

Primary care



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Efficacy and tolerability of selective serotonin reuptake inhibitors compared with tricyclic antidepressants in depression treated in primary care: systematic review and meta-analysis

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References to included and excluded studies appear on bmj.com

Abstract

Objective To compare the efficacy and tolerability of tricyclic antidepressants with selective serotonin reuptake inhibitors in depression in primary care.

Design Systematic review and meta-analysis of randomised controlled trials.

Data sources Register of the Cochrane Collaboration's depression, anxiety, and neurosis group. Reference lists of initial studies and other relevant review papers. Selected authors and experts.

Selection of studies Studies had to meet minimum requirements on: adequacy of sample size, adequate allocation concealment, clear description of treatment, representative source of subjects, use of diagnostic criteria or clear specification of inclusion criteria, details regarding number and reasons for withdrawal by group, and outcome measures described clearly or use of validated instruments.

Main outcome measures Standardised mean difference of final mean depression scores and relative risk of response when using the clinical global impression score. Relative risk of withdrawing from treatment at any time, and the number withdrawing due to side effects.

Results 11 studies (2951 participants) compared a selective serotonin reuptake inhibitor with a tricyclic antidepressant. Efficacy between selective serotonin reuptake inhibitors and tricyclics did not differ significantly (standardised weighted mean difference, fixed effects 0.07, 95% confidence interval -0.02 to 0.15; $z=1.59$, $P<0.11$). Significantly more patients receiving a tricyclic withdrew from treatment (relative risk 0.78, 95% confidence interval 0.68 to 0.90; $z=3.37$, $P<0.0007$) and withdrew specifically because of side effects (0.73, 0.60 to 0.88; $z=3.24$, $P<0.001$). Most studies included were small and supported by commercial funding. Many studies were of low methodological quality or did not present adequate data for analysis, or both, and were of short duration, typically six to eight weeks.

Conclusion The evidence on the relative efficacy of selective serotonin reuptake inhibitors and tricyclic

antidepressants in primary care is sparse and of variable quality. The study setting is likely to be an important factor in assessing the efficacy and tolerability of treatment with antidepressant drugs.

Introduction

Depression is the most common and costly mental health problem seen in general practice.¹ Antidepressants remain the mainstay of treatment. Although most patients with clinical depression are dealt with in primary care, research findings on which treatment decisions are based have included mostly patients in secondary care. However, research indicates that patients with major depressive disorders in primary care may have a different aetiology and natural history to patients in secondary care.^{2,3} Concern has therefore been expressed about the relevance of secondary care studies to primary care patients.⁴ Previous systematic reviews and meta-analyses have included mainly secondary care studies and have compared a range of newer antidepressants with tricyclic and related antidepressants.⁵⁻⁹

We conducted a systematic review and meta-analysis of only those studies that have been conducted concerning efficacy and tolerability of antidepressants among primary care patients, comparing the most commonly used classes of antidepressants in primary care (selective serotonin reuptake inhibitors and tricyclics).

Methods

Inclusion criteria

We included studies if they were randomised controlled trials comparing a selective serotonin reuptake inhibitor with a tricyclic antidepressant for the treatment of (predominantly adult) primary care patients with a depressive disorder.

Outcomes

The primary outcome was the efficacy of treatment comparing selective serotonin reuptake inhibitors with tricyclics. As a measure of efficacy we calculated standardised mean difference of final mean depression scores and relative risk of response when using the

clinical global impression score. Secondary outcomes were the number of patients withdrawing from treatment at any time and the number withdrawing because of side effects.

Identification of trials

We electronically searched the register of randomised controlled trials and controlled clinical trials located by the depression, anxiety, and neurosis group of the Cochrane Collaboration up to April 2002. We scrutinised the reference lists of initial studies identified and other relevant review papers. We also contacted selected authors and experts.

Data extraction and quality assessment

We assessed studies as being of low methodological quality if they did not meet minimum requirements on each of the following elements of study design: adequacy of sample size, adequate allocation concealment, clear description of treatment, representative source of subjects, use of diagnostic criteria or clear specification of inclusion criteria, details regarding number and reasons for withdrawal by group, and outcome measures described clearly or use of validated instruments.

Statistical analysis

For continuous outcomes we calculated the standardised mean difference or the weighted mean difference. For binary outcomes we calculated relative risk and the number needed to treat. We assessed heterogeneity by using the *Q* statistic. Any heterogeneity in the data was cautiously explored by using previously identified characteristics of the studies, particularly assessments of methodological quality, diagnostic category, and study length. We used a fixed effects model throughout. Where standard deviations were not provided by authors or were not available we conservatively used the highest known standard deviations from the included studies.

