Selective serotonin reuptake inhibitors (SSRIs) for major depression. Part 1: evaluation of the clinical literature

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Authors' objectives

To review the efficacy and safety of selective serotonin re-uptake inhibitors (SSRIs) when used to treat major depression.

Searching

MEDLINE, EMBASE, PsycINFO, International Pharmaceutical Abstracts, Pascal, Health Planning and Administration database, Mental Health Abstracts, and PharmacoEconomics and Outcomes News, were searched from 1980 to 1996. Details of the search terms used were provided. In addition, Current Contents was scanned during the course of the project, and journals received by the Canadian Coordinating Office for Health Technology Assessment library were handsearched. The bibliographies from retrieved papers, those provided by other researchers, and those from earlier publications on the subject were examined (see Other Publications of Related Interest nos.1-2).

Study selection

Study designs of evaluations included in the review

Double-blind randomised controlled trials (RCTs), including 2- and 3-arm trials, were eligible for inclusion.

Specific interventions included in the review

Antidepressant therapy of 4 to 12 weeks' duration, using SSRIs including fluoxetine, fluvoxamine, paroxetine and sertraline. The comparator regimens included placebo, an alternative SSRI, or other types of antidepressants. The latter included tricyclic antidepressants (TCAs) (amitriptyline, imipramine, clomipramine, dothiepin, doxepin, maprotiline, oxaprotiline, lofepramine, desipramine, nortriptyline) and others (mianserin, trazodone, moclobemide, bupropion, amineptine, nomifensine). The dose regimens varied across the trials and could be fixed or variable.

Participants included in the review

Adult or elderly patients with major depression, based on criteria of the American Psychiatric Association (DSM-III R or DSM-IV criteria), were included.

Outcomes assessed in the review

The outcome measures were: changes in the Hamilton Rate Scale for Depression (HRSD) or Clinical Global Impression (CGI), relative to baseline; the number of drop-outs; and the number of adverse events (analysis was restricted to consideration of the more common adverse events).

How were decisions on the relevance of primary studies made?

The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality

The authors do not state that they assessed quality.

Data extraction

The following data were extracted from all of the included studies: country of study; mean patient age; setting; clinical classification; history of recurrent episodes; intensity of current symptoms; fixed or variable drug dose regimens; level of dose; period of antidepressant treatment; concomitant drugs used; statistical tests employed; and quantitative data on change in HRSD and CGI scores and rates of adverse events were extracted from all included trials. In addition, data on

drop-outs and the reasons for their withdrawal, were recorded. However, the process of data extraction was not described, i.e. how many of the reviewers were involved and whether they conducted the data extraction independently.

Methods of synthesis

How were the studies combined?

To examine the change in HRSD as a result of treatment, the effect sizes were calculated for each individual trial and weighted by the inverse of the variance. The individual effect sizes were then pooled using a random-effects model. A funnel plot (individual effect sizes plotted against respective sample sizes) was generated for the comparison between SSRIs and all non-SSRI antidepressants, in order to examine the possible impact of publication bias.

The individual rate difference and associated 95% confidence intervals (CIs) were calculated for each trial, and weighted (method of weighting unclear) and pooled using hierarchical Bayesian meta-analyses (see Other Publications of Related Interest no.3), in order to examine the following:

the number of patients whose HRSD score improved by at least 50% following treatment;

the number of patients with a response of 1 or 2 in the CGI score (representing those who had improved very much or markedly);

the completion rates; and

adverse events,

How were differences between studies investigated?

Q statistics and respective p-values were calculated to assess homogeneity across the trials. Several subgroup analyses were undertaken in trials comparing SSRIs with TCAs. For one analysis, only trials explicitly excluding patients with major systemic diseases were included. In addition, the impact of the patients' age (18 to 60 years, or over 60 years), treatment setting (in- or out-patient), and drug dosage (low, standard, medium and high) were analysed.

Results of the review

One hundred and sixty-two RCTs (overall number of participants unclear) were included.

