Dose escalation for insufficient response to standard-dose selective serotonin reuptake inhibitors in major depressive disorder

Systematic review

HENRICUS G. RUHÉ, JOCHANAN HUYSER, JAN A. SWINKELS and AART H. SCHENE

Background Although selective serotonin reuptake inhibitors (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.

Method 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 summarised in an evidence table. Pooling was not justified because of heterogeneity of the identified studies.

Results Eight true dose-escalation studies and three 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 randomised controlled trials; methodological difficulties in the studies may account for this lack of evidence.

Declaration of interest None.

So far many countries have developed national clinical guidelines for the treatment of major depressive disorder (Depression Guideline Panel, 1993a,b; Rush et al, 1998; Mulrow et al, 1999; American Psychiatric Association, 2000; Anderson et al, 2000; Kennedy et al, 2001; National Institute for Clinical Excellence, 2004). In these guidelines pharmacotherapy is among the most important treatments, and in many 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 patients who do not respond to the first antidepressant administered (Thase & Rush, 1995; Kroenke et al, 2001). Strategies in case of non-response have been published in several narrative reviews (Thase & Rush, 1997; Nelson, 1998; Crismon et al, 1999; Fava, 2000a,b; O’Reardon et al, 2000; Marangell, 2001; Trivedi & Kleiber, 2001; Hirschfeld et al, 2002; Kennedy et al, 2002; Anderson, 2003; Kennedy & McDonough, 2003; McIntyre et al, 2003; Nelson, 2003) and in one systematic review (Stimpson et al, 2002). Three major strategies for non-response are recommended: dose escalation, augmenting the antidepressant by adding a second drug, and switching to another antidepressant of the same or a different class.

Available dose-finding studies do not provide evidence for initiating pharmacotherapy for major depressive disorder with SSRIs in higher than standard doses (Altamura et al, 1988; Beasley et al, 1990; Dunner & Dunbar, 1992; Tignol et al, 1992; Montgomery et al, 1994). For non-responders, all guidelines recommend dose escalation as the appropriate strategy, instead of continuing an apparently inadequate regimen (Depression Guideline Panel, 1993a,b; Rush et al, 1998; Mulrow et al, 1999; American Psychiatric Association, 2000; Anderson et al, 2000; Kennedy et al, 2001). Only the National Institute for Clinical Excellence (NICE) guideline is less definite (National Institute for Clinical Excellence, 2004), advising that if ‘there are no significant side-effects, a gradual increase in dose should be considered’. Moreover, surprisingly little systematic evidence is provided to support these recommendations. Because of the above recommendations and because of its simplicity, dose escalation is widely practised and often the first strategy applied (Byrne & Rothschild, 1997; Shergill & Katona, 1997; Fredman et al, 2000; Mischoulon et al, 2000). The aim of our study was to systematically review the evidence for dose escalation of SSRIs in major depressive disorder.

METHOD

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 regimen. In this review we consider three other methodological requirements for such studies. First, dose escalation should be deferred to 3–6 weeks after initiation of treatment, because several weeks are required for antidepressants to have clinical effect (Mischoulon, 1997). The practice of dose escalation and the demonstration of a dose–response relationship is based on selection of ‘true’ non-responders (Baker & Woods, 2003). As this might take 6–10 weeks (Quikin et al, 2003), dose-escalation studies with early randomisation diminish the possibility of proving 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 because of dose escalation.

Identification and selection of articles

First, systematic literature searches (updated 10 February 2005) were performed in four databases (MEDLINE, EMBASE, CINAHL, PsycInfo; 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 randomised controlled trials and systematic reviews, the Cochrane Collaboration Depression Anxiety and Neurosis group search-filter for major depressive disorder and MeSH-terms and text words for SSRIs. Primary selection (independently by H.R. and J.H.) was based on design and focused on dose–response relationships for SSRIs, by screening title and abstract of the article. Agreement on exclusion of irrelevant articles was 99.1%, with Cohen’s kappa for interrater agreement 0.62 (which is a substantial agreement (Munoz & Bangdiwala, 1997)). Discrepancies between initial selection were resolved by discussion and consensus.