Results

Study inclusion and characteristics

Altogether 130 of the initial 284 papers identified were potentially relevant and subjected to strict quality and eligibility assessment. We finally included 11 studies (2954 participants) comparing a selective serotonin reuptake inhibitor (1607 participants) with a tricyclic antidepressant (1347 participants). Details of included studies are shown on bmj.com

Most studies in the review included patients aged 18-70 (mean age 40.5). Typically about three quarters of participants were female. Most participants were white Europeans who were being treated by their general practitioner. Six of the studies took place in the United Kingdom; two in Denmark, Sweden, Norway, and Finland; one in Norway; and one in Australia. One study included 121 centres from 10 different countries, including Canada, France, Germany, Greece, Ireland, Portugal, and South Africa.

Four studies did not meet the minimum quality criteria on at least one of the key components of methodological quality. Two studies had inadequate allocation concealment; one study had inadequate allocation concealment and withdrawal details; and one study had a small sample size and inadequate details on

withdrawal. Funnel plots indicated no obvious publication or related bias. All included studies were either supported by commercial funding or included at least one author who was employed by a pharmaceutical company, or both.

Effectiveness

Final mean continuous depression scale scores

Six studies contributed to the analysis. Overall we made seven comparisons since one study had two groups of patients receiving a selective serotonin reuptake inhibitor at different dosages. Only three studies provided data in an unambiguous format and provided standard deviations.

The standardised weighted mean difference was 0.07 (95% confidence interval -0.02 to 0.15), which is a slight but non-significant effect in favour of tricyclic antidepressants (fig 1). If only the three studies that provide unambiguous data and standard deviations are included the effect that favours the tricyclics disappears (-0.03, -0.20 to 0.14) (fig 2). If three studies of low quality are also included in the overall analysis (thus 10 comparisons in all) the difference in favour of tricyclics is similar (0.05, -0.02 to 0.15).

Clinical global impression (improvement)

Three studies contributed four comparisons for this analysis; they included 740 patients of whom 441 received a selective serotonin reuptake inhibitor and 299 a tricyclic antidepressant. The difference between the two treatments does not seem to reach statistical significance (relative risk 1.11, 0.86 to 1.43). If the four low quality studies are included in the analysis there is still no suggestion of a difference (1.05, 0.87 to 1.27).

Tolerability

Number of patients withdrawing from treatment for any reason

Six studies contributed seven comparisons for this analysis. These included 2375 patients of whom 1275 received a selective serotonin reuptake inhibitor and 1100 a tricyclic antidepressant. Of patients receiving a selective serotonin reuptake inhibitor, 20.7% (264) withdrew from treatment, compared with 27.9% (307) of patients treated with a tricyclic. Pooled estimates significantly favoured the selective serotonin reuptake inhibitors (relative risk 0.78, 0.68 to 0.90, $P=0.0007$). The number needed to treat was 14 (95% confidence interval 10 to 27). The overall results remain broadly similar if the four low quality studies are also included in the analysis (0.81, 0.70 to 0.92).

Number of patients withdrawing from treatment because of drug related adverse events

Seven studies with eight comparisons provided data for the analysis (fig 2). Significantly fewer (11.6%; 9.9% to 13.3%) patients ($n=164$) receiving a selective serotonin reuptake inhibitor withdrew due to drug related adverse events than patients ($n=196$) treated with a tricyclic (17.0% (14.8% to 19.1%) (NNT 18, 12 to 33)). Results remained almost identical if the four low quality studies were included in the overall analysis (0.73, 0.61 to 0.88).

