Dose-escalation in the picture: pharmacological and imaging studies in depression

Ruhé, H.G.

Citation for published version (APA):
DOSE-ESCALATION FOR INSUFFICIENT RESPONSE TO A STANDARD DOSE OF A SELECTIVE SEROTONIN REUPTAKE INHIBITOR IN MAJOR DEPRESSIVE DISORDER: A SYSTEMATIC REVIEW.

British Journal of Psychiatry 2006; 189: 309-316

Henricus G. Ruhé¹
Jochanan Huyser¹
Jan A. Swinkels¹
Aart H. Schene¹

¹ Program for Mood Disorders, Department of Psychiatry, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands
Abstract

Background
Although SSRIs are frequently used for major depressive disorder, only 50-60% of patients respond to a standard dose. For non-responders dose-escalation is often applied.

Aim
To systematically review the evidence for dose-escalation of SSRIs.

Methods
A systematic literature search in MEDLINE, EMBASE, CINAHL and PsycInfo was performed. Randomised controlled trials and meta-analyses investigating dose-escalation of SSRIs were identified. Relevant articles were retrieved and critically appraised. Results were summarized in an evidence table. Pooling was not justified due to heterogeneity of the identified studies.

Results
Eight true dose-escalation studies and 3 meta-analyses were identified. The available data provided no unequivocal base for dose-escalation. Dose-escalation before 4 weeks of treatment at a standard dose appeared to be ineffective.

Conclusions
Dose-escalation of SSRIs is equivocally supported by evidence of RCTs, but methodological difficulties in the studies may account for this lack of evidence. Clinical implications and methodological considerations for future studies are discussed.
Introduction

Many countries developed national clinical guidelines for the treatment of Major Depressive Disorder (MDD).1-8 In these guidelines pharmacotherapy is among the most important treatments, while in many of the countries, Selective Serotonin Reuptake Inhibitors (SSRIs) have become the first line antidepressants. It is less clear what should be done in those 40-50% of the patients who do not respond to the first antidepressant given.9-10 Strategies in case of non-response have been published in several narrative reviews11-24 and in one systematic review.25 Three major strategies for non-response are recommended: 1) increase of the dose of the antidepressant (dose-escalation), 2) augmenting the antidepressant by adding a second drug, 3) switching to another antidepressant of the same or a different class.

Available dose-finding studies do not provide evidence to initiate pharmacotherapy for MDD with SSRIs in higher than standard doses.26-30 For non-responders, all guidelines recommend dose escalation as the appropriate strategy, instead of continuing an apparently insufficient regimen.1-7 Only the recent NICE guideline is less pronounced in this recommendation,8 and advises that if ‘there are no significant side effects, a gradual increase in dose should be considered’. Moreover, surprisingly little systematic evidence is provided to underscore these recommendations.

Due to the above recommendations and its simplicity, dose-escalation is widely practiced and often the first strategy applied.31-34 The aim of our study was to systematically review the evidence for dose-escalation of SSRIs in MDD.

Methods

Design of studies to be included

Ideally the design of dose-escalation studies is randomisation of non-responders to higher doses of an antidepressant or placebo after some weeks of a standard dose. In this review we consider three other methodological requirements for those studies. First, dose-escalation should be deferred, e.g. 3-6 weeks after the initiation of the treatment because antidepressants need several weeks to have a clinical effect.35 The practice of dose-escalation and the possibility to demonstrate a dose-response relationship is based upon a selection of ‘true’ non-responders.36 As this might take 6-10 weeks,37 dose-escalation studies with early randomisation unintentionally diminish the possibility to prove the usefulness of dose-escalation. The inclusion of unidentified late responders in both arms of the study reduces the contrast between the intervention and control. Second, an outstanding study will have sufficient power to be able to demonstrate a clinically relevant difference (e.g. 20%) between treatment arms, and third will describe the method of dose-escalation and describe the early drop-out rates due to dose-escalation.

