Dose Increase Versus Unchanged Continuation of Antidepressants After Initial Antidepressant Treatment Failure in Patients With Major Depressive Disorder:

A Systematic Review and Meta-Analysis of Randomized, Double-Blind Trials

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ABSTRACT

Objective: To evaluate the efficacy and tolerability of dose increase compared to dose continuation of the initially prescribed antidepressant in antidepressant treatment failure (ATF).

Data Sources: We searched CENTRAL, PubMed, Embase, and PsycINFO using generic terms for depression, dose increase, and randomized controlled trials (RCTs), without date or language restrictions.

Study Selection: Of 1,780 studies screened, 9 studies reporting on 1,273 patients were included for meta-analysis (PROSPERO Registration: CRD42017058389). Studies met the following predetermined inclusion criteria: randomized controlled trial, patients diagnosed with unipolar depression according to a standardized diagnostic instrument, ATF after a standard antidepressant trial (duration of ≥ 3 weeks at a standard dose), dose increase regimen, and control group of dose continuation.

Data Extraction: Two authors extracted data independently according to the Cochrane Handbook for Systematic Reviews. Analyses are based on random effects models.

Results: All studies reported on selective serotonin reuptake inhibitors (SSRIs); 1 study also reported on maprotiline. Meta-analyses resulted in a statistically nonsignificant summary effect size of 0.053 standardized mean difference (95% CI, −0.143 to 0.248) in favor of antidepressant dose increase. Subgroup and sensitivity analyses and secondary outcome analyses resulted in similar effect estimates and supported the robustness of the results.

Conclusions: With clinically and statistically nonsignificant effect estimates, there is evidence from RCTs against increasing the dose of SSRIs (with the possible exception of citalopram) in adult patients with major depression and ATF. Dose increase with other antidepressants (eg, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, monoamine oxidase inhibitors) and in other patient groups (minor depression, children and adolescents) or after long periods of first-line antidepressant therapy (ie, 8 weeks) have not been or not been sufficiently studied and, at this time, cannot be recommended in clinical practice.

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Failure after standard antidepressant treatment (antidepressant treatment failure [ATF]) remains relatively common in clinical practice. For example, rates of nonresponse have repeatedly been shown to reach 30% to 40%.[1–4] As a result, clinicians need evidence-based recommendations for treatment alternatives once a standard trial with an antidepressant has failed.[5,6] Current guidelines recommend different treatment options, such as antidepressant switch, augmentation with a second-generation antipsychotic or lithium, combination of antidepressants, and dose increase of the initially prescribed antidepressant.[7–13] In recent surveys, increasing the dose has been shown to be among the most popular strategies in ATF in everyday clinical routine: results varied, but with 11%,[14] 27%,[15] and 45%[16] preference among surveyed clinicians, dose increase is clearly a prevalent strategy.[17]

So far, however, results of randomized controlled trials of dose increase strategies in patients with ATF varied considerably or were inconclusive. For example, Licht and Qvitzau[18] found higher response rates in nonresponders when 100 mg sertraline per day was continued, relative to increasing the dose to 200 mg. On the other hand, Schweizer et al published statistically nonsignificant findings but recommended dose increase because their results trended toward dose increase.[19] In addition, some randomized controlled trials (RCTs) yielded inconclusive results because they were underpowered.[20–22] To our knowledge, the latest systematic literature review on the topic dates from 2006,[23] and, so far, no meta-analysis on the topic has been published.

Consequently, we carried out a systematic literature review and meta-analysis on dose increase of antidepressants as a treatment strategy for ATF.

Clinical Points

- Dose increase after antidepressant treatment failure has been examined in only a few randomized controlled trials, which have largely examined SSRI treatment in adults.
- Currently, dose increase cannot be recommended after antidepressant treatment failure. Other strategies such as antidepressant combination or augmentation with lithium or antipsychotics are preferable.
- More research is needed, particularly on antidepressants other than SSRIs and on longer prerandomization treatment periods.

METHODS

This is a systematic literature review and meta-analysis registered on PROSPERO (PROSPERO record registration no: CRD42017058389).

Literature Search and Data Extraction

We followed the methods described in the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0.[24] In our systematic search, we used generic terms for unipolar depression, dose increase, and randomized controlled trials (for details of the search algorithm, please refer to Supplementary Material), with no language and date restrictions applied and without excluding gray literature. We searched the CENTRAL database, and in order to avoid missing studies due to incomplete coverage in CENTRAL, we completed our results with systematic searches in PubMed, Embase, and PsycINFO for studies published after December 31, 2011 (last search update: February 20, 2017). We also hand-searched the references of 17 review articles on the topic of second-line treatment strategies and all references of studies selected for our analysis. Further, based on Web of Knowledge data, we screened all papers that cited the studies selected (forward search).

Titles and abstracts of all search results have been screened by 2 authors independently (L.R., C. Braun). All potentially eligible studies have been evaluated as full text. Disagreements were resolved by discussion among the authors (L.R., C. Braun, C. Baethge).

Inclusion criteria. Articles were included if they met all of the following criteria: (1) RCT with randomization of patients with ATF to either a dose increase regimen or unchanged continuation, (2) patients diagnosed with unipolar depression, and (3) standardized diagnosis of ATF. The term *ATF* refers to failure in a standardized antidepressant treatment trial.