Second, all potentially relevant articles were judged according to specific inclusion and exclusion criteria (criteria available from H.R. 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 available information.

Critical appraisal and summary
Next, selected articles were critically appraised and abstracted by H.R., using standardised forms derived from the Dutch Institute of Healthcare Improvement (Kwaliteitsinstituut voor de Gezondheidszorg CBO, 2000) and the Agency for Healthcare Policy and Research (Mulrow et al, 1999). The items used for critical appraisal were the same as proposed by the Scottish Inter-collegiate Guideline Network (2001) and Sackett et al (2000). Each study was assigned a ‘level of evidence’ (Table 1). Levels of evidence were based on the methodological robustness of studies. For the results, the highest level of evidence of the supporting scientific evidence (A1–D) was used.

To assess judgement bias of the person who performed the critical appraisal, inter-rater variation was determined in a slightly different set of 12 publications. We all critically appraised four publications, and 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); complete agreement existed for randomisation of the study, level of evidence and data extraction (kappa=1.0). This is in line with other reports of interrater agreement in appraisal of psychiatric research (Moncrieff et al, 2001).

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 Fig. 1. The 11 studies selected for this review are summarised in Table 2. A table of excluded studies is available from H.R. on request.

Characteristics of the studies
Our searches identified eight dose-escalation studies that increased dosages after at least 3 weeks of standard dosage (Dornseif et al, 1989; Schweizer et al, 1990, 2001; Fava et al, 1992, 1994, 2002; Benkert et al, 1997; Licht & Qvitzau, 2002). We further found three systematic reviews about dose–response relationships, which included, respectively, three (Bollini et al, 1999), three (Corryble & Guelfi, 2000) and four (Baker et al, 2003) of the eight identified dose-escalation studies. Across the studies different outcome definitions for end-points were used. In seven articles, response was defined as a reduction of $\geq 50\%$ in the Hamilton Rating Scale for Depression (HRSD) score (Dornseif et al, 1989; Schweizer et al, 1990, 2001; Benkert et al, 1997; Licht & Qvitzau, 2002; Baker et al, 2003). A Clinical Global Impression (CGI) improvement or severity score $\leq 2$ was used for response in one study (Schweizer et al, 2001). Partial response was used in three studies and defined as 25–50% decrease in HRSD score (Fava et al, 1992, 1994, 2002). In seven studies, remission-rates were reported. These were defined as HRSD score $\leq 7$ (Fava et al, 1994, 2002; Licht & Qvitzau, 2002) or HRSD score $\leq 8$ (Schweizer et al, 2001).

