Switching Antidepressants After a First Selective Serotonin Reuptake Inhibitor in Major Depressive Disorder: A Systematic Review

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Objective: Selective serotonin reuptake inhibitors (SSRIs) are frequently used as a first antidepressant for major depressive disorder but have response rates of 50% to 60% in daily practice. For patients with insufficient response to SSRIs, switching is often applied. This article aims to systematically review the evidence for switching pharmacotherapy after a first SSRI.

Data Sources: A systematic literature search (updated until Feb. 10, 2005) in MEDLINE, EMBASE, CINAHL, and PsychINFO (all indexed years) identified randomized, controlled trials (RCTs) and open studies investigating switching strategies. In the absence of specific keywords for switching, we performed "sensitive" searches using free text words with wildcards ($): "switch$" or ("alternat$" adj5 "treat$") or ("alternat$" adj5 "therap$") in combination with the Cochrane Collaboration search filter for RCTs, the Cochrane Collaboration Depression Anxiety and Neurosis Group search filter for major depressive disorder, and MeSH terms for antidepressants (in combination with additional text words for all antidepressive agents). Additionally, we included 4 recent Sequenced Treatment Alternatives to Relieve Depression publications. We limited searches to adults and humans but did not apply language restrictions.

Study Selection: Relevant articles were retrieved and critically appraised. The methodology of the studies, the results on efficacy and dropouts due to side effects, and remarks were summarized in an evidence table. Three studies comparing a switch to venlafaxine or SSRIs were pooled.

Data Synthesis: Eight RCTs and 23 open studies were identified, studying populations with different levels of treatment resistance. Definitions of response and remission rates varied between studies. Observed response rates after switching to any of the classes of antidepressants varied between 12% and 86%. Remission rates varied between 7% and 82%. The number of previous treatments with antidepressants was negatively correlated with treatment outcome. Rates of dropout due to side effects varied considerably across agents (5%–39%). Switching to venlafaxine showed a modest and clinically equivocal benefit over SSRIs (number needed to treat = 13 [95% CI = 9.1 to 25.0]).

Conclusions: After a first SSRI, any switch within or between classes of antidepressants appears legitimate (second SSRI, novel dual-acting antidepressants, selective norepinephrine or noradrenergic/dopaminergic agents, or tricyclic antidepressant or mianserin). No unequivocal evidence is available to prove an advantage of a between-class switch. More guidance by randomized empirical studies is needed. Clinical implications and methodological considerations for future studies are discussed.

(J Clin Psychiatry 2006;67:1836–1855)

See also Commentary on page 1833.

Received Aug. 1, 2005; accepted May 24, 2006. From the Department of Psychiatry, Program for Mood Disorders, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands.

This systematic review was realized by a grant for the development of a local evidence-based clinical practice guideline (No. SFA.07.012) from the Academic Medical Center, Amsterdam, The Netherlands. This guideline considering strategies for nonresponse to a standard dose of a first selective serotonin reuptake inhibitor is available on request from the first author (Dr. Ruhé).

Drs. Ruhé, Huyser, Swinkels, and Schene report no other financial affiliations relevant to the subject of this article.

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Major depressive disorder (MDD) is one of the most prevalent and disabling illnesses in psychiatry.[1] For the treatment of MDD, several national clinical guidelines were developed.[2–9] In these guidelines, pharmacotherapy is among the most important treatments; mostly, selective serotonin reuptake inhibitors (SSRIs) are the antidepressants of first choice. However, only 50% to 60% of patients respond to the first antidepressant given.[10,11] In a case of nonresponse, all treatment guidelines recommend 3 major strategies: (1) increasing the dose of the antidepressant (dose escalation), (2) switching to another antidepressant of the same or different class, and (3) augmenting the antidepressant by adding a second drug that by itself is not an antidepressant. By various authors, a fourth strategy of combination of antidepressants is proposed.[12–15]

Surprisingly very little systematic evidence exists to date to underscore the recommendations for nonresponders. One Cochrane review summarizes randomized, controlled trials (RCTs) of strategies in patients nonresponsive to at least 4 weeks of an antidepressant at the recommended dose.[16] With a thorough methodology, 16 RCTs were selected. Unintentionally, the studies included in this review represented more heterogeneous, difficult-to-treat populations, referred to as treatment-resistant depression (TRD). Although little information on previous treatments was found, the included studies especially considered tricyclic antidepressant (TCA) nonresponders. The switch options that were investigated in the included studies did not reflect clinical practice of switching to another antidepressant (1 of the above recommendations), but used a variety of other drugs (estrogen, benzodiazepines, ketoconazole, olanzapine). For the augmentation studies, meta-analyses were performed for 2 trials of lithium augmentation and for 3 pindolol trials. A clinically significant benefit was found only for lithium augmentation. Thus, this review does not provide helpful information for clinicians in the case of nonresponse to an (first) SSRI.[16]

Strategies for nonresponse have been summarized in several narrative reviews, focusing on all strategies together,[17–28] switching,[12,13,29–32] augmentation,[12,13,31,32] or combination.[12–15,33] Dose escalation was summarized in 2 meta-analyses,[34,35] 1 narrative,[36] and 1 recent systematic review.[37] The evidence for lithium augmentation was also summarized in meta-analyses by Bauer et al.[38,39]

Second to dose escalation, switching antidepressants is widely practiced.[40–42] Switching to a different pharmacologic class seems to be preferred by clinicians.[43] The above narrative reviews of switching strategies altogether provided a substantial overview. However, each review individually was limited in its presentation, predominantly by a lack of a well-defined search strategy, and none of the reviews presented data on critical appraisal of the identified studies as proposed by the Cochrane Collaboration.[44] The general conclusion today is that there is limited evidence available for switching antidepressants and that there is no clear proven advantage of one switch option over the others. Additionally, recently the results of a large study designed to elucidate sequential treatment strategies after nonresponse became available (Sequenced Treatment Alternatives to Relieve Depression; STAR*D).[45] This study provided prospective data on response and remission rates after randomized treatment allocations in patients who were not in remission after 1 to 4 sequential steps of treatment (further referred to as STAR*D levels I–IV).

Therefore, our primary objective was to systematically review and appraise the available research focusing on switching strategies for SSRI-nonresponders in MDD, including the recent STAR*D results. A secondary aim was to acknowledge and investigate the expected different levels of TRD as a source of variation between studies. Our principal question was whether the available evidence justifies distinct recommendations for next-step strategies after nonresponse to a first SSRI. We performed a systematic review following the Cochrane methodology and performed a meta-analysis of 2 switch options after a first SSRI: a second SSRI versus a serotonin-norepinephrine reuptake inhibitor (SNRI).

METHOD

Studies Included in the Review

We expected very few randomized, controlled, switch studies a priori, despite the widespread availability of SSRIs during the last decade. As best-available evidence, we included open and randomized studies in which at least 50% of participants used an SSRI previously in the current depressive episode. Thus, we excluded studies describing switching from TCAs to SSRIs. Studies performed in populations with TRD were also included if previous use of an SSRI (in ≥ 50% of subjects) was unambiguously documented.

Identification and Selection of Articles

We performed systematic literature searches (updated until February 10, 2005) in 4 databases (MEDLINE, EMBASE, CINAHL, and PsychINFO; all indexed years). In the absence of specific keywords for switching, we performed "sensitive" searches using free text words with wildcards ($): "switch$" or ("alternat$" adj5 "treat$") or ("alternat$" adj5 "therap$") in combination with the Cochrane Collaboration search filter for RCTs, the Cochrane Collaboration Depression Anxiety and Neurosis Group search filter for MDD, and MeSH terms for antidepressants (in combination with additional text words for all antidepressive agents). We limited searches to adults and humans, but did not apply language restrictions. Full queries are available on request. In addition, we included 4 identified studies released after these searches, including 3 studies from the STAR*D trial.[46–49]

The first and second authors (H.G.R., J.H.) independently screened titles and abstracts and selected articles on the basis of design and focus on switching antidepressants after SSRI treatment. Agreement on exclusion of irrelevant articles was 99.1%, with a Cohen's κ for interrater agreement of 0.62 (κ values between 0.45 and 0.75 indicate "substantial" agreement; values above 0.75 indicate "almost perfect" agreement.[50]). We resolved discrepancies between initial selection by discussion and consensus.

The first author (H.G.R.) judged all potentially relevant articles according to specific inclusion and exclusion criteria (full criteria available on request). In case of doubt, the article was fully read and assigned thereafter. We retrieved additional cross-references and checked reference lists of identified narrative reviews. We considered

Table 1. Levels of Evidence: Therapeutic Studies[a]

A1	Systematic review including at least some studies of A2 level; consistent results (homogeneity) across the included trials
A2	Randomized, controlled (double-blind) trial of good methodological quality, adequate size, and consistent results
B	Randomized, clinical trial of lower methodological quality or inadequate size; other comparative research (nonrandomized trial, comparative cohort study, case-control study)
C	Uncontrolled, open study
D	Expert opinion (guideline panel members)

[a]Reprinted with permission from the Dutch Institute of Healthcare Improvement.[51]

double publications together to reveal the maximum of available information.