As a consequence, we excluded studies investigating second-step strategies after antidepressant treatments below standard doses or lasting less than 3 weeks. ATF invariably covers nonremission of a depressive episode, but some authors defined ATF as nonresponse (eg, < 50% reduction in Hamilton Depression Rating Scale). We adopted authors' definition of ATF. Studies comparing different doses from the start of pharmacologic treatment were also excluded.

Exclusion criterion. Articles were excluded if they included interventions based on herbal medicine, nutritional supplements, or any non-antidepressant agent.

Data extraction. Data extraction and study ratings were carried out independently by 2 authors (L.R., C. Braun) using a standardized form (Excel, Microsoft; Redmond, Washington). In case of missing data, we contacted trial authors. For one study, unpublished as a journal article,[22] we decided to include data from the poster and not from the published abstract. We applied the Cochrane Collaboration Handbook tool for assessing risk of bias to rate all studies selected, and trials were rated according to the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Studies were defined to have a low risk of bias if they received a rating of "low" risk of bias in at least 5 of the 6 domains of the Cochrane risk of bias tool (Supplementary eTable 1).

Data Analysis

Primary outcome. The primary outcome was efficacy of dose increase compared with continuation of initially prescribed dose of antidepressants, expressed as standardized mean difference (SMD). We adopted efficacy assessments applied by trial authors, such as difference in depression rating scores or difference in change scores at endpoint. Continuous measurements were preferred, but we converted response and remission rates into SMDs if no other data were available (response preferred over remission if both were available). To convert dichotomous measures into SMDs, we calculated odds ratio (OR) using a 2-by-2 frequency table. The OR was then inserted into the following formula:

$$\mathrm{SMD} = \frac{\sqrt{3}}{\pi} \ln OR.$$ [24]

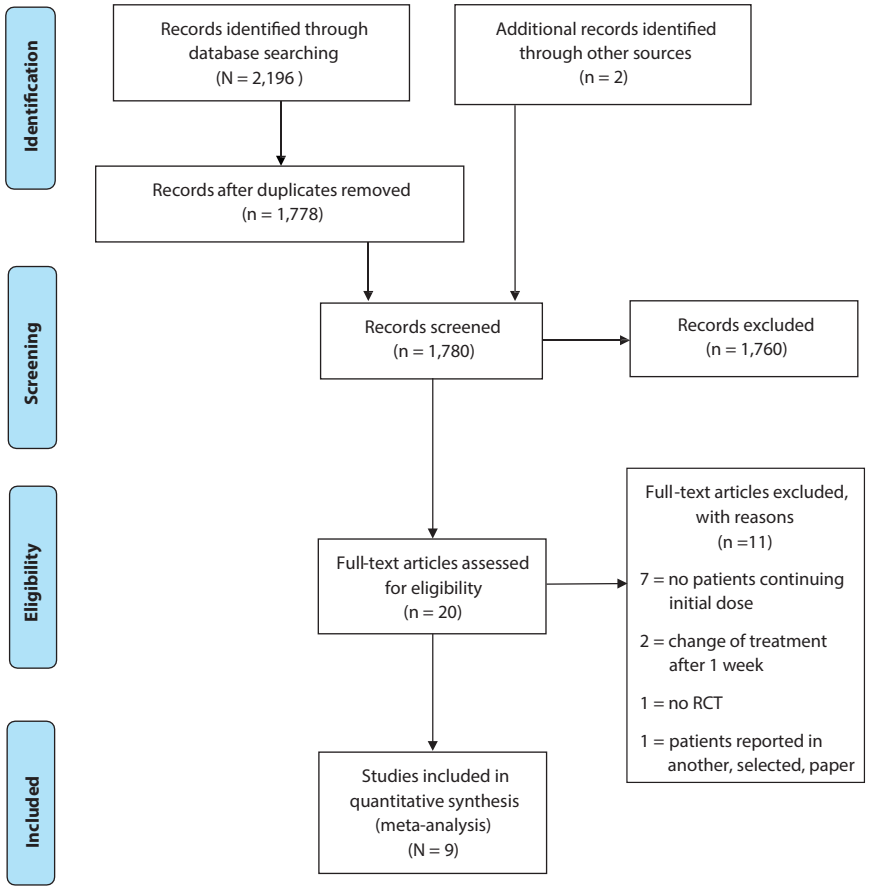
If available, we used intention-to-treat data and adopted study authors' method to account for missing data (eg, last observation carried forward).

Secondary outcomes. Secondary outcomes were predefined as follows: Response and remission rates (as defined by trial authors) using ORs, and tolerability expressed as dropout rates due to adverse events and dropout rates due to any reason (ORs).

Subgroup and sensitivity analyses. In subgroup analyses, we restricted calculations of the primary outcome to studies of (1) selective serotonin reuptake inhibitor (SSRI) only, (2) studies including adult patients only, (3) studies including only patients with major depressive disorder, and (4) studies of SSRI *and* adults *and* major depression. We also calculated SMD for studies with low risk of bias separately. To avoid undue reliance on single studies, we ran a sensitivity analysis with each study left out one at a time.

Publication bias analysis. Since power was too low for the Egger test, we inspected funnel plots of all analyses for indications of publication bias. We carried out trim-and-fill analyses (Duval and Tweedie's) for all prespecified

Figure 1. PRISMA Flowchart



meta-analyses. Orwin's fail-safe N was calculated based on the assumptions of an effect size of 0.5 SMD in missing studies and a summary effect estimate of 0.3 SMD in favor of dose increase regimens.