Different criteria were applied to decide whether a patient should be randomised: non-response according to CGI (Benkert et al, 1997), $<50\%$ decrease in HRSD score.
<table>
<thead>
<tr>
<th>Study</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>B</td>
<td>544</td>
<td>RCT of week 3</td>
<td>PAR 40 mg</td>
<td>PAR 20 mg</td>
<td>Response (≥50%</td>
<td>Study includes MinD (42% of randomised patients). Dose titration resulted in 18–20% new side-effects. No specified rates of drop-out. Response rate in placebo group 75%. Study also investigates maprotiline dose escalation (data N/A)</td>
</tr>
<tr>
<td>Dornseif et al (1989)</td>
<td>B</td>
<td>572</td>
<td>RCT of week 3</td>
<td>FLX 60 mg</td>
<td>FLX 20 mg</td>
<td>Response (≥50%</td>
<td>Masking is unclear. More side-effects in FLX 60 mg (n.s.). Response rate in placebo group 40.5%</td>
</tr>
<tr>
<td>Fava et al (1994)</td>
<td>B</td>
<td>41</td>
<td>RCT of week 3</td>
<td>FLX 40–60 mg</td>
<td>FLX 20 mg+DES</td>
<td>Remission (HRSD&lt;7)</td>
<td>Limited presentation of study population. No placebo control. Limited power, particularly in subgroup analyses</td>
</tr>
<tr>
<td>Fava et al (2002)</td>
<td>B</td>
<td>101</td>
<td>RCT of week 3</td>
<td>FLX 40–60 mg</td>
<td>FLX 20 mg+DES</td>
<td>Remission (HRSD&lt;7)</td>
<td>No placebo control. Limited power, particularly in subgroup analyses</td>
</tr>
<tr>
<td>Licht &amp; Qvitzau (2002)</td>
<td>A2</td>
<td>1629</td>
<td>RCT of week 6</td>
<td>SER 200 mg</td>
<td>SER 100 mg + PLAC</td>
<td>Response (≥50%</td>
<td>Dosage SER was increased from 50 mg to 100 mg 2 weeks before randomisation. Response rate in placebo-group 70.4%</td>
</tr>
<tr>
<td>Schweizer et al (1990)</td>
<td>B</td>
<td>108</td>
<td>RCT of week 3</td>
<td>FLX 60 mg</td>
<td>FLX 20 mg</td>
<td>Response (≥50%</td>
<td>Generalisation to other SSRIs might be difficult because of long half-life of FLX and its metabolite. Response rate in placebo group 51.2%</td>
</tr>
<tr>
<td>Study</td>
<td>LSE</td>
<td>n</td>
<td>Design</td>
<td>Intervention</td>
<td>Comparison</td>
<td>Outcome</td>
<td>Remarks</td>
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<tr>
<td>Boller et al. (1999)</td>
<td>A2</td>
<td>A2</td>
<td>SMR (MDD, Outp)</td>
<td>Medium-high dose and dose-escalation (3-5 weeks)</td>
<td>SMR (MDD, Outp)</td>
<td>Change in HRSD across dose-range: MDD = 9.3% (NS), ITT = 9.5% (NS)</td>
<td>Qualitative description of dose-response relationship per drug. Only for CIT and FLX.</td>
</tr>
<tr>
<td>Boller et al. (2000)</td>
<td>A2</td>
<td>A2</td>
<td>SMR (MDD, Outp)</td>
<td>High-dose SSRI (5 mg) for FLX used as reference for SME. ITT population used to estimate expressed dose-response relationship.</td>
<td>SMR (MDD, Outp)</td>
<td></td>
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</tbody>
</table>

**Table 2 (Continued)**

**Systematic reviews and meta-analyses**

Boller et al. (2000)

- Meta-analysis of 41 fixed-dose-controlled trials.
- Meta-analysis of 23 RCTs investigating MDD, Outp.
- Average daily dose across dose-range: CIT = 201-250 mg, FLX = 100-200 mg, IMI = 100-200 mg.

**Outcome**

- Change in HRSD across dose-range: MDD = 9.3% (NS), ITT = 9.5% (NS).
- Qualitative description of dose-response relationship per drug. Only for CIT and FLX.

**Remarks**

- Search of MEDLINE only. No appraisal of non-systematic bias particularly for SSRIs by conversion to IMI-equivalents.
- No pooling or exploration of differences between identified studies and dose-response relationship data per drug.
score (Dornseif et al, 1989; Schweizer et al, 1990; Fava et al, 1994, 2002) or no re-
mission (HRSD score ≤ 8 (Schweizer et al, 2001)). In the present studies no genetic
information of the cytochrome P450 (CYP) system nor drug blood levels were
reported.

The three previous reviews all had some methodological problems: Bollini et al (1999) pooled studies with completely
different designs and drug classes, and applied a dose equivalence strategy that
put differential doses of SSRIs together. Baker et al (2003) also pooled hetero-
geneous studies with different moments of
dose escalation, and used an unusually
low reference dose of fluoxetine (5 mg).
Carruba & Guelfi (2000) did not use an
adequate search strategy and only described
the dose–response relationships found in
their identified studies as flat, curvilinear
or linear.

We will briefly outline the dose-
investigated week-3 non-responders (n=371 out-patients) to fluoxetine, who
were randomised 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%, respectively. Drop-out rates
because of side-effects were significantly
different at 5.3% and 11.6%, respectively.
Schweizer et al (1990) investigated 77
non-responsive out-patients after 3 weeks’
administration of fluoxetine (20 mg/day),
with a randomisation to placebo increase
or dose escalation up to 60 mg/day for
weeks. Response rates were 51.2% and
50%, respectively, with non-significant
drop-out rates of 4.9% vs. 16.7%. In a simi-
lar study, Schweizer et al (2001) studied
dose escalation of sertraline in out-patient
non-remitters 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
because of side-effects were not reported.

