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SWITCHING ANTIDEPRESSANTS AFTER A FIRST SELECTIVE SEROTONIN REUPTAKE INHIBITOR IN MAJOR DEPRESSIVE DISORDER: A SYSTEMATIC REVIEW

CHAPTER

5

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Henricus G. Ruhé¹

Jochanan Huyser¹

Jan A. Swinkels¹

Aart H. Schene¹

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

Abstract

Background

Selective Serotonin Reuptake Inhibitors (SSRIs) are frequently used as a first antidepressant for major depressive disorder, but have response-rates of 50-60% in daily practice. For patients with insufficient response to SSRIs, switching is often applied.

Aim

To systematically review the evidence for switching pharmacotherapy after a first SSRI.

Methods

A systematic literature search (updated until Feb. 10, 2005) in MEDLINE, EMBASE, CINAHL and PsycInfo (all indexed years) identified randomised 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 STAR*D publications. We limited searches to adults and humans but did not apply language restrictions. Relevant articles were retrieved and critically appraised. The methodology of the studies, the results on efficacy and dropout s due to side effects, and remarks were summarized in an evidence table. Three studies comparing a switch to venlafaxine or SSRIs were pooled.

Results

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 (9.1-25.0))

Conclusions

After a first SSRI any switch within or between classes of antidepressants appear legitimate (second SSRI, novel dual acting antidepressants, selective noradrenergic or noradrenergic/dopaminergic agents, or TCA 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.

Introduction

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 non-response, all treatment guidelines recommend three 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 non-responders. One Cochrane review summarizes randomized, controlled trials (RCTs) of strategies in patients non-responsive 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) non-responders. The switch-options that were investigated in the included studies did not reflect clinical practice of switching to another antidepressant (one of the above recommendations), but used a variety of other drugs (oestrogen, benzodiazepines, ketoconazole, olanzapine). For the augmentation studies, meta-analyses were performed with 2 trials of lithium-augmentation and 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 non-response to a (first) SSRI.

Strategies for non-response 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 narrative³⁶ and 1 recent systematic review.³⁷ The evidence for lithium augmentation was also summarized in meta-analyses by Bauer et al.^{38;39}

After dose-escalation, switching antidepressants is widely practiced.⁴⁰⁻⁴² Switching to a different pharmacological 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 non-response 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 one to four sequential steps of treatment (further referred to as STAR*D level I-IV).

Therefore, our primary objective was to systematically review and appraise the available research focusing on switching strategies for SSRI non-responders 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 non-response to a first SSRI. We performed a systematic review following the Cochrane methodology and performed a meta-analysis of two switch options after a first SSRI: a second SSRI versus a serotonin-norepinephrine reuptake inhibitor (SNRI).

Methods

Studies included in the review

We expected very few randomised, 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 $\geq 50\%$ of subjects) was unambiguously documented.

Identification and selection of articles

We performed systematic literature searches (updated until February 10th 2005) in four 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 four identified studies released after these searches, including three 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 0.45-0.75 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 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 Improvement⁵¹ 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 Network⁵² and Sackett et al.⁵³ We assigned a 'level of evidence' (LoE; see table 4.1) 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 a priori preferred data for the Hamilton depression rating scale (HDRS;⁵⁴ 17-item version or other versions); otherwise we used data from the Montgomery Åsberg depression rating scale (MADRS),⁵⁵ clinical global impressions scale (CGI),⁵⁶ or other applied scales (e.g. the 16-item quick inventory for depressive symptoms-self-rated (QIDS-SR₁₆).⁵⁷ For tolerability, we took the dropout rate due to side effects as primary measure, followed by the overall dropout rate.

To assess judgement-bias by one 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

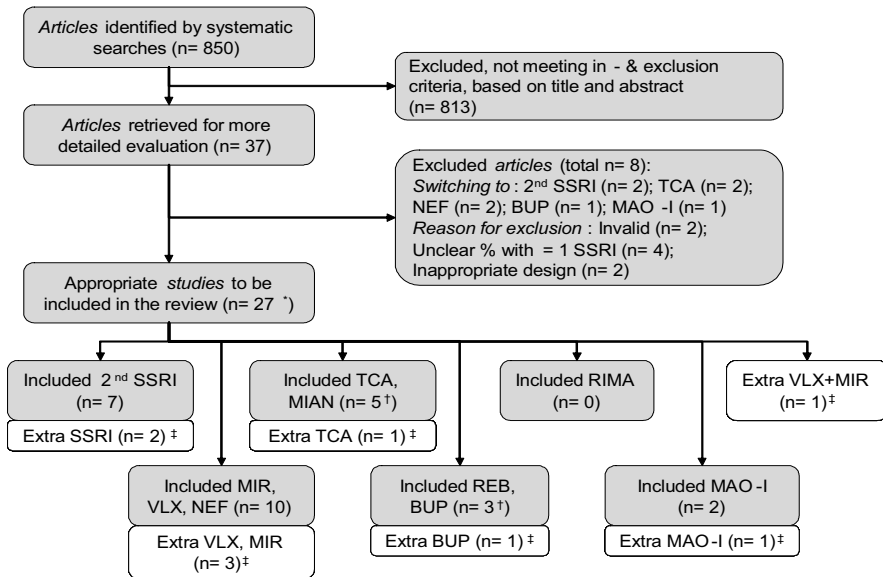
existed for the appraisal-items 'randomization of the study', 'level of evidence' and 'data extraction' ($\kappa = 1.0$). These results are in line with other reports of interrater agreement in appraisal of psychiatric research.⁵⁸

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 et al.^{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 homogenous randomised studies, we refrained from pooling in a meta-analysis, except for the three studies comparing the venlafaxine (SNRI) vs. second SSRI switch. We grouped antidepressants into six classes following the classification of the AHCPR.⁵

Results

We selected thirty-one studies for this review. Figure 5.1 shows the search results and selection of studies. Table 5.1 summarizes the included studies. A table of 8 excluded studies⁵⁹⁻⁶⁶ is available on request.

Figure 5.1. Selection of reported studies.



