MIRtazapine added to SSRIs or SNRIs for Treatment Resistant Depression in Primary Care: a placebo controlled randomised trial (MIR)

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Abstract

Objective: To investigate the effectiveness of combining mirtazapine with Serotonin-Noradrenaline Reuptake Inhibitor (SNRI) or Selective Serotonin Reuptake Inhibitor (SSRI) antidepressants for patients in primary care who had not responded to an antidepressant.

Design: A two parallel-group multi-centre, placebo controlled, randomised trial comparing the addition of mirtazapine to placebo for patients who had been adherent to an SSRI or SNRI for at least 6 weeks and were still depressed. Participants were stratified by centre and minimised by baseline Beck Depression Inventory score [BDI-II], gender and current psychological therapy. Participants, their General Practitioners (GPs), and the research team were blind to the allocation. Primary analyses compared the two groups as allocated without imputing missing data **Setting:** 106 general practices in 4 centres in the UK; Bristol, Exeter, Hull and North Staffordshire.

Participants: Between August 2013 and October 2015, we recruited 480 participants aged over 17 years, 69.1% of whom were female. Participants scored >13 using the BDI-II and fulfilled International Classification of Diseases [ICD]-10 criteria for depression. Exclusion criteria included bipolar disorder, psychosis and major alcohol/substance abuse. 431 (89.8%) were included in the (primary) 12-week follow-up.

Intervention: 241 participants were randomised to mirtazapine and 239 to placebo, both given in addition to their usual SSRI/SNRI medication. They were followed up at 12, 24 and 52 weeks.

Main outcome measures: Depressive symptoms at 12 weeks post-randomisation, measured using the BDI-II score as a continuous variable. Secondary outcomes include measures of anxiety, quality of life and adverse effects at 12, 24 and 52 weeks.

Results: BDI-II scores at 12 weeks were lower in the mirtazapine group after adjustment for baseline BDI-II and minimisation/stratification variables, although the confidence interval included the null (mean (SD) BDI-II scores at 12 weeks: 18.0 (12.3) in the mirtazapine group; 19.7 (12.4) in the placebo group; adjusted difference between means -1.83 (95% confidence interval: -3.92 to 0.27, p=0.087)). Adverse effects were more frequent in the mirtazapine group and associated with stopping the trial medication.

Conclusion: This study did not find evidence of a clinically important benefit for mirtazapine in addition to an SSRI or SNRI antidepressant over placebo in a treatment resistant group of

primary care patients with depression. This remains an area of important unmet need where there is limited evidence of effective treatment options.
376 words

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Introduction

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(1). People with depression are usually managed in primary care in the UK, and antidepressants are often the first-line treatment. The number of prescriptions for antidepressants has risen dramatically in recent years in the NHS, increasing by 6.8% (3.9 million items) between 2014 and 2015 (total 61million items)(2). However, many patients do not respond to antidepressants. The STAR*D study (Sequenced Treatment Alternatives to Relieve Depression) found that half of those treated did not experience at least a 50% reduction in depressive symptoms following 12-14 weeks of treatment with a single antidepressant(3). 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.

The National Institute for Health and Care Excellence (NICE) advises general practitioners (GPs) to reconsider treatment if there has been no response after 4 to 6 weeks of antidepressant medication(4). There is currently limited evidence to guide GPs in the management of patients who meet the International Classification of Diseases (ICD-10) criteria for depression after taking an SSRI or SNRI antidepressant at an adequate dose for a minimum of six weeks(5). Several pharmacological strategies have been proposed, including increasing the dose, switching antidepressants, combining two antidepressants and augmenting the antidepressant with another psychotropic drug, for example lithium or an antipsychotic. (6). A systematic review of antidepressant combinations for those who did not respond to a single drug found that the small number of trials and methodological drawbacks of those trials precluded definitive conclusions about effectiveness and some of the combinations carry substantial risk of adverse effects and are not considered appropriate for initiation in primary care (7). There is a pharmacological rationale for adding a second

antidepressant with a different and complementary mode of action to SSRIs or SNRIs. Mirtazapine, a noradrenaline (alpha2-adrenoreceptor) and serotonin (5HT-2 and 5HT-3) antagonist, has the potential for an additive and perhaps synergistic action with SSRIs and SNRIs and could enhance clinical response compared to monotherapy with SSRIs or SNRIs. There have been four trials of this combination against SSRI/SNRI monotherapy in both treatment resistant participants and in those without treatment failure, with mixed results (8-11).

The aim of this study was to determine the effectiveness of adding mirtazapine to an SSRI or SNRI in reducing depressive symptoms and improving quality of life at 12 weeks (primary follow-up), 24 and 52 weeks, compared with adding placebo for patients in primary care who are still depressed after an adequate course of treatment.