Critical Appraisal and Summary

The first author (H.G.R.), a certified epidemiologist, critically appraised and abstracted the articles, using standardized forms derived from the Dutch Institute of Healthcare Improvement[51] and the Agency of Healthcare Policy and Research (AHCPR).[5] We used the same items for critical appraisal as proposed by the Scottish Intercollegiate Guidelines Network[52] and Sackett et al.[53] We assigned a "level of evidence" (LoE; Table 1) to each study.[51] Levels of evidence are based upon the methodological robustness of studies. In the Results section, the LoE of the supporting scientific evidence (A1–D) is indicated. We extracted data on efficacy and tolerability from each study. As primary efficacy outcome, we took the percentage response or remission on an intention-to-treat (ITT) basis. If several scales were used, we used a priori–preferred data for the Hamilton Rating Scale for Depression[137] (HAM-D; 17-item version [HAM-D-17] or other versions); otherwise, we used data from the Montgomery-Asberg Depression Rating Scale[138] (MADRS), Clinical Global Impressions scale[139] (CGI), or other applied scales (e.g., the 16-item Quick Inventory for Depressive Symptoms-Self-Rated[140] [QIDS-SR16]). For tolerability, we took the dropout rate due to side effects as the primary measure, followed by the overall dropout rate.

To assess judgment bias by 1 person who performed the critical appraisal, we measured interrater variation in a slightly different set of 12 publications. Every other author (J.H., J.A.S., A.H.S.) critically appraised 4 publications. Cohen's κ values for the appraisal items were 0.49 (for "validity of the study") and 0.86 (for "concealment of allocation"), while complete agreement existed for the appraisal items "randomization of the study," "level of evidence," and "data extraction" (κ = 1.0). These results are in line with other reports of interrater agreement in appraisal of psychiatric research.[54]

We first described a qualitative summary with discussion of the results, restrictions, methodological flaws, and external validity of the studies in an evidence table and a separate document, of which a summary is provided in this article. For each study, we indicated the level of treatment resistance as proposed by Thase and Rush.[10,24] If possible, we calculated risk differences and corresponding numbers needed to treat (NNT) and harm (NNH), with 95% confidence intervals (95% CIs). Because of the lack of homogeneous, randomized studies, we refrained from pooling in a meta-analysis, except for the 3 studies comparing the venlafaxine (SNRI) versus second SSRI switch. We grouped antidepressants into 6 classes following the classification of the AHCPR.[5]

RESULTS

We selected 31 studies for this review. Figure 1 shows the search results and selection of studies. Table 2 summarizes the included studies. A table of 8 excluded studies[55–62] is available on request.

Second SSRI

We identified 7 open studies investigating a switch to a second SSRI.[63–69] In 1 of these studies, the nonresponse to the initial SSRI was determined prospectively, and switching was applied immediately.[65] In 4 studies, intolerance was determined retrospectively, with an (unclear) interval between the end of the previous SSRI and the next.[63,64,66,68] In the remaining 2 (SSRI-intolerance) studies, patients either started a second SSRI soon after the first SSRI or had an SSRI-free interval.[67,69]

Response rates of switching in SSRI nonresponders varied between 46% and 58% in 3 uncontrolled studies of variable methodological quality.[63–65] The response rate was lower (42%) in a fourth study with a heterogeneous group of inpatients.[66] However, response rates to a second SSRI varied between 56% and 72% when patients were intolerant to the first SSRI (4 studies).[64,67–69] Dropout rates due to side effects were between 5% and 21% in studies with initial nonresponders[65] and between 0% and 10% in SSRI-intolerant samples[67–69] (LoE: C).

In the SSRI arms of 3 RCTs, response rates varied between 26.7% and 71.1%, while remission rates were between 17.6% and 52.1%.[46,47,70] Dropout rates due to side effects varied between 4.8% and 21.0%. For results on the comparisons with other arms, see below (LoE: A2–B).

In summary, the data from the open studies and 1 of the RCTs[46] suggest that, after 1 SSRI, nonresponders and, notably, also SSRI-intolerant patients can benefit from a switch to a second SSRI with response rates of approximately 50% and 70%, respectively. However, the results in 2 RCTs[47,70] indicated much less advantageous response and remission rates for a second SSRI (26.7%–29.0% and ~17.6%, respectively).

TCAs and Mianserin

We identified 2 RCTs with a switch to a TCA,[48,71] with 1 having limited power due to a randomization into 3

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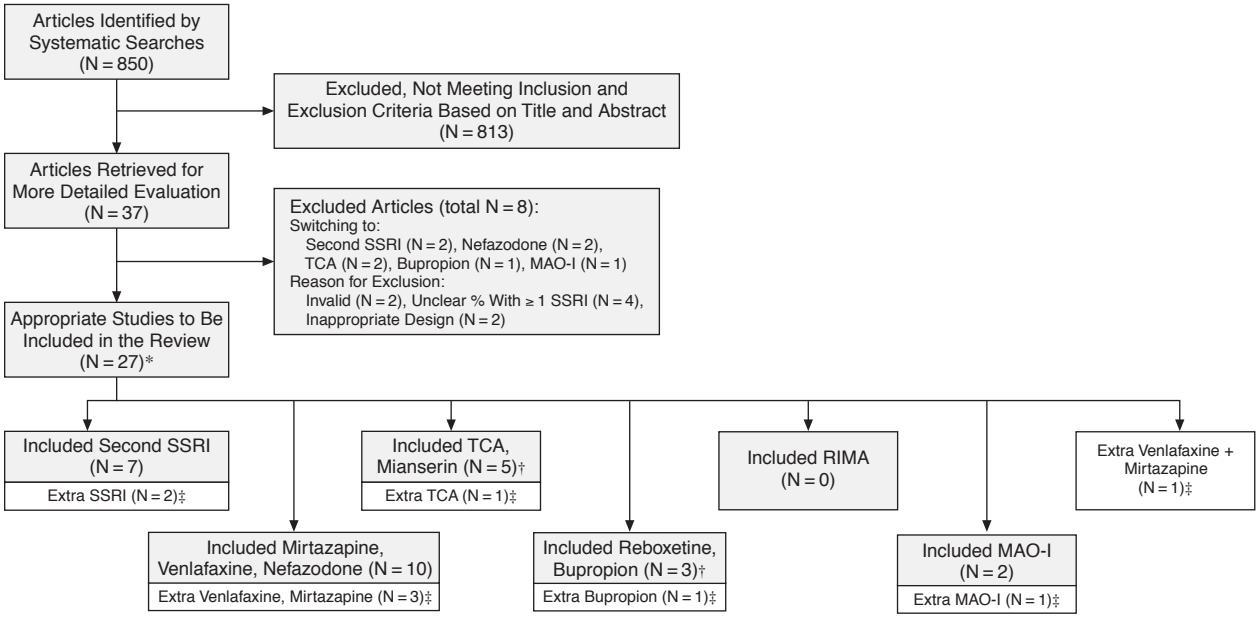
Figure 1. Selection of Reported Studies



*Two double publications† considered as 2 × 1 study.
‡In total, 4 extra publications with multiple contrasts released after systematic searches.
Abbreviations: MAO-I = irreversible inhibitor of monoamine-oxidase, RIMA = reversible inhibitor of monoamine-oxidase, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

arms.[71] Four open studies investigated a switch from an SSRI to a TCA.[72–76] The methodology of the open studies varied: 1 large crossover study was methodologically sound,[75,76] 1 small study was unequivocally poor,[74] and 2 studies were of reasonable quality (investigating populations with TRD).[72,73]

In the RCT of Ferreri et al.,[71] switching to mianserin (a noradrenergic tetracyclic) versus continuation of fluoxetine was investigated, with a third arm for their combination. No significant difference was found between switching to mianserin and continuation of fluoxetine (response: 48.5% and 36.8%, respectively; NNT = 9 [95% CI = 2.9 to ∞]) in an ITT analysis. The combination of fluoxetine and mianserin performed better than continuation of fluoxetine (response: 62.5% in the combination group; NNT = 4 [95% CI = 2.1 to 34.1]). Dropouts due to side effects were highest in the switch group (24%; NNH vs. continuation = 5 [95% CI = 2.6 to 10.4]) (LoE: B).

