Adverse effects associated with selective serotonin reuptake inhibitors and tricyclic antidepressants: a meta-analysis

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Authors' objectives
To examine the adverse reactions associated with the use of selective serotonin reuptake inhibitors (SSRIs) and older tricyclic antidepressants (TCAs).

Searching
The following data bases were searched from January 1980 to May 1996: MEDLINE; EMBASE; PsycINFO; International Pharmaceutical Abstracts; Pascal; Health Planning and Administration (Health); Mental Health Abstracts; and Adis PharmacoEconomics and Outcomes News. Regular searches were made of Current Contents: Clinical Medicine and hand scanning of Journals received by the Canadian Coordinating Office of Health Technology Assessment library throughout the study period. Keywords included the following: serotonin uptake inhibitor(s); SSRI(s); antidepressant(s); monoamine oxidase inhibitor(s); antidepressant agents; tricyclic; and the names of the various drugs. References from retrieved articles were scanned and further references obtained from bibliographies provided by other researchers. Additional references were identified from earlier publications on the topic including those by the US Agency for Health Care Policy and Research, clinical practice guidelines, and the UK National Health Service, Centre for Reviews and Dissemination.

Study selection
Study designs of evaluations included in the review
Double-blind randomised controlled trials (RCTs) that compared an SSRI with a TCA for major depression were included if they fulfilled the following criteria: study was of 4 to 12 weeks duration; trials had at least 20 patients in each arm; and study reported the number of patients with adverse effects in both the SSRI and TCA arm.

Specific interventions included in the review
Antidepressant treatment with SSRIs (including fluoxetine, fluvoxamine, paroxetine, and sertraline) and TCAs (including secondary, tertiary and quaternary amines) was studied.

Participants included in the review
The participants were patients for major depression as defined by American Psychiatric Association criteria (DSM-IV).

Outcomes assessed in the review
Outcomes were the following adverse reactions for which data from at least 6 trials was available: headache; tremor; urinary disturbances; hypotension; dry mouth; constipation; dizziness; sweating; blurred vision; palpitations; nausea; anorexia; diarrhoea; insomnia; nervousness; fatigue; agitation; and anxiety. Drop-outs due to adverse reactions were also considered.

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 validity.

Data extraction
Data extracted included the following: sample size by treatment arm; adverse reactions by drug treatment; drop-out
rates due to adverse reactions; and methods used to elicit information about adverse effects. The differences in rates of occurrence of specified adverse reactions between treatment arms was calculated for each trial.

**Methods of synthesis**
How were the studies combined?
For each adverse effect a pooled rate difference and 95% confidence interval was obtained by a Bayesian hierarchical meta-analysis.

How were differences between studies investigated?
The influence of the method of eliciting information on adverse reactions was tested by grouping the trials according to the method used, then calculating within each group the weighted pooled rate difference between the SSRI and TCA arms for 2 adverse reactions (nausea and dry mouth). Weighting was by variability of each trial.

Pooled rate differences were calculated for each of 4 SSRIs and TCAs as a whole. Rates of discontinuation due to adverse reactions were calculated for individual SSRIs or any SSRI and compared with rates for secondary, tertiary, quaternary amines or any TCA. A sub-set meta-analysis compared drop out rates for SSRIs vs TCAs for trials restricted to adult out-patients.

**Results of the review**
Eighty-four double-blind RCTs were included.

Crude rates of occurrence of adverse reactions SSRI vs TCA: constipation (49 trials) 11% vs 22%; dizziness (37 trials) 14% vs 23%; hypotension (8 trials) 9% vs 16%; dry mouth (56 trials) 22% vs 27%; blurred vision (19 trials) 10% vs 14%; sweating (27 trials) 10% vs 14%; urinary disturbance (14 trials) 6% vs 9%; palpitations (11 trials) 4% vs 5%; fatigue (23 trials) 10% vs 11%; tremor (37 trials) 15% vs 15%; anorexia (11 trials) 9% vs 8%; nervousness (14 trials) 14% vs 10%; agitation (11 trials) 12% vs 8%; headache (32 trials) 18% vs 14%; insomnia (32 trials) 12% vs 7%; anxiety (17 trials) 14% vs 7%; diarrhoea (15 trials) 16% vs 4%; nausea (56 trials) 26% vs 11%.

Adverse effects for which there was no statistically significant difference between any one of 4 SSRIs and TCAs: headache, tremor, urinary disturbance, and hypotension.

Adverse effects that occurred statistically significantly more often with TCAs than with at least one of the SSRIs: dry mouth, constipation, dizziness, sweating, blurred vision, and palpitations. Adverse effects that occurred statistically significantly more often with at least one of the SSRIs than with TCAs: nausea, anorexia, diarrhoea, insomnia, nervousness, and fatigue.

Adverse effects for which there was no significant rate differences between any individual SSRI and the group of TCAs: agitation and anxiety. Statistically significant difference noted for agitation and anxiety when SSRI data was pooled.

After pooling data for all SSRIs results were as follows: Adverse effects that occurred statistically significantly more often with SSRI: nausea, anorexia, diarrhoea, insomnia, nervousness, agitation and anxiety. Adverse effects that occurred statistically significantly more often with TCAs: dry mouth, constipation, dizziness, sweating and blurred vision.

Method of eliciting information about adverse effects. Details of the method was omitted from some studies. Rate differences were statistically significant for nausea with SSRIs compared with TCAs when information was sought using checklists, questions that indirectly addressed adverse effects, or spontaneous reporting by the patients, but not statistically significant when using Treatment Emergent Symptom Scale. Rate differences were statistically significant using all the above methods for dry mouth but were not statistically different from each other.

Drop-outs due to adverse effects (70 studies): No statistically significant differences in rates for individual SSRIs or any SSRI vs secondary, tertiary and quaternary amines or any of TCAs.
Sub-set analysis restricted to adult outpatients: 2% fewer drop-outs due to SSRIs (statistically significant).

**Authors’ conclusions**

SSRIs and TCAs are both associated with adverse effects although the key effects differ between classes. Further explanation of the adverse effects and their relation to discontinuation of medication will require better studies involving prospective collection of quality of life data.

**CRD commentary**

The aims and inclusion criteria are clearly stated. An extensive literature search was conducted. Some investigation was conducted into factors differing among trials. Discussion includes consideration of the following: potential difference between statistically significant and clinically significant rates; insufficient data available to allow comparison of rare event such as suicide; the potential influence of reporting methods on rates reported; unblinding of health professionals due to the profile of adverse reactions reported by patients; no definition of end points before commencement of individual trials; potential heterogeneity of population; high incidence of symptoms resembling adverse reactions among depressed patient before therapy was started; and lack of reporting of the intensity of symptoms or the impact on patient’s quality of life. The paper is based on a larger study of clinical trials of antidepressants (see Other Publications of Related Interest).

No details are given of methods used to select primary studies or extract data and no details are given of the individual trials. Neither validity nor heterogeneity among trials was assessed. Potential bias due to selective reporting of adverse effects cannot be ruled out because the relevant outcomes were not available in a large number of trials.

The conclusions are supported by the evidence presented.

**Implications of the review for practice and research**

Practice: The authors did not state any implications for practice.

Research: The authors consider that more systematic reporting of adverse effects is necessary to increase estimates of rate difference.

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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.