Methods

Study design and participants

The MIR Study was a two-parallel group multi-centre pragmatic placebo controlled randomised trial with allocation at the level of the individual. Participants were recruited from general practices in areas surrounding the four centres of Bristol, Exeter, Hull and Keele/North Staffs. Eligible participants were: over 17 years; currently taking an SSRI or SNRI antidepressant at an adequate dose, had done so for at least six weeks and had adhered to their medication; had a Beck Depression Inventory, 2nd version (BDI-II) score of at least 14(12); and fulfilled ICD-10 criteria for depression. We excluded patients with bipolar disorder, psychosis or major alcohol/substance abuse, a diagnosis of dementia, those who were unable to complete the questionnaires, and women who were pregnant, breast feeding, or planning 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 eligibility 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. GPs could also invite patients to take part in the study during a consultation, in which case the GP provided the patient with information

about the study and obtained permission to pass contact details to the research team. Those who agreed to be contacted were sent a postal questionnaire. This included questions about their depressive symptoms (BDI-II) and use of antidepressants.
Those who met the initial criteria of severity of depressive symptoms and adherence to an adequate dose of an antidepressant for at least six weeks were contacted by a researcher by telephone to ascertain their eligibility. Face to face baseline assessments were then conducted in the participants' 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 revised Clinical Interview Schedule)(13), had a BDI-II score of ≥14 and who were continuing to take the prescribed antidepressants at an adequate dose were eligible to participate in the trial.

Randomisation and Masking

Those who were eligible and gave written informed consent were randomised to one of two treatments: (i) one × 15mg encapsulated mirtazapine daily for 2 weeks followed by two × 15mg encapsulated mirtazapine for up to 50 weeks; or (ii) identical placebo.
Randomisation was by means of a computer-generated code, ensuring that allocation was concealed from the recruiting researcher. Randomisation was stratified by centre and minimised on baseline BDI-II score (mild <26; moderate 26–34; severe ≥ 35), gender (male/female), and current receipt of psychological services (yes/no).

The labelling of medication packs was Medicines and Healthcare Products Regulatory Authority (MHRA) approved. Each medication pack had an identification number, randomly generated to ensure mirtazapine and placebo medicine packs were indistinguishable to maintain allocation concealment. The random numbers were 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.

Participants were free to stop taking the study medication at any time. Participants, clinicians, outcome assessors and the research team were blinded to allocation. After the primary follow-up at 12 weeks, participants were offered the opportunity to be unblinded or to remain blind to allocation This was not in the original protocol but was required by the Research

Ethics Committee to ensure that those who had not improved had the option of reviewing their treatment. Those who elected to be unblinded no longer received the trial medication, but outcome measures continued to be collected. All participants continued with their GP care and usual antidepressants. Clinicians were not restricted in referring their patients to psychological services.

Procedures

Participants were followed up at 6 weeks, 12 weeks, 24 weeks and 52 weeks. To maximise response rates, follow-up assessments at 12, 24 and 52 weeks were conducted at a face-to-face appointment with a researcher. If this was not possible then questionnaires were posted or administered over the phone.

The primary outcome was BDI-II score at 12 weeks post-randomisation, measured as continuous variable, adjusted for baseline. We aimed to recruit 200 participants in each group, giving 91% power to detect a difference of 0.33 standard deviations at a two-sided 5% significance level. This would be equivalent to 3-4 points on the BDI-II, reported to be a clinically important difference(14). Allowing for 15% loss to follow-up at 12 weeks, we planned to recruit 472 participants.

Secondary outcomes were: 'response' defined as at least a 50% reduction in BDI-II score compared with baseline; 'remission', defined as a score on the BDI-II of less than 10; Patient Health Questionnaire (PHQ-9) (15), a brief depression measure included because it is widely used in primary care: anxiety symptoms measured with GAD-7(16); and adverse effects using the Antidepressant Side Effect Checklist (ASEC)(17); quality of life measured using the EQ-5D-5L(18); social and physical functioning using the SF-12(19); and adherence to antidepressants using a 4-item self-report measure(20). All these secondary outcomes were measured at 12, 24 (excluding ASEC) and 52 weeks, and again adjustments for baseline scores were made where appropriate. Cost effectiveness data will be presented in a separate publication.

Statistical Analysis

Analysis and reporting were in line with CONSORT(21) guidelines based on a pre-specified statistical analysis plan (SAP) approved by the Trial Steering Committee (22). Primary analyses were conducted comparing the two groups as randomised, without imputing missing values. Depending on the nature of the outcome variable (continuous or binary), linear or logistic regression models were used to compare the groups as randomised, adjusting for stratification and minimisation variables and (where available) the corresponding baseline value.

Secondary analyses of the primary and all secondary outcomes included additional adjustment for variables demonstrating marked imbalance at baseline (ascertained using descriptive statistics).

In all analyses we present regression coefficients (or odds ratios for binary outcomes), with 95% confidence intervals and p-values. Effect sizes are presented for the BDI-II outcomes and are calculated based on Cohen's *d* statistic.

We conducted pre-specified subgroup analyses by introducing appropriate interaction terms into the regression models, to investigate differential effects according to: baseline depression severity (BDI-II); and a multi-level measure of degree of treatment resistance based on duration of symptoms and prior treatment with antidepressants. This latter variable was categorised as: not prescribed anti-depressants in the past; prescribed anti-depressants in the past and depressed for less than 1 year; prescribed anti-depressants in the past and depressed for 1-2 years; prescribed anti-depressants in the past and depressed for more than 2 years.