Fava et al (1992) first openly treated
15 out-patients (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 17-item HRSD
score decreased 6.2 points in week-8 non-responders and 10.1 points in partial
responders. In a second study, Fava et al
(1994) randomised 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. No
placebo increase was practised. Remission
rates were 53%, 25% and 29%, respec-
tively, but these differences were non-
significant. Initial partial responders
appeared to benefit most from fluoxetine
dose increases (data non-significant).
Drop-out rates for side-effects were 0%,
17% and 7%, respectively. In a third study,
Fava et al (2002) repeated the three-arm
randomised 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 in-
creased but non-significant remission rates
(42.4%) compared with desipramine addi-
tion (29.4%) and lithium addition
(23.5%). Again initial partial responders
appeared to benefit more from fluoxetine
dose increases compared with initial non-
responders (differences non-significant).
No specific data on drop-out because of
side-effects were given.

Benkert et al (1997) investigated dose
escalation of paroxetine (20 mg/day) in
out-patients who were depressed or had
minor depression. Those who did not re-
spond after 3 weeks of treatment (n=86)
were randomised to receive 40 mg parox-
tine for 3 additional weeks or placebo
increase. Response rates were 75% in the
placebo increased group and 74% in the
40 mg group. Licht & Qvitza (2002)
investigated randomised dose escalation
of sertraline (up to 200 mg/day) v.
sertaline 100 mg/day (placebo increase)
or mianserin addition in 295 out-
patients non-responsive to sertraline
50 mg for 4 weeks and additionally in-
creased to 100 mg for 2 more weeks.
Response rates 5 weeks after randomis-
ation were significantly lower in the
dose-increase group (56%) than in the
sertraline 100 mg group (70%) and the
mianserin addition group (67%). Data on drop-out because of side-effects
were not specified.

Strengths, flaws and other details of all
selected studies are shown in Table 2. In
summary, we mention several methodo-
logical problems we encountered: absence
of placebo controls (Fava et al, 1992,
1994, 2002), inclusion of minor depression
(Benkert et al, 1997), insufficient data
presentation (Schweizer et al, 1990; Fava
et al, 1994), insufficient power (Schweizer
et al, 1990, 2001; Fava et al, 1992, 1994,
2002; Benkert et al, 1997), uncertainty
about masking (Dornseif et al, 1989;
Schweizer et al, 2001), earlier dose escal-
ation before the randomisation (Licht &
Qvitza, 2002), inadequate pooling of
heterogeneous data and problems with con-
version to dose equivalents (Bollini et al,
1999; Baker et al, 2003). None of the
studies provided information about the
method of dose escalation or described
the early drop-out rates because of dose
escalation.

Evidence for dose escalation?
From four of the eight dose-escalation stu-
dies it appeared that dose increments before
4 weeks were not effective (level of evi-
dence: A2) (Dornseif et al, 1989; Schweizer
et al, 1990, 2001; Benkert et al, 1997;
Bollini et al, 1999; Carruba & Guelfi,
2000; Baker et al, 2003). 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 participants who dropped out because
of side-effects were excluded from the
analysis (a so-called dose-tolerant sample)
proposed that differential drop-out
because of side-effects in the dose-
escalation group (compared with placebo
increase) conferred a substantial (negative)
bias to the potential dose–response re-
lationship. They argued that by applying a
last-observation-carried-forward approach
(frequent used in the original studies), more
participants dropping out early (because
of side-effects) in the high-dose groups
would unequally increase average severity
scores and decrease response rates compared
with the lower-dose (or placebo) groups.
This methodological problem could be
overcome by analysing only dose-tolerant
participants (those not dropping out because
of side-effects).

