Switching the Antidepressant After Nonresponse in Adults With Major Depression:

A Systematic Literature Search and Meta-Analysis

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ABSTRACT

Objective: Nonresponders to antidepressant monotherapy during acute treatment of major depression are often switched to a new antidepressant. The objective of this meta-analysis was to compare the efficacy of switching to a new antidepressant with continuation of the first antidepressant.

Data Sources: PubMed, Embase, PsycINFO, and Cochrane Central Register of Controlled Trials (CENTRAL) databases and additional sources were systematically searched independently by 2 authors up to March 2015 without language limitations. With employment of a sensitivity-enhancing search strategy, generic terms for major depression, switching, and randomized trials were combined.

Study Selection: Articles (3,234) were screened for trials of patients with major depression who had not responded to antidepressant monotherapy who were then randomized either to a new antidepressant or to continuation of the first antidepressant. Studies were subdivided into those not allowing for dose escalation in the continuation arm (strict analysis) and those allowing for dose escalation (broad analysis).

Data Extraction: Data were extracted and risk of bias was assessed independently by 2 authors, and data were pooled using random effects models.

Results: Four randomized controlled trials were included in the strict analysis and 8 in the broad analysis. In both analyses, switching was not superior to continuation: the standardized mean difference in the strict analysis was −0.17 (95% CI, −0.59 to 0.26; $P = .45$; $I^2 = 77.8\%$) and in the broad analysis was 0.031 (95% CI, −0.26 to 0.32; $P = .836$; $I^2 = 85.3\%$). All secondary outcome analyses (response and remission rates, low risk of bias studies only, leave-one-out analysis, dropouts) supported the results. There was no indication of publication bias.

Conclusions: There is a dearth of randomized controlled trials investigating switching. There is no high-level evidence that switching the antidepressant is effective when compared to simply continuing the initial antidepressant. Since there are better treatment options than switching, physicians should be cautious to switch antidepressants.

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Antidepressants are a cornerstone in the treatment of depression and are recommended in international guidelines.[1–6] Their efficacy has been shown in comparison to placebo in a host of randomized controlled studies[7] and meta-analyses.[8–11]

All antidepressants share a clinical shortcoming, a high rate of nonresponse (30% to 50%).[12] As a consequence, a major clinical challenge in the treatment of depression is to initiate an appropriate second-step strategy after nonresponse to monotherapy with an antidepressant. Recommended second-step strategies include augmentation (especially with lithium[13] or second-generation antipsychotics[14]), combining 2 antidepressants,[15] high-dose antidepressant therapy,[16] electroconvulsive therapy,[17] various psychotherapeutic approaches,[18] novel or experimental treatments,[19] and switching to a different antidepressant.[20]

In clinical practice, antidepressants are often switched,[21] but evidence for this strategy from controlled trials is unsatisfactory. Typically, observational studies (design 1 in Figure 1) show improvement when nonresponders are switched to a second antidepressant (eg, Souery et al[22]). Such pre-post comparisons, however, cannot elucidate whether the improvement results from the switch, from a placebo effect, or from the natural illness course.[7] A number of controlled studies compared switches to different antidepressants (design 2 in Figure 1), for example, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study.[23–25] In general, different second step antidepressants result in comparable outcomes. Without a placebo arm or without patients continuing on treatment with the first antidepressant, however, such studies are uninformative regarding the question of whether switching is better than continuation or placebo.

While it is interesting from a purely scientific point of view, we are aware of no study randomizing nonresponders to a first antidepressant to placebo. Consequently, we carried out a systematic literature review and meta-analysis of studies comparing switching to a new antidepressant with continuation of the first antidepressant in depressed adults who did not respond to an initial monotherapy with an antidepressant of adequate duration (design 3 in Figure 1).

This is an update and a refinement of a similar, earlier analysis that included studies until May 2007.[20] In that study, we found only 3 randomized studies, none of which showed a statistically significant difference in the clinical outcome between patients switched to a new antidepressant and those continuing the first antidepressant—findings that did not change in a meta-analysis of the studies. When we became

Clinical Points

- Nonresponders to an antidepressant are often switched to another antidepressant, although the evidence base of this strategy is unclear.
- Since our meta-analysis revealed no evidence that switching is more effective than continuation of the so-far ineffective antidepressant, switching cannot be considered first choice.

aware of new studies published on the subject, we decided to readdress this clinically important research question. To our knowledge, there are no other systematic reviews or meta-analyses of studies employing this design.

METHODS

This systematic review and meta-analysis has been registered at PROSPERO (international prospective register of systematic reviews; registration number CRD42015024870).