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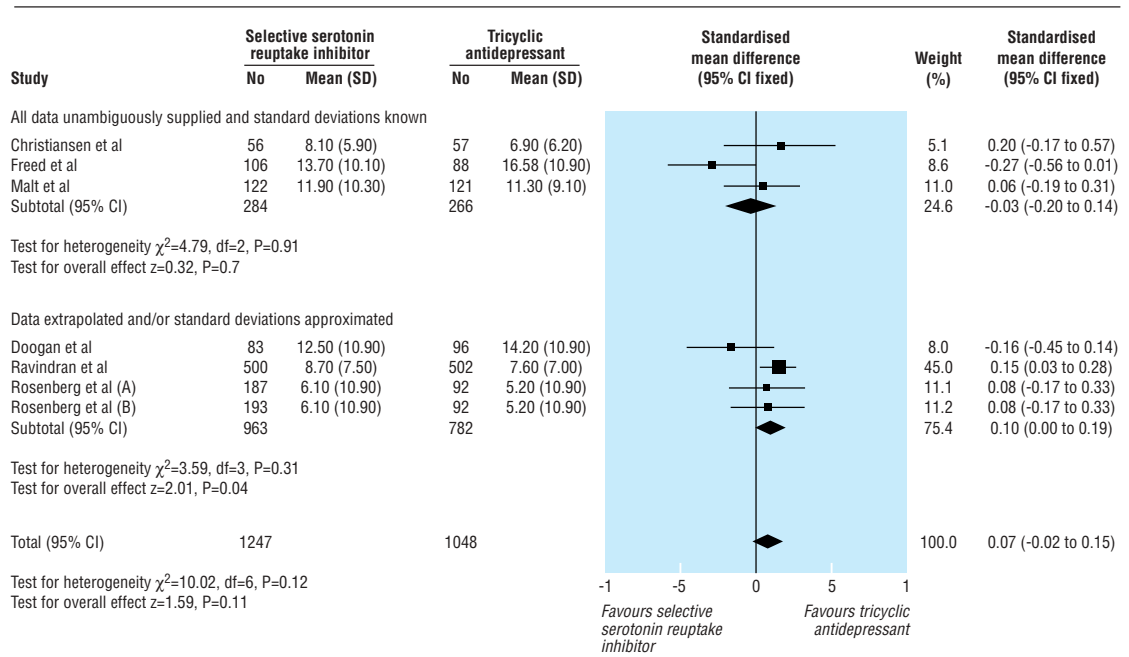


Fig 1 Effectiveness of treatments when using standardised continuous outcome measures. References to studies can be found on bmj.com

Discussion

Our results imply that, in the short term, no significant differences exist in efficacy between selective serotonin reuptake inhibitors and tricyclics in patients in primary care. We found significantly lower rates of dropout for selective serotonin reuptake inhibitors than for tricyclics. Previous reviews have also indicated that selective serotonin reuptake inhibitors are generally more tolerable than tricyclics, but evidence has been conflicting. Our results show lower dropout rates than those reported in other, non-primary care based reviews—10% less for selective serotonin reuptake inhibitors and 5.5% less for tricyclics.

Dropout rates are an imprecise index of tolerability, however, since patients may stop taking medication for many reasons. A more precise index of tolerability may be withdrawal from treatment because of problems with side effects. It should be noted, however, that patients may still find antidepressants

intolerable, although they may continue to adhere to treatment. Few previous reviews have included an analysis of withdrawal due to side effects; one has found that 15% of patients treated with a selective serotonin reuptake inhibitor and 19% of patients receiving a tricyclic antidepressant withdrew from treatment for such reasons.⁸ By comparison, we found very much lower rates of withdrawal when selective serotonin reuptake inhibitors were used and only slightly lower rates when tricyclics were used. This finding shows that primary care patients are not only more likely to continue taking a selective serotonin reuptake inhibitor than a tricyclic antidepressant but that they may also be more likely to continue with selective serotonin reuptake inhibitors than are secondary care patients.

None of the studies included in our review specifically examined minor depressive disorder, mild presentations of a major depressive disorder, or dysthymia. This is important because research indicates differences in outcome depending on diagnostic category. That there are no primary care based studies focused on such presentations, further highlight a need to conduct studies that include only minor or milder presentations.

We found only 11 studies based in primary care that met our inclusion criteria and provided evidence for the comparative efficacy and tolerability of selective serotonin reuptake inhibitors with tricyclics. This compares with considerably larger numbers of studies conducted with patients from all settings (123 trials in one review⁵ and 36 trials in a review including only United States based trials⁶). Given that we know that most depressed patients are treated in primary care only, we expected that a larger proportion of trials including only primary care patients would have been conducted. Furthermore, since differences

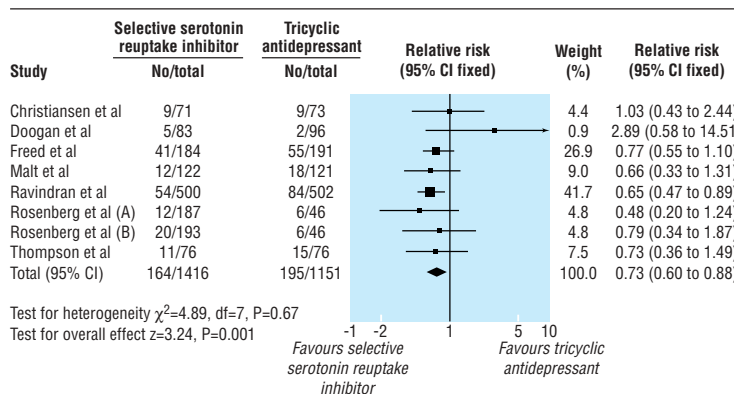


Fig 2 Number of patients withdrawing from treatment due to side effects

What is already known on this topic

Previous meta-analyses have included comparatively large numbers of secondary care based studies that indicate no significant differences in efficacy between selective serotonin reuptake inhibitors and tricyclics