The STAR*D level III study[48] compared a switch to nortriptyline versus mirtazapine in a randomized, unblinded design. All participants received citalopram plus either a switch to sertraline, venlafaxine, or bupropion or citalopram augmentation with buspirone or bupropion. Response rates (≥ 50% decrease in QIDS-SR16 score) were 16.5% for nortriptyline and 13.5% for mirtazapine (NNT = 32 [95% CI = 8.1 to ∞]). Remission rates (HAM-D-17 score ≤ 7) were 19.8% versus 12.4% for nortriptyline and mirtazapine, respectively (NNT = 14 [95% CI = 6.0 to ∞]). There were no differences in remission rates for those intolerant to the level II treatments versus those who tolerated their second trial of antidepressants. Dropout rates due to side effects were high both for nortriptyline (34.7%) and mirtazapine (33.3%) (LoE: A2).[48]

Thase et al.[75,76] investigated a switch to imipramine in nonresponders to sertraline in chronic depressive outpatients. They found a 44% ITT response rate, with a dropout rate due to intolerable side effects of 9%.[75,76] The methodologically poor study by Peselow et al.[74] (including SSRI-intolerant patients) found a 73% responder rate after a switch to imipramine in outpatients. In the studies that recruited TRD populations, response rates after switching to nortriptyline[72] and oxaprotiline[73] decreased to 39% in inpatients[73] and 42% in outpatients,[72] with a 35% overall dropout rate in the latter study (LoE: C).

In summary, for the switch to a TCA, response rates of approximately 16.5% to 48.5% were found.[48,71–73,75,76] Lower response rates were observed in studies that included more treatment-resistant patients.[48,72,73]

Mirtazapine, Nefazodone, or Venlafaxine (novel dual-acting agents)

We identified 13 switch studies to novel dual-acting agents.[46–48,70,77–86] The methodological quality varied. Four studies were RCTs: Poirier and Boyer[70] compared a switch to paroxetine versus venlafaxine, Baldomero et al.[46] compared a switch to venlafaxine extended release

Table 2. Effectiveness of Switching After ≥ 1 SSRI: Selected Studies

Study	Level of Evidence	N (diagnosis)	Design (follow-up)	Intervention[a]
Switch to a second SSRI				
Baldomero et al (2005)[46] See under Switch to mirtazapine, nefazodone, venlafaxine (dual-action agents)				
Brown and Harrison (1995)[67]	C	112 (MDD/TRD-I)	Open, multicenter trial of fluoxetine-intolerant outpatients (8 wk)	Sertraline 50–200 mg
Calabrese et al (2003)[69]	C	55 (MDD/TRD-I)	Open, multicenter trial of fluoxetine-intolerant outpatients (6 wk)	Citalopram 20–40 mg
Joffe et al (1996)[63]	C	55 (MDD/TRD-I)	Retrospective study of outpatients treated with a second SSRI in 2 y (≥ 5 wk)	Fluoxetine (N = 12) Fluvoxamine (N = 9) Paroxetine (N = 11) Sertraline (N = 23)
Poirier and Boyer (1999)[70] See under Switch to mirtazapine, nefazodone, venlafaxine (dual-action agents) Poirier (1999)[83]				
Rush et al (2006)[47]	A2	727 (MDD/TRD-I)	3-arm, multicenter, unblinded RCT; outpatients (14 wk)	1. Venlafaxine extended release 75–375 mg 2. Bupropion 150–400 mg
Thase et al (1997)[64]	C	106 (MDD/TRD-I)	Open, multicenter trial of sertraline nonresponders or intolerant subjects; outpatients (6 wk)	Fluoxetine 20–60 mg
Thase et al (2001)[65]	C	57 (MDD/TRD-I)	Open study of prospectively determined fluoxetine nonresponders; outpatients (12 wk)	Citalopram 20 mg (dosages could be increased to 60 mg)
Thase et al (2002)[68]	C	61 (MDD/TRD-I)	Open study in paroxetine-intolerant outpatients (6 wk)	Citalopram 20 mg (dosages could be increased to 40 mg)
Zarate et al (1996)[66]	C	39 (MDD, bipolar disorder, schizoaffective disorder, obsessive-compulsive disorder/TRD > I)	Retrospective chart review of inpatients previously taking fluoxetine (various durations of follow-up)	Sertraline mean ± SD dose = 93 ± 62 mg
Switch to a TCA or mianserin				
Fava et al (2006)[48]	A2	234 (MDD/TRD-II)	Multicenter, unblinded RCT; outpatients (14 wk)	Nortriptyline 50–200 mg

Comparison[a]	Outcome[b]	Remarks
…	Response (CGI-I score ≤ 2) = 71.8% Dropout overall = 21.4% Dropout side effects = 9.8%	No placebo control; fluoxetine intolerance before switch only
…	Response (CGI-I score ≤ 2) = 65.5% Dropout overall = 5% Dropout side effects = 0%	No placebo control; fluoxetine intolerance before switch only; no minimum level of HAM-D score required for study entrance; start of citalopram after placebo washout of 2–4 wk
…	Response (CGI-I score ≤ 2) = 51% No significant differences between various combinations of switching No side effects reported	No placebo control; methodologically poor: retrospective study, unclear definition of initial nonresponse, small numbers, no characteristics of population; unclear after how many wk response was determined
Sertraline 50–200 mg	Remission (HAM-D-17 score ≤ 7): Venlafaxine = 24.8% Bupropion = 21.3% Sertraline = 17.6% $NNT_{venlafaxine\text{-}sertraline}$ = 14 (7.0 to ∞) $NNT_{bupropion\text{-}sertraline}$ = 28 (9.3 to ∞) $NNT_{venlafaxine\text{-}bupropion}$ = 29 (9.2 to ∞) Response (≥ 50% decrease in QIDS-SR16 score): Venlafaxine = 28.2% Bupropion = 26.1% Sertraline = 26.7% $NNT_{venlafaxine\text{-}sertraline}$ = 66 (10.6 to ∞) $NNT_{bupropion\text{-}sertraline}$ = 189 (13.4 to ∞) $NNT_{venlafaxine\text{-}bupropion}$ = 49 (10.1 to ∞) Dropout side effects: Venlafaxine = 21.2% Bupropion = 27.2% Sertraline = 21.0% (nonsignificant differences)	Unblinded study, blinded assessors, no placebo group; methodologically well-performed effectiveness trial; all participants received citalopram 20–60 mg as prior treatment (level II STAR*D); because of high doses of citalopram in level I, 407 (56%) of 727 subjects were classified as citalopram intolerant; no washout applied
…	Response (≥ 50% decrease in HAM-D-17 score): Overall = 62% Initial intolerant subjects = 71% Initial nonresponders = 58%	No placebo control; nonresponse to sertraline was determined retrospectively (in most patients)
…	Response (CGI-I score ≤ 2) = 63%; (≥ 50% decrease in HAM-D-24 score) = 46% Dropout overall = 18% Dropout side effects = 5%	Well-performed open study; unknown placebo response rate; tolerance for citalopram after fluoxetine was good, despite direct switch; no increased rate of side effects in first wks of study
…	Response (CGI-I score ≤ 2) = 56% Dropout overall = 13% Dropout side effects = 10%	Open study; no minimal HAM-D score at entrance; unknown placebo response rate; tolerance for citalopram after paroxetine was good; 1-week washout; recurrence of the same side effects as during paroxetine treatment was 5%–30%
…	Response (CGI-I score ≤ 2) = 41.9% at discharge and 26% at follow-up	Methodologically very poor study; retrospective, nonsystematic follow-up; sertraline was not prescribed following fluoxetine; heterogeneous study population with heterogeneous history of previous treatments (including MAO-Is, electroconvulsive therapy); confounding by noncompliance and additional pharmacotherapy (in 69% of patients); possible recall bias
Mirtazapine 15–60 mg	Remission (HAM-D-17 score ≤ 7): Nortriptyline = 19.8% Mirtazapine = 12.4% $NNT_{nortriptyline\text{-}mirtazapine}$ = 14 (6.0 to ∞) (not different in level II intolerant group) Response (≥ 50% decrease in QIDS-SR16 score): Nortriptyline = 16.5% Mirtazapine = 13.5% $NNT_{nortriptyline\text{-}mirtazapine}$ = 32 (8.1 to ∞) Dropout side effects: Nortriptyline = 34.7% Mirtazapine = 33.3%	Unblinded study, blinded assessors, no placebo group; methodologically well-performed effectiveness trial; participants received citalopram 20–60 mg and venlafaxine or bupropion or sertraline or augmentation of citalopram with bupropion or buspirone or cognitive-behavioral therapy (level III STAR*D); 52.1% were considered level II intolerant; blood levels of nortriptyline allowed but not obligatory for dosing (33.9% measured); no washout applied

continued

Table 2. Effectiveness of Switching After ≥ 1 SSRI: Selected Studies (cont.)