Literature Search and Data Extraction

In March 2015, we conducted a systematic search in MEDLINE and PubMed Central via PubMed, in Embase, in PsycINFO, and in the Cochrane Central Register of Controlled Trials (CENTRAL) to identify studies on switching versus continuation of antidepressants in nonresponding depressed patients. We combined generic terms for major depression, switching, and randomized trials; the full search terms and history are specified in eAppendix 1.

Inclusion criteria. Inclusion criteria were as follows:

- Patients with a major depressive disorder (non-bipolar) according to generally accepted operationalized criteria, such as *DSM-III-R* or newer, *ICD-9* or *ICD-10*, Research Diagnostic Criteria, or Feighner Criteria
- Nonresponse (< 30% improvement) of every participant to a first treatment period of at least 2 weeks at standard or higher doses
- Nonresponse as well as treatment effects assessed using established instruments, eg, the Hamilton Depression Rating Scale (HDRS), Montgomery-Asberg Depression Rating Scale (MADRS), Bech-Rafaelsen Melancholia Rating Scale (BRMS), Beck Depression Inventory (BDI), or Clinical Global Impressions scale (CGI)
- Randomization of participants either to a new (second) antidepressant or to continuation of the first antidepressant (same dosage) for at least 2 weeks

Exclusion criteria. Exclusion criteria were as follows:

- Inclusion of bipolar depressed patients
- Interventions based on herbal medicine, nutritional supplements, or any non-antidepressive agents
- Maintenance therapy trials (treatment beyond the remission of acute depression)

Two authors (H.K. and T.B.) independently screened titles and abstracts retrieved in the literature search. We applied no language restrictions and did not exclude "gray" literature. Two raters (T.B. and C.B.) independently read full texts of articles potentially eligible. The bibliographies of all articles included were hand searched for relevant studies. Data from included studies were extracted independently by 2 authors (T.B. and C.B.) using an Excel-based standardized data extraction form in accordance with the Cochrane Collaboration Handbook.[26] All disagreements were solved by consensus.

All studies included were rated using the Cochrane Collaboration Handbook tool for assessing risk of bias.[26] As recommended, the following specific domains were taken into account: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, sponsorship, and other potential sources of bias. In accordance with the Cochrane Collaboration Handbook, studies were rated as holding overall "low risk of bias" only in cases where "low" or "unclear" risk of bias could be applied to all of the previously mentioned domains in the corresponding study.

Data Analysis

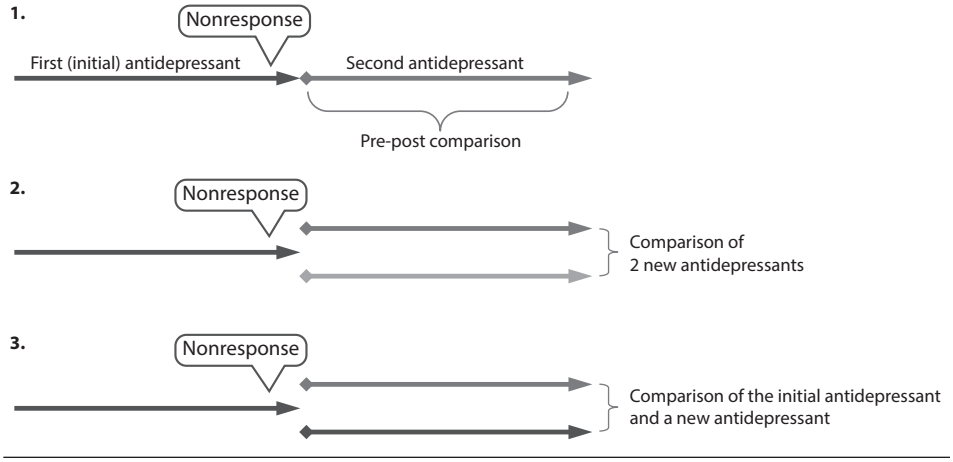
Primary outcome. The primary outcome was the comparison of antidepressive efficacy between the switch and the continuation arms of the included studies, operationalized as standardized mean difference (SMD) ± standard error (SE). SMDs were chosen because efficacy assessment of antidepressant treatment varies among studies. We computed SMDs from difference in depression rating scale scores or difference in change in scores on these scales (relative to baseline) at study endpoint. If no scores were available, SMDs were calculated from remission rates, defined as scores below determined thresholds on a depression rating scale (adopting remission criteria by study authors). If remission rates were not available, we used response rates, defined as a decrease of at least 50% in baseline symptoms on a depression rating scale. For "study endpoint," we adopted the time of assessment the authors chose for their primary outcome. In case of several time points, we chose the last one, but no longer than 12 weeks' continuation.

