Combining mirtazapine with SSRIs or SNRIs for treatment-resistant depression: the MIR RCT

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Scientific summary

The MIR Trial

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Scientific summary

Background

Depression is among the top five contributors to the global burden of disease and by 2030 is predicted to be the leading cause of disability in high-income countries. People with depression are usually managed in primary care and antidepressants are usually the first-line treatment. The number of prescriptions for antidepressants has risen dramatically in recent years, increasing by 6.8% (3.9 million items) between 2014 and 2015 (a total of 61 million items).

However, many patients do not respond to antidepressants. The STAR*D (Sequenced Treatment Alternatives to Relieve Depression) study found that half of those treated did not experience a reduction of $\geq$ 50% in depressive symptoms following 12–14 weeks of treatment with a single antidepressant. The reasons for non-response include non-adherence to medication. However, a substantial proportion of those who take their antidepressants in an adequate dose and for an adequate period do not experience a clinically meaningful improvement in their depressive symptoms. This can be termed treatment-resistant depression (TRD).

Definitions of TRD in research are varied. The National Institute for Health and Care Excellence advises general practitioners (GPs) to reconsider treatment if there has been no response after 4–6 weeks of antidepressant medication. Therefore, a definition of TRD that is relevant to UK primary care includes patients who still meet the *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10), criteria for depression after taking a selective serotonin reuptake inhibitor (SSRI) or a serotonin–noradrenaline reuptake inhibitor (SNRI) antidepressant at an adequate dose for a minimum of 6 weeks. However, there is currently limited evidence to guide GPs in the management of these patients.

Several pharmacological strategies have been proposed to treat those with TRD, including increasing the dose of antidepressant, switching antidepressants, combining two antidepressants and augmenting the antidepressant with another psychotropic drug. There is a pharmacological rationale for adding a second antidepressant with a different and complementary mode of action to SSRIs or SNRIs. Mirtazapine, an alpha2-adrenoreceptor antagonist, has the potential for a synergistic action with SSRIs and SNRIs and could enhance the clinical response compared with monotherapy. There have been three small trials of this combination of antidepressant, with encouraging results. However, these trials did not compare the combination in a treatment-resistant population.

Objectives

Our aim was to determine the clinical effectiveness and cost-effectiveness of adding mirtazapine to a SSRI or a SNRI prescription in reducing depressive symptoms and improving quality of life (QoL) at 12 and 24 weeks and 12 months, compared with adding placebo. A qualitative study explored the views and experiences of patients of taking either two antidepressant medications or an antidepressant and a placebo, their reasons for adhering to or stopping the medication and the views of GPs on prescribing combined antidepressant therapy.

Methods

The MIR trial was a two-parallel-group, multicentre, pragmatic, placebo-controlled randomised trial, with allocation at the level of the individual. Patients were recruited from general practices in four centres: (1) Bristol, (2) Exeter, (3) Hull/York and (4) Manchester/Keele.

Eligible patients (1) were aged ≥ 18 years; (2) were currently taking antidepressants, had done so for at least 6 weeks and had adhered to their medication; (3) had a Beck Depression Inventory-II (BDI-II) score of ≥ 14 points; and (4) fulfilled ICD-10 criteria for depression. We excluded patients with bipolar disorder, psychosis or major alcohol/substance abuse; those who were unable to complete the questionnaires; and women who were pregnant, breastfeeding or planning a pregnancy.

A three-stage recruitment process was used to identify potential participants. General practices searched their computerised records to identify patients who had received repeated prescriptions for an antidepressant during the previous 4 months and who were being prescribed an antidepressant at an adequate dose. GPs screened this list of patients and excluded patients based on study criteria. A letter of invitation and brief information about the study was sent to the potentially eligible participants, seeking permission for the research team to contact them.

The GPs could also invite patients to take part in the study during a consultation. GPs provided patients with information about the study and obtained permission to pass their contact details to the research team. Those who agreed were sent a postal questionnaire. This included questions about their depressive symptoms (BDI-II) and use of antidepressants.

Those who met the definition of TRD (based on severity of depressive symptoms and adherence to antidepressants for at least 6 weeks) were contacted by a researcher by telephone to ascertain their eligibility.

Baseline assessments to establish eligibility were conducted in the patients' own homes, at their GP surgeries or at nearby NHS/university premises. Only those patients who fulfilled ICD-10 criteria (category F32) for their current depressive episode (assessed using the Clinical Interview Schedule – Revised), had a BDI-II score of ≥ 14 points and were continuing to take the prescribed antidepressant at an adequate dose were eligible to participate in the trial.