Post hoc analysis. A post hoc analysis focused on different definitions of ATF (nonresponse vs nonremission).

Data Synthesis

We calculated SMDs with 95% CI and ORs with 95% CI using Comprehensive Meta-Analysis Versions 2 and 3 (Biostat; Englewood, New Jersey) and Practical Meta-Analysis Effect Size Calculator by David B. Wilson (George Mason University).[25] We applied random effects models in all analyses to account for sample and design differences inherent to the group of studies under investigation. Heterogeneity among studies is expressed as I^2. If data were available in graphs only, we used Plot Digitizer, version 2.6.8 (SourceForge Project; sourceforge.net), for data extraction. Power was calculated using G*Power 3.1 (http://www.gpower.hhu.de/en.html).

PICO Statement

We investigated in a systematic literature review and meta-analysis of randomized trials (design) whether antidepressant dose increase (intervention) is more effective, as measured in standardized mean difference (outcome), than unchanged continuation of an antidepressant (comparison) in patients with depression and antidepressant treatment failure (participants).

RESULTS

The literature search retrieved 2,196 articles, reduced to 1,780 articles after removing duplicates. Of 20 articles inspected at full-text level, 9 studies[18–22,26–29] met our predefined inclusion criteria (Figure 1). The studies selected included 1,273 patients (635 women), 628 of whom received dose increase after ATF (Table 1). All trials included were double-blind.

Efficacy and Tolerability

Primary outcome. All studies provided intent-to-treat data for primary outcome calculations. We calculated a statistically nonsignificant SMD of 0.053 (95% CI, −0.143 to 0.248) in favor of dose increase (Table 2, Figure 2A). After studies were removed one by one, SMD varied between −0.002 (−0.185 to 0.182) (excluding Kim et al[22]) and 0.106 (−0.082 to 0.294) (excluding Licht and Quitzau[18]).

Table 1. Characteristics of Double-Blind, Randomized Controlled Trials of Dose Increase Versus Unchanged Continuation in Patients With Antidepressant Treatment Failure (ATF)

Study (Publication Year)	Diagnosis	Double-Blind?	Age Range (y)	Women, %	Definition of ATF	Antidepressant (Dose per Day)	N Dose Increase/ Continuation	Sample Size Sufficient?[a]	Duration of Initial Phase/ Second Phase, wk
Benkert et al[26] (1997)	Min D or MD (modified RDC)	Yes	18–71	72[b]	According to CGI efficacy index	Paroxetine (20 mg, 40 mg) Maprotiline (100 mg, 150 mg)	90/84	Yes	3/3
Dornseif et al[29] (1989)	MD (*DSM-III*)	Yes	19–89	55[c]	<50% Reduction in HDRS-21	Paroxetine (20 mg, 60 mg)	180/189[d]	Yes	3/5
Heiligenstein et al[20] (2006)	MD (*DSM-IV*)	Yes	9–17	38[e]	<30% Decrease in CDRS-R	Fluoxetine (20 mg, 40–60 mg)	14/14	No	9/10
Kim et al[22] (2016)	MD (*DSM-IV-TR*)	Yes	18–65	76	MADRS > 10	Escitalopram (20 mg, 30 mg)	25/25	No	4/6
Kornstein et al[28] (2008)	MD (*DSM-IV-TR*)	Yes	19–83	61	HDRS-17 > 7	Duloxetine (60 mg, 120 mg)	118/130	Yes	6/8
Licht and Qvitzau[18] (2002)	MD (*DSM-IV*)	Yes	19–65	61	<50% Reduction in HDRS-17	Sertraline (100 mg, 200 mg)	97/98	Yes	(4 + 2)[f]/5
Ruhé et al[21] (2009)	MD (*DSM-IV*)	Yes	18–70	67[g]	<50% Reduction in HDRS-17	Paroxetine (20 mg, 30–50 mg)	30/27	No	6/6
Schweizer et al[27] (1990)	MD (*DSM-III*)	Yes	Mean (SD): 45 (13)	56	<50% Reduction in HDRS-17	Fluoxetine (20 mg, 60 mg)	36/41	No	3/5
Schweizer et al[19] (2001)	MD (*DSM-IV*)	Yes	18–65	55	HDRS-17 > 8	Sertraline (50 mg, 150 mg)	38/37	No	3/5

[a]Sample large enough to detect a medium-sized effect (Cohen *d* 0.5) with a power of 80%: 64 participants in each treatment group (2-tailed *t* test, α level: 5%).
[b]All patients included (responders and nonresponders).
[c]All patients eligible for randomization (N = 371).
[d]Response and remission rate were calculated on the basis of patients completing at least 3 weeks of the second phase.
[e]All patients eligible for randomization (N = 29).
[f]Prior to randomization, patients received 50 mg of sertraline for 4 weeks and 100 mg for 2 weeks.
[g]All patients eligible for randomization (N = 60).
Abbreviations: CDRS-R = Children's Depression Rating Scale-Revised, CGI = Clinical Global Impression, DSM = *Diagnostic and Statistical Manual of Mental Disorders*, HDRS = Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, MD = major depression, Min D = minor depression, RDC = Research Diagnostic Criteria.