Study	Level of Evidence	N (diagnosis)	Design (follow-up)	Intervention[a]
Switch to a TCA or mianserin				
Ferreri et al (2001)[71]	B	103 (MDD/TRD-I)	3-arm, multicenter RCT of nonresponders to fluoxetine 20 mg; inpatients and outpatients (6 wk)	1. Mianserin 60 mg 2. Fluoxetine 20 mg + mianserin 60 mg
Nierenberg et al (2003)[72]	C	92 (MDD/TRD > II)	Open phase of nortriptyline treatment in outpatients preceding a second RCT[136] (6 wk)	Nortriptyline 100 mg (adjusted to achieve 100 ng/mL)
Nolen et al (1988)[73]	C	31 (MDD/TRD-III)	Blinded, consecutive therapy after 4 wk of fluvoxamine; inpatients (4 wk)	Oxaprotiline 100–300 mg
Peselow et al (1989)[74]	C	15 + 10 (MDD/TRD-I)	Blinded, crossover design with original randomization; outpatients (6 wk)	Imipramine 65–275 mg
Thase et al (1995)[76] Thase et al (2002)[75]	C	117 (chronic MDD, MDD + dysthymia/TRD-I)	Blinded, multicenter crossover design with original randomization; outpatients (12 wk)	Imipramine 50–300 mg
Switch to mirtazapine, nefazodone, venlafaxine (dual-action agents)				
Baldomero et al (2005)[46]	B	3097 (MDD + minor depression + dysthymia/ TRD-I)	Multicenter, open design; RCT of venlafaxine vs CA in SSRI-nonresponsive or SSRI-intolerant outpatients (24 wk)	Venlafaxine 75–225 mg
Fava et al (2001)[77]	C	94 (MDD/TRD-I)	Multicenter, open design (RCT of direct switch vs washout); outpatients (8 wk)	Mirtazapine 15–45 mg
Fava et al (2006)[48] See under Switch to a TCA or mianserin				

Comparison[a]	Outcome[b]	Remarks
3. Fluoxetine 20 mg	Response (≥ 50% decrease in HAM-D-17 score): Mianserin = 48.5% Fluoxetine = 37% NNT = (1–3, mianserin vs fluoxetine): 9 (2.9 to ∞); (2–3): 4 (2.1 to 34.1) Remission (HAM-D-17 score ≤ 8): Mianserin = 36% Fluoxetine = 18% NNT = (1–3, mianserin vs fluoxetine): 6 (2.6 to ∞); (2–3): 4 (2.2 to 23.9) Dropout side effects: NNH = (1–3, mianserin vs fluoxetine): 5 (2.6 to 10.4); (2–3): 16 (6.8 to ∞) Dropout overall: NNH = (1–3, mianserin vs fluoxetine): 6 (2.6 to ∞); (2–3): 64 (4.9 to ∞)	Methodologically sound, small sample size for 3 arms, limited power; in the mianserin group because of long half-life of fluoxetine, first wks were also sort of "combination" therapy; low dose of continued fluoxetine in reference group; no washout applied, direct switch associated with increased intolerance and dropout
…	Response (≥ 50% decrease in HAM-D-17 score) = 42.4% Remission (HAM-D-17 score ≤ 7) = 11.9% Dropout overall = 34.7%	TRD defined as 1–5 failed adequate trials during current episode (mean ± SD = 2.3 ± 1.5); 95.7% of patients were treated with ≥ 1 SSRI; unknown placebo response rate
…	Response (≥ 50% decrease in HAM-D-17 score) = 38.7% Relapse = 19.4% within 6 mo	Modified ITT analysis, excluding patients who dropped out in first 2 wk; TRD: patients used ≥ 1 TCA before treatment with fluvoxamine; no data on dropouts
…	Response (≥ 50% decrease in HAM-D score or CGI-I score ≤ 2): Paroxetine switched to imipramine = 73%	Methodologically poor: unclear description of studied population, limited presentation of data; data of initial nonresponders to imipramine switched to paroxetine also provided
…	Response (CGI-I score ≤ 2, ≥ 50% decrease in HAM-D-24 score, HAM-D-24 score ≤ 15, and CGI-S score ≤ 3): Sertraline switched to imipramine = 44.4% Remission (HAM-D-24 score ≤ 7 and CGI-I score ≤ 2): Sertraline switched to imipramine = 23% Dropout overall = 25% Dropout side effects = 9%	Well-performed study; unknown placebo response rate; data of initial nonresponders to 12 wk imipramine switched to sertraline also provided; because of absence of second randomization, only tentative comparisons with switch from imipramine to sertraline available
CA: fluoxetine, paroxetine, citalopram 20–60 mg; sertraline 50–200 mg; mirtazapine 15–45 mg	Response (≥ 50% decrease in HAM-D-17 score): Venlafaxine = 77.3% SSRIs = 71.1% $NNT_{venlafaxine\text{-}SSRI}$ = 17 (10.5 to 35.0) Remission (HAM-D-17 score ≤ 7): Venlafaxine = 59.3% SSRIs = 52.1% $NNT_{venlafaxine\text{-}SSRI}$ = 14 (9.1 to 29.3) HAM-D-17 scores differ significantly but clinically irrelevant at wk 12 and 24 Dropout overall: Venlafaxine = 19.6% CA = 23.3% $NNH_{venlafaxine\text{-}CA}$ = 27 (15.1 to 120) Dropout side effects: Venlafaxine = 2.3% CA = 1.7% $NNH_{venlafaxine\text{-}CA}$ = 161 (62.1 to ∞)	Large randomized but unblinded study; some methodological problems; ^3.3% of included patients previously used an SSRI; inclusion of 8.7% with minor depression; no differentiation of first SSRI-intolerant and SSRI-unresponsive patients; modified ITT analysis of ≥ wk 4 completers; in CA-treated switch group, 22.7% received a non-SSRI; baseline HAM-D-17 scores were significantly higher in venlafaxine group; differential loss to follow-up was 26.2% venlafaxine vs 36.2% CA; only 3 time points over 24 wk; no separate dichotomous data for wk 12 response/remission
…	Response (≥ 50% decrease in HAM-D-17 score): SSRI nonresponsive = 48% SSRI intolerant = 53% Dropout overall = 43% Dropout side effects = 26%	Methodologically sound; unknown placebo response rate; washout phase offers no advantages

continued

Table 2. Effectiveness of Switching After ≥ 1 SSRI: Selected Studies (cont.)

Study	Level of Evidence	N (diagnosis)	Design (follow-up)	Intervention[a]
Switch to mirtazapine, nefazodone, venlafaxine (dual-action agents)				
Kaplan (2002)[78]	C	73 (MDD/TRD-I)	Retrospective, naturalistic study of SSRI nonresponders or nonsustaining SSRI responders; outpatients (6–8 wk + follow-up)	Venlafaxine 50–400 mg
Mischoulon et al (2004)[79]	C	13 (MDD/TRD > I)	Open design of SSRI-nonresponsive or SSRI-intolerant outpatients (12 wk)	Nefazodone 300–600 mg
Mitchell et al (2000)[80]	C	312 (MDD/TRD ≥ I)	Multicenter, open, unblinded design; setting unknown (8 wk)	Venlafaxine 75–300 mg
de Montigny et al (1999)[81]	C	152 (MDD/TRD-I)	Multicenter, open design; inpatients and outpatients (8 wk)	Venlafaxine 75–375 mg
Nierenberg et al (1994)[82]	C	70 (MDD/TRD-III)	2-center, open design; inpatients and outpatients (12 wk)	Venlafaxine 50–450 mg
Poirier and Boyer (1999)[70] Poirier (1999)[83]	A2	123 (MDD/TRD-II)	Multicenter RCT; inpatients and outpatients (4 wk)	Venlafaxine 75–300 mg
Reynaert-Dupuis et al (2002)[84]	C	688 (MDD/TRD-I)	Multicenter, naturalistic, open design; inpatients and outpatients (6 wk)	Venlafaxine 75–375 mg
Rush et al (2006)[47] See under Switch to a second SSRI				
Saiz-Ruiz et al (2002)[85]	C	69 (MDD/TRD-I)	Multicenter, naturalistic, open design; outpatients (24 wk)	Venlafaxine 75–375 mg
Wan et al (2003)[86]	C	24 (MDD/TRD ≥ II)	Retrospective chart review of consecutive subjects who failed response to ≥ 1 TCA and ≥ 1 SSRI; unknown setting (2 wk–3 y)	Mirtazapine 15–45 mg