† Two double publications † considered as 2 x 1 study

‡ in total 4 extra publications with multiple contrasts published after systematic searches

Abbreviations: BUP = bupropion, MAO-I= irreversible inhibitor of monoamine-oxidase, MIAN = mianserin, MIR = mirtazapine, NEF = nefazodone, REB = reboxetine, RIMA = reversible inhibitor of MAO, SSRI = selective serotonin reuptake inhibitors, TCA = tricyclic antidepressant, VLX = venlafaxine

Table 5.1. Effectiveness of switching after ≥ 1 SSRI: Selected studies.

Study (year) ^{reference}	LoE	N	Design (follow-up)	Intervention*	Comparison*	Outcomes†	Remarks
5.1.A. to 2nd SSRI							
Baldomero et al. (2005) ⁴⁶	C	See under 5.2.C.					
Brown et al. (1995) ⁷¹	C	112 MDD OutP TRD-I	Open multicenter trial of FLX intolerant subjects (8 weeks)	SER 50-200mg	-	Response (CGI-I \pm SE) 71.8% Dropout overall = 21.4% Dropout SE = 9.8%	No placebo control. FLX-intolerance before switch only.
Calabrese et al. (2003) ⁷³	C	55 MDD OutP TRD-I	Open multicenter trial of FLX intolerant subjects (6 weeks)	CIT 20-40mg	-	Response (CGI-I \pm SE) 65.5% Dropout overall = 5% Dropout SE = 0%	No placebo control. FLX-intolerance before switch only. No minimum level of HDRS required for study-entrance. Start of CIT after placebo wash-out of 2-4 weeks.
Joffe et al. (1996) ⁶⁷	C	55 MDD OutP TRD-I	Retrospective study of patients who were treated with a second SSRI in 2 years. (≥ 5 weeks)	FLX (n=12) FLV (n=9) PAR (n=11) SER (n=23)	-	Response (CGI-I \pm SE) 51% No significant differences between various combinations of switching. No SE reported.	No placebo control. Methodologically poor: retrospective study, unclear definition of initial non-response, small numbers, no characteristics of population. Unclear after how many weeks response was determined.
Poirier et al. (1999) ^{74;87}	See under 5.1.C.						
Rush et al. (2006) ⁴⁷	A2	727 MDD OutP TRD-I	3 arm Multi center unblinded RCT (14 weeks)	1. VLX+XR 75-375mg 2. BUP 150-400mg	SER 50-200mg	Remission (HDRS ₁₇ ≤ 7) VLX = 24.8%, BUP = 21.3%, SER = 17.6% NNT _{VLX-SER} = 14 (7.0- ∞), NNT _{BUP-SER} = 28 (9.3- ∞) NNT _{VLX-BUP} = 29 (9.2- ∞) Response ($\geq 50\%$ \downarrow in QIDS ₁₆) VLX = 28.2%, BUP = 26.4%, SER = 26.7% NNT _{VLX-SER} = 66 (10.6- ∞), NNT _{BUP-SER} = 189 (13.4- ∞) NNT _{VLX-BUP} = 49 (10.1- ∞) Dropout SE VLX = 21.2%, BUP = 27.2%, SER = 21.0% (Nonsignificant differences)	Unblinded study, blinded assessors, no placebo group. Methodologically well performed effectiveness trial. Participants all received CIT 20-60mg as prior treatment (level II STAR*D). Due to high doses of CIT in 'level I' 407/727 (56%) of subjects in this study were classified as CIT-intolerant. No washout applied.
Thase et al. (1997) ⁶⁸	C	106 MDD OutP TRD-I	Open multicenter trial of SER nonresponders or intolerant subjects (6 weeks)	FLX 20-60mg	-	Overall 62% initial/intolerant subjects 71%, initial nonresponders 58%.	No placebo control. Nonresponse to SER was determined retrospectively (in most patients).
Thase et al. (2001) ⁶⁹	C	57 MDD OutP TRD-I	Open study of prospectively determined FLX nonresponders (12 weeks)	CIT 20mg (dosages could be increased to 60mg)	-	Response (CGI-I \pm SE) 63% ($\geq 50\%$ \downarrow in HDRS ₂₄) 46% Dropout overall = 18% Dropout SE = 5%	Well performed open study. Unknown placebo response rate. Tolerance for CIT after FLX is good, despite direct switch. No increased rate of SE in first weeks of study.

Table 5.1. Effectiveness of switching after ≥ 1 SSRI: Selected studies. (Continued)