Identification and selection of articles

First, systematic literature searches (updated until February 10th 2005) were performed in four databases (MEDLINE, EMBASE, CINAHL, PsychInfo; all indexed years). As there are no specific keywords for dose-escalation studies, ‘sensitive’ searches were performed with the following terms: (((dose[textword(tw)] or dosage[tw]) and increase[tw]) or ((dose[tw] or dosage[tw]) and maxim*[tw]) or (upward[tw] and titrat*[tw])) OR dose-response relationship, drug[MeSH] in combination with the Cochrane Collaboration search-filter for RCTs and systematic reviews, the Cochrane Collaboration Depression Anxiety and Neurosis group (CCDAN) search-filter for MDD and MeSH-terms and text words for SSRIs. Primary selection (independently by the first and second author) was based on design and focus on dose-response relationships for SSRIs, by screening title and abstract of the article. Agreement on predominantly exclusion of irrelevant articles was 99.1%, with Cohen’s Kappa for interrater agreement of 0.62 (a ‘substantial’ agreement).38 Discrepancies between initial selection was resolved by discussion and consensus.
Second, all potentially relevant articles were judged according to specific inclusion and exclusion criteria (criteria available on request). In case of doubt an article was read fully and assigned afterwards. Additionally, relevant cross-references were retrieved. Double-publications were considered together to reveal the maximum of available information.

**Critical Appraisal and summary**

Selected articles were critically appraised and abstracted by the first author, using standardized forms derived from the Dutch Institute of Healthcare Improvement\(^39\) and the AHCPR.\(^4\) The items used for critical appraisal were the same as proposed by SIGN\(^40\) and Sackett et al.\(^41\) Each study was assigned a 'level of evidence' (LoE; Table 4.1).\(^39\) Levels of evidence are based upon the methodological robustness of studies. For the results, the highest LoE of the supporting scientific evidence (A1-D) is indicated.

**Table 4.1. Levels of Evidence: Therapeutic studies.**

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>Systematic review including at least some studies of A2-level. Consistent results (homogeneity) across the included trials.</td>
</tr>
<tr>
<td>A2</td>
<td>Randomized controlled (double-blind) trial of good methodological quality, adequate size and consistence of results.</td>
</tr>
<tr>
<td>B</td>
<td>Randomized clinical trial of lower methodological quality or inadequate size. Other comparative research (e.g. non-randomized trial, comparative cohort-study, case-control study)</td>
</tr>
<tr>
<td>C</td>
<td>Uncontrolled, open study</td>
</tr>
<tr>
<td>D</td>
<td>Expert opinion, e.g. guideline-panel members</td>
</tr>
</tbody>
</table>

Source: Dutch Institute of Healthcare Improvement.\(^39\)

To assess judgement-bias by one person who performed the critical appraisal, intrarater variation was determined in a slightly different set of 12 publications. Every other author critically appraised 4 publications, agreement for the appraisal-items was expressed by Cohen's Kappa. Kappa values were 0.49 (for 'validity of the study'), 0.86 (for 'concealment of allocation'), while complete agreement existed for the appraisal-items 'randomization of the study', 'level of evidence' and 'data extraction' (Kappa = 1.0). This is in line with other reports of intrarater agreement in appraisal of psychiatric research.\(^42\)

A qualitative summary with discussion of the results, restrictions, methodological flaws and external validity of the studies was described in an evidence table and a separate document, of which a summary is provided in this paper. Because of the apparent heterogeneity in timing of the dose-escalation between the studies, results were not pooled in a meta-analysis.

**Results**

Search results and selection of studies are presented in Figure 4.1. The 11 studies selected for this review are summarized in Table 4.2. A table of excluded studies is available on request.

*Figure 4.1. Selection of reported studies.*
Characteristics of the studies

Our searches identified 8 dose-escalation studies that increased dosages after at least 3 weeks of standard dosages.43-50 We further found 3 systematic reviews about dose response relationships, which included respectively three,51 three,52 and four53 of the eight identified dose-escalation studies.

Across the studies different outcome definitions for end-points were used. In 7 articles response was defined as a reduction of ≥50% in the Hamilton depression rating scale (HDRS).43,44,47,50,53 A Clinical global impression (CGI) improvement or severity score ≤2 was used for response in one study.48 Partial response was used in 3 studies and defined as 25-50% decrease in HDRS.45-49 In 7 studies remission-rates were reported. These were defined as a HDRS ≤7,46,49,50 or HDRS ≤8.48

Different criteria were used to decide whether a patient should be randomized: non-response (by CGI,47 <50% decrease in HDRS43,44,46,49), or no remission (HDRS ≤848). In the present studies no genetic information of the CYP P450 system, nor drug blood levels were reported.