Comparison[a]	Outcome[b]	Remarks
…	Response (HAM-D-25 score ≤ 10 and PGI-21 score ≥ 5) = 86% Remission (HAM-D-25 score ≤ 8) = 82% Dropout side effects = 5.5%	Methodologically very poor; open, unblinded design; 1 researcher; retrospective data obtained; mild depression included also; unclear, but probable selection bias; recruitment of SSRI responders who did not sustain their response (52%) might increase response rate; ITT results not mentioned in study
…	Response (> 50% decrease in HAM-D-6 score and/or CGI-S score ≤ 2) = 31% Dropout side effects = 39%	Small sample (pilot study); unknown placebo response rate; 61.5% attrition, especially in previous fluoxetine users; washout of 4–7 d applied; heterogeneous group with TRD, approximately 46% ≥ stage II; no significant differences in response rates and side effects compared with 13 patients treated with nefazodone as first applied antidepressant (but low power)
…	Response (> 50% decrease in MADRS score) = 52.6% Remission (MADRS score < 12) = 40.7% Dropout side effects = 11%	Methodologically sound; unclear setting; unknown placebo response rate; unclear which proportion used ≥ 1 SSRI (41%–68%); probably chronically depressed subjects
…	Response (≥ 50% decrease in HAM-D-21 score) = 58%; (≥ 50% decrease in MADRS score) = 62%; (CGI-S score ≤ 3) = 66% Remission (≥ 75% decrease in HAM-D-21 score) = 21% Dropout side effects = 7.9%	TRD: at least 1 previous TCA or SSRI or moclobemide, trazodone, or nefazodone; majority of patients used an SSRI; mean duration of episode 2 y (range, 2 mo–12.5 y); unknown placebo response rate
…	Response (≥ 50% decrease in HAM-D-21 score) = 32.9%; (≥ 50% decrease in MADRS score) = 30%; (CGI-I score ≤ 2) = 40% Remission (HAM-D-21 score ≤ 8) = 15.7%; (MADRS score ≤ 12) = 18.6%; (CGI-I score = 1) = 22.9% Dropout side effects = 9.6%	TRD: at least ≥ 3 drugs of ≥ 2 different classes, ≥ 1 TCA, and ≥ 1 augmentation; unclear what proportion of patients used ≥ 1 SSRI; chronically depressed group (median duration of 2.5 y); unknown placebo response rate
Paroxetine 20–40 mg	Response (≥ 50% decrease in HAM-D-17 score): Venlafaxine = 45.0% Paroxetine = 29.0% $NNT_{venlafaxine\text{-}paroxetine}$ = 7 (3.0 to ∞) Remission (HAM-D-17 score ≤ 10): Venlafaxine = 36.7% Paroxetine = 17.7% $NNT_{venlafaxine\text{-}paroxetine}$ = 6 (2.9 to 28.9) Dropout side effects: Venlafaxine = 8.2% Paroxetine = 4.8% $NNH_{venlafaxine\text{-}paroxetine}$ = 30 (8.3 to ∞)	Methodologically sound; short follow-up during study; dosing schedules were different between venlafaxine and paroxetine
…	Response (≥ 50% decrease in HAM-D-21 score) = ±61% (in previous SSRI-treated patients)	86.3% of patients were switched to venlafaxine because of inefficacy; of 41.7% who were switched from an SSRI, separate response rates were given; immediate switching applied (except from MAO-Is); unclear presentation of data; dropout rate not mentioned; type of previous SSRI did not significantly affect venlafaxine efficacy
…	Response (≥ 50% decrease in HAM-D-17 score) = 69.6%; (CGI-I score ≤ 2) = 63.8% Dropout overall = 30.4% Dropout side effects = 8.7% Side effects occurred in 54%	Selection of nonresponse to a previous SSRI in at least a standard dose for 4 wk; limited presentation of data; in the article, a modified ITT analysis was applied for wk 4 completers; endpoint of study was only reported for wk 24
…	Response (CGI-I score ≤ 2) = 16.7% Partial response (CGI-I score = 3) = 20.8% Dropout side effects = 20.8%	Methodologically very poor; in 17.2% of eligible patients, data were insufficient for inclusion; highly treatment-resistant population (mean of 7 previous drug trials [range, 2–13]); unclear what response indicated switch to mirtazapine; CGI data determined by chart review; chronic depression in 45.8%; high level of comorbidity with anxiety disorders; comedication with antidepressants and antipsychotics in 41.7%

continued

Table 2. Effectiveness of Switching After ≥ 1 SSRI: Selected Studies (cont.)

Study	Level of Evidence	N (diagnosis)	Design (follow-up)	Intervention[a]
Switch to reboxetine or bupropion (selective NRI or noradrenergic and dopaminergic agents)				
Fava et al (2003)[90]	C	128 (MDD/TRD-I)	Multicenter, open design of fluoxetine-nonresponding outpatients (8 wk)	Reboxetine 8–10 mg
Fava et al (2003)[88]	C	29 (MDD/TRD-I)	2-center open design of prospectively determined fluoxetine-nonresponding outpatients (8 wk)	Bupropion-sustained release 150–400 mg
Rush et al (2006)[47] See under Switch to a second SSRI				
Walker et al (1993) [89]	C	39 (MDD/TRD-I)	Open design of patients with sexual side effects taking fluoxetine; partial fluoxetine nonresponders: N = 16; outpatients (8 wk)	Bupropion 150–450 mg
Switch to an MAO-I				
McGrath et al (2006)[49]	B	109 (MDD/TRD ≥ II)	Multicenter, unblinded RCT; outpatients (12 wk)	Tranylcypromine 10–60 mg
Nolen et al (1985)[92]	B	26 (MDD/TRD ≥ II)	Randomized, unblinded, crossover design; inpatients (4 wk)	Tranylcypromine 20–100 mg
Nolen et al (1988)[91]	B	21 (MDD/TRD ≥ II)	RCT with secondary crossover; inpatients (4 wk)	Tranylcypromine 40–100 mg

[a]All dosages in mg/day.
[b]Intention-to-treat (ITT) results unless specified.
Abbreviations: CA = conventional antidepressant (paroxetine, fluoxetine, sertraline, citalopram, mirtazapine, and other antidepressants not specified), CGI = Clinical Global Impressions scale, CGI-I = CGI-Improvement scale, CGI-S = CGI-Severity of Illness scale, HAM-D = Hamilton Rating Scale for Depression (6-item = HAM-D-6, 17-item = HAM-D-17, 21-item = HAM-D-21, 24-item = HAM-D-24, 25-item = HAM-D-25, 28-item = HAM-D-28), L5HTP = L-5-hydroxy-tryptophan, MADRS = Montgomery-Asberg Depression Rating Scale, MAO-I = irreversible inhibitor of monoamine-oxidase, MDD = major depressive disorder, NNH = number needed to harm (95% CIs are also included),

Comparison[a]	Outcome[b]	Remarks
…	Response (≥ 50% decrease in HAM-D-25 score and CGI-I score ≤ 2) = 44.5% Response (≥ 50% decrease in HAM-D-17 score) = 45.3% Dropout side effects = 13.3%	Methodologically well-performed open study; unknown placebo response rate; fluoxetine nonresponders determined at end of fluoxetine treatment; direct switch to reboxetine well tolerated; because of long half-life of fluoxetine, first 4 wk were "combination" therapy
…	Modified ITT (N = 26) Response (≥ 50% decrease in HAM-D-17 score) = 34.6% Partial response (25%–49% decrease in HAM-D-17 score) = 30.8% Remission (HAM-D-17 score ≤ 7) = 23.1%	Methodologically well performed but small open study; unknown placebo response rate; no specified dropout rates; fluoxetine nonresponders prospectively determined; direct switch to bupropion; no documentation of effects of this switch; because of long half-life of fluoxetine, first 4 wk were "combination" therapy
…	All (N = 36): Decrease in HAM-D-28 mean ± SD score = 16.6 ± 7.8 to 8.4 ± 8.3 Dropout side effects = 10.3% Dropout inefficacy = 10.3% Baseline HAM-D-28 score ≥ 18 (N = 16): decrease in HAM-D-28 mean ± SD score = 25.4 ± 5.8 to 10.9 ± 10.8	Initial design of switching because of sexual side effects; limited data provided for depressed subjects, eg, no response rates; unknown placebo response rate; improvement of orgasm function (84%), satisfaction (78%), and libido (78%) after switch; 2-wk washout applied; disappearance of sexual dysfunction linear with fluoxetine washout
Venlafaxine-extended release 75–300 mg + mirtazapine 15–45 mg	Remission (HAM-D-17 score ≤ 7): Tranylcypromine = 6.9% Venlafaxine-mirtazapine = 13.7% NNH = 15 (5.5 to ∞) Response (≥ 50% decrease in QIDS-SR16 score): Tranylcypromine = 12.1% Venlafaxine-mirtazapine = 23.5% NNH = 9 (3.9 to ∞) Dropout side effects: Tranylcypromine = 41.4% Venlafaxine-mirtazapine = 21.6% NNH = 6 (2.7 to 35.2)	Unblinded study, blinded assessors; participants received at least 1 SSRI, a second SSRI or venlafaxine or bupropion or citalopram augmentation (bupropion or buspirone) and some cognitive-behavioral therapy, and a third treatment with nortriptyline or mirtazapine (level IV STAR*D)
L5HTP 20–200 mg	Response (≥ 50% decrease in HAM-D-17 score): Tranylcypromine = 42.9% L5HTP = 0% NNT = 3 (1.5 to 5.9) Tranylcypromine side effects = 61.5% cardiovascular, 15.4% insomnia	Small study, allocation of initial treatment not clearly described; study groups differed significantly in baseline HAM-D-17 score; stage II–III TRD patients; in the article, data of second 4 wk (crossover phase) were also given; limited presentation of data
Nomifensine 150–250 mg	Response (≥ 50% decrease in HAM-D-17 score): Tranylcypromine = 45.5% Nomifensine = 10.0% NNT = 3 (1.4 to 154.8) Tranylcypromine side effects = 58% cardiovascular, 33% insomnia	Stage II–III TRD patients; unclear method of randomization; in the article, data of second 4 wk (crossover phase) were also given; limited presentation of data