We used intention-to-treat data whenever possible and accepted the method of the authors to account for missing data (eg, last observation carried forward or mixed-model repeated measures).

Secondary outcomes and subgroup analyses. The following predefined secondary outcomes were analyzed: remission and response rates, as defined above, using odds ratios (ORs) with 95% confidence intervals (95% CIs) for comparison; and tolerability, operationalized as dropout rates due to adverse events and due to any reason (OR with 95% CI). As a subgroup analysis, studies with a low risk of bias were analyzed separately.

Post hoc analyses. Our literature search revealed several studies allowing for a dose escalation in the continuation arm. We decided post hoc to select such studies for meta-analysis to avoid the loss of important data and labeled the

Figure 1. Three Different Study Designs to Test the Switch Strategy in Depressed Patients Who Did Not Respond to an Initial Treatment Trial With an Antidepressant



analysis including such studies "broad analysis." In contrast, the "strict analysis" included only studies without dose escalation (in accordance with our predefined criteria). To avoid undue reliance on single studies, we left out 1 study at a time with regard to the primary outcome in both strict and broad analyses (leave-one-out analysis).

Data Synthesis

Data analyses were performed using Comprehensive Meta-Analysis (Version 2) following the procedures detailed in the Cochrane Collaboration Handbook.[26] In all analyses, random effects models were applied. Statistical heterogeneity between studies is reported as I^2 statistic. Publication bias was assessed using a funnel plot and the Egger test. Finally, we estimated the potential effect of missing studies in our literature search and determined the Orwin fail-safe N: the number of missed studies necessary to achieve a moderate summary effect size of 0.3 (SMD) in favor of switching, under the assumption that all missed studies had a medium effect size of 0.5 in favor of switching.

RESULTS

Database searches retrieved 4,841 hits (cf PRISMA flowchart, Figure 2). After removal of duplicates, we searched 3,234 articles at title and abstract level. Full texts of 37 articles were read, and 8 publications were eventually included. Authors of 5 studies were contacted by e-mail because additional information was needed to decide if our inclusion and exclusion criteria were met. Four studies met criteria for the strict analysis,[27–30] and 4 additional studies[31–34] were identified for the broad analyses (dose escalation in the continuation arm allowed). One study was published as an abstract only[34] and another one in Chinese language only.[31] On request, both first authors provided sufficient details for their data to be included. All 8 studies used the HDRS or the MADRS.

Table 1 provides an overview of all studies included. In total, continuation arms of strict analysis studies comprised 204 and switching arms 255 patients. The broad analysis used data on 783 and 844 patients, respectively.

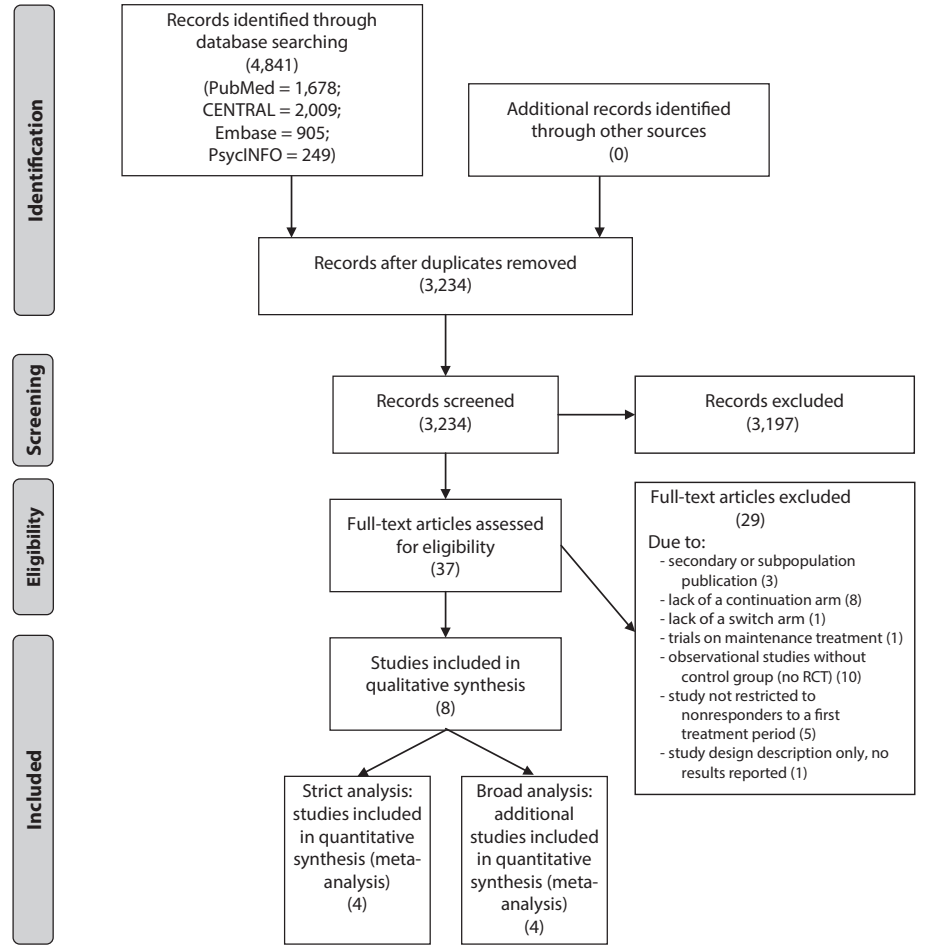
Analysis of Studies With No Dose Escalation in the Continuation Arms (strict analysis)