Study (year) ^{reference}	LoE	N	Design (follow-up)	Intervention*	Comparison*	Outcome†	Remarks
These et al. (2002) ⁷²	C	61 MDD OutP TRD-I	Open study in PAR intolerant patients (6 weeks)	CIT 20mg (dosages could be increased to 40mg)	-	Response (CG-I \pm SE) 5.6% Dropout overall = 13%; Dropout SE = 10%	Open study, no minimal HDRS-score on entrance. Unknown placebo response rate. Tolerance for CIT after PAR is good, 1 week washout. Recurrence of the same SE as during PAR treatment is 5-30%.
Zarate et al. (1996) ⁷⁰	C	39 MDD, BipD, SchA, OCD InP TRD->I	Retrospective study of patient charts in using FLX (various durations offollow-up)	SER mean dose 93 \pm 62 mg	-	Response (CG-I \pm SE) 41.9% on discharge, 26% at follow-up.	Methodologically very poor study: retrospective, nonsystematic follow-up. SER was not prescribed following FLX, heterogeneous study population with heterogeneous history of previous treatments (including MAO-I, ECT). Confounding by non-compliance and additional pharmacotherapy (in 69% of patients). Possible recall-bias.
5.1.B. to a TCA or mianserin							
Fava et al. (2006) ⁴⁸	A2	234 MDD OutP TRD-II	Multi center unblinded RCT (14 weeks)	NOR 50-200mg	MIR 15-60mg	Remission (HDRS ₁₇ \leq 7) NOR = 19.8%, MIR = 12.4% NNT _{NOR-MIR} = 14 (6.0- ∞) Not different in level II intolerant group. Response (\geq 50% \downarrow in QIDS ₁₆) NOR = 16.5%, MIR = 13.5% NNT _{NOR-MIR} = 32 (8.1- ∞) Dropout _{SE} NOR = 34.7%, MIR = 33.3%	Unblinded study, blinded assessors, no placebo-group. Methodologically well performed effectiveness trial. Participants received CIT 20-60mg and VLX or BUP or SER or augmentation of CIT with BUP or BUS or CBT (level III STAR*D). 52.1% was considered level II intolerant. Blood-levels of NOR allowed but not obligatory for dosing (33.9% measured). No washout applied.
Ferreri et al. (2007) ⁷⁵	B	103 MDD InP + OutP TRD-I	3 arm multicenter RCT of FLX 20mg-NR (6 weeks)	1. MIAN 60mg 2. FLX 20mg + MIAN 60mg	3. FLX 20mg	Response (\geq 50% \downarrow in HDRS ₁₇) Mianserine = 48.5%, Fluoxetine = 37% NNT _{MIAN-FLX} =9 (2.9- ∞); NNT _{MIAN-FLX-FLX} =4 (2.1-34.1) Remission (HDRS ₁₇ \leq 8) Mianserine = 36%, Fluoxetine = 18% NNT _{MIAN-FLX} =6 (2.6- ∞); NNT _{MIAN-FLX-FLX} =4 (2.2-23.9) Dropout _{SE} NNH _{MIAN-FLX} =5 (2.6-10.4); NNH _{MIAN-FLX-FLX} =16 (6.8- ∞) Dropout overall NNH _{MIAN-FLX} =6 (2.6- ∞); NNH _{MIAN-FLX-FLX} =64 (4.9- ∞)	Methodologically sound, small sample size for three arms, limited power; in MIAN-group due to long half-life of FLX, first weeks also sort of 'combination'-therapy. Low dose of continued FLX in reference group. No washout applied, direct switch associated with increased intolerance and dropout.
Nierenberg et al. (2003) ⁷⁶	C	92 MDD OutP TRD->II	Open phase of NOR treatment preceding a 2 nd RCT ⁴⁶ (6 weeks)	NOR 100mg (adjusted to achieve 100 ng/ml)	-	Response (\geq 50% \downarrow in HDRS ₁₇) = 42.4% Remission (HDRS ₁₇ \leq 7) = 11.9% Dropout _{overall} = 34.7%	TRD defined as 1-5 failed adequate trials during current episode (mean \pm SD 2.3 \pm 1.5). 95.7% of patients was treated with ≥ 1 SSRI. Unknown placebo response rate.
Nolen et al. (1988) ⁷⁷	C	31 MDD InP TRD-III	Blinded consecutive therapy after 4 weeks of FLV (4 weeks)	OXA 100-300mg	-	Response (\geq 50% \downarrow in HDRS ₁₇) = 38.7% Relapse = 19.4% within 6 months	Modified ITT analysis, excluding patients who dropped-out in first 2 weeks. TRD: patients used ≥ 1 TCA before treatment with FLV. No data on dropouts.

Table 5.1. Effectiveness of switching after ≥1 SSRI: Selected studies. (Continued)

Study (year) ^{reference}	LoE	N	Design (follow-up)	Intervention*	Comparison*	Outcome†	Remarks
Peselow et al. (1989) ⁷⁸	C	15 + 10 MDD OutP TRD-I	Blinded cross-over design with original randomization (6 weeks ?)	IMI 65-275mg	-	Response (±50% ↓ in HDRS _{unknown} or CGI-I ±2) PAR → IMI = 73%	Methodologically poor: unclear description of studied population, limited presentation of data. Data of initial nonresponders to IMI switched to PAR also provided.
Thase et al. (2002) ^{79,80}	C	117 Chron MDD, MDD + Dys OutP TRD-I	Blinded, multicenter cross-over design with original randomization (12 weeks)	IMI 50-300mg	-	Response (CGI-I ±2, ±50% ↓ in HDRS ₂₄ ⁴⁷ , HDRS ₂₄ ^{51,5} and CGI-S ±3) SER → IMI = 44.4% Remission (HDRS ₂₄ ⁴⁷ and CGI-I ±2) SER → IMI = 23% Dropout _{overall} = 25%; Dropout _{SE} = 9%	Well-performed study. Unknown placebo response rate. Data of initial nonresponders to 12 weeks IMI switched to SER also provided. Due to absence of second randomization only tentative comparisons with switch IMI → SER available.
5.1.C. to mirtazapine, nefazodone, venlafaxine (dual action agents)							
Baldomero et al. (2005) ⁴⁶	B	3097 MDD + MinD + Dys OutP TRD-I	Multicenter, open design; RCT of VLX vs CA in SSRI-NR or intolerant patients (24 weeks)	VLX 75-225mg	CA: FLX, PAR, CIT 20-60mg SER 50-200mg MIR 15-45mg	Response (±50% ↓ in HDRS ₁₇): VLX = 77.3%, SSRIs = 71.1% NNT _{VLX,SSRI} = 17 (10.5-35.0) Remission (HDRS ₁₇ ≤ 7): VLX = 59.3%, SSRIs = 52.1% NNT _{VLX,SSRI} = 14 (9.1-29.3) HDRS ₁₇ scores differ significantly but clinically irrelevant at week 12 and 24 Dropout _{overall} : VLX = 19.6%, CA = 23.3% NNH _{VLX,CA} = 27 (15.1-120) Dropout _{SE} : VLX = 2.3%, CA = 1.7% NNH _{VLX,CA} 161 (62.1-∞)	Large randomized but unblinded study. Some methodological problems. 63.3% of included patients previously used a SSRI. Inclusion of 8.7% MinD. No differentiation of first-SSRI intolerant and unresponsive patients. Modified ITT analysis of ≥week 4 completers; in CA-treated switch group 22.7% received a non-SSRI. Baseline HDRS-scores sign. higher in VLX group; differential loss to follow up 26.2% VLX vs 36.2% CA Only 3 time-points over 24 weeks. No separate dichotomous data for week 12 response/remission
Fava et al. (2001) ⁸¹	C	94 MDD OutP TRD-I	Multicenter, open design (RCT of direct switch vs. washout) (8 weeks)	MIR 15-45mg	-	Response (±50% ↓ in HDRS ₁₇) SSRI _{NR} = 48%, SSRI _{intol.} = 53% Dropout _{overall} = 43%; Dropout _{SE} = 26%	Methodologically sound. Unknown placebo response rate. Washout-phase offers no advantages.
Fava et al. (2006) ⁴⁸	See under 5.1.B						
Kaplan (2002) ⁸²	C	73 MDD OutP TRD-I	Retrospectivenaturalistic study of SSRI-NR or non-sustaining SSRI responders (6-8 weeks + follow-up)	VLX 50-400mg	-	Response (HDRS ₃₅ ≤ 10 and CGI-I-21 ≤ 5) = 86% Remission (HDRS ₃₅ ≤ 8) = 82% Dropout _{SE} = 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.