Abbreviations continued: NNT = number needed to treat (95% CIs are also included), NRI = norepinephrine reuptake inhibitor, QIDS-SR16 = 16-item Quick Inventory of Depressive Symptomatology-Self-Rated, PGI-21 = 21-item Patient Global Improvement scale, RCT = randomized, controlled trial, SSRI = selective serotonin reuptake inhibitor, STAR*D = Sequenced Treatment Alternatives to Relieve Depression, TCA = tricyclic antidepressant, TRD = treatment-resistant depression (stages: I = failure of 1 adequate trial of 1 major antidepressant class, II = stage I + failure of an adequate trial of 1 distinctly different antidepressant class, III = stage II + failure of an adequate trial of a TCA, IV = stage III + failure of an adequate trial of an MAOI, V = stage IV + failure of a course of bilateral electroconvulsive therapy[10,24]).

versus switching to any other antidepressant (77% of these switches used paroxetine, citalopram, sertraline, or fluoxetine) in an unblinded design, and the level II and III STAR*D switch studies, which were also unblinded studies, compared a switch after citalopram to venlafaxine extended release, bupropion, or sertraline[47] and the switch thereafter to nortriptyline or mirtazapine.[48] Other studies described open studies with mirtazapine,[77,86] nefazodone,[79] and venlafaxine.[78,80–82,84,85] In 7 of the studies, all patients received an SSRI before switching.[47,48,77–79,85,86] Five studies included patients with variable but higher levels of treatment resistance[48,70,79,82,86]; in 2 studies, this was unclear.[77,80] In contrast, 1 study included patients (52%) who initially responded to an SSRI but did not sustain their response.[78]

In the RCT performed by Poirier and Boyer,[70] switching to venlafaxine was more efficacious than paroxetine when remission (HAM-D-17 score ≤ 10) was considered (remission rates: 36.7% and 17.7%, respectively), with an NNT of 6 (95% CI = 2.9 to 28.9). For a response criterion (≥ 50% reduction in HAM-D-17 score), the difference was insignificant (response rates: venlafaxine = 45% and paroxetine = 29%; NNT = 7 [95% CI = 3.0 to ∞]). Dropout rates due to side effects were comparable (8.2% for venlafaxine and 4.8% for paroxetine; NNH = 30 [CI = 8.3 to ∞]) (LoE: A2).

In the randomized, unblinded study by Baldomero et al.,[46] venlafaxine showed a significantly increased remission (HAM-D-17 score ≤ 7) rate (59.3%) compared with conventional antidepressants (51.5%) after 24 weeks of treatment, with an NNT of 13 (95% CI = 8.9 to 23.7).[46] In the conventional antidepressant group, 77.3% of the patients used a second SSRI; for SSRIs, the remission rate was 52.1% (NNT = 14 [95% CI = 9.1 to 29.3]). Response (≥ 50% reduction in HAM-D-17 score) rates also showed a modest but significant advantage: 77.3% for venlafaxine versus 71.1% for SSRIs (NNT = 17 [95% CI = 10.5 to 35.0]). Overall dropout rate was slightly lower in the venlafaxine group when compared with all conventional antidepressants (19.6% vs. 23.3%; NNH = 27 [95% CI = 15.1 to 119.9]). Dropout rates due to side effects were not significantly different between venlafaxine and conventional antidepressants (2.3% vs. 1.7%, respectively; NNH = 160.8 [95% CI = 62.1 to ∞]) (LoE: B).

The level II STAR*D trial did not find significant differences between the switches to venlafaxine, bupropion, and sertraline.[47] Before the switch, all participants received citalopram (20–60 mg for a maximum of 14 weeks). Patients were randomized over different randomization possibilities for which they were at equipoise.[87] The assessors of the primary outcome (17-item HAM-D-17) were blind to the treatment. After 14 weeks of treatment, response rates (≥ 50% decrease in QIDS-SR16 score) were 28.2% for venlafaxine, 26.1% for bupropion, and 26.7% for sertraline (not significant). Remission rates (HAM-D-17 score ≤ 7) were not significantly different for venlafaxine, bupropion, and sertraline (24.8%, 21.3%, and 17.6%, respectively). For corresponding NNTs, see Table 2. The dropout rate due to side effects was not statistically different for venlafaxine (21.2%), bupropion (27.2%), and sertraline (21.0%) (LoE: A2).

The level III switch study[48] was described earlier. Mirtazapine response, remission, and side effect–related dropout rates were 13.5%, 12.4%, and 33.3%, respectively, (LoE: A2).

In open studies, mirtazapine, nefazodone, and venlafaxine showed response rates between 17% and 86%, with decreased response rates at increased levels of treatment resistance (LoE: C).[77–82,84–86] Dropout rates due to adverse effects varied between 5.5% and 11.0% for venlafaxine[78,80–82,85] and between 20.8% and 25.7% for mirtazapine,[77,86] and the rate was 38.5% in 1 study with nefazodone[79] (LoE: A2, C).

We performed a meta-analysis of the 3 RCTs that compared switching to venlafaxine versus SSRIs, although the differences in duration of follow-up introduced some heterogeneity (ranging from 4 weeks by Poirier and Boyer[70] to 24 weeks by Baldomero et al.[46]). As shown in Figure 2, the weighted difference in remission rates (fixed-effects model) was 8% (4%–11%) in favor of venlafaxine (NNT = 13 [95% CI = 9.1 to 25.0]) and for response was 6% (1%–10%) (NNT = 17 [95% CI = 10.0 to 100.0]). Omission of the methodologically poorer study of Baldomero et al.[46] increased the difference in remission rates (10% [95% CI = 3 to 16] fixed-effects model; NNT = 10 [95% CI = 6.3 to 33.3]), but decreased the difference in response rates (4% [–3% to 12%] fixed-effects model; NNT = 25 [95% CI = 8.3 to ∞]). The dropout rate due to side effects was only reported in 2 studies[47,70]; the weighted difference was 1% (–5% to 7%) (fixed-effects model), with more dropouts for venlafaxine.

In summary, heterogeneous studies considering switching to mirtazapine, nefazodone, and venlafaxine showed response rates of approximately 28% to 50% in subjects without obvious TRD, while in subjects with increased levels of TRD, response percentages dropped (investigated for venlafaxine and mirtazapine). Pooling of results showed a modest and clinically equivocally advantageous increased remission rate for venlafaxine over SSRIs (NNT = 13 [95% CI = 9.1 to 25.0]).

Bupropion and Reboxetine (agents specifically affecting dopaminergic and/or noradrenergic neurotransmission)

We identified 1 RCT and 2 small open studies of switching to bupropion.[47,88,89] The STAR*D level II switch study including bupropion was described earlier.[47] There were no significant differences in remission or response rates for bupropion compared with venlafaxine or sertraline. In this study, bupropion had the (statistically insig-

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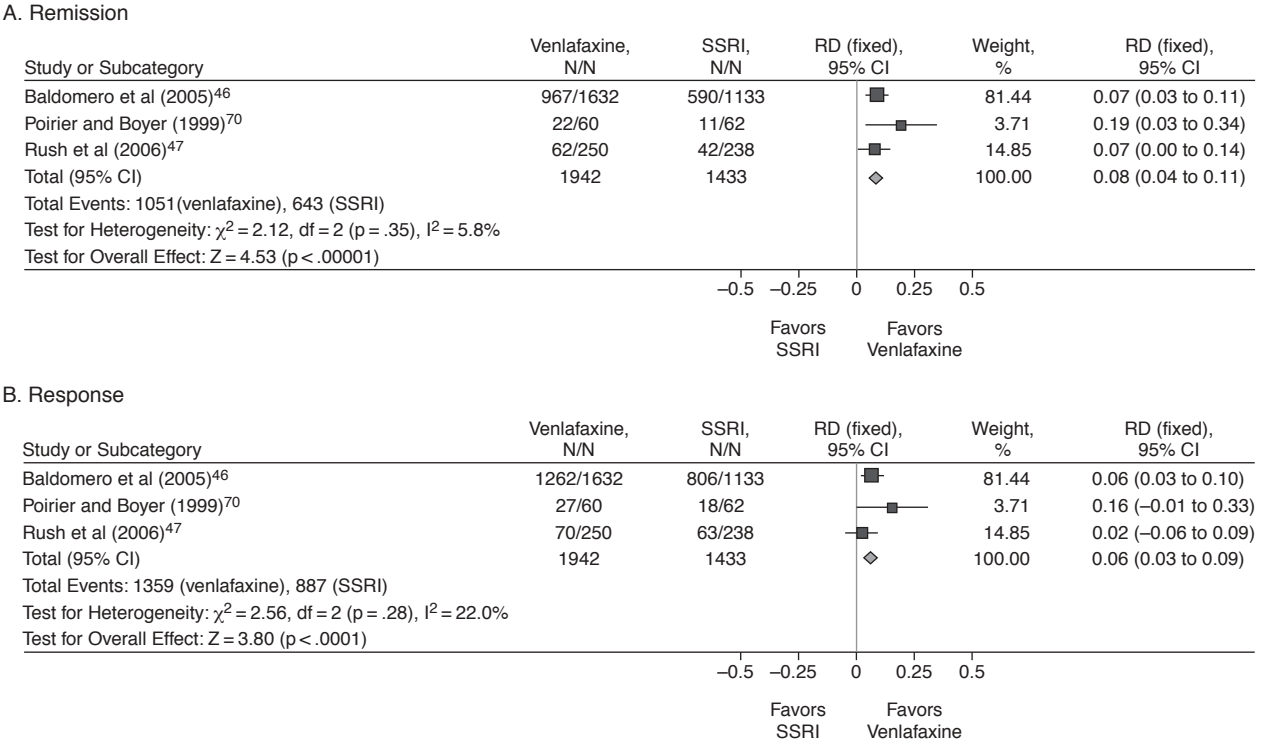
Figure 2. Meta-Analysis of Switch Studies Comparing a Switch to Venlafaxine Versus a Second SSRI



