Mirtazapine: a review of its use in major depression
Holm K J, Markham A

Authors' objectives
To evaluate the use of mirtazapine in patients with major depression.

Searching
AdiBase, MEDLINE and EMBASE were searched from 1966 with no language restrictions. AdiBase search terms were 'mirtazapine', '6-azamianserin', 'azamianserin', 'mepirzapin', 'Org-3770' and 'depression'. MEDLINE and EMBASE search terms were 'mirtazapine' and 'depression'. Additional references were identified from the reference lists of published articles. Bibliographic information, including contributory unpublished data, was requested from the company developing the drug.

Study selection
Study designs of evaluations included in the review
Double-blind randomised controlled trials (RCTs) and meta-analysis or reviews of RCTs. Most analysis was performed on an intention-to-treat (ITT) basis and included all randomised patients who had >/=1 post-baseline efficacy assessment and had received >/=1 dose of study medication. A number of studies stated that end-point analyses were performed using the last observation carried forward method.

Specific interventions included in the review
Mirtazapine (in the majority of trials dosage regimes were titrated according the patients' responses) given at an initial dosage of 5-20mg/day and maximum dosages of 35 to 80mg/day in all studies apart form one in which patients received higher dosages (40 to 100mg/day). Comparator drugs included tricyclic antidepressants (amitriptyline 30-280mg/day, clomipramine 50-200mg/day, doxepin 75-300mg/day, imipramine 38-450mg/day); selective seratonin reuptake inhibitors (fluoxetine 20-40mg/day, paroxetine 20-40mg/day); atypical antidepressant trazodone 40-450mg/day; or placebo.

Participants included in the review
Hospitalised patients and outpatients meeting American Psychiatric Association DSM-III, DSM-III-R or DSM-IV criteria for major depression were included. Patients had moderate or severe (17-item Hamilton Depression Rating Scale (HDRS) score 18 to 24 or >/=25, respectively) depression at baseline. Mean baseline HDRS scores were >/= 25 in a number of studies.

Outcomes assessed in the review
Outcomes were not defined a-priori. The main clinical assessment tool used in included studies was the HDRS. In general, patients were considered to be responders if they had a >/= 50% reduction in HDRS score from baseline. Remission and relapse rates (the proportion of patients with 17-item HDRS scores </=7 and >/= 16, respectively) at study end-point were also reported in a few studies. A number of other scales were also used to assess antidepressant efficacy. Information about any experienced adverse effects was also collected.

How were decisions on the relevance of primary studies made?
Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. No further information was presented on how decisions on the relevance of primary studies were conducted.

Assessment of study quality
The authors do not report the criteria used to assess validity, or how the validity assessment was performed.
Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

Methods of synthesis
How were the studies combined?
Studies were combined in a narrative.

How were differences between studies investigated?
The authors do not state how differences between the studies were investigated.

Results of the review
There was a minimum of 12 RCTs (1,944 evaluable patients) included in the review, however, the exact number of included studies was not presented.

Therapeutic efficacy:
The proportion of responders according to HDRS generally ranged from 51 to 80% with mirtazapine. In short term studies (4-7 weeks), the drug was as effective as amitriptyline, clomipramine and doxepin, and it was at least as effective as trazodone, in patients with moderate or severe depression, including those with baseline anxiety symptoms or sleep disturbance or the elderly. Mirtazapine was less effective than imipramine in a single study performed in a heterogeneous population including previous non responders to antidepressants. Single comparisons between mirtazapine and selective serotonin reuptake inhibitors (SSRIs) demonstrated superior efficacy of mirtazapine versus fluoxetine at week 3 and 4, versus paroxetine at week 1 and versus citalopram at week 2, suggesting an earlier onset of efficacy with mirtazapine than with the SSRIs (total assessment times were 6 or 8 weeks). Mirtazapine had equivalent efficacy to the SSRIs at study end-point. In trials where additional scales were used to assess antidepressant efficacy, quality of life, general psychopathology, global functioning and global clinical impression changes in scores correlated with HDRS results. In a continuation trial, mirtazapine was associated with higher sustained remission rates than amitriptyline and the drugs had similar efficacy for the prevention of relapse. Initial evidence suggests that mirtazapine may also be effective as an augmentation or combination therapy with a number of other classes of antidepressant in patients with refractory depression.

Tolerability:
Data from meta-analyses of placebo-controlled trials indicate that dry mouth, drowsiness/ sedation, increase in appetite and bodyweight gain are the most common adverse experiences with short term (5-6 weeks) mirtazapine therapy. A reduction in the incidence of sedation-related symptoms over time with higher mirtazapine dosages was seen in some studies and is thought to have a pharmacological basis. Anticholinergic symptoms and events such as drowsiness, tremor and dyspepsia tend to occur less frequently with mirtazapine than with tricyclic antidepressants or trazodone. Typical SSRI adverse events were less common with mirtazapine than with fluoxetine and placebo, although overall mirtazapine appears to have a similar tolerability profile to those of the SSRIs fluoxetine, citalopram and paroxetine. Increased appetite and bodyweight are the only events that have been reported to be more common with mirtazapine than with antidepressant comparators. The drug appears to be well tolerated in elderly patients. Mirtazapine has not been associated with clinically significant changes in vital signs in clinical trials. Changes in laboratory parameters with mirtazapine does not increase the incidence of suicide attempts in patients with depression compared with active comparators, although this parameter was not specifically assessed in clinical trials of any antidepressant. Patients have recovered without adverse sequelae from mirtazapine overdose of up to 30 times the recommended daily amount.

Cost information
A cost effectiveness analysis was performed and included two studies. Mirtazapine was more cost effective that fluoxetine or amitriptuline for the treatment of major depression form the perspectives of the national health funder in France and Australia, despite high acquisition costs for the drug in these countries.
**Authors' conclusions**

Mirtazapine is effective and well tolerated for the treatment of patients with moderate to severe major depression. Further research is required to define the comparative efficacy of mirtazapine in specific patient groups, including the elderly and those with severe depression. Clarification of its efficacy as an augmentation therapy and in patients with refractory depression and its role in improving the efficacy and reducing the extrapyramidal effects of antipsychotic drugs would also help to establish its clinical value. The low potential for interaction with drugs that are metabolised by CYP2D6, including antipsychotics, tricyclic antidepressants and some SSRI's, may also make mirtazapine an important option for the treatment of major depression in patients who require polytherapy. Mirtazapine also appears to be useful in patients with depression who present with anxiety symptoms and sleep disturbance.

**CRD commentary**

The review includes a clear objective, a good literature search and an attempt was made to identify unpublished studies. However, very little information is presented on the methodology used to conduct the review, for example, what were the specific inclusion/exclusion criteria used, how were decisions made on the inclusion of primary studies, how was the validity of included studies assessed and what criteria were used. No information was presented on whether heterogeneity between studies was investigated.

The authors' conclusions seem to follow from the results but should be interpreted with caution in view of the above comments.

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

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

**Research:** The authors recommend that further research is required to define the comparative efficacy of mirtazapine in specific patient groups, including the elderly and those with severe depression.

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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.