Those who were eligible and gave written informed consent were randomised, using a computer-generated code. Participants were randomly assigned to one of two treatments: (1) one × 15-mg mirtazapine capsule daily for 2 weeks followed by two × 15-mg mirtazapine capsules for up to 50 weeks or (2) identical placebo capsules.

Randomisation was carried out using a computerised system and was stratified by centre and minimised on baseline BDI-II score (mild < 26 points; moderate 26–34 points; severe ≥ 35 points), sex (male/female) and receipt of psychological services (yes/no).

The labelling of medication packs was approved by the Medicines and Healthcare products Regulatory Agency. Each medication pack had an identification number, randomly generated to ensure that mirtazapine and placebo medicine packs were indistinguishable to maintain allocation concealment. The random number was generated by the Bristol Randomised Trials Collaboration and provided to the manufacturer.

Participants and GPs were advised to use with caution other serotonergic drugs, such as tramadol or the triptan group of drugs, and those taking monoamine oxidase inhibitors were excluded.

Participants were free to withdraw from the medication at any time. Participants, clinicians, outcome assessors and the research team were blinded to allocation. After collection of the primary outcome measure at 12 weeks, participants were offered the opportunity to be unblinded or to remain blind to allocation. Those who elected to be unblinded would no longer receive the trial medication but outcome measures would be collected. All participants continued with their GP care and their usual antidepressants. Clinicians were not restricted in referring their patients to psychological services.

Participants were followed up at 2, 6, 12, 24 and 52 weeks. To maximise response rates, follow-up assessments at 6, 12, 24 and 52 weeks were conducted at a face-to-face appointment with a researcher. If this was not possible, questionnaires were posted or completed over the telephone. Only the 2-week follow-up data were collected solely by telephone.

The primary outcome was change in BDI-II score at 12 weeks post randomisation, measured as a continuous variable. With 200 participants in each group, we would have 91% power to detect a difference of 0.33 standard deviations (SDs) at the 5% level. This is equivalent to 3–4 points on the BDI-II, a clinically important difference. Allowing for 15% loss to follow-up at 12 weeks, we needed to recruit 472 patients.

Secondary outcomes were 'response', defined as a $\geq$ 50% reduction in BDI-II score compared with baseline; 'remission', defined as a BDI-II score of $<$ 10 points; change in anxiety symptoms, measured using the Generalised Anxiety Disorder-7 questionnaire; adherence to antidepressants; QoL, measured using the EuroQoL-5 Dimensions, five-level version; social and physical functioning, measured using the Short Form questionnaire-12 items; and adverse events (AEs), measured using the Antidepressant Side-Effect Checklist (ASEC). All of these secondary outcomes were measured at 12, 24 (excluding ASEC) and 52 weeks.

The primary comparative analyses of clinical effectiveness were conducted according to the principle of intention to treat (ITT), without imputation of missing data.

Cost-effectiveness was measured using self-report resource use questionnaires at 12 and 24 weeks and at 12 months, in addition to primary care practice data on consultations, services and prescriptions over the 12-month trial period. The perspective for the primary analysis is that of the NHS and personal social services. Personal costs and productivity costs for patients who missed work are included in a secondary analysis from the societal perspective.

We conducted semistructured interviews with people who were invited to participate in the trial but who declined, trial participants and GPs. We explored reasons for declining to participate, reasons for adhering to or stopping medication and views and experiences of GPs about managing people with depression, with a focus on prescribing.

A purposeful sampling strategy was used to ensure that interviews were held with individuals in both groups of the trial in all four centres. Interviews were conducted either by telephone (patients who declined participation in the trial and GPs) or face to face. Analysis was conducted within each data set and then comparison was carried out across the data sets. NVivo 10 (QSR International, Warrington, UK) was used to store data and aid with analysis.

Results

A total of 480 patients were randomised (mirtazapine and usual care, $n = 241$; placebo and usual care, $n = 239$), of whom 431 (89.8%) were followed up at 12 weeks, 403 (84.0%) at 24 weeks and 390 (81.3%) at 12 months.

The two groups were similar in baseline characteristics, but there was some evidence that patients in the mirtazapine group had more severe depression. Patients randomised to mirtazapine were more likely to have a prior history of depression and a higher proportion had had suicidal thoughts.

At 12 weeks, the mean BDI-II score was 18.0 points (SD 12.3 points) in those randomised to the mirtazapine group compared with 19.7 points (SD 12.4 points) in those randomised to the placebo group. There was a small difference in favour of the intervention after adjustment for baseline BDI-II score, centre, baseline BDI-II score terciles, sex and whether or not the patient was receiving psychological therapy at baseline.