The three previous reviews all had some methodological problems: Bollini et al. pooled studies with completely different designs and drug-classes, and applied a dose-equivalence strategy that lumped differential doses of SSRIs together.51 Baker et al. also pooled heterogeneous studies with different moments of dose-escalation, and used an unusual low reference dose of fluoxetine (5mg).53 Corruble et al. did not use an adequate search strategy and only described the dose-response relationships found in their identified studies as ‘flat’ ‘curvilinear’ or ‘linear’.52

Outline of dose-escalation studies

We will briefly outline the dose-escalation studies. Dorseif et al. first investigated week 3 non-responders (n= 371 outpatients) to fluoxetine who were randomized to continuation with 20 mg or increase to 60 mg/day for 5 weeks. Response rates were 40.5% and 44.7% respectively and remission rates 33.3% and 36.2%. Drop-out rates due to side-effects were significantly different with 5.3% and 11.6% respectively.43 Schweizer et al. investigated 77 non-responsive outpatients after 3 weeks of fluoxetine 20 mg/day, with a randomization to placebo-increase or dose-escalation up to 60 mg/day for 5 weeks. Response rates were 51.2% and 50% respectively, with nonsignificant drop-out rates of 4.9% versus 16.7%.44 In a similar study Schweizer et al. studied dose-escalation of sertraline in outpatient nonremitters after 3 weeks of sertraline 50 mg/day (n= 75). Doses were randomly either kept at 50 mg/day or increased to 150 mg/day. Remission rates after 5 weeks were 32% and 47% respectively (non-significant). Specified drop out rates due to side effects were not reported.48

