Switching antidepressants after a first selective serotonin reuptake inhibitor in major depressive disorder: a systematic review
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CRD summary
The authors concluded that, after a first SSRI, switching within or between any of the current classes of antidepressants appears reasonable. However, little randomised evidence is available. There is no conclusive evidence of any advantage in switching between classes. The review was well-conducted in most respects and these conclusions seem likely to be reliable.

Authors' objectives
To evaluate strategies for switching antidepressants among adults with insufficient response to selective serotonin re-uptake inhibitors (SSRIs).

Searching
MEDLINE, EMBASE, CINAHL and PsycINFO were searched from inception to February 2005; the search terms were provided. There were no language restrictions. The references of articles retrieved were checked. Four more recent papers were also included.

Study selection
Studies of pharmacological switching strategies for adults with major depressive disorder nonresponsive to SSRIs were eligible for inclusion. Both randomised and non-randomised studies were eligible, provided at least 50% of the participants had either used an SSRI in the current depressive episode or, in the case of treatment-resistant depression, had well-documented prior use of an SSRI. The primary review outcomes were response (preferably measured by the Hamilton Rating Scale for Depression), remission and tolerability (defined as the drop-out rate due to side-effects). The overall drop-out rate was a secondary outcome. Studies describing switching from tricyclic antidepressants (TCAs) to SSRIs were excluded.

The participants in the included studies were intolerant or unresponsive to SSRIs and/or treatment resistant. Most were out-patients. The studies varied widely with respect to the extent and degree of treatment resistance among participants, the antidepressants used, and the definition of response and remission. The primary outcome in most of the included studies was response. A variety of outcome assessment tools and cut-off scores was used. Study duration varied from 4 to 24 weeks.

Two reviewers independently selected studies potentially eligible for inclusion, with any discrepancies resolved by consensus.

Assessment of study quality
Study validity was assessed using Scottish Intercollegiate Guidelines Network criteria (SIGN 2001) and by assigning a level of evidence to each study based on design and quality.

The first author conducted the validity assessment and other authors checked a sample of 12 studies to ascertain inter-rater reliability.

Data extraction
Where possible, risk differences (RDs) and numbers-needed-to-treat for benefit (NNT) or harm were calculated, with 95% confidence intervals (CIs). Antidepressants were classified as follows: SSRIs; TCAs and mianserin; novel dual-acting agents (mirtazapine, nefazodone and venlafaxine); agents affecting dopaminergic and/or adrenergic neurotransmission (bupropion and reboxetine); reversible monoamine-oxidase A inhibitors (MAOIs); and MAOIs. Levels of treatment resistance in each study were categorised from I to III as proposed by Thase 1995.
It appears that the first author extracted the data and that other authors checked a sample of 12 studies to ascertain inter-rater reliability.

**Methods of synthesis**
The studies were combined in a narrative or, if homogeneous data were available, RD were pooled in a fixed-effects model. Findings were grouped by class of antidepressant. Statistical heterogeneity was assessed using the $\chi^2$ test and $I^2$ statistic. Potential sources of heterogeneity were discussed in the text, with an a priori focus on treatment-resistant depression.

**Results of the review**
Thirty-one studies were included: 8 randomised controlled trials (RCTs; n approximately 4,000) and 23 non-randomised trials (13 controlled trials, n=1,219; 7 uncontrolled trials, n=1,086; 3 chart reviews, n=1,222).

Most of the studies were unblinded and/or uncontrolled. Only 6 studies described the prospective definition of SSRI nonresponders, and several failed to treat nonresponders promptly after stopping the unsuccessful drug. Other common methodological problems were unclear definition of initial nonresponse (5 studies), limited presentation of results (7 studies) and small sample size (9 studies).

**Efficacy of switch strategies.**
- **Second SSRI** (3 RCTs and 7 non-randomised trials): 2 RCTs reported response and remission rates of 26.7 to 29% and 17.6%, respectively. However, the other studies (1 RCT and 7 non-randomised trials) reported response rates of around 50% in nonresponders and 70% in SSRI-intolerant patients.
- **TCAs and mianserin** (2 RCTs and 4 non-randomised trials): the response rates varied from 16.5 to 48.5%, with lower response rates in studies with higher rates of treatment-resistant depression.
- **Mirtazapine, nefazodone and venlafaxine** (4 RCTs and 9 non-randomised trials): the pooling of 3 RCTs showed a small but statistically significant increase in remission and response rates associated with switching to venlafaxine versus SSRI (respectively: RD 8%, 95% CI: 4, 11; NNT 13, 95% CI: 9, 25; and RD 6%, 95% CI: 1, 10; NNT 17, 95% CI: 10, 100). Across all studies, the response rates were 28 to 50% in patients without overt treatment-resistant depression, and lower in studies with higher rates of treatment-resistant depression.
- **Bupropion and reboxetine** (1 RCT and 2 non-randomised trials): the response rates were 26 to 35% for bupropion and 45% for reboxetine.
- **MAOI inhibitors**: no studies using reversible MAOI inhibitors were found. Three RCTs reported efficacy rates for tranylcypromine, two with response rates of 43 to 46%. The third reported remission and response rates of 7% and 12%, respectively.

**Drop-out rates.**
RCTs found no significant differences in drop-outs related to side-effects, except for tranylcypromine versus combined venlafaxine/mirtazapine (12% versus 24%). Across all studies, rates varied as follows: second SSRI and venlafaxine, 5 to 21%; TCAs, bupropion and reboxetine, 10 to 35%; mirtazapine, 20 to 33%; nefazodone 39%; tranylcypromine 41%. The overall drop-out rate ranged from 5 to 62%.

**Authors’ conclusions**
After a first SSRI, switching within or between any of the current classes of antidepressants appears reasonable. However, little randomised evidence is available. There is no conclusive evidence of any advantage in switching between classes.

**CRD commentary**
The study objectives and inclusion criteria were clear and the search was adequate, although it was unclear whether
unpublished studies were sought and publication bias does not appear to have been assessed. Appropriate criteria were used to assess study quality and the findings of the better quality studies were highlighted. Steps were taken to reduce the risk of error and bias by having more than one reviewer involved in the study selection and by double-checking the validity assessment and data extraction for a sample of studies. However, the whole process would ideally have been undertaken by more than one independent reviewer. There was marked clinical and methodological heterogeneity between the studies, thus it was appropriate that most of the findings were reported as a narrative review. Where meta-analysis was conducted, suitable statistical methods were used to pool the data and assess statistical heterogeneity. Potential sources of heterogeneity were discussed in the text. The review was well-conducted in most respects and the authors' conclusions seem likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that after nonresponse to a first SSRI it is reasonable to switch to a second SSRI, or to an antidepressant from another current class, although MAOI inhibitors should not normally be prescribed because of the risk of side effects. Intolerance of a first SSRI does not appear to increase the risk of intolerance to a second.

Research: The authors stated that randomised algorithm-based studies with at least three arms should compare switching strategies within and/or between drug classes versus a new or augmented approach and versus continuation of the original therapy. Levels of treatment-resistant depression should be considered an important variable, and patient perspectives should be considered.

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