Our primary outcome was the SMD in efficacy between the 2 arms. None of the 4 studies fulfilling strict inclusion criteria reported a statistically significant advantage of switching the antidepressant over continuation with the so far ineffective one, but 1 study[27] found continuation to be superior to switching (SMD = −0.95 [95% CI, −1.51 to −0.38], $P = .001$) (Figure 3A). The meta-analytic estimate of all 4 studies combined showed that, numerically, switching was less effective than continuation but without reaching statistical significance and with considerable heterogeneity (SMD = −0.17 [95% CI, −0.59 to 0.26], $P = .45$; $I^2 = 77.8\%$). Meta-analyses of remission and response rates (secondary outcomes) confirmed this finding, but with lower heterogeneity (OR [95% CI] = 0.90 [0.41 to 1.97], $I^2 = 48.2\%$ and 0.78 [0.46 to 1.30], $I^2 = 35.7\%$, respectively, with ORs > 1 indicating superiority of switching) (Figure 3B and 3C). We removed 1 study at a time from the analysis to detect effects of outlier studies; however, none of the ensuing analyses resulted in statistically significant summary estimates (point estimates ranging from −0.30 to 0.04 SMD).

Analysis of Studies Allowing for Dose Escalation in the Continuation Arms (broad analysis)

In 4 additional studies, a dose increase was allowed for patients randomized to the continuation arm; these 4 studies were included in the broad analysis with the 4 studies from the strict analysis. With regard to our primary outcome (SMD), 5 studies found no significant difference between the 2 strategies of switching and continuation (Figure 4A). In addition to the study by Souery et al,[27] a second study (Bose et al[33]) demonstrated a statistically significant inferiority of switching, and a Chinese study[31] reported a statistically significant superiority of switching (SMD = 1.25 [95% CI, 0.77 to 1.74], $P < .001$). Upon our request for complete data,

Figure 2. PRISMA Flowchart



Abbreviations: CENTRAL = Cochrane Central Register of Controlled Trials, RCT = randomized controlled trial.

Table 1. Characteristics of Studies Included In a Systematic Meta-Analysis Comparing Switching to a New Antidepressant Versus Continuation of the Initial Antidepressant in Patients With Major Depressive Disorder After Nonresponse to Antidepressant Monotherapy

Study/First Author	Year of Publication	Initial and Continuation Antidepressant	Switch Antidepressant	Follow-Up Time (wk)	N After Randomization[a]	Dose Escalation Allowed in the Continuation Arm?	Low Risk of Bias According to Cochrane Collaboration Tool for Assessing Risk of Bias?
Ferreri[28]	2001	Fluoxetine	Mianserin	6	71	No	Yes
Corya[29]	2006	Venlafaxine	Fluoxetine	12	119	No	No
Souery[27]	2011	Desipramine or citalopram	Desipramine or citalopram	4	59	No	Yes
Shelton[30]	2005	Nortriptyline	Fluoxetine	8	210	No	No
Romera[32]	2012	Escitalopram	Duloxetine	4	566	Yes	Yes
Bose[33]	2012	Escitalopram	Duloxetine	8	472	Yes	Yes
Petrescu[34]	2014[b]	Any SSRI	Duloxetine	8	52	Yes	No
Zhu[31]	2003	Various SSRIs	Mirtazapine	6	78	Yes	No

[a]A total of 1,627 patients were included in the meta-analysis.
[b]Published as abstract only.
Abbreviation: SSRI = selective serotonin reuptake inhibitor.