Sensitivity analyses were conducted to assess the robustness of our primary analysis. These included per protocol analyses of the primary outcome at 12 and 52 weeks and, since these were likely to be biased, a Complier Average Causal Effect (CACE) analysis at 12, 24 and 52(23). In this analysis 'compliers' were defined as those who had continued taking their trial medication up until 12 weeks. An additional sensitivity analysis at 24 and 52 weeks examined between-group differences in BDI-II score in those who remained blinded throughout the trial. We also investigated the influence of missing data by performing

analyses of the primary outcome under different assumptions: “best” and “worst” case scenarios (representing the lowest and highest possible BDI-II scores) and multiple imputation by chained equation (MICE) to impute missing data(24). When using MICE, 25 datasets were generated, and 10 switching procedures were undertaken. The imputation model included all variables predictive of missingness as well as all the variables used in the primary analysis.
Analyses were performed using Stata v14.(25)

Role of the funding source

The funding source had no role in study design, data collection, data analysis, interpretation of data or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The screening process commenced on the 1st of August 2013, and the final patient was randomised to the trial on 6th October 2015. All follow-up data were collected between August 2015 and the end of October 2016.We identified 856 patients as potentially eligible and invited them to attend a baseline appointment, but 105 (12%) declined. Those who declined were comparable to attenders on age, sex and home ownership, but less likely to be educated to A-level or above (31% vs 48%). At baseline, one patient was eligible but declined, one was alcohol-dependent, one had recently had their dose of antidepressant altered and 268 did not satisfy the ICD-10 criteria for a major depressive episode and/or had a BD-II score of <14 A total of 480 participants were randomised (mirtazapine and SSRI/SNRI: n=241; placebo and SSRI/SNRI n=239); 431 (89.8%) were followed up at 12 weeks, 403 (84.0%) at 24 weeks and 390 (81.3%) at 52 weeks (figure).

The two groups were similar in baseline characteristics, but there was some evidence that participants in the mirtazapine group had more severe depression (Table 1). Participants randomised to mirtazapine were more likely to have a prior history of depression, and a higher proportion had had suicidal thoughts in the past.

Table 1: Baseline characteristics of randomised participants

		Allocated groups			
		Mirtazapine + SSRI/SNRI (n=241)		**Placebo + SSRI/SNRI (n=239)**	
Stratification variable					
Centre: n(%)	Bristol	89	36.9%	88	36.8%
	Exeter	61	25.3%	61	25.5%
	Keele/North Staffs	41	17.0%	41	17.2%
	Hull	50	20.7%	49	20.5%
Minimisation variables					
Female: n(%)		168	69.7%	164	68.6%
Baseline BDI-II: n(%)	14-25	77	32.0%	79	33.1%
	26-34	78	32.4%	78	32.6%
	>=35	86	35.7%	82	34.3%
Currently receiving psychological services: n(%)		33	13.7%	29	12.1%
Socio-demographic variables					
Age (years): mean (SD)		50.4	13.8	49.9	12.5
Ethnic group: n(%)	White	233	96.7%	235	98.3%
	Non-white	8	2.3%	4	1.7%
Marital status: n(%)	Married/Living as married	142	58.9%	135	56.5%
	Single	47	19.5%	53	22.2%
	Separated/Divorced/ Widowed	52	21.6%	51	21.3%
Employment status: n(%)	Not working	132	54.8%	104	43.5%
Educational attainment: n(%)	A-level or higher	115	47.7%	115	48.1%
	GSCE; Standard Grade; O-level or equivalent	72	29.9%	78	32.6%
	No formal qualification	54	22.4%	46	19.2%
Financial wellbeing: n(%)	Just about getting by or worse	130	53.9%	126	52.7%
Alcohol use score*: median (IQR)		2.0	(1.0, 4.0)	2.0	(1.0, 4.0)
Number of life events in the past 6 months: mean (SD)		1.0	1.0	1.1	1.0
Social support score: mean (SD)		12.2	4.1	12.8	4.0
Caring responsibilities					
Providing care for someone who is disabled; n(%)		30	12.4%	37	15.5%
Measures of depression					
Suffered from depression in the past: n(%)		206	85.5%	190	79.5%
Previous referral to a psychiatrist for depression: n(%)[a]		71	34.5%	60	31.6%

Number of prior episodes of depression: n(%)[b]	None	3	1.5%	5	2.6%
	One	14	6.8%	8	4.2%
	Two to four	82	39.8%	79	41.6%
	Five or more	107	51.9%	98	51.6%
Length of current course of antidepressants: n(%)	<6 months	26	10.8%	20	8.4%
	6 or more months	215	89.2%	219	91.6%
ICD-10 primary diagnosis: n(%)	Mild	38	15.8%	44	18.4%
	Moderate	138	57.3%	144	60.3%
	Severe	65	27.0%	51	21.3%
CIS-R score: mean (SD)		28.3	8.2	27.0	8.3
BDI-II score: mean (SD)		31.5	10.2	30.6	9.6
GAD-7 score: mean (SD)[c]		11.3	4.8	10.7	4.8
PHQ-9 score: mean (SD)		16.7	5.5	16.0	5.5
EQ-5D-5L score: mean (SD)[d]		0.65	0.26	0.69	0.22
SF-12 aggregate physical functioning score: mean (SD)[e]		45.7	13.8	46.4	13.1
SF-12 aggregate mental functioning score: mean (SD)[e]		27.9	9.6	29.2	9.7
Suicidal ideation (CIS-R thoughts/plans): n(%)	No suicidal thoughts	81	33.6%	119	49.8%
	Patient feels life isn't worth living	59	24.5%	44	18.4%
	Suicidal thoughts/Plans	101	41.9%	76	31.8%

Note: Number of missing observations by treatment group:

[a] n=35 mirtazapine, n=49 placebo;[b] n=35 mirtazapine, n=49 placebo; [c] n=3 mirtazapine, n=0 placebo; [d] n=1 mirtazapine, n=1 placebo;[e] n=7 mirtazapine, n=4 placebo