Abbreviations: RD = risk difference (remission/response rate in venlafaxine vs. SSRI), SSRI = selective serotonin reuptake inhibitor.

nificant) highest dropout rate (27.2) due to side effects (LoE: A2).[47]

In 2 open studies with bupropion, Fava et al.[88] prospectively determined fluoxetine nonresponse in a small but well-performed study, and Walker et al.[89] recruited patients who were primarily suffering sexual side effects of fluoxetine and only reported a decrease in 28-item HAM-D scores. One larger, well-performed, open study investigated the switch to reboxetine in fluoxetine nonresponders.[90]

Thus, switching from fluoxetine was investigated, with reported response rates of 34.6% for bupropion[88] and 45.3% for reboxetine.[90] For bupropion, specified dropout rates were not reported in 1 study.[88] The side effect–related dropout rate was 10.3% in subjects with sexual dysfunction while taking fluoxetine.[89] For reboxetine, the dropout rate due to side effects was 13.3% (LoE: C).[90]

In summary, switching to bupropion or reboxetine was scarcely studied but was a possible option with response rates of 26.1% to 34.6% and 45.3%, respectively.[47,88–90] The remission rate of switching to bupropion was not different compared with venlafaxine or sertraline.

Reversible Inhibitor of Monoamine-Oxidase A

We identified no studies that investigated switching from an SSRI to a reversible inhibitor of monoamine-oxidase A.

Monoamine-Oxidase A Inhibitor

We identified 1 RCT[49] from STAR*D (level IV) and 2 small, interrelated, randomized studies[91,92] after 4 weeks of treatment with at least 1 SSRI (fluvoxamine) and oxaprotiline. We identified no studies of SSRI nonresponders in atypical depression. Two studies were RCTs[49,91] and 1 was an unblinded, randomized, crossover study.[92] The STAR*D study investigated outpatients[49]; the studies by Nolen et al.[91,92] were performed in treatment-resistant inpatients.

Nolen et al.[91] found tranylcypromine to be more efficacious than nomifensine; in their studies, the response rates for tranylcypromine were 42.9% and 45.5%.[91,92] All patients previously received at least fluvoxamine and oxaprotiline. Fifty-eight percent to 62% had side effects affecting their blood pressure levels (LoE: B).

The STAR*D level IV study[49] included patients who had not been in remission after citalopram treatment (level I); who received venlafaxine, bupropion, sertraline, or citalopram augmentation with buspirone or bupropion (level II); and who additionally received nortriptyline or mirtazapine (level III).[49] These patients were randomized between tranylcypromine and a combination of venlafaxine with mirtazapine. Of the included patients, 32.1% were intolerant of the level III medication. Remission rates (HAM-D-17 score ≤ 7) were low for tranylcypromine (6.9%) and the combination treatment (13.7%;

NNH = 15 [95% CI = 5.5 to ∞]). Response rates (≥ 50% decrease in QIDS-SR16 score) were also not significantly different: 12.1% vs. 23.5% for tranylcypromine and venlafaxine with mirtazapine, respectively (NNH = 9 [95% CI = 3.9 to ∞]).[49]

Dropout rates due to side effects were higher for tranylcypromine: 41.4% versus 21.6% for venlafaxine with mirtazapine (NNH = 6 [95% CI = 2.7 to 35.2]).[49]

Additional Concerns for Clinicians Regarding Switching

Little evidence is available about the optimal way to switch.[20,29,65,84,93] Abrupt reduction or discontinuation of SSRIs may produce somatic and psychological withdrawal symptoms, of which occurrence is inversely related to the plasma half-life of the initial SSRI.[94,95] Overlap of antidepressants during switching is generally avoided.[20,29]

Direct switching (without a washout phase) from an initial SSRI (fluoxetine at the standard dose or citalopram at high dosages) to another SSRI (paroxetine, citalopram, sertraline),[47,65,93] nortriptyline,[48] mirtazapine,[48,77] bupropion,[47] reboxetine,[90] or venlafaxine was well tolerated.[47,84] Also, direct switching reduced the emergence of side effects compared with placebo in a 1-week washout phase (which might have been discontinuation symptoms).[93]

In case of higher than standard doses of SSRIs, some data for tolerance of direct switching were generated by STAR*D.[47–49] However, the results published so far do not specify dropout rates in the first 2 weeks after switching. Also, because tapering of high doses of previous antidepressants was not applied in STAR*D, this trial was not designed to examine the optimal switch strategy if higher than standard doses were used before the switch. Thus, if necessary, direct switching of high-dose antidepressant therapy appears possible after citalopram as a first SSRI.[47]

In a case of switching from an SSRI to a TCA, other reviewers did not recommend a washout period.[20,29] In 1 included study, a direct switch to mianserin was less well tolerated.[71] For switching to nefazodone, in 1 study, a 4-day to 7-day washout was applied but not investigated.[79] A 1-week washout period is suggested for switching to a reversible inhibitor of monoamine-oxidase A, and a 1-week to 2-week washout period is recommended for switching to a monoamine-oxidase A inhibitor.[20,29] For fluoxetine, these washout periods should be prolonged to 5 weeks because of the long half-life of fluoxetine and norfluoxetine.[20] The inhibition of cytochrome P450 subenzymes by SSRIs may increase the levels of some TCAs during the first to fifth (fluoxetine) week.[20]

DISCUSSION

This report systematically reviewed and appraised the available research focusing on switching strategies for SSRI-nonresponders in MDD, including the recent STAR*D results. We found that the available evidence does not justify distinct recommendations for next-step strategies after nonresponse to a first SSRI. The pooled difference in remission rates of switching to venlafaxine (an SNRI) versus a second SSRI showed a modest and clinically equivocal advantage of venlafaxine (NNT = 13 [95% CI = 9.1 to 25.0]), this difference increased when the largest and methodologically poorest study was omitted (NNT = 10 [95% CI = 7 to 34]).

In summary, after a first SSRI, switching to any of the current classes of antidepressants has approximately a 50% chance of response. Still, a direct comparison of the rates across the predominantly open studies is methodologically not justified. In STAR*D, response and remission rates were lower (respectively, 26.8% and 21.3% at level II,[47] 15% and 16.2% at level III,[48] and 17.4% and 10.1 at level IV[49]). Rush et al.[47] attributed these lower remission rates to the inclusion of patients who were more chronically depressed, had lower socioeconomic status, and suffered from more comorbid somatic and psychiatric diseases. In general, the level of TRD[10] of included studies was inversely correlated with treatment outcome. Although this finding carries the risk of an ecological fallacy, it is worrisome, as is also apparent in the STAR*D results. After the second antidepressant, the chances of response or remission by switching again are becoming rather low, challenging us to find new approaches.[96–98]

Dropouts due to side effects varied between 5% and 21% for a second SSRI and venlafaxine; 10% and 35% for TCAs, bupropion, and reboxetine; 20% and 33% for mirtazapine; 39% for nefazodone; and 41.4% for tranylcypromine. It should be noted, however, that these percentages cannot simply be compared with each other, because of heterogeneous populations and open-study designs. In randomized comparisons, no significant differences in side effect–related dropout were found, except for tranylcypromine versus a combination of venlafaxine with mirtazapine.[49]

With 8 RCTs,[46–49,70,71,91,92] switching options after a first SSRI were generally investigated with open studies. In these open studies, switching to a second SSRI (7 studies) and venlafaxine (7 studies) were studied most frequently. Furthermore, the studies were of variable methodological quality. In our opinion, the available evidence for switching strategies allows general recommendations only. Switching is open to all studied antidepressant classes (second SSRI, novel dual-acting antidepressants, selective norepinephrine and noradrenergic/dopaminergic agents, or TCA or mianserin) without clear recommendations other than those that apply for the selection of initial treatment. In the choice of an initial antidepressant, some reports promoted TCAs for treatment of inpatients[99–102]; however, it is unclear what special feature is associated

with inpatients (e.g., severity), and studies investigating switching strategies after an SSRI in inpatients were not identified. From the available studies, it must be emphasized that side effects to a first SSRI did not reduce the chance of response or increase the chance of intolerance for a second SSRI. Because of side effects, we think that monoamine-oxidase A inhibitors should not be prescribed as a second antidepressant after a first SSRI. A possible exception—but not investigated after a first SSRI—is for atypical depression.