In a subgroup analysis restricted to adult patients with major depression treated with SSRIs, including 1,121 patients from 8 studies, after exclusion of Heiligenstein et al[20] as well as the maprotiline and minor depression subgroups from Benkert et al,[26] we found a nonsignificant SMD of 0.079 (−0.118 to 0.276) (Figure 2B). In studies with a low risk of bias (Kornstein et al,[28] Licht and Qvitzau,[18] Ruhé et al[21]), the SMD summary estimate was −0.148 (−0.369 to 0.074) (Table 2).

Secondary outcomes. Secondary outcome analyses, namely, response and remission, confirmed the results of the primary outcome analysis, with statistically nonsignificant odds ratios of 1.124 (0.778 to 1.625) for response (all 9 studies included, Table 2) and 1.01 (0.694 to 1.469) for remission (6 studies included[18,19,21,22,28,29]). There were no statistically significant findings regarding dropouts due to any reason or due to adverse events: Slightly fewer patients dropped out of the dose increase arms (OR = 0.964 [0.584 to 1.590], Table 2), but, numerically, there were more dropouts due to adverse events in dose increase arms than in continuation groups (OR = 1.244 [0.450 to 3.441]), with 5 studies providing data on dropouts due to adverse events.[20,21,27–29]

Throughout analyses, I^2 values ranged between around 50% and 75% but were consistently lower in subgroup analyses (Table 2).

Publication Bias

Trim-and-fill analyses. A funnel plot of all 9 studies included in the primary outcome analysis indicated the possibility of publication bias, and a trim-and-fill analysis with 1 study filled to the left of the mean resulted in a reduced effect size (SMD = 0.004 [−0.201 to 0.209]). Trim-and-fill analyses of secondary outcomes, if indicated, yielded similar results (Table 3).

Fail-safe N. In the primary outcome analysis, to achieve a SMD of 0.3, one would need 13 additional studies with an effect size of 0.5 SMD. Calculations of Orwin's fail-safe N for secondary outcomes resulted in similar findings (Table 3).

Post Hoc Analysis

Summary effects of studies employing nonresponse definitions of ATF[18,20,21,27,29] were similar to those of studies that used nonremission definitions[19,22,26,28]: SMD = 0.018 (−0.277 to 0.314) versus 0.107 (−0.209 to 0.423), respectively (P = .69).

DISCUSSION

This systematic literature review and meta-analysis yielded 2 main results, as follows. (1) There is no clinically or statistically significant effect of SSRI dose increase after

Table 2. Meta-Analyses of Double-Blind, Randomized Controlled Trials of Dose Increase Versus Unchanged Continuation in Patients With Antidepressant Treatment Failure

Analysis	SMD	Response	Dropouts Due to Any Reason
All studies	SMD = 0.053 [95% CI, −0.143 to 0.248] *P* = .598 I^2: 60.2% (9 studies; n = 1,273)	OR = 1.124 [95% CI, 0.778 to 1.625] *P* = .532 I^2: 50.5% (9 studies; n = 1,197)	OR = 0.964 [95% CI, 0.584 to 1.590] *P* = .885 I^2: 45.2% (7 studies; n = 1,036)
Major depression, SSRI, adults	SMD = 0.079 [95% CI, −0.118 to 0.276] *P* = .432 I^2: 53.1% (8 studies; n = 1,121)	OR = 1.110 [95% CI, 0.753 to 1.636] *P* = .599 I^2: 49.3% (8 studies; n = 1,048)	OR = 0.909 [95% CI, 0.519 to 1.592] *P* = .598 I^2: 53.9% (6 studies; n = 1,008)
SSRI	SMD = 0.083 [95% CI, −0.103 to 0.270] *P* = .381 I^2: 52.3% (9 studies; n = 1,185)	OR = 1.132 [95% CI, 0.770 to 1.665] *P* = .528 I^2: 50.6% (9 studies; n = 1,110)	OR = 0.964 [95% CI, 0.584 to 1.590] *P* = .885 I^2: 45.2% (7 studies; n = 1,036)
Major depression	SMD = 0.098 [95% CI, −0.089 to 0.285] *P* = .305 I^2: 52.1% (9 studies; n = 1,208)	OR = 1.167 [95% CI, 0.798 to 1.705] *P* = .426 I^2: 51.3% (9 studies; n = 1,133)	OR = 0.964 [95% CI, 0.584 to 1.590] *P* = .885 I^2: 45.2% (7 studies; n = 1,036)
Adults	SMD = 0.018 [95% CI, −0.176 to 0.211] *P* = .859 I^2: 59.6% (8 studies; n = 1,245)	OR = 1.042 [95% CI, 0.736 to 1.475] *P* = .816 I^2: 45.3% (8 studies; n = 1,169)	OR = 0.909 [95% CI, 0.519 to 1.592] *P* = .738 I^2: 53.9% (6 studies; n = 1,008)
Low risk of bias	SMD = −0.148 [95% CI, −0.369 to 0.074] *P* = .191 I^2: 24.8% (3 studies; n = 500)	OR = 0.711 [95% CI, 0.495 to 1.021] *P* = .065 I^2: 0% (3 studies; n = 500)	OR = 1.008 [95% CI, 0.366 to 2.772] *P* = .988 I^2: 67.7% (3 studies; n = 512)

Abbreviations: SMD = standardized mean difference, SSRI = selective serotonin reuptake inhibitor.

failure in antidepressant pharmacotherapy. (2) Studies on dose increase of antidepressants other than SSRIs (and of citalopram) are needed.