SSRIs were significantly more effective than placebo. The overall mean difference in effect size was 0.55 (95% CI: 0.40, 0.70) when using data from 48 trials (n=4,803). There were no significant differences in effect size between different SSRIs (10 trials), nor between SSRIs and other antidepressants (overall analysis of 117 trials: pooled effect size difference -0.01, 95% CI: -0.08, 0.06). The latter was robust when SSRIs were compared with different subgroups of non-SSRI antidepressants (classical TCAs and all other antidepressants). The patient mix, patients' age, treatment setting, and drug dose and regimen did not affect the results. Analysis by dichotomous (rate) outcomes showed similar results. The funnel plot for the comparison between SSRIs and non-SSRI antidepressants was symmetrical, suggesting that there was little publication bias.

Completion rates with SSRIs were significantly better than with placebo (overall analysis of 43 trials, n=4,986: pooled mean completion rate difference 8%, 95% CI: 4, 13), but did not differ significantly between different SSRIs (11 trials) or between SSRIs and other antidepressants (116 trials). The rates were not influenced by the patients' age or the treatment setting. The differences in drop-outs between the SSRI and TCA groups, due to lack of effect, worsening of symptoms, or adverse events, were not statistically significant. However, there were significantly fewer drop-outs (2%) due to adverse events with SSRIs than with TCAs when the adult (i.e. elderly patients excluded) and out-patient (i.e. in-patients excluded) groups were combined.

SSRIs were associated with significantly higher rates of nausea, anorexia, diarrhoea, anxiety, agitation, insomnia and nervousness when compared with TCAs. TCAs were associated with significantly higher rates of dry mouth, constipation, blurred vision, sweating and dizziness when compared with SSRIs. There were no statistically-significant differences between SSRIs and TCAs for incidence of palpitations, urinary disturbance, fatigue, tremor, headache and hypotension. The findings were not influenced by the method of eliciting information on adverse effects.

Authors' conclusions

Use of placebo can produce improvement. However, SSRIs were significantly more effective than placebo in terms of improved symptoms, and were associated with significantly greater completion rates. There were no statistically-significant differences in efficacy or completion rates between individual SSRIs, or between SSRIs and other antidepressants. There were no statistically-significant differences in drop-out rates between SSRIs and TCAs, except when the adult and out-patient groups were combined; in this case, significantly fewer drop-outs due to adverse effects were seen with the SSRIs. SSRIs and TCAs were each associated with certain adverse effects, the incidence of which differed in terms of the statistical significance between the two groups of drugs.

CRD commentary

Overall, this was a thorough and well-conducted systematic review. The research question, literature search, selection criteria, and methods used to pool the data were all clearly presented. Some details of the primary studies were tabulated, but more information, particularly relating to the participants, would have been useful. There was no quality assessment of the included trials. Although only double-blind RCTs were eligible for inclusion, a presentation of the methodological quality would have been useful; study validity is likely to vary across groups of trials. In addition, there were no details concerning the process of the review, i.e. how many of the reviewers were involved, how decisions were made about selecting the studies, and whether the trials were assessed independently.

The authors' conclusions reflect the evidence found in the review.

Implications of the review for practice and research

The authors did not state any implications for practice or further research.

Bibliographic details

Trindade E, Menon D. Selective serotonin reuptake inhibitors (SSRIs) for major depression. Part 1: evaluation of the clinical literature. Ottawa, ON, Canada: Canadian Coordinating Office for Health Technology Assessment (CCOHTA). 1997

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http://www.cadth.ca/index.php/en/hta/reports-publications/search/publica tion/27

Other publications of related interest

1. United States Agency for Health Care Policy and Research. Depression in primary care: detection, diagnosis, and treatment. Rockville (MD): The Agency; 1993. 2. NHS Centre for Reviews and Dissemination. The treatment of depression in primary care: which treatments are effective in the management of depression in primary care? Effective Health Care 1993;1(5). 3. Hedges LV, Olkin I. Statistical methods for meta-analysis. San Diego (CA): Academic Press; 1985.

This additional published commentary may also be of interest. Review: selective serotonin reuptake inhibitors differ from tricyclicantidepressants in adverse events. Evid Based Med 1998;3:86-7.

Indexing Status

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.