CNS or classic drugs for the treatment of pain in functional dyspepsia? A systematic review and meta-analysis of the literature

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CRD summary
The review concluded that both central nervous system (CNS) drugs and classic gastrointestinal drugs (prokinetic and antisecretory drugs) were associated with significant pain reduction in functional dyspepsia. Given some limitations of the review process, uncertainties about the quality of included studies, and the small size of the studies of CNS drugs, the reliability of the authors' conclusions is unclear.

Authors' objectives
To compare the efficacy of central nervous system (CNS) drugs and classic (gastrointestinal) drugs for the treatment of pain in functional dyspepsia.

Searching
MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Database of Systematic Reviews were searched from January 1997 to June 2007 for publications in English; search terms were reported. Bibliographies of each retrieved article were handsearched. Published books, articles, indexed abstracts, journals and proceedings were included.

Study selection
Double-blind randomised controlled trials (RCTs) that compared the efficacy of CNS drugs (antidepressants and anti-anxiety agents) with classic drugs (antisecretory and prokinetic drugs) for the treatment of pain and abdominal discomfort in functional dyspepsia (according to the Rome diagnostic criteria) were eligible for inclusion. Eligible trials had to measure dyspeptic symptoms on a continuous clinical scale and report the mean and standard deviation (SD) of dyspeptic symptoms before and after treatment (or report other statistical parameters that enabled calculation of these values). Since relatively few RCTs of CNS drugs were identified, the authors also included open-label trials of CNS drugs. Case studies or series were excluded.

The primary outcomes were dyspeptic symptoms/pain scores.

In included trials, the antisecretory (classic) drugs used were omeprazole, lansoprazole, escabet sodium, cimetidine, rebamipide and famotidine; the prokinetic (classic) drugs used were cisapride, itopride, mosapride and ABT-229; the CNS drugs used were levulosupiride, amitriptyline, fluoxetine and tandospirone. Dosage details were provided; some trials compared different dosage regimes. The duration of treatment ranged from three to eight weeks. The mean age of included patients ranged from 35.5 to 63.1 years; the percentage of males ranged from 21.1 to 87.5%.

The authors did not state how many reviewers selected studies for the review.

Assessment of study quality
A formal validity assessment was not performed, but the authors recorded blinding.

Data extraction
Individual or global dyspeptic symptom scores were extracted and used to calculate mean differences (MDs) from baseline to immediately after treatment, with 95% confidence intervals (CI). Authors were contacted for missing data.

One reviewer performed the extraction, which was checked by a second reviewer. Discrepancies were resolved by consensus or by consultation with a third reviewer.

Methods of synthesis
Standardised mean differences (SMD; Cohen's d) were calculated with 95% confidence intervals. Results were pooled initially to evaluate the effectiveness of CNS and classic drugs separately, then the effect sizes of the two types of treatment were compared. Effect sizes were also determined for antisecretory and prokinetic drugs.

Since relatively few RCTs of CNS drugs were identified, the standardised mean difference for open studies of CNS drugs was determined, followed by the standardised mean difference of RCT and open studies were combined. Pooled effects were determined using both fixed-effect and random-effects models. Heterogeneity was determined using the Q statistic.

Sensitivity analyses were performed omitting studies one by one from the analysis.

Publication bias was assessed using Egger's test and visually using funnel plots.

**Results of the review**

Eighteen relevant studies were identified (n=2,746 patients), including 15 RCTs (n=2,628 patients, range 7 to 569) and three open-label trials (n=118, range 16 to 62) of central nervous system (CNS) drugs. There were four RCTs of CNS drugs (n=219 patients) and eleven RCTs of classic drugs (n=2,409 patients). The classic drugs RCTs included six of prokinetic drugs and five of antisecretory drugs. Twelve RCTs were reported as double-blind and one as blind. Eight RCTs were placebo-controlled, with three cross-over studies, one parallel study and one multicentre study.

CNS drugs significantly reduced dyspeptic symptoms/pain scores (SMD 1.48, 95% CI 0.75 to 2.22; four RCTs; random-effects model). No significant heterogeneity was found.

Prokinetic drugs (SMD 1.63, 95% CI 1.28 to 1.97; six RCTs) and antisecretory agents (SMD 0.93, 95% CI 0.57 to 1.29; five RCTs) significantly reduced dyspeptic symptoms/pain scores. Both analyses used a random-effects model and had significant heterogeneity.

Sensitivity analyses did not change the overall effects. There was no significant difference between prokinetic drugs and CNS drugs, but there was a significant difference between antisecretory drugs and CNS drugs (p<0.01); CNS drugs were slightly more effective (further details were not provided).

The pooled analysis of the RCTs and the open studies of CNS drugs gave a slightly higher effect in reducing dyspeptic symptoms (SMD 1.96, 95% CI 0.82 to 3.11; seven studies; random-effects model); there was significant heterogeneity.

There was no evidence of publication bias.

**Authors' conclusions**

CNS drugs may be as effective as classic gastrointestinal therapies (prokinetic and antisecretory drugs) in the treatment of functional dyspepsia; both types of drugs were associated with significant pain reduction in functional dyspepsia.

**CRD commentary**

The review addressed a well-defined question in terms of participants, interventions, study design and relevant outcomes. Relevant databases were searched. Only studies published in English were sought, so language bias was a possibility, and relevant studies may have been missed. There was no evidence of publication bias. Although data extraction was carried out with efforts to reduce error and bias, it was not clear whether this process applied to study selection.

Study quality was not assessed and, given the relatively few relevant details provided, it was difficult to judge the quality of included studies. Relevant study details were reported. There was little data on the placebos used. Statistical heterogeneity was assessed; there was evidence for heterogeneity with most outcomes. The statistical method used for the meta-analysis of the RCTs may be inappropriate, since the study designs and drugs investigated were very varied, and few of the RCTs directly compared CNS and classic drugs. Sensitivity analyses were performed.

In view of some potential limitations arising from the review process, uncertainties about the quality of included studies are inevitable.
studies, and the small size of many of the included studies (particularly those of the CNS drugs), the reliability of the authors’ conclusions is unclear.

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

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

**Research:** The authors identified a need for larger clinical trials with head-to-head comparisons between CNS and classic drugs and the investigation of new approaches such as combination therapy of anti-anxiety and anti-depressive agents with prokinetic or antisecretory agents.

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