Despite its frequent use in clinical practice, we found no sufficient evidence for the efficacy of antidepressant dose increase after failure of an antidepressant treatment in patients with major depressive disorder. With a standardized mean difference of 0.053, the clinical effect of dose increase is negligible. While heterogeneity of our main analysis was considerable, subgroup and sensitivity analyses strongly supported our main finding: SMDs varied between −0.15 and +0.1 in subgroup analyses, and effects on response and remission were always close to an OR of 1 and never became statistically or clinically significant. As expected, heterogeneity was smaller in subgroup analyses and centered around 50%. Of note, in studies with a low risk of bias, the summary effect of dose increase was negative and the lower confidence interval (−0.37) indicated the possibility of a weak detrimental effect of dose increase in SSRIs. Moreover, our leave-one-out analysis indicated that no study dominated the calculation (SMDs between 0.0 and 0.1). Consideration of possible publication bias resulted in even smaller SMDs. Calculation of fail-safe Ns resulted in numbers of studies that were invariably larger than the number included in this meta-analysis, rendering it unlikely that the effect we saw will be offset by unpublished or overlooked studies. Further, upper confidence limits never crossed 0.3 standardized mean differences—a moderate and common effect size in antidepressant pharmacotherapy,[30–32] even in second-step pharmacotherapy.[33,34] Finally, the results do not depend on the definition of ATF because analyses based on studies using nonremission as criterion or nonresponse yielded similar results.

At the study level, 2 investigations showed significant effects: Kim et al[22] observed that raising the dose of citalopram from 20 mg/d to 30 mg/d led to a sizable improvement in Montgomery-Asberg Depression Rating Scale scores (SMD = 0.66 [0.1 to 1.2]). So far, however, this study has been published only as a poster. It is also a small study (N = 50), and its primary outcome (remission) did not reach statistical significance. In contrast, in Licht and Qvitzau's well-powered trial,[18] doubling the dose of sertraline led to worse outcomes in comparison to dose continuation (SMD = −0.35 [−0.68; −0.03]). While a recent meta-analysis[35] could not support a dose-dependent efficacy of sertraline in general, the results of this trial in nonresponders cannot easily be discounted because it is large (N = 195) and methodologically sound. As a result, it is among the few studies in this field with low risk of bias, even though the time to achieve response after dose increase was very short (2 weeks).

One possible explanation for the lack of efficacy of dose increase in the studies included in this meta-analysis is that increasing the doses of SSRIs has not led to increased serotonin transporter occupancy[36]: In the only study investigating this hypothesis, Ruhé et al[21] found that SERT occupancy was not higher after increasing paroxetine dose from 20 mg to 40 mg.

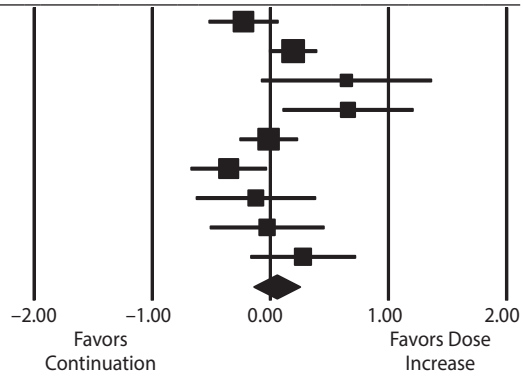
Dose escalation and continuation arms only slightly, and not statistically significantly, differed in regard to treatment discontinuation due to side effects. Since several adverse effects have been reported to be dose dependent, for example, hypertension,[37] QT prolongation,[38] sexual dysfunction,[39] fracture risk,[40] or liver injury,[40] the statistical power of the combined studies in this meta-analysis may have been too low. Alternatively, side effects did not occur more often or occurred but were tolerated in this group of severely affected patients. Notably, high doses of SSRIs have recently been linked to the risk of withdrawal symptoms once doses are decreased or discontinued.[41]

Taken together, the summary estimates for increasing the dose in antidepressant pharmacotherapy after an initial trial have failed to indicate negligible effects. From the confidence intervals, however, we cannot rule out a weak positive or a very weak negative effect of dose increase.

Figure 2. Dose Increase Versus Unchanged Continuation of Antidepressant Pharmacotherapy After Initial Treatment Failure

