*, a curvilinear dose-response curve was demonstrated by the majority of studies, indicating the existence of a "therapeutic window", with a positive correlation between plasma level and clinical effect in the middle plasma level range, and no linearity of correlation at either lower or higher levels [10, 51, 70, 77, 119]. It has even been suggested that several patients who were non-responsive at blood levels above the therapeutic window (e. g. > 200 ng/ml), responded after reduction of blood levels to the proposed therapeutic range (i. e. 50–150 ng/ml) [52]. A linear effect is shown for *desipramine*, when administered as the parent drug [71, 77]. Friedel, in his review, reports a therapeutic window for desipramine (125–170 ng/ml) at least for less severely ill patients [34]. For *amitriptyline*, the relationship is discussed controversially as being linear [20, 53, 120], curvilinear [65, 69, 77, 108, 111], and not correlated [21, 58, 64,

Table 5 Comparative dose studies of different modern antidepressants in patients not resistant to treatment

Author (year)	Drug(s)	Dosage (I = group 1, II = group 2, etc.)	No. of participants, study design, trial length	Results
Rudolph et al. (1998)	Venlafaxine	I: 75 mg II: 225 mg III: 375 mg	N = 358, RCT, DB, MC, 6 weeks	Significantly greater improvement of 225 mg and 375 mg group
Mendels et al. (1995)	Nefazodone	I: 50–300 mg II: 100–600 mg	N = 240, RCT, PCB controlled, DB, 6 weeks	Significantly greater improvement of 100–600 mg group. No differences between 50–300 mg group and PCB
Fontaine et al. (1994)	Nefazodone	I: 50–250 mg NEF II: 100–500 mg NEF III: 50–250 mg IMI	N = 180, RCT placebo controlled, DB, 6 weeks	Significant difference in improvement from PCB in high-dose range as compared to low-dose range
Mendels et al. (1993)	Venlafaxine	I: 25 mg II: 50–75 mg III: 150–200 mg	N = 312, RCT, PCB controlled, DB, MC, 6 weeks	Significantly positive dose response relationship beginning at week 1
Schweizer et al. (1991)	Venlafaxine	I: 75 mg II: 225 mg III: 375 mg	N = 60, PCB controlled DB, MC, 6 weeks	Trend toward greater and quicker improvement in 225 mg and 375 mg groups
Kane et al. (1983)	Bupropion	I: 150 mg BUP II: 300–450 mg BUP III:75–200 mg IMI	N = 38, RCT, DB, 4 weeks	No significant differences between dosages

RCT randomized controlled trial; *DB* double-blind; *PCB* placebo; *MC* multicentric; *BUP* bupropion; *NEF* nefazodone; *IMI* imipramine

91]. In a recent study of 25 moderately to severely depressed inpatients, a curvilinear serum-level response relationship with a therapeutic window was described for amitriptyline [110]. For *clomipramine* and its metabolite desmethyl-clomipramine, a statistically significant but modest correlation between clinical response and serum concentration was recently shown [23]. Very limited and controversial data are available concerning other tri- and tetracyclic compounds such as doxepine [56] and maprotiline [89]. In summary, secondary amines, such as nortriptyline, seem to show curvilinear relationships whereas tertiary amines, such as amitriptyline and imipramine, show linear relationships of plasma level and clinical response. This is confirmed by a review [74] concluding that a consistent concentration-effect relationship can be established for imipramine and nortriptyline, whereas the effects of amitriptyline and clomipramine are less clear in spite of the large number of studies.

Selective serotonin reuptake inhibitors (SSRIs)

The lack of dose-dependent clinical response is confirmed by a study failing to show any correlation between dose-dependent serum concentrations of fluoxetine and its metabolite norfluoxetine and clinical improvement in 13 patients [49]. As a whole, a clinically useful correlation between serum levels of SSRI and clinical response could not be shown [49, 83, 103]. Available evidence considering the dose-response relationship for SSRIs is highly suggestive of a flat dose-response curve with no increase in clinical response above the minimum effective dose and with 70–80 % of platelet serotonin uptake being inhibited [60]. This correlation is confirmed by a recent study on the benefit of therapeutic drug monitoring that used three different SSRIs, paroxetine, sertraline and citalopram [59]. SSRI doses were adjusted by the treating physician based on TDM results and clinical impression. In half of the patients, antidepressant doses were reduced according to TDM outcome without any change in clinical response indicating equal efficacy and sufficient serum levels of a minimum SSRI dose.

Monoamine-oxidase inhibitors (MAO-I)

Regarding MAO-I, only a small drug monitoring study on 16 patients treated with moclobemide (at 300 mg/d) was found. Plasma concentrations were not shown to be correlated to clinical response [35].