**AUDIT score (26)*

At 12 weeks, the mean BDI-II score in those randomised to the usual care and mirtazapine group was 18.0 (SD=12.3) compared with 19.7 (SD=12.4) in those randomised to usual care and placebo (Table 2). There was a small difference in favour of the intervention after adjustment for baseline BDI-II score and the stratification and minimisation variables, centre, baseline BDI-II score tertiles, gender and whether the patient was receiving psychological therapy at baseline. The confidence interval (CI) included the null; it is therefore possible that there was no difference between the two treatment groups (adjusted difference in means = -1.83 (95% CI -3.92 to 0.27, p=0.087); Table 2). Slightly larger differences were observed in a per protocol and CACE analyses (Table A1). Further adjustment for characteristics showing an imbalance at baseline did not materially affect the results of the primary analysis (Table A2).

At 24 and 52 weeks, the adjusted difference in BDI-II between the two groups was smaller and again included the null (24 weeks: adjusted difference in means = -0.85 (95% CI -3.12 to 1.43); 52 weeks: adjusted difference in means = 0.17 (95% CI -2.13 to 2.46)) (Table 2). Adopting per protocol and CACE approaches to analysis of these outcomes yielded similar or slightly larger differences (Table A1).

Table 2: Means and difference in mean BDI-II scores between treatment groups at 12, 24 and 52 weeks

	Mirtazapine + SSRI/SNRI		**Placebo + SSRI/SNRI**		**Comparison**		
	N	*Mean (SD)*	*N*	*Mean (SD)*	*Adjusted* difference in means (95% CI)*	*p-value*	*Effect size (Cohen's d)*
Baseline	*241*	*31.5 (10.2)*	*239*	*30.6 (9.6)*	*-*	*-*	*-*
Primary outcome							
12 weeks	*214*	*18.0 (12.3)*	*217*	*19.7 (12.4)*	*-1.83 (-3.92 to 0.27)*	*0.09*	*0.148*
Secondary outcomes							
24 weeks	*196*	*17.3 (12.9)*	*206*	*18.2 (12.6)*	*-0.85 (-3.12 to 1.43)*	*0.46*	*0.066*
52 weeks	*190*	*16.8 (12.7)*	*198*	*16.7 (12.2)*	*0.17 (-2.13 to 2.46)*	*0.89*	*0.014*

**: adjusted for baseline BDI-II score and the stratification and other minimisation variables*

Participants were able to request unblinding after the primary outcome at 12 weeks. The results in table 2 at 24 and 52 weeks include all those who remained in the trial, whether they were unblinded or not. In the mirtazapine group 83 individuals requested unblinding by 52 weeks, and 103 individuals in the placebo group. A sensitivity analysis at 24 and 52 weeks found no between-group differences in BDI-II score amongst those who remained blinded throughout the trial (Table A3).

The between-group differences in all the secondary outcome scores at 12 weeks were in favour of the intervention, including a second measure of depressive symptoms, the PHQ -9. However, the differences were small and, in almost every case (apart from the GAD-7, which measures anxiety symptoms, and the mental health component of the SF-12) the CI for the difference included the null (Table 3). Adherence to the trial medication was substantially

lower in the intervention group compared with placebo (Table 3). Outcomes at later time points showed smaller between-group differences (Table A4).

Table 3: Secondary outcomes at 12 weeks

	Mirtazapine + SSRI/SNRI			**Placebo + SSRI/SNRI**			**Comparison**		
	N	N (%)	Mean (SD)	N	N (%)	Mean (SD)	Adjusted OR* (95% CI)	Adjusted* difference in means (95% CI)	p-value
12 weeks									
"Response"	214	94 (43.9)	-	217	78 (35.9)	-	1.39 (0.94 to 2.07)	-	0.099
"Remission"	214	63 (29.4)	-	217	53 (24.4)	-	1.29 (0.82 to 2.02)	-	0.266
GAD-7	214	-	7.15 (5.63)	217	-	7.89 (5.78)	-	-0.98 (-1.93 to -0.03)	0.044
EQ-5D-5L	213	-	0.72 (0.27)	216	-	0.73 (0.25)	-	0.01 (-0.02 to 0.05)	0.400
SF-12 (physical)	208	-	44.09 (12.87)	210	-	45.85 (12.54)	-	-1.09 (-2.75 to 0.57)	0.196
SF-12 (mental)	208	-	39.94 (12.27)	210	-	36.33 (12.53)	-	3.91 (1.63 to 6.20)	0.001
PHQ-9	212	-	9.74 (6.35)	217	-	10.63 (6.21)	-	-1.05 (-2.14 to 0.04)	0.058
Adherence	210	156 (74.3)	-	214	180 (84.1)	-	0.55 (0.34 to 0.89)	-	0.015
ASEC	184	-	10.13 (7.02)	206	-	9.77 (7.93)	-	0.35 (-1.04 to 1.73)	0.624

* Adjusted for baseline values of the outcome and stratification and minimisation variables except in the case of adherence at 12 weeks where adjustment was made solely for stratification and minimisation variables

There was no between-group difference in adverse effects using the ASEC at 12 weeks (Table 3). We also collected spontaneous participant reports of adverse effects. In the first 12 weeks most reported adverse effects were minor. There were 11 Serious Adverse Events

resulting in hospitalisation, eight of which occurred in the intervention group (Table A5). More patients in the intervention group reported non-serious adverse effects, and 46 participants reporting adverse effects in this group stopped their medication compared to 9 in the placebo group (Table 4).