Previous meta-analyses are conflicting regarding the relative tolerability between selective serotonin reuptake inhibitors and tricyclics, but do suggest a small but significant difference in favour of selective serotonin reuptake inhibitors

Such meta-analyses show notable heterogeneity

What this study adds

Selective serotonin reuptake inhibitors are better tolerated than tricyclics by primary care patients and may be better tolerated by primary care patients than secondary care patients

Study setting seems to be important and should be considered before licences are given to specific antidepressants

Although there are limited high quality data, available evidence shows that the most commonly prescribed classes of antidepressants in primary care (selective serotonin reuptake inhibitors and tricyclics) are equally effective in the short term for primary care patients, but the literature has many gaps

in tolerability of medicines may exist between patients treated in different settings, it may be appropriate for bodies that grant licences for drugs to ensure that studies have been carried out in appropriate settings before granting specific antidepressants their licence.

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- 1 Katon W, Schulberg H. Epidemiology of depression in primary care. *Gen Hosp Psychiatry* 1992;14:237-47.
- 2 Suh T, Gallo JJ. The management of depression among general medical service providers. *Psychol Med* 1999;27:1051-63.
- 3 Arya R. The management of depression in primary health care. *Curr Opin* 1999;12:103-7.
- 4 Gill D. Prescribing antidepressants in general practice. Systematic review of all pertinent trials is required to establish guidelines. *BMJ* 1997;314:826-7.
- 5 Williams JW Jr, Mulrow CD, Chiquette E, Noel PH, Aguilar C, Cornell J. A systematic review of newer pharmacotherapies for depression in adults: evidence report summary. *Ann Intern Med* 2000;132:743-56.
- 6 Steffens DC, Krishnan KR, Helms MJ. Are SSRIs better than TCAs? Comparison of SSRIs and TCAs: a meta-analysis. *Depress Anxiety* 1997;6:10-18.
- 7 North of England Evidence Based Guideline Development Project. *The choice of antidepressants for depression in primary care: evidence based clinical practice guideline*. Newcastle upon Tyne: Centre for Health Services Research, University of Newcastle UK, 1998.
- 8 Song F, Freemantle N, Sheldon TA, House A, Watson P, Long A, et al. Selective serotonin reuptake inhibitors: meta-analysis of efficacy and acceptability. *BMJ* 1993;306:683-7.
- 9 Anderson IM, Tomenson BM. Treatment discontinuation with selective serotonin reuptake inhibitors compared with tricyclic antidepressants: a meta-analysis. *BMJ* 1995;310:1433-8.

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One hundred years ago

The evil effects of the corset

Generations of medical men and some few enthusiastic reformers have repeatedly protested against the use of corsets, and have ascribed to them many of the ailments which are relatively common amongst women who wear them, but no more comprehensive accusation has been brought against the use of these articles of female attire than that contained in a paper by Dr. W. Williams of Liverpool, published in the *Reports* of the Royal Southern Hospital. Dr. Williams asserts that the injurious pressure of the corset on the lower ribs and the abdominal viscera interferes with digestion and assimilation, and produces dilatation of the stomach and gastric ulceration with subsequent anaemia, whilst at the same time by compressing the base of the thorax corsets throw the diaphragm out of action, and thus are responsible for the thoracic respiration of females which is described as both abnormal and insufficient. In addition, however, to these injurious results, lateral curvatures of the spine are also said to be due to the

injurious pressure of the corset upon the spinal muscles, and Dr. Williams concludes his heavy indictment with the statement that by the use of corsets the majority of women are permanently deformed as to their skeletons at 24 years of age, and permanently crippled at 30. Most observers will admit that numerous evils result from the abuse of corsets, nevertheless it is a fact that many women live to old age in good health, in spite of the compression to which they subject themselves, and it is difficult to see how the use of corsets is to be dispensed with so long as it is the custom to wear skirts and petticoats, which are most conveniently suspended from a structure which has a basis of support upon the hips... Until some series of garments is devised for female wear as becoming and comfortable as those which are at present customary but capable of being worn without corsets, there is little hope that the latter article will be dispensed with. (BMJ 1903;i:388)