Table 5.1. Effectiveness of switching after ≥ 1 SSRI: Selected studies. (Continued)

Study (year) ^{reference}	LoE	N	Design (follow-up)	Intervention*	Comparison*	Outcome†	Remarks
Mischoulon et al. (2004) ⁸⁵	C	13 MDD OutP TRD->I	Open design of SSRI-NR or in tolerable patients (12 weeks)	NEF 300-600mg	-	Response ($\geq 50\%$ \downarrow HDRS ₆ and/or CGI-S ≤ 2) 31% Dropout SE = 39%	Small sample (pilot study). Unknown placebo response rate; 61.5% attrition; especially in previous VLX-users. Washout of 4-7 days applied. Heterogeneous group of TRD app. 46% \geq stage II. No significant differences in response rates and side effects compared to 13 patients treated with NEF as first applied antidepressant (but low power).
Mitchell et al. (2000) ⁸⁴	C	312 MDD Setting? TRD->I	Multicenter, open unblinded design (8 weeks)	VLX 75-300mg	-	Response ($\geq 50\%$ \downarrow in MADRS) = 52.6% Remission (MADRS < 12) = 40.7% Dropout SE = 11%	Methodologically well. Unclear setting. Unknown placebo response rate. Unclear which proportion used ≥ 1 SSRI (41-68%). Probably chronically depressed subjects.
De Montigny et al. (1999) ⁸⁵	C	152 MDD InP & OutP TRD-I	Multicenter, open design (8 weeks)	VLX 75-375mg	-	Response ($\geq 50\%$ \downarrow in HDRS ₂₁) = 58%; ($\geq 50\%$ \downarrow in MADRS) = 62%; (CGI-S ≤ 3) = 66% Remission ($\geq 75\%$ \downarrow in HDRS ₂₁) = 21% Dropout SE = 7.9%	TRD: at least 1 previous TCA or SSRI or MOC or TRAZ or NEF, majority of patients used a SSRI. Mean duration of episode 2 years (range 2 months - 12.5 years). Unknown placebo response rate.
Nierenberg et al. (1994) ⁸⁶	C	70 MDD InP & OutP TRD-III	2 center, open design (12 weeks)	VLX 50-450mg	-	Response ($\geq 50\%$ \downarrow in HDRS ₂₁) = 32.9%; ($\geq 50\%$ \downarrow in MADRS) = 30%; (CGI-I ≤ 2) = 40% Remission (HDRS ₂₁ ≤ 8) = 15.7%; (MADRS ≤ 12) = 18.6%; (CGI-I = 1) = 22.9% Dropout SE = 9.6%	TRD: at least 2-3 drugs of 22 different classes, ≥ 1 TCA and ≥ 1 augmentation. Unclear what proportion of patients used ≥ 1 SSRI. Chronically depressed group (median duration 2.5 years). Unknown placebo response rate.
Poirier et al. (1999) ^{41;87}	A2	123 MDD InP & OutP TRD-II	Multicenter RCT (4 weeks)	VLX 75-300mg	PAR 20-40mg	Response ($\geq 50\%$ \downarrow in HDRS ₁₇): VLX = 45.0%, PAR = 29.0% NNT _{VLX-PAR} = 7 (3.0-∞) Remission (HDRS₁₇ ≤ 10): VLX = 36.7%, PAR = 17.7% NNT_{VLX-PAR} = 6 (2.9-28.9) Dropout SE: VLX = 8.2%, PAR = 4.8% NNT_{VLX-PAR} = 30 (8.3-∞)}}}	Methodologically well. Short follow-up during study. Dosing schedules are different between VLX and PAR.
Reynaert-Dupuis et al. (2002) ⁸⁸	C	688 MDD InP & OutP TRD-I	Multicenter, naturalistic, open design (6 weeks)	VLX 75-375mg	-	Response ($\geq 50\%$ \downarrow in HDRS ₂₁) = 46% (in previous SSRI-treated patients)	86.3% of patients were switched to VLX due to inefficacy, of 41.7% who were switched from a SSRI separate response rates are given. Immediate switching applied (except from MAO-is). Unclear presentation of data. Dropout rate not mentioned. Type of previous SSRI not significantly affected VLX-efficacy.
Rush et al. (2006) ⁴⁷	See under 5.1.A						

Table 5.1. Effectiveness of switching after ≥ 1 SSRI: Selected studies. (Continued)