Table 4: Most frequent types and most common examples of adverse events spontaneously reported by participants in the 12 weeks from randomisation*

	Mirtazapine + SSRI/SNRI (n=241)		Placebo + SSRI/SNRI (n=239)	
	Number of patients reporting AE (% of patients randomised reporting AE)	Number of patients reporting AE who stopped IMP	Number of patients reporting AE (% of patients randomised reporting AE)	Number of patients reporting AE who stopped IMP
Anti-cholinergic *Dry mouth, blurred vision or urinary difficulties*	16 (6.6%)	3	4 (1.7%)	0
Central Nervous System *Drowsiness, feeling light headed, headache and unpleasant dreams*	59 (24.5%)	23	20 (8.4%)	2
Increase in appetite/weight gain	26 (10.8%)	7	8 (3.3%)	0
Psychiatric *Increase in anxiety*	8 (3.3%)	4	5 (2.1%)	0

Other*:* *Restless legs nausea and peripheral oedema*	47 (19.5%)	13	47 (19.7%)	8
Any	121 (50.2%)	46	71 (29.7%)	9

* Patients may have reported more than one type of adverse event therefore column totals are greater than the total number of individuals reporting adverse effects

We compared our analyses of the primary outcome using complete cases with analyses that addressed missing data. The findings using complete cases appeared to be robust to various assumptions regarding missing data (Table A6).

Regarding the two pre-planned subgroup analyses, we found no evidence that either had any effect on the difference between the mirtazapine and placebo groups (p-value for interaction with treatment group for baseline depression severity: p=0.101; p-value for interaction with treatment group for treatment resistance: p=0.30).

Discussion

Statement of principal findings

This study did not find convincing evidence of a clinically important benefit for mirtazapine over placebo when given in addition to an SSRI or SNRI antidepressant for patients who had remained depressed after at least 6 weeks of an antidepressant, recruited from primary care. In the primary analysis at 12 weeks, the placebo group improved from a baseline BDI-II score of 30.6 to a mean of 19.7 and the intervention group from a baseline BDI-II score of 31.5 to a mean of 18.0. We based our sample size calculation on detecting a between group difference equivalent to 3 to 4 BDI-II points, which we posited would be clinically important. The adjusted difference (in means) between the groups after 12 weeks was less than this at -1.83 (95% CI; -3.92 to 0.27, p=0.087) points on the BDI-II in favour of the intervention group. Despite the fact that the lower limit of the 95% confidence interval for this difference includes the possibility of a clinically meaningful effect, the CI also includes the null and the most likely (mean) effect is small, making clinical benefit unlikely.

Similar observations of small differences between the treatment groups in favour of the mirtazapine group were observed for the secondary outcomes at 12 weeks, but for most outcomes the 95% confidence intervals surrounding the difference between groups included the null. This weak evidence of a small effect at 12 weeks is supported by changes in favour of the intervention group in the SF-12 aggregate mental health score (between-group difference 3.91 (95% CI 1.63 to 6.20)) and GAD-7 (between-group difference -0.98 (95%CI -1.93 to -0.03)) where confidence intervals did not include the null, although the clinical importance of these small differences is not clear. Outcomes at later time points showed smaller between-group differences with no evidence of benefit over the longer term. CACE and per protocol analyses for the primary outcome, designed to estimate treatment effects in those who complied with their allocated treatment, showed slightly larger between group differences than the primary analyses but these were still consistent with a chance observation, and per-protocol analyses are known to be biased. Pre-specified subgroup analyses based on severity and degree of treatment resistance did not yield any evidence of effect modification.

In the mirtazapine group 46 participants who reported adverse effects stopped their medication, compared with nine in the placebo group. Adherence was therefore substantially lower in the mirtazapine group compared with placebo and is likely to have been a consequence of adverse effects. Whilst there was no difference between the two groups in their rating of adverse effects using the ASEC scale, this may be in part due to the lower rate of adherence to the trial medication in the intervention group. The number of SAEs was small in both groups and none were directly attributable to the intervention.

Strengths and weaknesses of the study

Participants, investigators and assessors were all blind to the allocation up to and including the primary outcome at 12 weeks. Follow-up rates throughout the trial were good at all sites, with the overall follow-up rates of 90% at 12 weeks, 84% at 24 weeks and 81% at 52 weeks. Sensitivity analyses were conducted to assess the impact of missing data on the analysis of the primary outcome. Whether estimating the missing data assuming a “best” or “worst” case scenario or using multiple imputation, the observed difference in BDI-II scores at 12 weeks between treatment groups was small. There were some minor baseline imbalances between the two groups but adjustment for these did not materially affect the outcome of the trial results.

The criteria for defining inadequate response to treatment that we adopted have been used elsewhere in primary care research(27) and were designed to be inclusive while reflecting NICE treatment guidelines(4). Our approach accords with the Maudsley staging method where treatment failure following an adequate dose of an antidepressant for 6 weeks is an important starting point on a continuum of treatment failure (28). The authors also point out that in addition to treatment failure, severity and duration of depression are also important dimensions of treatment resistance. Nearly all (90%) of our participants had been taking an antidepressant for at least six months and the range of symptom severity in our sample was evenly spread between 3 terciles; mild to moderate, moderate to severe and severe. In addition most participants reported previous episodes of depression. Hence the population recruited to the study is representative of the group for whom there is uncertainty around ongoing management in primary care.

