Citalopram therapy for depression: a review of 10 years of European experience and data from US clinical trials

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Authors' objectives
To review a decade of experience with citalopram, focusing mainly on efficacy, safety, and tolerability data derived from randomised, well-controlled clinical trials of patients with depression.

Searching
MEDLINE was searched from 1966 to 2000 to identify relevant English language publications, using the following terms: 'citalopram', 'SSRI', 'TCA', 'depression' and 'clinical'. Published biographies were cross-referenced to locate additional primary sources of information. Data presented at major medical conferences and published in abstract form were also reviewed.

Study selection
Study designs of evaluations included in the review
Double-blind, randomised controlled trials (RCTs) to determine the efficacy of citalopram were included. Pharmacokinetic studies and case reports were reviewed to supplement the evaluation of citalopram's safety and tolerability.

Specific interventions included in the review
Studies were included if they compared citalopram with placebo, tricyclic or tetracyclic antidepressants (amitriptyline, clomipramine, imipramine, maprotiline, mianserin) or other selective serotonin re-uptake inhibitors (SSRIs, i.e. fluoxetine and fluvoxamine). Citalopram was administered once daily, either in the morning or at bedtime.

Participants included in the review
Studies were included if citalopram was used in the treatment of depression. Most of the trials enrolled patients with moderate-to-severe major depression, as defined by American Psychiatric Association criteria (DSM-III, DSM-III-R or DSM-IV); however, some studies also included patients with bipolar disorder or melancholia. The average age of participants in the clinical trials was approximately 40 years. Some studies included geriatric patients, and three exclusively enrolled patients aged above 60 years.

Outcomes assessed in the review
The primary efficacy measures used in the trials were the Hamilton Rating Scale for Depression (HAM-D), the Montgomery-Asberg Depression Rating Scale for Depression (MADRS), and/or the Clinical Global Impression Improvement scale (CGI-I). In most cases more than one rating instrument was used. Responders were assessed using the conventional 50% reduction from baseline rating scale score, or a CGI-I score of 1 or 2. Reports of adverse events were assembled using a variety of means, including specific symptom checklists, the open-question technique, and spontaneous reportage and investigator observation.

How were decisions on the relevance of primary studies made?
The author does not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The author does not state that they assessed validity.

Data extraction
The author does not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. Data were extracted on: author, year, patient type and age, duration of treatment (weeks), the number of evaluable patients, daily dose (mg), assessment method, concomitant medicine, results and comments.

Methods of synthesis
How were the studies combined?
A narrative synthesis was undertaken.

How were differences between studies investigated?
Differences between the included studies were discussed in the narrative synthesis.

Results of the review
Thirty double-blind RCTs, containing approximately 4,800 patients, were included in the review.

Antidepressant efficacy versus placebo (11 RCTs):

Three large multicentre trials comparing citalopram (10 to 80 mg) with placebo found significantly greater improvement in HAM-D, MADRS and CGI scores for depressed patients receiving citalopram. Three meta-analyses of placebo-controlled trials generated results consistent with those seen in the multicentre trials. A 6-week placebo-controlled trial of citalopram (20 to 30 mg) in depressed elderly patients with or without dementia found similar improvements, plus improvements on several individual items on the Gotfries-Brane-Steen scale of cognitive functioning.

Efficacy of citalopram versus placebo in the prevention of relapse (n=2):

When using citalopram as a continuation therapy for the prevention of relapse, patients who responded to citalopram (after 6 or 8 weeks) were randomly assigned to citalopram (20 to 60mg) or placebo for a further 24 weeks. In both trials, the rates of relapse (defined by a threshold MADRS score of 22 in one trial, 25 in the other) were significantly lower for citalopram than placebo.

Efficacy of citalopram in preventing recurrence of depression (n=2):

In one study, patients with a history of at least 2 prior depressive episodes, who responded to treatment with citalopram, received 16 weeks of continuous treatment at their established effective dose. Patients who continued to respond were randomised to at least 48 weeks of double-blind treatment with either continued citalopram or placebo. Eighty percent of citalopram-treated patients remained free of recurrence (MADRS score 22) throughout the maintenance phase of the study, compared with 50% of patients assigned to placebo (p<0.0001). In the second study with a similar design, citalopram was shown to be effective in the prevention of depression recurrence in patients aged over 65 years.

Comparative efficacy of citalopram versus tricyclic and tetracyclic antidepressants:

In 3 double-blind studies, citalopram (20 to 60 mg/day) and amitriptyline (50 to 225 mg/day) were found to be similarly efficacious among patients with major depression and elderly depressed patients.