Fava et al. first openly treated 15 outpatients (who were week 8 non-responders to fluoxetine at 20 mg/day) with increased doses of fluoxetine titrated up to 80 mg/day for 4 weeks. No response rates were given, but the mean HDRS17-score decreased 6.2 points in week 8 non-responders and 10.1 points in partial responders.45 In a second study Fava et al. randomized week 8 non-responders to fluoxetine 20 mg/day (n= 41) to either fluoxetine 40-60 mg, desipramine addition or lithium-addition for 4 weeks. Remission rates were 53%, 25% and 29% respectively, but these differences were nonsignificant. Initial partial responders appeared to benefit most from fluoxetine dose-increases (data nonsignificant). Drop-out rates for side effects were 0%, 17%, and 7% respectively.46 In a third study Fava et al. repeated the 3-arm randomized design from their 1994 study with a stratification for partial or non-response at week 8 (n= 101). After 4 weeks, the high-dose fluoxetine group showed increased but nonsignificant remission rates (42.4%) compared to desipramine addition (29.4%) and lithium-addition (23.5%). Again initial partial responders appeared to benefit more from fluoxetine dose-increases compared to initial non-responders (differences nonsignificant). No specific data on dropout due to side effects were given.49
### Table 4.2. Effectiveness of increasing the dose: Selected studies.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Reference</th>
<th>LoE</th>
<th>N</th>
<th>Design (follow-up)</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcome</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benkert et al. (1997)</td>
<td>47</td>
<td>B</td>
<td>544</td>
<td>MDD, MinD OutP</td>
<td>RCT of week 3 nonresponders (n= 86) (3 weeks)</td>
<td>PAR 40mg</td>
<td>PAR 20mg</td>
<td>Response (≥50% ↓ in HDRS17) all: NNT_{PAR40mg} = 100 (5.1-∞) For MDD only: NNT_{PAR40mg} = 8 (2.4-∞) For baseline HDRS ≥ 24: NNT_{PAR40mg} = 6 (1.7-∞)</td>
</tr>
<tr>
<td>Dornseif et al. (1989)</td>
<td>43</td>
<td>B</td>
<td>572</td>
<td>MDD OutP</td>
<td>RCT of week 3 nonresponders (n= 371) (5 weeks)</td>
<td>FLX 60mg</td>
<td>FLX 20mg</td>
<td>Response (≥50% ↓ in HDRS21) NNT = 25 (6.5-∞) Remission (HDRS21 ≤ 7) NNT = 36 (7.3-∞) Response (CGI-I ≤ 2) NNT = 20 (6.5-∞) Drop-out SE NNH = 16 (8.3-144)</td>
</tr>
<tr>
<td>Fava et al. (1992)</td>
<td>45</td>
<td>C</td>
<td>15</td>
<td>MDD OutP</td>
<td>Open trial of nonresponders to 8-12 weeks of FLX 20mg (4 weeks)</td>
<td>FLX 40-80mg (if tolerated)</td>
<td>Decrease in HDRS17-scores in NR (-6.2) and PR (-10.1) (p&lt;0.05) Decrease in CGI-S NR (-0.9; n.s.) and PR (-2.0 p&lt;0.05)</td>
<td>Highly selected population (tertiary care). No placebo control. Limited power</td>
</tr>
<tr>
<td>Fava et al. (1994)</td>
<td>46</td>
<td>B</td>
<td>41</td>
<td>MDD Setting?</td>
<td>RCT of nonresponders to 8 weeks of FLX 20mg (4 weeks)</td>
<td>FLX 20mg + DES 25-50mg FLX 20mg + Li 300-600mg</td>
<td>Remission (HDRS17 ≤ 7) NNT_all = 4 (1.6-∞) NNT_{NR} = 6 (1.5-∞) (vs. Li) NNT_{PR} = 2 (0.9-2.8) (vs. Li) Drop-out_{SE} NNH = 6 (2.6-∞) (vs. Li)</td>
<td>Limited presentation of study-population. No placebo control. Limited power, especially in subgroup analyses</td>
</tr>
<tr>
<td>Fava et al. (2002)</td>
<td>49</td>
<td>B</td>
<td>101</td>
<td>MDD OutP</td>
<td>RCT of nonresponders to 8 weeks of FLX 20mg (4 weeks)</td>
<td>FLX 40-60mg (if tolerated)</td>
<td>FLX 20mg + DES 25-50mg FLX 20mg + Li 300-600mg</td>
<td>Remission (HDRS17 ≤ 7) NNT_all = 6 (2.4-∞) (vs. Li) NNT_{NR} = 5 (2.0-∞) (vs. Li) NNT_{PR} = 6 (2.0-∞) (vs. Li) Drop-out_{SE} NA</td>
</tr>
<tr>
<td>Licht et al. (2002)</td>
<td>50</td>
<td>A2</td>
<td>1629</td>
<td>MDD OutP</td>
<td>RCT of week 6 nonresponders (n= 295) (5 weeks)</td>
<td>SER 200 mg</td>
<td>SER 100 mg + PLAC</td>
<td>Response (≥50% ↓ in HDRS17) NNT = 7 (3.6-74.4) Response (CGI-I ≤ 2) NNH = 6 (3.4-16.4) Remission (HDRS17 ≤ 7) NNT = 12 (4.5-∞) Drop-out_{SE} not sign. different</td>
</tr>
<tr>
<td>Schweizer et al. (1990)</td>
<td>44</td>
<td>B</td>
<td>108</td>
<td>MDD OutP</td>
<td>RCT of week 3 nonresponders (n = 77) (5 weeks)</td>
<td>FLX 60mg</td>
<td>FLX 20mg</td>
<td>Response (≥50% ↓ in HDRS17) NNT = 82 (4.2-∞) Drop-out_{SE} NNH = 9 (3.9-∞) SE increased in FLX 60mg (trend)</td>
</tr>
<tr>
<td>Schweizer et al. (2001)</td>
<td>48</td>
<td>B</td>
<td>91</td>
<td>MDD OutP</td>
<td>RCT of week 3 non-remitters (n = 75) (5 weeks)</td>
<td>SER 150mg</td>
<td>SER 50mg</td>
<td>Response (CGI-I ≤ 2) NNT 7 (2.7-∞) Dropout NNH = 34 (8.5-∞) SE both increased or decreased (trend) in SER 150mg</td>
</tr>
</tbody>
</table>
### 4.2b. Systematic reviews and meta-analyses