Study (year) ^{reference}	LoE	N	Design (follow-up)	Intervention*	Comparison*	Outcome†	Remarks
Saiz-Ruiz et al. (1998) ⁹⁹	C	69 MDD OutP TRD-I	Multicenter, naturalistic, open design (24 weeks)	VLX 75-375mg	-	Response ($\geq 50\%$ \downarrow in HDRS ₁₇) = 69.6%; (CGI-I ≤ 2) = 63.8% Dropout _{overall} = 30.4% Dropout _{SE} = 8.7% SE occur in 54%	Selection of NR to a previous SSRI in at least a standard dose for 4 weeks. Limited presentation of data. In the paper a modified ITT analysis is applied for week 4 completers. Endpoint of study is only reported for week 24.
Wan et al. (2003) ⁹⁰	C	24 MDD Setting? TRD- ≥ 1 I	Retrospective chart review of consecutive subjects who failed response to ≥ 1 TCA and ≥ 1 SSRI (2 weeks - 3 years)	MIR 15-45mg	-	Response (CGI-I ≤ 2) = 16.7% Partial response (CGI-I = 3) = 20.8% Dropout _{SE} = 20.8%	Methodologically very poor. In 17.2% of eligible patients data were insufficient for inclusion. Highly treatment resistant population (average 7 previous drug-trials [range 2-13]). Unclear what response indicated switch to MIR. 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%.
5.1.D. to reboxetine or bupropion (selective NRI or noradrenergic & dopaminergic agents)							
Fava et al. (2003) ⁹⁴	C	128 MDD OutP TRD-I	Multicenter, open design of FLX-NR (8 weeks)	REB 8-10mg	-	Response ($\geq 50\%$ \downarrow in HDRS ₂₃ and CGI-I ≤ 2) = 44.5% Response ($\geq 50\%$ \downarrow in HDRS ₁₇) = 45.3% Dropout _{SE} = 13.3%	Methodologically well performed open study; unknown placebo response rate. FLX-NR determined at end of FLX-treatment; direct switch to REB well tolerated. Due to long half-life of FLX, first 4 weeks 'combination'-therapy.
Fava et al. (2003) ⁹²	C	29 MDD OutP TRD-I	Two-center open design of prospectively determined FLX-NR (8 weeks)	BUP-SR 150-400mg	-	Modified ITT (n = 26) Response ($\geq 50\%$ \downarrow in HDRS ₁₇) = 34.6% Partial response (≥ 25 -49% \downarrow in HDRS ₁₇) = 30.8% Remission (HDRS ₁₇ ≤ 7) = 23.1%	Methodologically well performed, but small open study; unknown placebo response rate. No specified dropout rates. FLX-NR prospectively determined; direct switch to BUP; no documentation of effects of this switch. Due to long half-life of FLX, first 4 weeks 'combination'-therapy.
Rush et al. (2006) ⁴⁷	See under 5.1.A						
Walker et al. (1993) ⁹³	C	39 MDD OutP TRD-I	Open design of patients with sexual side-effects on FLX (partially FLX-NR; n = 16) (8 weeks)	BUP 150-450mg	-	All (n = 30): \downarrow HDRS ₃₈ ; 16.6 (± 7.8) \rightarrow 8.4 (± 8.3) Dropout _{SE} = 10.3% Dropout _{efficacy} = 10.3% Bsl HDRS ₃₈ ≥ 18 (n = 16): \downarrow HDRS ₂₃ ; 8-25; 4 (± 5.8) \rightarrow 10.9 (± 10.8)	Initial design of switching due to sexual side-effect; limited data provided for depressed subjects; e.g. no response-rates; unknown placebo response rate. Improvement of orgasm function (84%), satisfaction (78%) and libido (78%) after switch. 2 weeks washout applied; disappearance of sexual dysfunction linear with FLX-washout

Table 5.1. Effectiveness of switching after ≥1 SSRI: Selected studies. (Continued)

Study (year) ^{reference}	LoE	N	Design (follow-up)	Intervention*	Comparison*	Outcome†	Remarks
5.1.E. to a MAOI							
McGrath et al. (2006) ⁷⁴⁹	B	109 MDD OutP TRD-≥11	Multicenter unblinded RCT (12 weeks)	TCP 10-60mg	VLX-XR 75-300mg + MIR 15-45mg	Remission (HDRS ₁₇₋₂₁) TCP: 6.9%, VLX-MIR: 13.7% NNH = 15 (5.5-∞) Response (≥50% ↓ in QIDS-SR) TCP: 12.1%, VLX-MIR: 23.5% NNH = 9 (3.9-∞) Dropouts _{SE} TCP: 41.4%, VLX-MIR: 21.6% NNH = 6 (2.7-35.2)	Unblinded study, blinded assessors. Participants received at least 1 SSRI, a 2 nd SSRI or VLX or BUP or CIT-augmentation (BUP or BUS) and some CBT and a 3 rd treatment with NOR or MIR (level IV STAR*D).
Nolen et al. (1985) ⁹⁶	B	26 MDD InP TRD-≥11	Randomized unblinded crossover design (4 weeks)	TCP 20-100mg	L5HTP 20-200mg	Response (≥50% ↓ in HDRS ₁₇) TCP: 42.9%, L5HTP: 0% NNT = 3 (1.5-5.9) tranylcypromine side effects = 62% cardiovascular; 15% insomnia	Small study, allocation of initial treatment not clearly described. Study-groups differ significantly in baseline HDRS-score. Stage II-III TRD-patients. In the paper data of second 4 weeks (cross-over phase) are also given. Limited presentation of data.
Nolen et al. (1988) ⁹⁵	B	21 MDD InP TRD-≥11	RCT with secondary cross-over (4 weeks)	TCP 40-100mg	NOM150-250mg	Response (≥50% ↓ in HDRS ₁₇) TCP: 45.2% NOM: 10.0% NNT = 3 (1.4-154.8) TCP _{SE} = 58% cardiovascular, 33% insomnia	Stage II-III TRD-patients. Unclear method of randomization. In the paper data of second 4 weeks (cross-over phase) are also given. Limited presentation of data.

* All dosages in mg/day. † Intention to treat (ITT)-results unless specified.

Abbreviations: AD = antidepressant, CA = 'Conventional antidepressants' (PAR, FLX, SER, CIT, MIR and other antidepressants not specified), CBT = Cognitive Behavior therapy, CGI-I = Clinical global impression -Improvement scale, Dys = dysthymia, HDRS; = Hamilton depression rating scale (? indicates number of items), InP = in-patients, MADRS= Montgomery Åsberg Depression Rating Scale, MDD = major depressive disorder, MinD = Minor Depression, NNH/T = number needed to harm/treat, NR = nonresponders, OCD = Obsessive compulsive disorder, OutP = Out-patients, PGI = Patient global improvement scale, QIDS-SR = Quick inventory of depressive symptomatology self-rated, Scha = Schizoaffective disorder, SE = Side-effects, TRD = treatment resistant depression, stages I: failure of an adequate trial of 1 major AD class; II: Stage I + failure of an adequate trial of 1 distinctly different AD class; III: stage II + failure of an adequate trial of TCA; IV: Stage III + failure of an adequate trial of an MAOI; V: Stage IV + failure of a course of bilateral ECT.¹⁰²⁴ Drugs: BUP = bupropion, BUS = buspirone, CIT = citalopram, FLV= fluvoxamine, FLX = fluoxetine, IMI = imipramine, L5HTP = L-5-hydroxytryptophan, MAO-I = irreversible inhibitor of monoamine-oxidase, MIR = mirtazapine, MOC = moclobemide, NEF = nefazodone, NOM = nomifensine, NOR = nortriptyline, NRI = noradrenalinine reuptake inhibitor, OXA = oxaprotidine, PAR = paroxetine, PLAC = placebo, REB = reboxetine, SER = sertraline, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressants, TCP = tranylcypromine, TRAZ = trazodone, VLX = venlafaxine.