In the well-performed study with ser-
traline by Licht & Qvitza (2002) (not
included in the three reviews), dose escal-
after 6 weeks was found to be less
effective than continuation of the standard
dose, or augmentation with mianserin (level
of evidence: A2). After 8 weeks of treat-
ment, increased dosages of fluoxetine were
more effective than augmentation with
lithium or desipramine (Fava et al, 1994,
2002), although in the later study this
was not significant (level of evidence: B).
In these studies no placebo dose escalation
was performed. Both studies showed a
non-significant trend of increased efficacy

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of dose escalation compared with augmentation (lithium or desipramine), particularly for partial responders (level of evidence: B).

Across all studies, higher doses were related to increased drop-out rates, which were associated with more side-effects in some studies (level of evidence: A2) (Bollini et al., 1999). It appeared that the occurrence of side-effects did not increase equally when dosages were gradually escalated for initial non-responders, compared with 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 how dose increase should be practised. Also, the maximum dosage to be achieved was not investigated well.

**DISCUSSION**

Our systematic review provided eight studies about dose escalation of SSRIs. Only one of these studies approached our rather stringent criteria (Licht & Qvitzau, 2002). We found no evidence of increased efficacy by 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 because of 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 as it is generally practised (Byrne & Rothschild, 1997; Shergill & Katona, 1997; Fredman et al., 2000; Mischoulon et al., 2000). Contrary to this challenge, many patients who have 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 from 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; i.e. 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 (National Institute for Clinical Excellence, 2004). 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 (Weller et al., 2004). From this report it was unclear which studies were taken as evidence. Three previous reviews concerning higher doses of antidepressants were published (Bollini et al., 1999; Corruble & Guelfi, 2000; Baker et al., 2003), the methodological shortcomings of which have already been 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, according to their dose-tolerance analysis. All reports summarised studies performed until 1997; thereafter, the study by Licht & Qvitzau (2002) further challenged the efficacy of dose escalation.

**Possible explanations for a dose–response relationship**

A possible explanation of the clinical observation that response might occur after dose escalation is initial lower levels of the drug in the bloodstream. This may be related to increased metabolism because of genetic polymorphisms of the CYP enzyme system (Bertilsson et al., 1985; Steimer et al., 2001; Charlier et al., 2003; Brooks, 2004). The incidence of increased metabolism by (multi-)idiplicated genes of CYP 2D6 varies between 1–2% in White populations in Sweden, 3.6% in Germany and 7–10% in Spain and Sicily, and also varies between ethnic groups (e.g. 29% in Black Ethiopians) (Bertilsson et al., 2002). A few studies showed equivocal evidence for the involvement of CYP polymorphisms (responsible for rapid metabolism) as an explanation of non-response to a standard dose of SSRIs (Bertilsson et al., 1997, 2002; Steimer et al., 2001; Brooks, 2004; Kawanishi et al., 2004). However, a clear relationship between blood levels of SSRIs and response was never found (Beasley et al., 1990; Norman et al., 1993; Baumann, 1996; Amsterdam et al., 1997; Bourdeaux et al., 1998; DeVane, 1998). Perhaps genetic variability of the central target of these drugs, the serotonin reuptake transporter, may be responsible more directly for the effects of SSRIs (Hahn & Blakely, 2002; Smits et al., 2004).
From in-vitro and ex-vivo studies it appears that, at higher doses, selective antidepressants such as SSRIs may become dual-action agents that, like noradrenaline, also affect other monoamine systems (Owens et al., 1997; Gorman & Sullivan, 2000; Gilmore et al., 2002). From the current data on dose escalation in SSRIs, this theoretical hypothesis can neither 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. (2003) was considered inappropriate for addressing this problem, as the number of studies gave insufficient power; moreover, gender, age, outcome definition and type of SSRI ideally should be included in such a model.

The grading system for studies does not represent 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 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 randomisation and refraining from (additional) interventions before dose escalation is applied. The minimum period that can be reconciled with recommendations in current guidelines and that is acceptable for clinical practice is 6 weeks. 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 such 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 and SERT polymorphisms) and plasma SSRI-level sampling would be interesting in the further examination of potential explanations for the clinically observed efficacy of dose escalation, and to identify potential prognostic variables.

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Development of a quality assessment instrument of Kappa and B statistics measures of agreement.

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