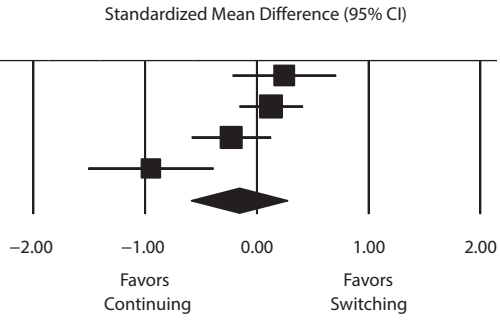
the authors of the latter study realized an error in their results. Since we used the corrected data (with written permission of Zhu Haibing, MD), the numbers in our meta-analysis are in contrast to the published version of the article by Zhu et al.[31]

Our meta-analysis of all 8 studies combined confirmed the result of the strict analysis: no statistically significant difference between switching and continuation (SMD = 0.031 [95% CI, −0.26 to 0.32], $P = .836$; $I^2 = 85.3\%$) (Figure 4A). Meta-analyses of remission and response rates (secondary outcomes) supported this finding (OR = 1.05 [95% CI, 0.65 to 1.69], $I^2 = 66.6\%$ and 0.97 [95% CI, 0.69 to 1.36], $I^2 = 51.2\%$, respectively; ORs > 1 indicate superiority of switching) (data not shown in detail). After removing 1 study at a time, summary estimates did not differ substantially from the

Figure 3. Strict Analysis (no dose escalation in the continuation arms): Switching to a New Antidepressant Versus Continuation of the Initial Antidepressant in Patients With Major Depressive Disorder After Nonresponse to Antidepressant Monotherapy

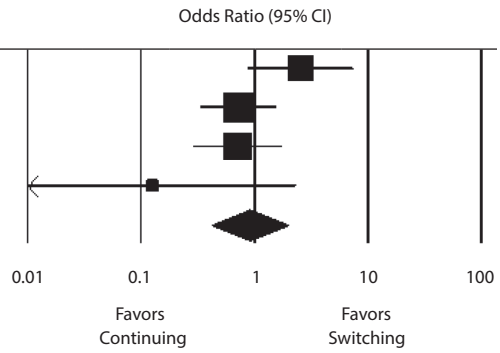
A. Standardized Mean Differences

Study/ First Author	Standardized Mean Difference	Standard Error	Variance	Lower Limit	Upper Limit	*Z* Value	*P* Value	Sample Size, n: Switch	Sample Size, n: Continuation
Ferreri 2001[28]	0.245	0.239	0.057	−0.223	0.713	1.025	.305	33	38
Shelton 2005[30]	0.127	0.148	0.022	−0.162	0.416	0.862	.389	142	68
Corya 2006[29]	−0.229	0.184	0.034	−0.589	0.132	−1.244	.213	60	59
Souery 2011[27]	−0.948	0.289	0.083	−1.513	−0.382	−3.285	.001	20	39
Combined estimate	−0.165	0.219	0.048	−0.594	0.264	−0.756	.450		



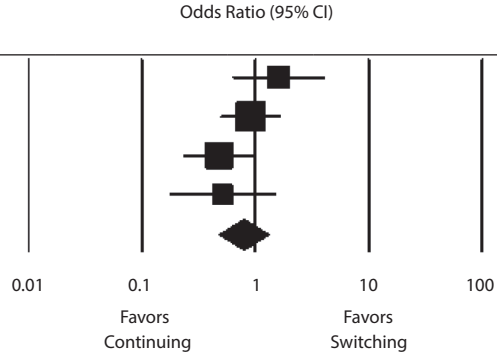
B. Remission

Study/ First Author	Odds Ratio	Lower Limit	Upper Limit	*Z* Value	*P* Value	Remission n/ Total n: Switch	Remission n/ Total n: Continuation
Ferreri 2001[28]	2.531	0.856	7.484	1.678	.093	12/33	7/38
Shelton 2005[30]	0.721	0.328	1.586	−0.813	.416	19/142	12/68
Corya 2006[29]	0.708	0.283	1.770	−0.739	.460	10/60	13/59
Souery 2011[27]	0.126	0.007	2.351	−1.388	.165	0/20	6/39
Combined estimate	0.899	0.410	1.968	−0.267	.789		



C. Response

Study/ First Author	Odds Ratio	Lower Limit	Upper Limit	*Z* Value	*P* Value	Response n/ Total n: Switch	Response n/ Total n: Continuation
Ferreri 2001[28]	1.613	0.625	4.168	0.988	0.323	16/33	14/38
Shelton 2005[30]	0.909	0.484	1.705	−0.299	0.765	41/142	21/68
Corya 2006[29]	0.479	0.227	1.011	−1.932	0.053	19/60	29/59
Souery 2011[27]	0.515	0.172	1.541	−1.186	0.235	8/20	22/39
Combined estimate	0.776	0.464	1.298	−0.966	0.334		



analysis of all 8 studies (point estimates ranging from −0.10 to 0.13 SMD).