Second SSRI

We identified 7 open studies investigating a switch to a second SSRI.^{67;68;68-73} In one of these studies, the non-response to the initial SSRI was determined prospectively, and switching was applied immediately.⁶⁹ In 4 studies, intolerance was determined retrospectively, with an (unclear) interval between the end of the previous SSRI and the next.^{67;68;70;72} In the remaining 2 (SSRI-intolerance) studies, patients either started a second SSRI soon after the first SSRI or had an SSRI-free interval.^{71;73}

Response rates of switching in SSRI non-responders varied between 46% and 58% in three uncontrolled studies of variable methodological quality.⁶⁷⁻⁶⁹ The response rate was lower (42%) in a fourth study with a heterogeneous group of inpatients.⁷⁰ However, response rates to a second SSRI varied between 56% and 72% when patients were intolerant to the first SSRI (4 studies).^{68;71-73} Dropout rates due to side effects were between 5% and 21%, in studies with initial non-responders⁶⁹ and between 0% and 10% in SSRI-intolerant samples⁷¹⁻⁷³ (LoE: C).

In the SSRI-arms of three RCTs, response rates varied between 26.7% and 71.1%, while remission rates were between 17.6-52.1%.^{46;47;74} Dropout rates due to side effects varied between 4.8-21.0%. For results on the comparisons with other arms see below (LoE: A2-B).

In summary, the data from the open studies and one of the RCTs⁴⁶ suggest that, after 1 SSRI, non-responders 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 two RCTs^{47;74} indicated much less advantageous response and remission rates for a second SSRI (26.7-29.0% and ~17.6% respectively).

Tricyclic Antidepressants and mianserin

We identified 2 RCTs with a switch to a TCA,^{48;75} with one having limited power due to a randomization into 3 arms.⁷⁵ Four open studies investigated a switch from an SSRI to a TCA.⁷⁶⁻⁸⁰ The methodology of the open studies varied: one large cross-over study was methodologically sound,^{79;80} one small study was unequivocally poor,⁷⁸ and two studies were of reasonable quality (investigating populations with TRD).^{76;77}

In the RCT of Ferreri et al. switching to mianserin (a noradrenergic tetracyclic) versus continuation of fluoxetine was investigated, with a third arm for their combination.⁷⁵ 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-∞)) 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 2.1-34.1)). Dropouts due to side effects were highest in the switch-group (24%; NNH vs continuation= 5 (95% CI 2.6-10.4)) (LoE: B).

The STAR*D level III study compared a switch to nortriptyline versus mirtazapine in a randomized unblinded design.⁴⁸ All participants received citalopram plus either a switch to sertraline, venlafaxine or bupropion or citalopram augmentation with buspirone or bupropion. Response rates ($\geq 50\%$ decrease in QIDS-SR₁₆ score) were 16.5% for nortriptyline and 13.5% for mirtazapine (NNT= 32 (95% CI 8.1-∞)). Remission rates (HDRS₁₇ ≤ 7) were 19.8% vs 12.4% for nortriptyline and mirtazapine, respectively (NNT= 14 (95% CI 6.0-∞)). 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).

Thase et al. investigated a switch to imipramine in non-responders to sertraline in chronic depressive out-patients. They found a 44% ITT response rate, with a dropout rate due to intolerable side effects of 9%.^{79;80} The methodologically poor study by Peselow et al. (including also SSRI-intolerant patients) found a 73% response rate after a switch to imipramine in outpatients.⁷⁸ In the studies that recruited TRD populations, response rates after switching to nortriptyline⁷⁶ and oxaprotiline⁷⁷ decreased to 39% in in-patients⁷⁷ and 42% in outpatients,⁷⁶ 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. Lower response rates were observed in studies that included more treatment resistant patients.

Mirtazapine, nefazodon or venlafaxine (novel dual acting agents)

We identified 13 switch studies to novel dual acting agents.^{46-48;74;81-90} The methodological quality varied. Four studies were randomized controlled trials: Poirier and Boyer compared a switch to paroxetine versus venlafaxine,⁷⁴ Baldomero et al. compared a switch to venlafaxine extended release versus switching to any other antidepressant (77% of these switches used paroxetine, citalopram, sertraline, or fluoxetine) in an unblinded design,⁴⁶ 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 sertraline⁴⁷ and the switch thereafter to nortriptyline or mirtazapine.⁴⁸ Other studies described open studies with mirtazapine,^{81;90} nefazodone,⁸³ and venlafaxine.^{82;84-86;88;89} In seven of the studies, all patients received an SSRI before switching.^{47;48;81-83;89;90} Five studies included patients with variable but higher levels of treatment resistance;^{48;74;83;86;90} in 2 studies, this was unclear.^{81;84} In contrast, one study included patients (52%) who initially responded to an SSRI but did not sustain their response.⁸²