We based our view of the minimal clinically important difference (MCID) between intervention and placebo groups of 3-4 points in BDI-II score on previous recommendations from NICE(4). Since our protocol was written an approach towards establishing MCID using self-rated global ratings of improvement has been developed(14). This approach gives an estimate of an MCID in depression of 17.5% reduction in BDI-II score for a depressed primary care population, but suggests that the MCID is higher, at 32% in a non-responsive population similar to that studied here. This translates to BDI-II differences of 3.5 and 5.9 BDI-II points respectively. It therefore seems unlikely that mirtazapine would provide a clinically important benefit, although there is still considerable uncertainty around the clinically important difference in treatment outcome for this group of patients.

Comparison to other studies

Two earlier small studies in patients, one of which was in treatment resistant patients (8), and one in those who had not failed previous treatment(9) reported that mirtazapine in combination with an SSRI gave a greater improvement than monotherapy. A further recent study also reported benefit in non-resistant patients and that it was well tolerated in combination with either an SSRI or venlafaxine (an SNRI) (10). The STAR*D study(3) compared venlafaxine plus mirtazapine, to tranylcypromine, a MAOI antidepressant. Although there was a modest advantage for the combination of venlafaxine and mirtazapine over the MAOI, there was no placebo group in this comparison. The large CO-MED

randomised trial compared the combination of venlafaxine and mirtazapine to escitalopram (an SSRI) and placebo in patients who had either recurrent depression or chronic depression lasting at least 2 years(11). There was no difference in response rates between the two groups but the burden of adverse effects was greater in the combined antidepressant group. Those recruited into CO-MED differ from our study population in that they were not necessarily taking an antidepressant at baseline.

Conclusion and unanswered questions

Half of those who take antidepressants in an adequate dose for an adequate duration remain depressed(3, 29). This represents a substantial burden of illness and an unmet or inadequately met need. Although many patients in this group can benefit from CBT, it is not always easily available, nor is it universally effective (27). In primary care, where most initial encounters between people with depression and clinicians take place, antidepressants are still very widely prescribed and remain a first line treatment. Several pharmacological strategies have been developed to help those who do not respond to first line treatment, bu the evidence supporting them is not of very high quality(6). There is therefore a lack of clear guidance for clinicians in an area of unmet need, and this is particularly important in primary care because of the size of the population that does not improve on antidepressants (29). The lack of clear evidence of benefit in our study, combined with the increased burden of adverse effects in the mirtazapine group, means that we cannot recommend this combination as a routine strategy in primary care for those who remain depressed after adequate treatment with SSRI/SNRI antidepressants.

Word count, excluding abstract, tables and references 3810

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Ethical Approval was granted by the South East Wales Research Ethics Committee C (ref 12/WA/0350) on the 25th January 2013. All participants gave informed consent before taking part in the study.

Transparency Statement: The Lead author affirms that the manuscript is an honest, accurate and transparent account of the study and that no important aspects of the study have been omitted.

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Possible competing interests:

Drs Kessler and Round and Professors Lewis, Wiles and Peters report grants from NIHR-HTA during the conduct of the study

Professor Anderson reports personal fees from Lundbeck-Otsuka, Takeda and Lundbeck outside the submitted work

Contributorship Statement

DK, GL, SD, NW, TP, WH, IA, JC, CD, C C-G, UM were responsible for the original proposal, and securing funding for the trial. DT joined them in drafting the original protocol. DK as chief investigator had overall responsibility for the management of the study and the Bristol site, and as co-investigators JC and CD had responsibility for the Exeter site, UM for the Hull-York site and CC-G for the Keele site. All authors contributed to the refinement of the protocol. DT and AB had overall responsibility for the data collection and were supported by CJ, MC, TS and HG. SM, TP and NW wrote the statistical analysis plan. SM did the main analyses with input from TP, NW and DK. DK wrote the initial draft of the report. All authors contributed to and approved the final report.

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Data Sharing Statement

Individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures, and appendices) will be available beginning 3 months and ending 5 years after article publication to researchers who provide a methodologically sound proposal. The study protocol and statistical analysis plan will also be available. To gain access, data requestors will need to sign a data access agreement. Proposals should be directed to david.kessler@bristol.ac.uk.

Patient involvement statement

Patient and service user groups from Bristol and Manchester (PRIMER) were involved in the development of the full application and commented on the Plain English Summary. All those consulted said they recognised the value of the trial and offered advice about recruitment strategies. The West Hub Mental Health Research Network, (now Clinical Research Network) Research Materials Advisory Service worked with the trial team to develop materials, including patient information materials and consent forms. Study documents were reviewed by a panel of service users prior to being sent for ethical approval. A patient representative sat on the Trial Steering Committee. A patient group met regularly to contribute to the nested qualitative study; this group advised on topic guides, contributed to analysis of all qualitative data sets, and advised on dissemination activities.