Switching from a failed TCA treatment was reviewed earlier.[7,10,32,76,103] The response rates for within-class switching with SSRIs appear more favorable than a TCA-TCA switch: in 2 small trials, response rates of a within-class TCA switch were 9%[104] and 30%.[105] The SSRI results challenge the belief that any within-class switch should be considered illogical. The between-classes switching strategies from a TCA to an SSRI (investigated in 10 trials[73–75,105–111]; response rates varying between 4% [inpatients] and 75% [outpatients]) to a heterocyclic antidepressant (e.g., bupropion, trazodone, nomifensine, oxaprotiline; 6 studies[73,91,112–115]; response rates between 10% and 56%) and to a monoamine-oxidase A inhibitor (6 trials[91,92,116–119]; response rates between 29% and 83%) showed similar broad ranges of response rates. These ranges reflect differences in heterogeneous study populations as well. Again, it is inappropriate to simply compare these rates determined in different studies.

On theoretical grounds, it is logical (and often recommended) to switch to an antidepressant with different or combined sites of action (e.g., norepinephrine uptake inhibition after unsuccessful serotonergic uptake inhibition).[120–122] Others pointed out the complex interaction of monoamine systems alone, proposed other possible etiologic mechanisms, and considered the monoamine hypothesis only partially explanative for depression and the response to antidepressants.[123–127] Six RCTs so far compared different pharmacologic approaches in nonresponders (venlafaxine vs. paroxetine,[70] venlafaxine vs. an SSRI,[46] venlafaxine vs. sertraline or bupropion,[47] nortriptyline vs. mirtazapine,[48] fluoxetine vs. mianserin or a mianserin-fluoxetine combination,[71] and tranylcypromine vs. a venlafaxine-mirtazapine combination[49]). These RCTs found equivocal superiority of dual-action pharmacotherapy. However, in STAR*D,[47–49] the empirical proof of this theoretical strategy was not found.

Apart from switching, augmentation or combination and addition of (or switching to) psychotherapy are possible options. Only Ferreri et al.[71] and McGrath et al.[49] compared switching versus combination (the latter at a higher level of TRD). In STAR*D, a switch to or augmentation with cognitive-behavioral therapy was possible after citalopram,[45] and augmentation of citalopram with buspirone or bupropion was also studied.[128] A direct comparison between switching and augmentation after citalopram was not feasible.[47] Therefore, clear recommendations about choosing one of these strategies relative to each other are not possible. In most countries, SSRIs are generally prescribed as first-line treatment, often provided in primary care. We think that switching strategies after a first SSRI will be preferred, especially in primary care, in which augmentation and combination strategies may be unfamiliar to physicians. This hypothesis is supported by audits, even among psychiatrists.[40–42]

Limitations of the Identified Studies

Well-designed switch studies are difficult to carry out, and, therefore, it does not surprise that the evidence to date is limited in several ways. We found predominantly open, uncontrolled studies, with a risk of more positive results than in blinded studies and without a possibility to actively compare strategies. There were few studies that clearly described the inclusion of prospectively determined SSRI nonresponders.[47–49,65,71,75,88] This finding is of importance, as, in retrospectively determined nonresponders, current depression may cause recall bias. Furthermore, in some studies nonresponders were not treated directly after cessation of the unsuccessful drug, which might have biased results; for example, depression worsened after cessation, or—the other way around—depression may have improved because of the natural course of depression.[129,130]

Several other problems were encountered: unclear criteria for initial nonresponse,[63,68,69,78,86] inclusion of mild or minor depression,[46,78] possible selection bias,[78] limited presentation of results,[46,74,84,85,89,91,92] absence of ITT data,[78] small sample sizes ($N < 40$),[66,73,74,79,86,88,89,91,92] and low statistical power.[71,79] In general, less robust studies found more positive results for the drug of interest. Table 2 presents a summary of these problems.

The STAR*D trials[47–49] were randomized but unblinded effectiveness trials. The primary outcome (remission by HAM-D-17) was determined by blind assessors; the secondary outcomes by the QIDS-SR16 were self-rated by the unblinded patients. The a priori definition of *nonremission* for missing data will have decreased remission rates because of attrition, but this a priori definition was considered noninfluential after sensitivity analyses. The aggressive dose increases in STAR*D trials prevented undertreatment, but might have increased attrition, and definitely increased the percentages of treatment-intolerant patients at all levels. Especially in the level IV trials, the treating physicians might have been unfamiliar with the prescribed medication (tranylcypromine, venlafaxine-mirtazapine combination), reducing the vigor of the applied pharmacologic intervention.[49]

Future Switching Studies

After the STAR*D trials, the question arises as to whether many randomized direct comparisons between

switches among drug classes are fruitful to develop fully evidence-based recommendations for switching. Results of some studies might still be published.[131–133] Also, the predictors of poor response and nonremission need to be further clarified. In order to structure directions of research, the recommended approaches in guidelines should be evaluated for each treatment step. The Texas Medication Algorithm Project proved that algorithms are beneficial for patient care[134]; however, our next challenge is to investigate which steps within these algorithms are better compared with each other.

Ideally, 3 or more armed studies should be designed. Switching within the same class or to different classes of drugs should be compared with an augmentation or new approach, while an arm for continuation of the initial therapy should also be included. The latter arm would then represent a form of placebo control. Naturally, these studies are hard to carry out, may have to overcome resistance and doubts concerning the ethics of the continuation arm, or may suffer from selective patient withdrawal from this continuation arm. The STAR*D project has been a major step in this direction, especially by proving the feasibility of such large multicenter trials and the methodology of (equipoise) randomization. At the same time, the effectiveness approach with many centers, high levels of comorbidity, chronicity, and many arms of treatment might have reduced the ability to find differences.

We found that the response rates in switch studies decreased with increased levels of TRD. Therefore, future studies must consider the level of TRD as an important effect-modifying variable. Ideally, in future research, clear populations of prospectively determined treatment resistance should be selected or analyzed in a priori–defined subgroups to increase our knowledge about confounding or effect-modifying variables. Finally, to improve the acceptance of switching in daily clinical practice, more studies of patients' perspectives of switching of antidepressants are needed.

Limitations of the Review

Several limitations of this review should be mentioned. First, a review like this cannot overcome the paucity of high-quality evidence to date. The Cochrane Collaboration primarily rejects open studies as high-quality evidence. If this criterion had been applied, only 8 studies would have qualified for the review, obviously limiting its applicability. The majority of included studies had methodological flaws; 2 studies were excluded for clear invalidity.[57,58] We decided a priori to include open studies and—even more—to include studies in which 50% to 100% of patients initially used an SSRI, introducing different levels of TRD. Of course, the latter decision is debatable from a methodological point of view.

Second, in the selected trials, mostly response was used as the primary outcome, while currently remission of depression is the clinical aim of treatment.[135] Only 13 of 31 studies (42%) included remission as an outcome criterion.[46–49,70–72,75,78,80–82,88] Only STAR*D primarily investigated the practice of switching in order to achieve remission.[47–49]

Third, patients studied in the included trials represented selected populations, reducing the generalizability of the findings to the "real world" clinical practice; as an effectiveness trial, the STAR*D results overcame this problem. Fourth, critical appraisal was performed by 1 reviewer (H.G.R.), while ideally this should have been performed by 2 raters. However, we found our interobserver agreement to be moderate to good and no worse than in previous interrater attempts in psychiatry.[54] Fifth, 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.

Strengths of the Review

This is the first review that applied the thorough methodology to search for, identify, and appraise articles as used in Cochrane reviews. The applied methodology and transparent presentation of data allow clinicians to make their own judgments and, if necessary, to retrieve the source of data. Apart from the relevant up-to-date information for clinicians, this review could well serve national guideline committees as a building stone for the development of treatment guidelines for MDD.

CONCLUSION

This systematic review about switching identified 8 RCTs and mostly open switch studies of variable methodological quality in heterogeneous populations. The STAR*D results largely increased the amount and quality of the available evidence, but did not show differential class effects to guide switching. After a first SSRI, switching is open to all studied antidepressant classes (except irreversible monoamine-oxidase A inhibitors), without clear recommendations other than those that apply for the selection of initial treatment. For recommendations about when to choose between switching, augmentation, combination, or psychotherapeutic strategies as a next step, hardly any evidence of comparisons of these strategies relative to each other exists. Future algorithm-based switch studies and studies of patient perspectives regarding switching will have to improve our knowledge to guide treatment for SSRI nonresponders.

Drug names: bupropion (Wellbutrin and others), buspirone (BuSpar and others), citalopram (Celexa and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), ketoconazole (Nizoral and others), lithium (Eskalith, Lithobid, and others), mirtazapine (Remeron and others), nortriptyline (Pamelor and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), pindolol (Visken),

sertraline (Zoloft and others), tranylcypromine (Parnate and others), trazodone (Desyrel and others), venlafaxine (Effexor and others).

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