Tolerability

Five studies provided data on dropouts due to adverse events (Figure 4B). In the study by Ferreri et al,[28] 8 of 33 participants switched to a new antidepressant dropped out due to adverse events, but none of the 38 participants who continued their initial antidepressant did so (OR = 25.667, $P = .028$). In the other 4 studies, dropout rates did not differ significantly between the 2 groups. The meta-analysis revealed a statistically nonsignificant odds ratio of 1.20 [95% CI, 0.36 to 4.07] in favor of continuation.

Seven studies reported on dropout rates for any reason (Figure 4C). In the study by Romera and colleagues,[32] significantly more patients in the continuation arm dropped out, whereas the other 6 studies found no significant differences, and neither did our meta-analysis (OR = 0.82 [95% CI, 0.44 to 1.51]).

Studies With Low Risk of Bias

Four studies[27,28,32,33] were judged to be of a high methodological standard with a low risk of bias. Our meta-analysis of these studies showed no statistically significant difference between switching and continuation (Figure 4D) (SMD = −0.132 [95% CI, −0.48 to 0.21], $I^2 = 84.1\%$).

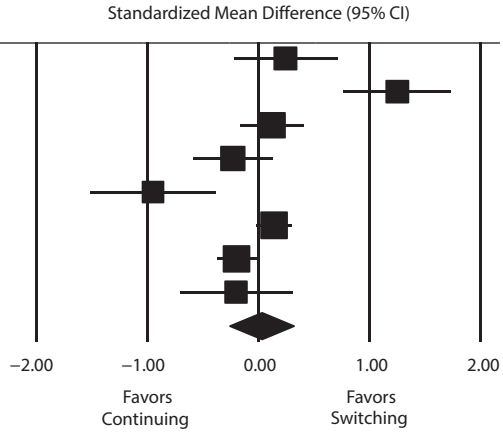
Publication Bias

Since the strict analysis included only 4 studies, we did not search for publication bias. A funnel plot of the 8 studies

Figure 4. Broad Analysis (dose escalation allowed in the continuation arms): Switching to a New Antidepressant Versus Continuation of the Initial Antidepressant in Patients With Major Depressive Disorder After Nonresponse to Antidepressant Monotherapy

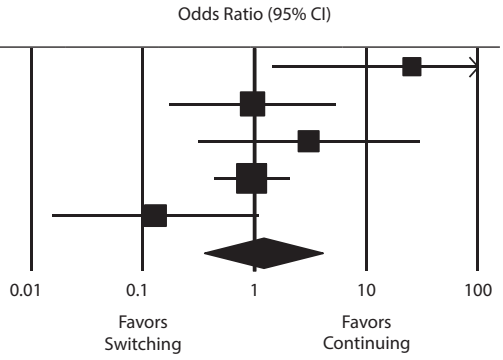
A. Standardized Mean Differences

Study/First Author	Standardized Mean Difference	Standard Error	Variance	Lower Limit	Upper Limit	*Z* Value	*P* Value
Ferreri 2001[28]	0.245	0.239	0.057	−0.223	0.713	1.025	.305
Zhu 2003[31]	1.251	0.248	0.061	0.766	1.737	5.052	.000
Shelton 2005[30]	0.127	0.148	0.022	−0.162	0.416	0.862	.389
Corya 2006[29]	−0.229	0.184	0.034	−0.589	0.132	−1.244	.213
Souery 2011[27]	−0.948	0.289	0.083	−1.513	−0.382	−3.285	.001
Romera 2012[32]	0.143	0.084	0.007	−0.022	0.308	1.694	.090
Bose 2012[33]	−0.196	0.092	0.009	−0.377	−0.015	−2.121	.034
Petrescu 2014[34]	−0.200	0.260	0.067	−0.709	0.308	−0.772	.440
Combined estimate	0.031	0.147	0.022	−0.258	0.319	0.207	.836