The confidence interval (CI) included the null, consistent with the possibility that there was no difference between the two treatment groups (difference –1.83 points, 95% CI –3.92 to 0.27 points; $p = 0.087$). Further adjustment for characteristics showing an imbalance at baseline did not change this result meaningfully. At 24 weeks and 12 months, the adjusted differences in BDI-II scores between the two groups became smaller (24 weeks: difference –0.85 points, 95% CI –3.12 to 1.43 points; 12 months: difference 0.17 points, 95% CI –2.13 to 2.46 points).

Similar trends of small differences between the treatment groups in favour of the mirtazapine group were observed for other secondary outcomes at 12 weeks, including response to treatment [odds ratio (OR) 1.39, 95% CI 0.94 to 2.07], remission of depression symptoms (OR 1.29, 95% CI 0.82 to 2.02), anxiety symptoms (difference in GAD-7 scores –0.98 points, 95% CI –1.93 to –0.03 points), quality of life (difference in EQ-5D-5L scores 0.01 points, 95% CI –0.02 to 0.05 points), difference in SF-12 aggregate physical functioning score –1.09 points, 95% CI –2.75 to 0.57 points) and difference in SF-12 aggregate mental functioning score 3.91 points, 95% CI 1.63 to 6.20 points). This was also true for the complier-average causal effect (CACE) analysis (difference in mean BDI-II scores –2.39 points, 95% CI –5.18 to 0.40 points) and a per-protocol analysis (difference in mean BDI-II scores –2.18 points, 95% CI –4.60 to 0.24 points).

There was no important between-group difference in AEs, measured using the ASEC. Most reported AEs were minor and no serious AEs were directly attributable to the intervention. In the intervention group, 167 participants reported AEs, 46 of whom reported AEs associated with stopping the trial medication, whereas 91 participants in the placebo group reported AEs, only nine of whom stopped the trial medication.

No clinically important differences in quality-adjusted life-years (QALYs) or costs were observed between the two groups at 12 or 52 weeks. At the primary outcome end point of 12 weeks, participants in the active treatment arm reported QALYs of 0.163 and participants in the control arm reported QALYs of 0.162, a difference of 0.002 QALYs (95% CI –0.002 to 0.005 QALYs). The active treatment arm at 12 weeks had higher costs (£65) than the control arm (£63). The difference in costs was small (£2, 95% CI –£27 to £31). At 52 weeks, participants in the treatment arm had an incremental gain of 0.009 QALYS (95% CI –0.016 to 0.035 QALYs) and an incremental cost of £69 (95% CI –£74 to £206) compared with the placebo arm.

In the qualitative study, participants described the ‘hard work’ of managing depression. Those in the study often described a ‘crisis point’ motivating their desire for change, whereas those who declined participation were concerned that additional treatment might disrupt their hard-won equilibrium. GPs were concerned that the use of two antidepressants would result in more AEs for those on long-term treatment.

Conclusions

- This study did not find convincing evidence of a clinically important benefit for mirtazapine in addition to a SSRI or SNRI antidepressant over placebo in a treatment-resistant group of depressed patients in primary care.
- The corrected mean difference in BDI-II score between the groups after 12 weeks was 1.83 points (95% CI –3.92 to 0.27 points) in favour of the intervention, which was less than the prespecified clinically significant difference of 3–4 points. Although the lower limit of the 95% CI (–3.92 points) means that it is not possible to exclude a clinically meaningful effect, the CI included the null, indicating that there may be no difference in outcomes between the groups.
- The evidence for clinical effectiveness is similarly weak for the secondary outcomes of response and remission at 12 weeks. Outcomes at later time points showed smaller between-group differences.
- Complier-average causal effect and per-protocol analyses, which are designed to estimate treatment effects in those who comply, showed slightly larger differences than the ITT analyses, but CIs included the null.
- Prespecified subgroup analyses based on severity and degree of treatment resistance did not show any evidence of effect modification.
- No clinically important differences in QALYs or costs were observed between the two groups at 12 or 52 weeks.

Implications for health care

- The evidence presented in this study does not support the addition of mirtazapine to SSRI or SNRI antidepressants for TRD in routine primary care.
- Minor AEs associated with stopping the trial medication were more likely in the mirtazapine group.
- General practitioners have concerns about the burden of AEs for those who are taking two antidepressants long term. Patients who declined to join the MIR trial were concerned about disturbing an 'equilibrium' that they had reached with a single antidepressant.

Implications for future research

- There is a need for further research into combination and augmentation treatments for people with TRD that can be prescribed or delivered in primary care.
- It is important that future studies in this area define TRD in a way that is appropriate to primary care, where there is the greatest potential for access to care.

Trial registration

This trial is registered as ISRCTN06653773 and EudraCT number 2012-000090-23.

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