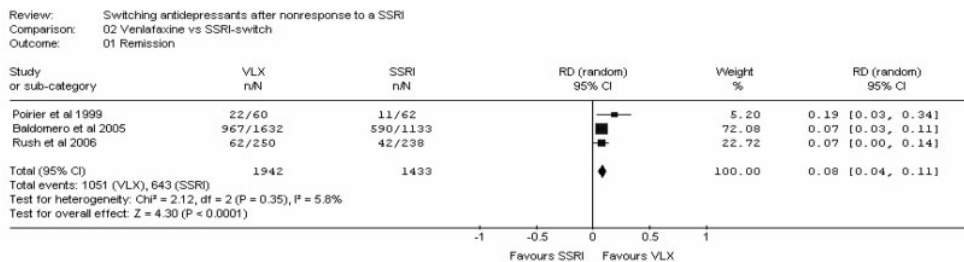
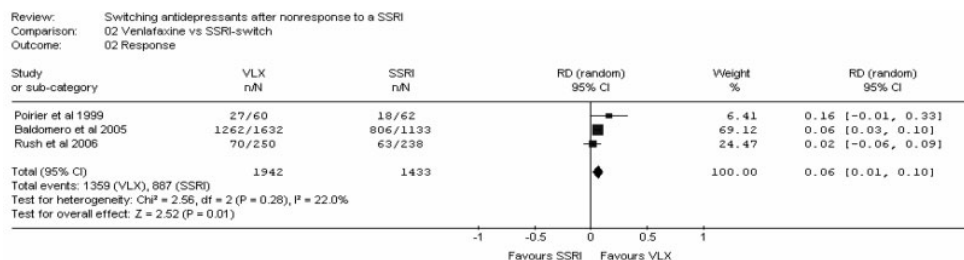
In the RCT performed by Poirier and Boyer, switching to venlafaxine was more efficacious than paroxetine when remission ($\text{HDRS}_{17} \leq 10$) was considered (remission rates: 36.7% and 17.7% respectively), with a NNT of 6 (95% CI 2.9-28.9).⁷⁴ For a response criterion ($\geq 50\%$ reduction in HDRS_{17}), the difference was insignificant (response rates: venlafaxine= 45% and paroxetine= 29%; NNT= 7 (95% CI 3.0- ∞)). Dropout rates due to side effects were comparable (8.2% for venlafaxine and 4.8% for paroxetine; NNH= 30 (95% CI 8.3- ∞)) (LoE: A2).

In the randomized, unblinded study by Baldomero et al., venlafaxine showed a significantly increased remission ($\text{HDRS}_{17} \leq 7$) rate (59.3%) compared with conventional antidepressants (51.5%) after 24 weeks of treatment, with a NNT of 13 (95% CI 8.9-23.7).⁴⁶ In the conventional antidepressants group, 77.3% of the patients used a second SSRI; for SSRIs, the remission rate was 52.1% (NNT= 14 (95% CI 9.1-29.3)). Response ($\geq 50\%$ reduction in HDRS_{17}) rates also showed a modest but significant advantage: 77.3% for venlafaxine versus 71.1% for SSRIs (NNT= 17 (95% CI 10.5-35.0)). Overall dropout was slightly lower in the venlafaxine group when compared with all conventional antidepressants (28.3% vs 32.8%; NNH= 27 (95% CI 15.1-120)). Dropout rates due to side effects were not significantly different between venlafaxine and conventional antidepressants (12% vs 7.3% respectively; NNH= 161 (95% CI 62.1- ∞)) (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.⁹¹ The assessors of the primary outcome (HDRS_{17}) were blind to the treatment. After 14 weeks of treatment, response rates ($\geq 50\%$ decrease in QIDS-SR_{16}) were 28.2% for venlafaxine, 26.1% for bupropion and 26.7% for sertraline (not significant). Remission rates ($\text{HDRS}_{17} \leq 7$) were not significantly different for venlafaxine, bupropion, and sertraline (24.8%, 21.3% and 17.6% respectively). For corresponding NNTs see table 5.1. 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 was described earlier.⁴⁸ Mirtazapine response, remission and side-effects 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).^{81-86;88-90} Dropout rates due to adverse effects varied between 5.5% and 11% for venlafaxine, between 20.8% and 26% for mirtazapine and was 39% in one study with nefazodone (LoE: A2, C).

Figure 5.2. Meta-analysis of switch-studies comparing a switch to venlafaxine versus a second SSRI.**A****B**

A: Remission. B: Response. V LX = venlafaxine. References to studies: Poirier et al.,⁷⁴ Baldomero et al.,⁴⁶ Rush et al.⁴⁷

We performed a meta-analysis of the three RCTs that compared switching to venlafaxine versus SSRIs,^{46;47;74} although the differences in duration of follow-up introduced some heterogeneity (ranging from 4 weeks by Poirier and Boyer⁷⁴ to 24 weeks by Baldomero et al.⁴⁶). As shown in figure 5.2, the weighted difference in remission-rates (fixed effects model) was 8% (4 – 11%) in favour of venlafaxine (NNT= 13 (95% CI 9.1 – 25.0), and for response 6% (1 – 10%), (NNT= 17 (95% CI 10.0 – 100.0)). Omission of the methodologically poorer study of Baldomero et al. increased the difference in remission rates (10% (95% CI 3-16%) fixed effects model; NNT= 10 (95% CI 6.3-33.3)), but decreased the difference in response rates (4% (-3-12%) fixed effects model; NNT= 25 (95% CI 8.3-∞)). The dropout rate due to side effects was only reported in two studies^{47;74}; the weighted difference was 1% (95% CI -5-7%) (fixed effects model) with more dropouts for venlafaxine.

In summary, heterogeneous studies considering switching to mirtazapine, nefazodone and venlafaxine showed response rates of approximately 28-50% 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 (NN_T= 13 (95% CI 9.1-25.0).

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

We identified one RCT and two small open studies of switching to bupropion.^{47;92;93} 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 to venlafaxine or sertraline. In this study, bupropion had the (statistically insignificant) highest dropout rate (27.2%) due to side effects (LoE : A₂).

In two open studies with bupropion, Fava et al prospectively determined fluoxetine nonresponse in a small but well performed study,⁹² and Walker et al. recruited patients that were primarily suffering sexual side-effects of fluoxetine, and only reported a decrease in 28-item HDRS-scores.⁹³ One larger, well-performed, open study investigated the switch to reboxetine in fluoxetine non-responders.⁹⁴

Thus, switching from fluoxetine was investigated, with reported response rates of 34.6% for bupropion⁹² and 45.3% for reboxetine.⁹⁴ For bupropion, specified dropout rates were not reported in one study.⁹² The side effect-related dropout rate was 10.3% in subjects with sexual dysfunction while taking fluoxetine.⁹³ For reboxetine, the dropout rate due to side effects was 13.3% (LoE: C).

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

Reversible Inhibitor of Monoamine-oxidase A

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

Monoamine-oxidase A inhibitor

We identified one RCT from STAR*D⁴⁹ (level IV) and two small, interrelated randomized studies after 4 weeks of treatment with at least one SSRI (fluvoxamine) and oxaprotiline.^{95;96} We identified no studies of SSRI non-responders in atypical depression. Two studies were RCTs^{49;95} and one an unblinded, randomized, cross-over study.⁹⁶ The STAR*D study investigated outpatients; the studies by Nolen et al.^{95;96} were performed in treatment resistant in-patients.