<table>
<thead>
<tr>
<th>Study (year) reference</th>
<th>LoE</th>
<th>N</th>
<th>Design (follow-up)</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcome</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baker et al. (2002)</td>
<td>A2</td>
<td>1102</td>
<td>MDD Setting</td>
<td>Meta-analysis of 1) 4 fixed dose RCTs (3-7 weeks) and 2) 4 dose-escalation RCTs (3-5 weeks) of NR in week 3-8. (SSRIs only).</td>
<td>1) Medium / High dose 2) Dose-escalation</td>
<td>1) Low dose 2) adding PLAC (or LI/DES)</td>
<td>Increase in Response rate (≥50% ↓ in HDRS) across dose-range: 1) ITT: -9.5% (n.s.) DT: 7.8% (p&lt;0.01) 2) ITT: 6% (n.s.). DT: 9.3% (n.s.) Change of HDRS-decrease across dose-range: 1) ITT: -2.0% (p&lt;0.001). DT: unavailable. 2) ITT: 1.93% (p&lt;0.01). DT: unavailable.</td>
</tr>
<tr>
<td>Bollini et al. (1999)</td>
<td>A2</td>
<td>584</td>
<td>MDD InP &amp; OutP</td>
<td>Meta-analysis of 33 RCTs (1997-1997) with various antidepressants. (3-156 weeks)</td>
<td>Higher doses IMI-equivalent 201-250 (a) and &gt;250mg (b)</td>
<td>Average daily dose (IMI-equivalent 100-200mg)</td>
<td>Efficacy in ITT analysis: 53.3% (ref), 46.3% (a), 48.3% (b) Completers analysis: 69% (ref), 67.3% (a), 76% (b) Dropout rates: 22% (ref), 28% (a), 35% (b). SE: 30% (ref), 36% (a), 48% (b)</td>
</tr>
</tbody>
</table>

---

*All dosages in mg/day. † Intention to treat (ITT)-results unless specified. ‡ CGI-efficacy index: minimal or no change in depression with no or non-interfering side effects. § <50% reduction in HDRS-score. ¶ HDRS$_{>8}$

Abbreviations: CGI-I/S = Clinical global impression improvement/severity, DT = Dose tolerant sample, HDRS$_{xx}$ = Hamilton depression rating scale (xx denote number of items used), InP = Inpatients, ITT = Intention to treat, MDD = Major depressive disorder, MinD = Minor depression, N/A = not applicable, NNH/T = Number needed to harm/treat, NR = Nonresponders, OutP = Outpatients, PR = Partial responders, RCT = Randomized controlled trial, SE = side effects.

**Drugs:** CIT = citalopram, FLX = fluoxetine, IMI = imipramine, PAR = paroxetine, PLAC = placebo, SER = sertraline, TCA = Tricyclic antidepressants.
Benkert et al. investigated dose-escalation of paroxetine 20 mg/day in outpatients that were depressed or had minor depression. Those who did not respond after 3 weeks of treatment (n=86) were randomized to receive 40 mg paroxetine for 3 additional weeks or placebo-increase. Response rates were 75% in the placebo-increased group and 74% in the 40 mg group. Licht et al. investigated randomized dose-escalation of sertraline (up to 200 mg/day) versus sertraline 100 mg/day (placebo-increase) or mianserin addition in 295 outpatients non-responsive to sertraline 50 mg for 4 weeks and additionally increased to 100 mg for 2 more weeks. Response rates 5 weeks after randomization were significantly lower in the dose-increase group (56%) than in the sertraline 100 mg group (70%) and the mianserin-addition group (67%). Drop-outs due to side effects were not specified.

Strengths, flaws and other details of all selected studies are provided in table 4.2. In summary we mention several methodological problems we encountered: absence of placebo controls, inclusion of minor depression, insufficient data-presentation, insufficient power, uncertainty about blinding, earlier dose-escalation before the randomisation, inadequate pooling of heterogeneous data and problems with conversion to dose-equivalents. None of the studies provided information about the method of dose-escalation nor described the early drop-out rates due to dose-escalation.

**Evidence for dose-escalation?**

From 4 of the 8 dose-escalation studies it appeared that dose-increments before 4 weeks were not effective (LoE: A2). However, in the meta-analysis of some of these studies by Baker et al., a potential dose-response relationship was found for dose-escalation if dropouts due to side effects were excluded from the analysis (a so called dose-tolerant sample). Baker et al. proposed that differential dropout due to side effects in the dose-escalation group (compared to placebo-increase) gave a substantial (negative) bias of the potential dose-response relationship. They argued that by applying a last-observation carried forward approach (often used in the original studies), more early drop-outs (due to side-effects) in the high-dose groups would unequally increase average severity scores and decrease response rates compared to the lower dose (or placebo) groups. This methodological problem could be overcome by analysing only dose-tolerant subjects (those not dropping out due to side effects).