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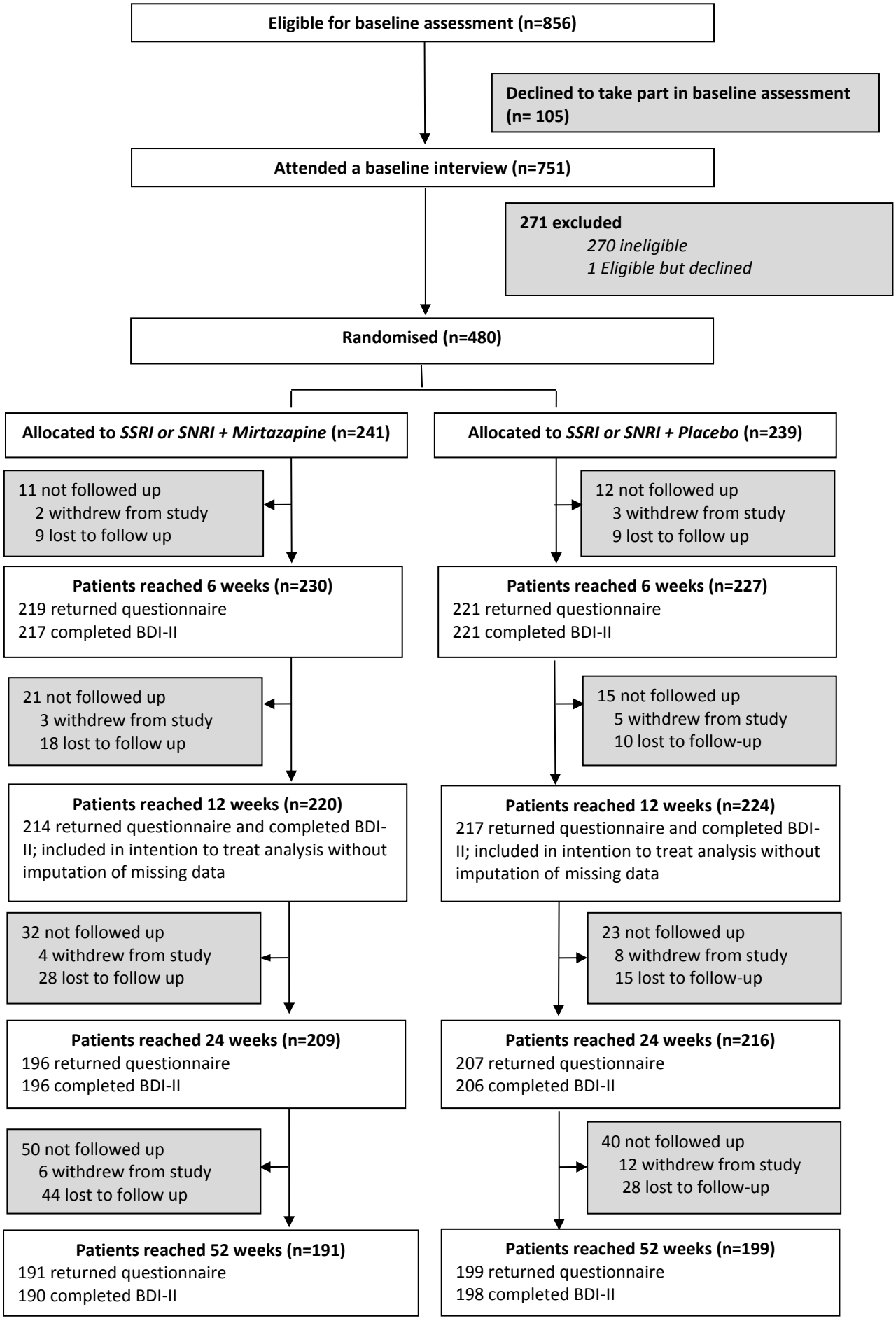
Figure


Eligible for baseline assessment (n=856)
Declined to take part in baseline assessment (n= 105)
Attended a baseline interview (n=751)
271 excluded
270 ineligible
1 Eligible but declined
Randomised (n=480)
Allocated to SSRI or SNRI + Mirtazapine (n=241)
Allocated to SSRI or SNRI + Placebo (n=239)
11 not followed up
2 withdrew from study
9 lost to follow up
12 not followed up
3 withdrew from study
9 lost to follow up
Patients reached 6 weeks (n=230)
219 returned questionnaire
217 completed BDI-II
Patients reached 6 weeks (n=227)
221 returned questionnaire
221 completed BDI-II
21 not followed up
3 withdrew from study
18 lost to follow up
15 not followed up
5 withdrew from study
10 lost to follow-up
Patients reached 12 weeks (n=220)
214 returned questionnaire and completed BDI-II; included in intention to treat analysis without imputation of missing data
Patients reached 12 weeks (n=224)
217 returned questionnaire and completed BDI-II; included in intention to treat analysis without imputation of missing data
32 not followed up
4 withdrew from study
28 lost to follow up
23 not followed up
8 withdrew from study
15 lost to follow-up
Patients reached 24 weeks (n=209)
196 returned questionnaire
196 completed BDI-II
Patients reached 24 weeks (n=216)
207 returned questionnaire
206 completed BDI-II
50 not followed up
6 withdrew from study
44 lost to follow up
40 not followed up
12 withdrew from study
28 lost to follow-up
Patients reached 52 weeks (n=191)
191 returned questionnaire
190 completed BDI-II
Patients reached 52 weeks (n=199)
199 returned questionnaire
198 completed BDI-II

Appendix

Table A1 Per protocol and CACE analyses of BDI-II scores

	Number of patients in model	**Difference in means***		**95% CI**	**p-value**
	CACE				
12 weeks	427	-2.39		-5.18 to 0.40	0.093
24 weeks	396	-1.02		-3.04 to 1.90	0.494
12 months	379	0.17		-2.91 to 3.25	0.914
	Per protocol				
12 weeks	327	-2.18		-4.60 to 0.24	0.077
12 months	138	-1.08		-5.11 to 2.95	0.598