Discussion

Our study revealed that there are very limited clinical data on high-dose antidepressant therapy. Only nine studies directly addressed the question of effectiveness of maximum-dose antidepressant treatment in refractory depression. Seven of these studies have been conducted using a randomized double-blind design [17, 24, 29, 31, 57, 97, 99] and all of them have examined SSRI high-dose treatment. Furthermore, many of the reviewed studies are based on small sample sizes which allow only limited conclusions and reflect the difficulty in realizing large scale studies with a homogenous sample of treatment-refractory patients with depression. There-

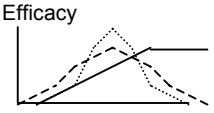
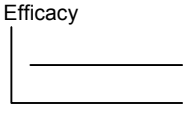
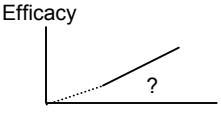
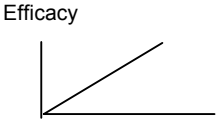
	Tri-/Tetracyclic Antidepressants	SSRI	MAO Inhibitors	Other
Dose-efficacy relationships				
Comments	Evidence for the effectiveness of high-dose treatment mainly from comparative dose studies and therapeutic drug monitoring (TDM) studies.	High dose treatment ⇒ more side effects without increase of efficacy TDM ⇒ reduction of dosage without loss of efficacy [59]	Ultra-high dose treatment of *tranylcypromine* ⇒ sympathomimetic (amphetaminergic) effect compensates sympatholytic side effects	Positive dose-response relationship suggested for *venlafaxine* mainly from comparative dose studies

Fig. 1 Dose-efficacy relationships of different antidepressant classes

fore, the primary result of this analysis is that evidence supporting the common strategy of maximizing the dose of antidepressants is particularly scarce at the level of clinical studies that directly address this topic for non-SSRI antidepressants.

Most of the comparative dose studies included in this overview dealt with the recently marketed selective antidepressants, partly because of the present requirements from regulatory bodies to provide such data. Yet, studies with treatment refractory patients remain rare even for these substances. The reasons are two-fold: 1) comparative fixed-dose studies are difficult to design and expensive to conduct; 2) attention has been focussed on the serum level-response relationship rather than the dose-response relationship [19]. Comparative dose studies bear the limitation that they are generally conducted to find the minimal dosage that results in a response based on population averages.

Twenty-seven drug monitoring studies and several reviews concerning the topic were included. The relationship between administered drug doses, serum concentration and clinical response is far from being established. For example, a rather linear relationship exists between drug dose and serum concentration for SSRIs, but there is hardly any correlation between serum concentration and clinical response or between drug dose and clinical response for these compounds [16]. One limitation of the drug-monitoring studies is that data suggest an up to 10- to 40-fold difference in antidepressant plasma concentrations, at least for tricyclic antidepressants, between individuals receiving the same dose of a drug [79].

There are different reasons for the lack of studies directly addressing the efficacy of high-dose antidepressant treatment in non-responders to a previous medium-dose treatment. One major reason is the difficulty to obtain large enough sample sizes of patients who are treatment refractory, according to predefined operationalized criteria. Another reason may be that variations in pharmacokinetics and other influencing factors such as genetic differences and concomitant medication, which are strongly confounding variables, result in the need for very large patient samples to control for these variables in clinical trials [16]. A further

major confounding factor is the latency of antidepressant response which makes it difficult to conduct longitudinal dose-effect studies in a given patient sample [23].

As a whole, including comparative dose studies and therapeutic drug monitoring studies, the knowledge about high dose treatment with antidepressants for patients who have not responded to a medium-dose treatment trial remains limited. What, then, is to be concluded from the studies in this overview? In the following we will briefly discuss the conclusions for the different subclasses of antidepressants and the conclusions for clinical practice and future research.

For tricyclic and tetracyclic antidepressants, available data from comparative dose studies suggest a positive dose-response relationship in the majority of studies [23, 44, 101, 113, 116] although two studies failed to show a positive correlation [117, 118]. The major limitation concerning tri- and tetracyclic substances is the existence of only one dose maximization study in non-responders [17]. One of the comparative dose-studies, however, is a placebo-controlled stepwise dose-increase study of non-responders to the tricyclic nortriptyline [73] but only to a maximum of 150 mg/d. TDM studies showing a relationship between serum concentration and clinical response are a source of moderate evidence supporting high-dose treatment with TCA. However, relationships between administered drug doses, serum levels and clinical response have to be differentiated. The existence of a "therapeutic window" as was best shown in TDM studies of secondary amines, particularly for nortriptyline, can be associated with a loss of efficacy in maximum dose ranges depending on individual pharmacokinetics. In summary, maximum dose escalation in patients who are refractory to medium-dose treatment with a tricyclic should be considered, bearing in mind the insufficient data addressing the question.