In the well performed study with sertraline by Licht et al. (not included in the three reviews), dose-escalation after 6 weeks was found to be less effective than continuation of the standard dose, or augmentation with mianserin (LoE: A2). After 8 weeks of treatment, increased dosages of fluoxetine were more effective than augmentation with lithium or desipramine, although in the latter study this was not significant (LoE: B). In these studies no placebo dose-escalation was performed. Both studies showed a non-significant trend of increased efficacy of dose-escalation compared to augmentation (lithium or desipramine) especially for partial responders (LoE: B).

Across all studies, higher doses were related to increased dropout rates, which were associated with more side effects in some studies (LoE: A2). It appeared that the occurrence of side effects did not increase equally when dosages were gradually escalated in initial non-responders compared to fixed-dose trials. However, this could not be compared straightforwardly between the studies, and was not investigated specifically.

**Additional concerns for clinicians**

We identified no evidence to recommend on how dose-increase should be practiced. Also the maximum dosage to be achieved was not investigated well.
Discussion

Our systematic review provided 8 studies about dose-escalation in SSRIs. Only one of these approached our rather stringent criteria. We found no evidence for increased efficacy of dose-escalation within the first 4 weeks. Dose-escalation after 6 weeks appeared less effective than continuing the same dose. We found some, but limited evidence for efficacy of dose-escalation after 8 weeks, particularly in partial responders. This effect was seen within 4 weeks after dose-escalation. Irrespective of efficacy, dose-escalation unequivocally increased side-effects, but effects on drop-out rates due to side effects were less straightforward. Thus, in the absence of methodologically well designed studies we can neither unequivocally state that dose-escalation is useful, nor discard it as useless.

These findings may challenge the current beliefs and recommendations about dose-escalation, underscored by the fact that dose-escalation is generally practiced. Contrarily to this challenge, many patients that only partially responded are too often treated with long-term obviously insufficient treatments (e.g. standard doses of SSRIs). For these patients, one could argue that it is better to try dose-escalation than to continue inadequate treatment. Presumably, in the absence of clear guidance by trial-data, clinicians do not have many alternatives for non-responders or partial responders, and clinicians all have their case-histories of improvement after dose-escalation. A more sophisticated question must therefore also be asked: which subgroup of patients will benefit from dose-escalation?

So far, only the NICE guideline displayed some reserve in the general recommendation about dose-escalation. The British Medicines and Healthcare products Regulatory Agency’s Committee on Safety of Medicines examined the available evidence for dose-escalation as provided by pharmaceutical companies, and recommended the lowest efficacious dose (MHRA, 2004 Internet: www.mhra.gov.uk). From this report it was unclear which studies were taken as evidence. Three previous reviews concerning higher doses of antidepressants were published, of which the methodological shortcomings were already mentioned. The findings in these reviews previously challenged the belief of a dose-response relationship, but Baker et al. proposed a potential dose-response relationship, based on their dose-tolerant analysis. All reports summarized studies performed until 1997, thereafter the study by Licht et al. further challenged the efficacy of dose-escalation.

Limitations of the identified studies

Four major issues of concern in the 8 identified studies should be mentioned. First, the methodological quality of these studies varied between poor and good according to our classification. We summarized these methodological problems in the results section and table 4.2.

Second, and more in general, all dose-escalation studies (except the studies of Fava and colleagues, that lacked a placebo-control) suffered a methodological problem of the timing of dose-escalation. Even the most robust study by Licht et al. hampered its own design by a nonrandomized dose-increase 2 weeks prior to randomization. This problem might explain the high placebo response rates in some of the dose-escalation studies (up to 75%).

Third, in most studies no data were provided on the selective drop-out, nor the schedule of dose-increments. Because patients randomised to true dose-escalation might drop out more frequently and earlier after randomisation (with associated high severity scores) compared to those receiving placebo, this might have biased the intention to treat analyses in which last-observations are usually carried forward to study endpoints. This especially happens when dose-escalation is performed rapidly. The analysis of a dose-tolerant sample in such studies would indeed provide additional information, but these data were not provided.