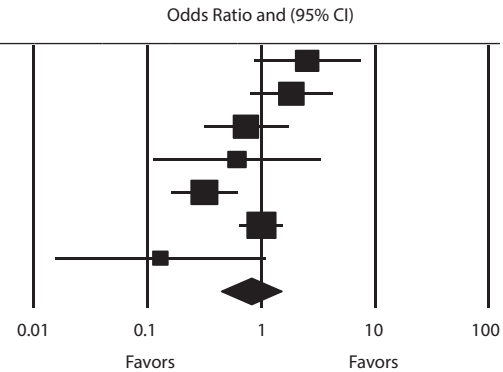
B. Dropouts Due to Side Effects

Study/First Author	Odds Ratio	Lower Limit	Upper Limit	*Z* Value	*P* Value	Dropout n/ Total n	
						Switch	Continuation
Ferreri 2001[28]	25.667	1.418	464.484	2.196	.028	8/33	0/38
Shelton 2005[30]	0.957	0.171	5.355	−0.051	.960	4/142	2/68
Corya 2006[29]	3.053	0.308	30.220	0.954	.340	3/60	1/59
Bose 2012[33]	0.939	0.426	2.071	−0.156	.876	13/243	13/229
Petrescu 2014[34]	0.130	0.015	1.098	−1.874	.061	1/25	9/37
Combined estimate	1.203	0.355	4.074	0.297	.766		



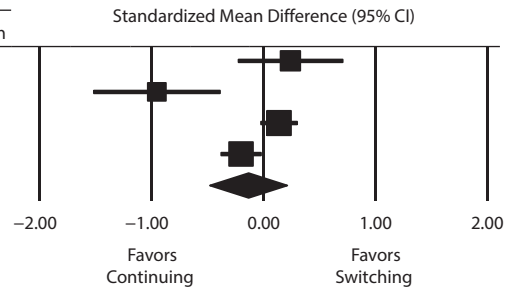
C. Dropouts Due to Any Reason

Study/First Author	Odds Ratio	Lower Limit	Upper Limit	*Z* Value	*P* Value	Dropout n/ Total n	
						Switch	Continuation
Ferreri 2001[28]	2.531	0.856	7.484	1.678	.093	12/33	7/38
Shelton 2005[30]	1.842	0.791	4.291	1.416	.157	28/142	8/68
Corya 2006[29]	0.733	0.310	1.737	−0.705	.481	12/60	15/59
Souery 2011[27]	0.611	0.112	3.346	−0.568	.570	2/20	6/39
Romera 2012[32]	0.316	0.161	0.623	−3.329	.001	12/282	35/284
Bose 2012[33]	1.003	0.642	1.568	0.014	.989	50/243	47/229
Petrescu 2014[34]	0.130	0.015	1.098	−1.874	.061	1/25	9/37
Combined estimate	0.818	0.444	1.507	−0.644	.520		



D. Standardized Mean Differences in Studies With Low Risk of Bias

Study/First Author	Standardized Mean Difference	Standard Error	Variance	Lower Limit	Upper Limit	*Z* Value	*P* Value	Sample size, n	
								Switch	Continuation
Ferreri 2001[28]	0.245	0.239	0.057	−0.223	0.713	1.025	.305	33	38
Souery 2011[27]	−0.948	0.289	0.083	−1.513	−0.382	−3.285	.001	20	39
Romera 2012[32]	0.143	0.084	0.007	−0.022	0.308	1.694	.090	282	284
Bose 2012[33]	−0.196	0.092	0.009	−0.377	−0.015	−2.121	.034	243	229
Combined estimate	−0.132	0.177	0.031	−0.479	0.214	−0.749	.454		



in the broad analysis revealed no sign of publication bias, and the Egger test was negative ($P = .92$). We estimated the number of missed studies with a medium effect size of 0.5 SMD to achieve a moderate overall effect size of 0.3 SMD to be 8 and 12 in the strict and broad analyses, respectively.

DISCUSSION

With only 4 studies selected in the strict and 8 in the broad analysis, it is evident that switching antidepressants after a first antidepressant has failed is only poorly studied—a worrisome finding particularly because it is a treatment strategy frequently employed in clinical practice. Moreover, none of the trials in the strict and only 1 in the broad analysis[31] found switching to be superior to continuation. Two other articles[27,33] reported a statistically significant difference in favor of continuation. Our meta-analyses of primary and secondary outcomes, which were supported by a risk-of-bias analysis and a leave-one-out calculation, consistently resulted in small and statistically nonsignificant summary effects (eg, primary outcome: SMD = −0.165 in the strict and 0.031 in the broad analysis). These results support the conclusions of our earlier meta-analysis[20] including studies until 2007.