For SSRIs a good relationship has been shown between dose and serum levels whereas the relationship between serum levels and clinical response, as well as administered dose and clinical response, seems to be poor. Nevertheless, SSRIs are the best studied drug class for dose maximization in non-responders. Available data suggest a flat dose-response relationship. Minimal effective doses (MED) of SSRIs lead to a 70 % serotonin reuptake inhibition. Above MED, serotonin reuptake inhibition and clinical improvement rates do not increase considerably [83]. Increase of dosage above the minimal effective dose is likely to increase the occurrence of side effects without increasing therapeutic efficacy.

The irreversible MAO-I tranylcypromine might show an increase of clinical efficacy in the ultra-high dose range between 90 and 180 mg/d suggesting a positive dose-efficacy correlation. However, there seems to be a flat relationship in the normal to high dose range when MAO-inhibition is the main pharmacological mechanism [4, 5]. The clinical effect of ultra-high dosages of tranylcypromine is hypothesized to be related to an amphetaminergic effect, which occurs in the high-dose range. MAO-inhibition is not likely to be solely responsible for the clinical effect in high-dose treatment since a sufficient portion (90 %) of MAO is already inhibited by the administration of 10 mg tranylcypromine per day [95]. This treatment is reported to be relatively safe with side effects decreasing while doses increase. However, when considering these open studies of ultra-high-dose effectiveness of the MAO-I tranylcypromine, it is important to note that before the double blind studies with fluoxetine were carried out, this agent was regarded as a promising candidate for high-dose treatment based on the results of one open study [28].

For phenelzine, a positive dose-response relationship in the medium to high-dose range has been suggested [108], whereas data for the reversible MAO-I moclobemide are less clear [9, 36, 85].

Venlafaxine [61, 62, 93, 98, 100] and nefazodone [32, 63, 82] show higher efficacy in the maximum dose range, suggesting dose escalation might be useful in patients who are not responding to lower doses. Bupropion does not appear to have increasing efficacy with increasing drug dose [40, 48, 78, 80].

For clinical practice, one has to bear in mind that individual patients may benefit from higher doses even if dose increase for a particular compound has not been shown effective in large dose-finding trials. Furthermore, as indicated by the variations in the plasma levels of antidepressants, there may be fluctuations in the response of a given patient to a high-dose treatment over time. It is also important to note that overdosing might deteriorate clinical response when side-effects rise disproportionately compared to response.

Because standard analyses of clinical trials require the therapeutic response to fixed doses be expressed only for patients who complete the protocol and do not drop out, Bollini and coworkers performed a meta-analysis of dose-effect relationships in randomized clinical trials with different compounds on an intention-to-treat basis [19]. Response rates were calculated as the proportion responding after randomization. This analysis, however, did not show markedly different response rates between any doses of drugs. The authors conclude that there is no positive dose-effect relationship for antidepressants in general and that conventional therapeutic doses of antidepressants are as effective as higher doses. In addition, MED treatment is only marginally less effective than medium dose treatment in the therapeutic range and produces significantly less adverse events. As a result, high dose treatment should be an option for patients who do not respond to other strategies, such as lithium augmentation.

An essential aspect of antidepressant drug dosing is the growing evidence of the impact of genetic polymorphisms in cytochrome P450 enzymes (CYP) on the disposition of antidepressant drugs. This has best been shown for CYP2D6 and CYP2D19 polymorphisms on the pharmacokinetics of almost all tricyclic antidepressants and many other antidepressive compounds [50]. Genetic classification into poor (PM), intermediate

(IM), extensive (EM) and ultrarapid (UM) metabolizers may explain non-response to a medium dose treatment in EM and UM and lead to a genotype-based dosing strategy in the future.

Whether dose escalation for certain classes of antidepressants is a profitable strategy in initially refractory patients can only be answered by studies that are strictly designed for approaching this problem prospectively. Such would be a randomized trial involving well diagnosed and characterized non-responders and comparing dose increase of the initial antidepressant with other strategies, i. e. lithium augmentation [12]. Such a study is currently underway within the multi-center algorithm-project of the German competence network on depression [1].

Filling the gaps of strongly needed evidence for a rationale medical-decision making in the treatment of patients who fail to respond sufficiently to an initial treatment trial is also the major aim of two large-scale National Institute of Mental Health-funded, multisite clinical trials. The Texas Medication Algorithm Project (TMAP) demonstrated the superior efficacy of an algorithm-guided treatment procedure compared to treatment as usual in patients with major depressive disorder [107]. Sequenced Treatment Alternatives to Relieve Depression (STAR*D) compares different treatment strategies in patients who are not responding to an initial antidepressant trial [94].

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