Fourth, in the selected trials, mostly response was used as primary outcome, while currently remission of depression is the clinical aim of treatment. If dose-escalation would be effective, the question remains whether dose-escalation will also further improve initial responders that were nonremitters. So far only Schweizer et al. addressed this topic with equivocal effects of dose-escalation.
Possible explanations for a dose-response relationship

A possible explanation of the clinical observation that response might occur after dose-escalation, can be initial lower blood levels. This may be related to increased metabolism due to genetic polymorphisms of the cytochrome P450 (CYP P450) enzyme system.\textsuperscript{55-58} The incidence of increased metabolism by (multi-)duplicated genes of the CYP P450 2D6 genes varies between 1-2\% in Swedish Caucasians, 3.6\% in Germany and 7-10\% in Spain and Sicily, and varies between ethnic groups (e.g. 29\% in Black Ethiopians).\textsuperscript{59} A few studies showed equivocal evidence for the involvement of CYP P450 polymorphisms (responsible for rapid metabolism) as an explanation of non-response to a standard dose of SSRIs.\textsuperscript{56;58-61} However, a clear relationship between blood levels of SSRIs and response was never found.\textsuperscript{26;62-66} Perhaps, genetic variability of the central target of these drugs, the serotonin reuptake transporter, may be responsible more directly for the effects of SSRIs.\textsuperscript{67;68}

From in vitro and ex-vivo studies it appears that at higher doses selective antidepressants like SSRIs may become dual action agents that will also affect other monoamine systems like norepinephrine.\textsuperscript{69-71} From the current data of dose-escalation in SSRIs this theoretical hypothesis cannot be falsified nor proven. In addition, we are unaware of an acceptable method to test whether specific sites of action are responsible for the observed treatment-effects.

Limitations of the review

No meta-analysis was performed because the differences in timing of dose-escalation between the identified studies introduced substantial heterogeneity. An extension of the meta-regression approach as performed by Baker et al.\textsuperscript{53} was considered impossible to acknowledge this problem as the number of studies to explore this heterogeneity will lack power, moreover as age, sex, outcome definition and type of SSRI ideally should also be included in such a model.

The grading system for studies is not representing the appraised methodological dimensions of evidence. This improved the applicability of the results for busy clinicians, but reduced their strength.

Finally, patients studied in trials are generally selected populations, reducing external validity for the ‘real world’ clinical practice. All identified studies excluded psychotic depression, bipolar depression, depression in children or adolescents, and depressive disorder with severe psychiatric and somatic comorbidity.

Future dose-escalation studies

For future dose-escalation trials methodological issues should be considered. First, for optimal contrast in the study, an appropriate group of non-responders should be selected by postponing randomization and refraining from (additional) interventions before dose-escalation is applied. Six weeks is the minimum which can be reconciled with recommendations in current guidelines and is acceptable for clinical practice. Second, studies should have enough power to detect significant differences. This implies a large sample to start with, as approximately 50\% of patients will show a response in the first 6 weeks. Third, the method of dose-escalation should be described and applied in a way that few patients drop-out. Fourth, adequate results should be presented: response and remission rates in intention to treat analyses and for the group that could be described as dose tolerant. Fifth, efficacy should be tested in predefined subgroups (e.g. partial responders at week 6). Sixth, genetic sampling (e.g. CYP P450 and SERT polymorphisms) and plasma SSRI level sampling would be interesting to further examine potential explanations for the clinically observed efficacy of dose-escalation and to identify potential prognostic variables.

Clinical implications and conclusion

For clinicians this review may challenge the belief in dose-escalation of SSRIs for patients who show insufficient response to a standard dose. This review points out that dose-escalation of SSRIs in a standard dose before the fourth week of treatment does not seem to be more
beneficial for patients. Thereafter dose-escalation is one of the easiest thing to do, but – to our opinion – should not be performed obligatory, as the evidence for this strategy is not compelling. Contrary dose-escalation appears more adequate to try than to continue an inadequate treatment, maybe partial responders will benefit most. Side-effects will most likely increase and might induce drop-out of treatment. For more clinical guidance well-performed new dose-escalation studies are needed. In order to fill this gap, for the introduction and registration of (new) antidepressants, clinical studies with an adequate dose-escalation design should be required by the U.S. Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products (EMEA).

Acknowledgements
This systematic review was realised by a grant for the development of a local evidence-based clinical practice guideline (No SFA.07.012) from the Academic Medical Center, Amsterdam, the Netherlands. This guideline considering strategies for non-response to a standard dose of a first SSRI is available on request.

Conflicts of interest
None

References

Chapter 4

Review of SSRI dose-escalation in MDD