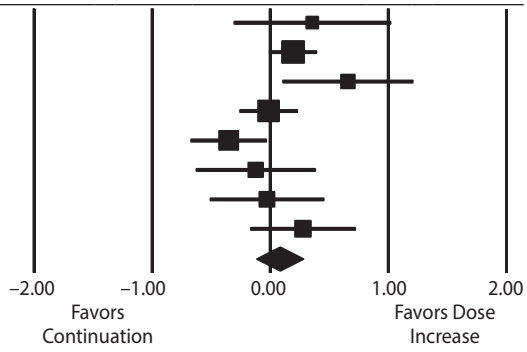
A. All studies

Study	SMD	Statistics for Each Study: Standard Error	Lower Limit	Upper Limit	*P* Value	Sample Size: Dose Increase	Continuation
Benkert et al 1997[26]	−0.227	0.151	−0.523	0.069	0.133	90	84
Dornseif et al 1989[29]	0.193	0.104	−0.011	0.397	0.063	180	189
Heiligenstein et al 2006[20]	0.645	0.370	−0.079	1.369	0.081	14	14
Kim et al 2016[22]	0.658	0.283	0.104	1.213	0.020	25	25
Kornstein et al 2008[28]	−0.014	0.127	−0.261	0.234	0.915	118	130
Licht and Qvitzau 2002[18]	−0.352	0.165	−0.676	−0.029	0.033	97	98
Ruhé et al 2009[21]	−0.122	0.260	−0.631	0.387	0.638	30	27
Schweizer et al 1990[27]	−0.027	0.248	−0.513	0.459	0.914	36	41
Schweizer et al 2001[19]	0.278	0.228	−0.169	0.725	0.223	38	37
	0.053	**0.100**	**−0.143**	**0.248**	**0.598**	**628**	**645**



B. Adults, major depression, SSRI

Study	SMD	Statistics for Each Study: Standard Error	Lower Limit	Upper Limit	*P* Value	Sample Size: Dose Increase	Continuation
Benkert et al 1997[26]	0.357	0.340	−0.310	1.023	0.295	32	18
Dornseif et al 1989[29]	0.193	0.104	−0.011	0.397	0.063	180	189
Kim et al 2016[22]	0.658	0.283	0.104	1.213	0.020	25	25
Kornstein et al 2008[28]	−0.014	0.127	−0.261	0.234	0.915	118	130
Licht and Qvitzau 2002[18]	−0.352	0.165	−0.676	−0.029	0.033	97	98
Ruhé et al 2009[21]	−0.122	0.260	−0.631	0.387	0.638	30	27
Schweizer et al 1990[27]	−0.027	0.248	−0.513	0.459	0.914	36	41
Schweizer et al 2001[19]	0.278	0.228	−0.169	0.725	0.223	38	37
	0.079	**0.100**	**−0.118**	**0.276**	**0.432**	**556**	**565**



Abbreviations: SMD = standardized mean difference, SSRI = selective serotonin reuptake inhibitor.

Limitations

Our findings pertain mainly to SSRIs (with the possible exception of citalopram) and to adult patients with major depression. Other dose increase regimens, for example, in tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), or serotonin-norepinephrine reuptake inhibitors (SNRIs), have not been investigated in depressed patients with ATF, and, thus, a clinically meaningful effect cannot be ruled out for those substances. One study,[26] however, showed that increasing the dose of the tetracyclic compound maprotiline to 150 mg/d was inferior to continuing on maprotiline 100 mg. The only study in children and adolescents[20] turned out to be inconclusive: in their small trial, Heiligenstein et al reported a statistically nonsignificant but possibly strong effect. As a consequence, while dose increase in children and adolescents or with SNRIs, TCAs, and MAOIs cannot be recommended on an evidence-based level, studies are clearly warranted. Citalopram may have to be viewed differently because the Kim et al[22] study provides preliminary evidence for beneficial effects of increasing its dose (see above) and because there is some evidence that citalopram may be slightly more efficient at 40 mg than at 20 mg.[42] To our knowledge, similar data are not available for fluvoxamine.[43]

The limitations of our systematic review and meta-analysis are those inherent to the studies included. For example, only 3 studies were considered to be low risk of bias studies.[18,21,28] Still, even in low risk of bias trials, blinding may be compromised, and, unfortunately, none of the trials included assessed the success of blinding.[44] As power calculations show, several studies[19–22,27] were too small to detect intermediate effects (SMD = 0.5), and all but 1 study[29] were too small to detect a common effect of 0.3 SMD. Meta-analysis, however, is one means to overcome the disadvantages of underpowered studies. ATF comprises both nonresponse and nonremission, and by combining both criteria, we ensured that we would not miss an effect of dose increase due to lack of power.

In spite of our highly sensitive search, carried out independently by 2 researchers in various databases, and in spite of a forward search in Web of Knowledge, it is possible that we missed relevant trials. Therefore, it is important to note that the number of trials necessary to flip our summary result to a positive impression of dose increase is high: For

Table 3. Publication Bias Analysis in Meta-Analyses of Randomized Controlled Trials of Dose Increase Versus Unchanged Continuation in Patients With Antidepressant Treatment Failure

Analysis	Orwin's Fail-Safe N	Trim-and-Fill Studies	Trim-and-Fill Point Estimate [95% CI]
All studies (9 studies)	13	1	0.004 [−0.201 to 0.209]
Major depression, SSRI, adults (8 studies)	10	1	0.026 [−0.184 to 0.236]
SSRI (9 studies)	11	1	0.038 [−0.159 to 0.235]
Major depression (9 studies)	10	2	0.016 [−0.185 to 0.217]
Adults (8 studies)	12	NA	NA
Low risk of bias (3 studies)	7	NA	NA

Abbreviations: NA = not applicable, SSRI = selective serotonin reuptake inhibitor.

example, regarding SSRIs in adults with major depression, 10 studies showing a SMD of 0.5 in favor of dose increase were needed to change the picture. It seems unlikely that so many studies with a relatively strong effect should not have been published or overlooked in our search and in the pertaining literature.