Among the quantity of theoretically conceivable switch strategies, only a limited number were investigated (Table 1): in 3 of the 8 studies, nonresponders to selective serotonin reuptake inhibitors (SSRIs) were switched to duloxetine, and in 2 other studies, nonresponders (to venlafaxine and to nortriptyline, respectively) were switched to fluoxetine. Therefore, our results cannot be generalized to other switch sequences.

Although all antidepressants employed for switching in the studies selected have been shown to be effective in placebo-controlled studies, an argument can be made that there may be no specific efficacy of any switching strategy: nearly all antidepressants share related modes of action,[7] leading to the enhancement of monoamines in the synaptic cleft, either by inhibiting the reuptake from the synaptic cleft (SSRIs, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants), by blocking presynaptic autoreceptors (mirtazapine, mianserin), or by inhibiting monoamine oxidase activity (monoamine oxidase inhibitors). Therefore, switching to a new antidepressant may not start a truly new neuropharmacologic action and, if so, cannot be more effective than continuation of the first antidepressant. It is conceivable that switching simply means to start anew with the waiting time for the onset of action.

As a consequence, studies comparing the switch strategy with second-step strategies that are well-based on evidence and employ different modes of action are warranted.[12] Examples include combining 2 antidepressants,[15] lithium augmentation,[13] sleep deprivation, electroconvulsive therapy,[17] psychotherapy,[18] and augmentation with second generation antipsychotics,[14] although the latter drug class shares some mechanism with antidepressants. In addition, nonresponders might benefit from therapeutic drug monitoring[35] and, at least regarding some antidepressants, from dose escalation.[16]

Limitations

Our results have to be viewed in light of several limitations. The number of studies included is small, and we also may have missed pertinent trials. On the other hand, we searched 4 large databases, applied no language restrictions, did not exclude gray literature, and contacted authors to include abstract publications.

Heterogeneity was substantial, rendering results and conclusions more uncertain. Still, all of our 9 analyses arrived at the same result, although it has to be kept in mind that the broad analysis was conducted post hoc. Moreover, while heterogeneity results from different effect estimates, 7 of 8 studies consistently showed no statistically significant effect of switching, a homogeneous distribution on the level of clinically important outcomes. Finally, in a failsafe N analysis assuming comparatively strong effect sizes in potentially missed studies, the number of studies missed in order to achieve a moderate overall effect was higher than the number of studies included (12 and 8 in the broad and strict analyses, respectively). As a result, we consider it unlikely that publication bias is an important factor in explaining our results. As always, however, future studies may change the conclusions from this current meta-analysis, and the final word is still out because the confidence intervals do not exclude effect sizes large enough to warrant clinical consideration (eg, approx. 0.3 SMD in the broad analysis). In addition, in clinical practice (without double-blind conditions), switching the antidepressant may induce greater expectations of benefit than continuation. A greater expectation of benefit typically leads to a larger placebo effect.

So far, there is no evidence from high quality studies supporting switching the antidepressant over continuation in nonresponders with major depression. There is an urgent need for further controlled studies on switching, as nonresponse to antidepressants continues to be a serious clinical problem. Pending better evidence, physicians should be cautious with switching antidepressants and prefer one of several treatment strategies better evaluated in nonresponders to antidepressant treatment.

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Drug names: citalopram (Celexa and others); desipramine (Norpramin and others); duloxetine (Cymbalta); escitalopram (Lexapro and others); fluoxetine (Prozac and others); mirtazapine (Remeron and others); nortriptyline (Pamelor, Aventyl, and others).

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Supplementary Material

Article Title: Switching the Antidepressant After Nonresponse in Adults With Major Depression: A Systematic Literature Search and Meta-Analysis

Author(s): Tom Bschor, MD; Hannah Kern; Jonathan Henssler, MD; and Christopher Baethge, MD

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List of Supplementary Material for the article

1. **eAppendix 1** Search terms and their combination used for a systematic literature search in MEDLINE and PubMed Central via PubMed, Central, Embase, and PsycINFO in March 2015

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<u>eAppendix 1.</u> Search terms and their combination used for a systematic literature search in MEDLINE and PubMed Central via PubMed, Central, Embase, and PsycINFO in March 2015

(depress* or dysthymi* or adjustment disorder* or mood disorder* or affective disorder or affective symptoms)
AND
(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 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 tianeptin* or tranylcypromin* or trazodon* or trimipramin* or venlafaxin* or viloxazin*)
AND
(switch* or crossover or cross-over or crossed-over or change* or changing or remain* or stay* or continu*)
AND
(respond* or remiss* or remit* or resistant* or improv*)