

Review: Selective serotonin reuptake inhibitors are more tolerable than tricyclic antidepressant drugs

Barbui C, Hotopf M, Freemantle N, et al. Selective serotonin reuptake inhibitors versus tricyclic and heterocyclic antidepressants: comparison of drug adherence. *Cochrane Database Syst Rev.* 2000;(4):CD002791 (latest version 13 Jul 2000).

QUESTION

On the basis of patient discontinuation rates, are selective serotonin reuptake inhibitors (SSRIs) more tolerable than tricyclic and heterocyclic antidepressant drugs?

DATA SOURCES

Studies were identified by searching MEDLINE (1966 to 1999) and EMBASE (1974 to 1999) with drug names; conference abstracts; government documents; and the 1997 to 1999 Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register. Specialist journals and reference lists of relevant studies and systematic reviews were hand searched.

STUDY SELECTION

Randomized, blinded, controlled trials involving patients (age ≥ 18 y) diagnosed with depression were selected if they compared an SSRI (fluoxetine, fluvoxamine, sertraline, paroxetine, or citalopram) with old tricyclics (amitriptyline or imipramine), newer tricyclics (clomipramine, desipramine, dothiepin, doxepin, lofepramine, or nortriptyline), or heterocyclic and related drugs (amineptine, bupropion, maprotiline, mianserin, or trazodone) and if data on dropouts (patients not completing study after allocation) were available.

DATA EXTRACTION

Data were extracted on study and patient characteristics, total dropouts, dropouts from inefficacy, and dropouts from side effects after randomization.

MAIN RESULTS

136 randomized controlled trials met the criteria. 84% of the studies had a follow-up of ≤ 6 weeks (4 wk to 1 y), 58% were in outpatient settings, and $< 25\%$ were done completely in inpatient settings. Patients receiving SSRIs had a lower total dropout rate than did those receiving old and newer tricyclics and did not differ from those receiving heterocyclics (Table). SSRIs had a higher dropout rate from inefficacy than did all other antidepressant drugs combined. SSRIs

had a weighted dropout rate from side effects of 12% vs 18% for old tricyclics (odds ratio [OR] 0.62, 95% CI 0.54 to 0.71) and 10% vs 13% for newer tricyclics (OR 0.78, CI 0.63 to 0.98).

CONCLUSION

On the basis of patient discontinuation rates, selective serotonin reuptake inhibitors are somewhat more tolerable than the old and newer tricyclic antidepressant drugs.

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Dropout rates with selective serotonin reuptake inhibitors (SSRIs) vs other antidepressant drugs (fixed-effects model)*

Comparison	Unweighted event rate	RRR (95% CI)	NNT (CI) based on weighted event rates
SSRIs vs old tricyclics	31% vs 35%	12% (6 to 17)	22 (15 to 41)
SSRIs vs newer tricyclics	23% vs 26%	13% (4 to 22)	30 (18 to 108)
SSRIs vs heterocyclics	21% vs 24%	12% (-4 to 25)	Not significant
SSRIs vs all others†	27% vs 30%	13% (8 to 17)	26 (20 to 43)

*Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

†All others = old tricyclics, newer tricyclics, and heterocyclics.

COMMENTARY

Despite higher costs, SSRIs might be more cost-effective if they were better tolerated. This potential advantage has been calculated assuming the risk for dropout to be 8% to 12% lower for SSRIs. The systematic review by Barbui and colleagues found a 3% difference in overall adherence, which is not clinically significant: The number of patients needing treatment to prevent 1 additional dropout is 26. However, generalizing from randomized controlled trials to routine practice may not be justifiable.

First, most trials in the review continued for only 6 weeks, but in practice, medication is offered for approximately 6 months. Second, most trials in the review included only patients with no comorbid conditions, whereas in practice we need to consider drug interactions and side effects, such as the effect of tricyclics on heart disease.

Further evidence from real world practice is surprisingly scant. An observational study of the ratio of SSRI treatment discontinuations to inceptions in U.K. general practice found an 11% difference in

favor of the SSRIs, and the practitioners in the study reported that in their view, lack of tolerability rather than inefficacy explained most of this difference (1). SSRIs also have the advantage of being prescribed at a dose that is therapeutic from the beginning; tricyclics often have to be titrated upward.

Although advantages may be overrated, in primary care practice, SSRIs have become the drug of first choice for most patients with depression, particularly because the drugs have started to come off patent with resultant lower costs.

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Reference

1. Martin RM, Hilton SR, Kerry SM, Richards NM. General practitioners' perceptions of the tolerability of antidepressant drugs: a comparison of selective serotonin reuptake inhibitors and tricyclic antidepressants. *BMJ.* 1997;314:646-51.