Of note, the duration of treatment before randomization was relatively short in some studies, eg, in Licht and Qvitzau's trial.[18] Given the latency in antidepressant efficacy, the time span to achieve response may have been too short (Sequenced Treatment Alternatives to Relieve Depression,[45] Henssler et al[46]). For example, Fava et al,[47,48] in studies without continuation arms, have documented beneficial effects of dose increase after patients had been treated for more than 4 weeks with a stable dose of fluoxetine (20 mg). It is also possible that a postrandomization response may have been the result of a dose increase prior to randomization. These effects may have confounded our results and thus limit what can be concluded from the studies under review. From a methodological view, therefore, studies with longer prerandomization periods are clearly desirable. However, from a clinical viewpoint, such rigorous studies are difficult to carry out because, for the research question at hand, it is methodologically imperative to retain a group of nonresponders in a continuation arm: Many nonresponders may not be willing to remain on the dose that has not been helpful for 8 weeks. It is also worth noting that in the studies of Ruhé et al[21] and Kornstein et al[28] in adults, with their 6-week treatment duration prior to randomization, results indicated no superiority of dose escalation.

Finally, this is not a meta-analysis comparing different doses right from the start of antidepressant pharmacotherapy. Furthermore, it is not an analysis of early dose increase studies. We consider antidepressant dose increase after very early signs of future nonresponse a different clinical scenario than ATF after a standardized antidepressant trial.[49] Therefore, studies like the one by Ueno et al,[50] who randomized patients after 1 week of initial treatment, were not included. Interestingly, even though their design did not meet our eligibility criteria, Ueno and colleagues' results are compatible with our findings: Patients randomized to 30 mg/d of mirtazapine had no statistically significantly superior results compared to those continuing on 15 mg/d.

CONCLUSIONS

Clinically, and pending studies in children, with other antidepressants, and with longer initial treatment durations, we recommend not increasing the dose of antidepressants after initial treatment failure in antidepressant pharmacotherapy. Currently, evidence from meta-analyses favors other second-line treatments, such as lithium augmentation[51–53] or augmentation with a second-generation antipsychotic.[54] A recent systematic literature review and meta-analysis[33] showed that combining a reuptake inhibitor with an antagonist of presynaptic α_2-autoreceptors is superior to an antidepressant monotherapy, but it is unclear whether this finding translates into patients with ATF. Switching antidepressants has been shown to be unsuccessful in this difficult-to-treat subgroup of patients.[55]

In conclusion, we found evidence that increasing the dose of SSRIs (with the possible exception of citalopram) is not beneficial for adult patients who failed to respond to an antidepressant treatment trial of 3 to 6 weeks' duration. Dose increase regimens with other groups of antidepressants, or after longer durations of initial treatment with antidepressants, are understudied and, therefore, cannot be recommended in clinical practice at this time but should be investigated in RCTs.

Additionally, special populations, for example, rapid metabolizers, should be the subject of RCTs to examine whether they benefit from different therapeutic strategies than other populations.

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Supplementary material follows this article.

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Supplementary Material

Article Title: Dose Increase Versus Unchanged Continuation of Antidepressants After Initial Antidepressant Treatment Failure in Patients With Major Depressive Disorder: A Systematic Review and Meta-Analysis of Randomized, Double-Blind Trials

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List of Supplementary Material for the article

1. **eAppendix 1** Search Strategy
2. **eTable 1** Risk of Bias

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

eAppendix 1: Search strategy

Databases searched:

Cochrane/CENTRAL

Embase

MEDLINE and PubMed Central via PubMed

PsycINFO

Search terms and their combination:

CENTRAL:

(depress* or dysthymi* or adjustment disorder* or mood disorder* or affective disorder or affective symptoms)

AND

(antidepressant* or agomelatin* or amineptin* or amitriptylin* or amoxapin* or bupropion* or butriptylin* or chlorimipramin* or citalopram* or clomipramin* or desipramin* or desvenlafaxin* or dibenzepin* or dosulepin* or dothiepin* or doxepin* or duloxetin* or escitalopram* or fluoxetin* or fluvoxamin* or imipramin* or isocarboxazid* or lofepramin* or levomilnacipran* or MAOI* or "monoamine oxidase inhibitors" or maprotilin* or mianserin* or milnacipran* or mirtazapin* or moclobemid* or nefazodon* or nortriptylin* or paroxetin* or phenelzin* or protriptylin* or reboxetin* or selegilin* or sertralin* or setiptilin* or SSRI or SSNRI* or SNRI* or "selective serotonin reuptake inhibitors" or "serotonin-norepinephrine reuptake inhibitors" or tetracyclic* or tianeptin* or tranylcypromin* or trazodon* or trimipramin* or tricyclic* or venlafaxin* or viloxazin* or vortioxetin*)

AND

(((dose OR dosage) AND (increase OR escalat* OR elevat* OR raise)) OR ((dose OR dosage) AND ((maxim*) OR (upward AND titrat*)))

OR dose–response relationship, drug OR dose-effect OR high-dose

Embase:

((((depress* or dysthymi* or adjustment disorder* or mood disorder* or affective disorder or affective symptoms)