A 5-week study of 102 depressed patients found citalopram (40 mg/day) to be less effective than clomipramine (150 mg/day). The rate of complete recovery (HAM-D score of 7 or less) was 60% in the clomipramine group and 30% in the citalopram group (p<0.005).

A large multicentre study in 400 depressed patients found patients receiving citalopram (10 to 30 mg/day; 20 to 60 mg/day) or imipramine (50 to 150 mg/day) experienced similar reductions in HAM-D scores at the end of both 6 and 22 weeks of treatment.

Two double-blind comparative trials concluded that citalopram was as effective as maprotiline in reducing HAM-D, MADRS and CGI scores from baseline.
Two small studies compared the efficacy of citalopram with mianserin in patients with depression. In one of these, citalopram appeared to produce a more rapid onset of effect as measured by both the MADRS and the CGI score. In the other study, citalopram (40 to 60 mg/day) and mianserin (60 to 90 mg/day) were equally effective in patients with endogenous depression, but mianserin was more effective among nonendogenously depressed patients.

A retrospective meta-analysis of 5 trials comparing citalopram (30 to 60 mg) with tricyclic antidepressants (amitriptyline, clomipramine, nortriptyline and amitriptyline) showed that, on the basis of a 50% reduction in HAM-D total scores, the efficacy of citalopram was similar to that of tricyclic antidepressants.

Comparative efficacy of citalopram versus other SSRIs:

The efficacy of citalopram was compared with that of fluoxetine in two 8-week trials among psychiatric patients and among patients from general medical practice. In the psychiatrist-based trial, citalopram (40 mg) and fluoxetine (20 mg) were equally efficacious, as measured by reductions in MADRS, HAM-D and CGI-S assessments. Citalopram was found to be significantly more efficacious than fluoxetine for severely depressed patients with HAM-D scores of at least 25 (p=0.0003). Similar outcomes were found in the general medical practice setting, where the two treatments were similarly efficacious; except for a subgroup of patients not receiving benzodiazepines, the mean reduction in total MADRS scores favoured citalopram at 2, 4, 6 and 8 weeks.

Two multicentre trials comparing citalopram with sertraline found both to be similarly effective in producing a meaningful reduction in total MADRS score, although one study found citalopram to be associated with anti-anxiety effects.

A 6-week, double-blind multicentre study found citalopram (20 to 40 mg/day) and fluvoxamine to be similarly effective. Complete plus partial response rates (based on HAM-D scores) were 42 and 39% in the citalopram and fluvoxamine groups, respectively. CGI and Zung self-rating depression scores provided similar results with regard to efficacy.

Safety and tolerability:

In comparison with placebo, citalopram was shown to be safe and well-tolerated in both the short- and long-term. The side-effects observed in patients treated with citalopram included somnolence, nausea, dry mouth, increased sweating and short-term anorgasmia. One study also found that asthenia, tiredness, lassitude and emotional indifference occurred significantly more frequently in elderly patients treated with citalopram, than in those receiving placebo.

As with other SSRIs, citalopram is generally better tolerated than the tricyclic antidepressants. In particular, citalopram appears to produce fewer and less severe central nervous system and anticholinergic effects. The available data suggest that the tolerability profile of citalopram is similar to that of other SSRIs.

Evidence included in the review suggested that citalopram does not have any adverse effects in terms of psychomotor function or cardiovascular safety, and is safe in overdose.

Authors' conclusions

Data published over the last decade suggest that citalopram is (1) superior to placebo in the treatment of depression; (2) has efficacy similar to that of the tricyclic and tetracyclic antidepressants and to other SSRIs; and (3) is safe and well tolerated in the therapeutic dose range of 20 to 60 mg/day. Distinct from some other agents in its class, citalopram exhibits linear pharmacokinetics and minimal drug interaction potential.

CRD commentary

The inclusion criteria used were appropriate to the review question, but the literature search was not as thorough as it could have been. References lists of retrieved papers were scanned and attempts to identify unpublished literature were made. However, relevant papers may have been missed as the search was limited to a single database and only English language papers were retrieved. The validity of individual studies was not assessed and study quality was not taken into consideration during synthesis; however, only double-blind RCTs, which provide a stronger level of evidence than other
study designs, were included. It is unclear how many reviewers were involved at any stage of the review process. The narrative synthesis was organised under appropriate headings and provided details of individual studies, though it is unclear why only a selection of the included studies were displayed in tables. The author's conclusions appear to follow from the evidence presented in the review, but they should be treated with some caution considering the above-mentioned caveats.

**Implications of the review for practice and research**
Practice: The author states that citalopram exhibits linear pharmacokinetics and minimal drug interaction potential, making it an attractive treatment agent for the treatment of depression, especially among the elderly and patients with co-morbid illness.

Research: The author did not state any implications for further research.

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