Nolen et al. found tranylcypromine to be more efficacious than nomifensine,⁹⁵ in both studies the response rate for tranylcypromine was 42.9 and 45.5%.^{95;96} All patients previously received at least fluvoxamine and oxaprotiline. Fifty-eight to 62% had side effects affecting their blood pressure levels (LoE: B).

The STAR*D level IV study included patients that had not been in remission after citalopram (level I), either venlafaxine, bupropion, sertraline or citalopram augmentation with buspirone or bupropion (level II), and 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 for the level III medication. Remission rates (HDRS₁₇ ≤ 7) were low for tranylcypromine (6.9%) and the combination treatment (13.7%; NNH= 15 (95% CI 5.5-∞)). Response rates (≥50% decrease in QIDS-SR₁₆) were also not significantly different: 12.1% vs 23.5% for tranylcypromine and venlafaxine with mirtazapine, respectively (NNH= 9 (95% CI 3.9-∞)). Dropout rates due to side effects were higher for tranylcypromine: 41.4% versus 21.6% for venlafaxine with mirtazapine (NNH= 6 (95% CI 2.7-35.2)).

Additional concerns for clinicians regarding switching

Little evidence is available about the optimal way to switch.^{20;29;69;88;97} 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.^{98;99} 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;69;97} nortriptyline,⁴⁸ mirtazapine,^{48;81} bupropion,⁴⁷ reboxetine,⁹⁴ or venlafaxine^{47;88}) was well tolerated. Also, direct switching reduced the emergence of side effects compared with placebo in a 1-week washout phase (which might have been discontinuation symptoms).⁹⁷

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 one included study a direct switch to mianserin was less well tolerated.⁷⁵ For switching to nefazodone, in one study a 4-day to 7-day washout was applied but not investigated.⁸³ 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 MAO-I.^{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 non-responders in MDD, including the recent STAR*D results. We found that the available evidence does not justify distinct recommendations for next-step strategies after non-response 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 9.1-25.0)), this difference increased when the largest and methodologically poorest study was omitted (NNT= 10 (95% CI 7-34)).

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 IV⁴⁹). Rush et al. attributed these lower remission rates to the inclusion of patients who were more chronically depressed, had lower socio-economic status and suffered from more co-morbid somatic and psychiatric diseases.⁴⁷ In general, the level of TRD¹⁰ of included studies was inversely correlated with treatment outcome. Although this finding carries the risk of an ecological fallacy, it is worrisome, which further appears from 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.¹⁰⁰⁻¹⁰²

Dropout rates due to side-effects varied between 5-21% for a second SSRI and venlafaxine; 10-35% for TCAs, bupropion, and reboxetine; 20-33% for mirtazapine; 39% for nefazodone and 41.4% for tranylcypromine. It should be noted 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 eight RCTs,^{46-49;74;75;95;96} 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 noradrenergic 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;¹⁰³⁻¹⁰⁶ 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 MAO-I 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;80;107} The response rates for within-class switching with SSRIs appear more favourable than a TCA-TCA switch: in two small trials,^{108;109} response-rates of a within-class TCA switch were 9%¹⁰⁸ and 30%.¹⁰⁹ 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;^{77;79;109-115} response rates varying between 4% (inpatients) and 75% (out-patients)), to a heterocyclic antidepressant (e.g. bupropion, trazodone, nomifensine, oxaprotiline; 6 studies;^{77;95;116-119} response rates between 10%-56%) and to a MAO-I (6 trials;^{95;96;120-123} response rates between 29-83%) 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).¹²⁴⁻¹²⁶ 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.¹²⁷⁻¹³¹ Six RCTs so far compared different pharmacologic approaches in non-responders (venlafaxine versus paroxetine,⁷⁴ venlafaxine versus an SSRI⁴⁶, venlafaxine versus sertraline or bupropion,⁴⁷ nortriptyline versus mirtazapine,⁴⁸ fluoxetine versus mianserin or a mianserin-fluoxetine combination⁷⁵, and tranylcypromine versus a venlafaxin-mirtazapine combination⁴⁹). These RCTs found equivocal superiority of dual-action pharmacotherapy. However, in STAR*D 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.⁷⁵ 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 behaviour therapy was possible after citalopram (unpublished yet), and augmentation of citalopram with buspirone or bupropion was also studied.¹³² 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 non-responders.^{47-49;69;75;79;92} This finding is of importance, as in retrospectively determined non-responders, current depression may cause recall-bias. Furthermore, in some studies non-responders 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.^{133;134}

Several other problems were encountered: unclear criteria for initial non-response,^{67;72;73;82;90} inclusion of mild or minor depression,^{46;82} possible selection-bias,⁸² limited presentation of results,^{46;78;88;89;93;95;96} absence of ITT-data,⁸² small sample sizes ($n < 40$),^{70;77;78;83;90;92;93;95;96} and low statistical power.^{75;83} In general, less robust studies found more positive results for the drug of interest. Table 5.2 presents a summary of these problems.

The STAR*D trials⁴⁷⁻⁴⁹ were randomized but unblinded effectiveness trials. The primary outcome (remission by HDRS₁₇) 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 vigour 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.¹³⁵⁻¹³⁷ 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;¹³⁸ however, our next challenge is to investigate which steps within these algorithms are better compared with each other.

Ideally, three 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 also an arm for continuation of the initial therapy should 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 co-morbidity, 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, two studies were excluded for clear invalidity.^{61;62} We decided a priori to include open studies, and—even more—to include studies in which 50-100% of patients initially used an SSRI, introducing different levels of TRD. Of course, the latter decision is debateable 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.¹³⁹ Only 13 of 31 studies (42%) included remission as an outcome criterion.^{46-49;74-76;79;82;84-86;92} 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 one reviewer (H.G.R.), while ideally this should have been performed by two raters. However, we found our interobserver agreement to be moderate to good and no worse than in previous interrater attempts in psychiatry.⁵⁸ 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 judgements 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 MAO-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 non-responders.

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Conflicts of interest

None

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