AND

(antidepressant* or agomelatin* or amineptin* or amitriptylin* or amoxapin* or bupropion* or butriptylin* or chlorimipramin* or citalopram* or clomipramin* or desipramin* or desvenlafaxin* or dibenzepin* or dosulepin* or dothiepin* or doxepin* or duloxetin* or escitalopram* or fluoxetin* or fluvoxamin* or imipramin* or isocarboxazid* or lofepramin* or levomilnacipran* or MAOI* or monoamine oxidase inhibitors or maprotilin* or mianserin* or milnacipran* or mirtazapin* or moclobemid* or nefazodon* or nortriptylin* or paroxetin* or phenelzin* or protriptylin* or reboxetin* or selegilin* or sertralin* or setiptilin* or SSRI or SSNRI* or SNRI* or tca or selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors or tetracyclic* or tianeptin* or tranylcypromin* or trazodon* or trimipramin* or tricyclic* or venlafaxin* or viloxazin* or vortioxetin*)

AND

(((dose OR dosage) AND (increase OR escalat* OR elevat* OR raise)) OR ((dose OR dosage) AND ((maxim*) OR (upward AND titrat*))) OR dose–response relationship OR dose-effect OR high-dose)

AND

(random* or factorial* or crossover* or placebo* or assign* or allocat* or volunteer* or doubleblind* or singleblind* or double-blind* or single-blind* or double blind* or single blind*)

PubMed:

((((depress* or dysthymi* or adjustment disorder* or mood disorder* or affective disorder or affective symptoms)

AND

(antidepressant* or agomelatin* or amineptin* or amitriptylin* or amoxapin* or bupropion* or butriptylin* or chlorimipramin* or citalopram* or clomipramin* or desipramin* or desvenlafaxin* or dibenzepin* or dosulepin* or dothiepin* or doxepin* or duloxetin* or escitalopram* or fluoxetin* or fluvoxamin* or imipramin* or isocarboxazid* or lofepramin* or levomilnacipran* or MAOI* or "monoamine oxidase inhibitors" or maprotilin* or mianserin* or milnacipran* or mirtazapin* or moclobemid* or nefazodon* or nortriptylin* or paroxetin* or phenelzin* or protriptylin* or reboxetin* or selegilin* or sertralin* or setiptilin* or SSRI or SSNRI* or SNRI* or tca or "selective serotonin reuptake inhibitors" or "serotonin-norepinephrine reuptake inhibitors" or tetracyclic* or tianeptin* or tranylcypromin* or trazodon* or trimipramin* or tricyclic* or venlafaxin* or viloxazin* or vortioxetin*)

AND

((((dose[tw] OR dosage[tw]) AND (increase[tw] OR escalat* OR elevat* OR raise)) OR ((dose[tw] OR dosage[tw]) AND ((maxim*[tw]) OR (upward[tw] AND titrat*[tw]))) OR ((dose–response relationship, drug[MeSH] OR dose-effect OR high-dose) OR ("dose-response relationship"))

AND

(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti]

NOT

(animals[mh] NOT humans [mh])))))

PsycInfo:

(depress* or dysthymi* or adjustment disorder* or mood disorder* or affective disorder or affective symptoms)

AND

(antidepressant* or agomelatin* or amineptin* or amitriptylin* or amoxapin* or bupropion* or butriptylin* or chlorimipramin* or citalopram* or clomipramin* or desipramin* or desvenlafaxin* or dibenzepin* or dosulepin* or dothiepin* or doxepin* or duloxetin* or escitalopram* or fluoxetin* or fluvoxamin* or imipramin* or isocarboxazid* or lofepramin* or levomilnacipran* or MAOI* or "monoamine oxidase inhibitors" or maprotilin* or mianserin* or milnacipran* or mirtazapin* or moclobemid* or nefazodon* or nortriptylin* or paroxetin* or phenelzin* or protriptylin* or reboxetin* or selegilin* or sertralin* or setiptilin* or SSRI or SSNRI* or SNRI* or tca or "selective serotonin reuptake inhibitors" or "serotonin-norepinephrine reuptake inhibitors" or tetracyclic* or tianeptin* or tranylcypromin* or trazodon* or trimipramin* or tricyclic* or venlafaxin* or viloxazin* or vortioxetin*)

AND

((((dose[tw] OR dosage[tw]) AND (increase[tw] OR escalat* OR elevat* OR raise)) OR ((dose[tw] OR dosage[tw]) AND ((maxim*[tw]) OR (upward[tw] AND titrat*[tw]))) OR ((dose–response relationship, drug[MeSH] OR dose-effect OR high-dose) OR ("dose-response relationship"))

AND

(SU.EXACT("Treatment Effectiveness Evaluation") OR SU.EXACT.EXPLODE("Treatment Outcomes") OR SU.EXACT("Placebo") OR SU.EXACT("Followup Studies") OR placebo* OR random* OR "comparative stud*" OR clinical NEAR/3 trial* OR research NEAR/3 design OR evaluat* NEAR/3 stud* OR prospectiv* NEAR/3 stud* OR (singl* OR doubl* OR trebl* OR tripl*) NEAR/3 (blind* OR mask*))

E-table 1: Risk of bias

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Benkert 1997	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk	High risk
Dornseif 1989	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk	Low risk
Heiligenstein 2006	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk
Kim 2016	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk	Low risk
Kornstein 2008	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Licht 2002	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Ruhé 2009	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk
Schweizer 1990	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Unclear risk
Schweizer 2001	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Unclear risk