* Adjusted for baseline BDI-II score, stratification and minimisation variables

Table A2: Means and differences in mean BDI-II scores at 12 weeks, 24 weeks and 12 months adjusting for baseline BDI-II scores, stratification and other minimisation variables, history of depression, length of current course of antidepressants and suicidal ideation

	Mirtazapine + SSRI/SNRI		**Placebo + SSRI/SNRI**		**Comparison**	
	N	*Mean (SD)*	*N*	*Mean (SD)*	*Adjusted difference in means (95% CI)*	*p-value*
Primary outcome						
12 weeks	*214*	*18.0 (12.3)*	*217*	*19.7 (12.4)*	*-2.12 (-4.25 to 0.02)*	*0.052*
Secondary outcomes						
24 weeks	*196*	*17.3 (12.9)*	*206*	*18.2 (12.6)*	*-1.26 (-3.57 to 1.05)*	*0.28*
12 months	*190*	*16.8 (12.7)*	*198*	*16.7 (12.2)*	*-0.29 (-2.61 to 2.03)*	*0.81*

*Table A3: Means and difference in mean BDI-II scores between treatment groups at 24 and 52 weeks among those remaining blinded**

	Mirtazapine + SSRI/SNRI		**Placebo + SSRI/SNRI**		**Comparison**	
	N	*Mean (SD)*	*N*	*Mean (SD)*	*Adjusted** difference in means (95% CI)*	*p-value*
*24 weeks ******	*152*	*17.4 (13.0)*	*141*	*17.0 (12.7)*	*0.26 (-2.41 to 2.94)*	*0.846*
*52 weeks ******	*120*	*16.5 (13.1)*	*110*	*15.1 (11.4)*	*1.48 (-1.57 to 4.53)*	*0.341*

**This is a post-hoc exploratory analysis and was not part of the original SAP*

***: adjusted for baseline BDI-II score and the stratification and other minimisation variables*

****: One patient in the placebo group returned a 24-week questionnaire without a BDI-II measure as did one patient in the mirtazapine group at 52 weeks*

Table A4: Secondary outcomes at 24 weeks and 12 months (except BDI-II)

	Mirtazapine + SSRI/SNRI			**Placebo + SSRI/SNRI**			**Comparison**		
	N	N (%)	Mean (SD)	N	N (%)	Mean (SD)	Adjusted OR* (95% CI)	Adjusted* difference in means (95% CI)	p-value
24 weeks									
"Response"	196	96 (49.0)	-	206	100 (48.5)	-	1.01 (0.67 to 1.50)	-	0.977
"Remission"	196	65 (33.2)	-	206	59 (28.6)	-	1.28 (0.81 to 2.01)	-	0.287
GAD-7	195	-	6.83 (5.89)	206	-	7.17 (5.86)	-	-0.56 (-1.56 to 0.44)	0.274
EQ-5D-5L	196	-	0.72 (0.25)	207	-	0.74 (0.25)	-	0.01 (-0.02 to 0.05)	0.464
SF-12 (physical)	191	-	42.88 (13.02)	201	-	45.37 (12.75)	-	-1.54 (-3.23 to 0.15)	0.075
SF-12 (mental)	191	-	39.89 (13.92)	201	-	37.91 (12.43)	-	2.32 (-0.17 to 4.80)	0.068
12 months									
"Response"	190	97 (51.1)	-	198	101 (51.0)	-	0.99 (0.66 to 1.49)	-	0.978
"Remission"	190	63 (33.2)	-	198	67 (33.8)	-	0.96 (0.62 to 1.50)	-	0.873
GAD-7	189	-	6.81 (6.23)	198	-	6.80 (5.73)	-	-0.17 (-1.23 to 0.90)	0.755
EQ-5D-5L	189	-	0.72 (0.28)	199	-	0.75 (0.25)	-	0.001 (-0.04 to 0.04)	0.950
SF-12 (physical)	182	-	43.34 (13.42)	191	-	44.32 (12.49)	-	-0.47 (-2.19 to 1.24)	0.587
SF-12 (mental)	182	-	40.54 (13.80)	191	-	39.25 (13.09)	-	1.42 (-1.20 to 4.04)	0.287

ASEC	119		9.50 (7.65)	136	-	9.59 (8.26)	-	-0.43 (-2.19 to 1.33)	0.630

* Adjusted for baseline values of the outcome and stratification and minimisation variables except in the case of adherence at 12 weeks where adjustment was made solely for stratification and minimisation variables

Table A5 Serious Adverse Events in the 12 weeks up to the primary outcome (all requiring hospitalisation).

Allocation	**Brief description of event**	**Relatedness to IMP as rated at follow-up**
Mirtazapine	Fall leading to minor injury, observed overnight	Not related
Mirtazapine	Admitted to hospital as a day case for pre-planned gynaecological procedure (D&C).	Not related
Mirtazapine	Deep Vein Thrombosis	Not related
Mirtazapine	Transient Ischaemic Attack	Unlikely to be related
Mirtazapine	Dental Extraction	Not related
Mirtazapine	Suicidal ideation and self-harm	Possibly related
Mirtazapine	Deliberate Overdose	Possibly related
Mirtazapine	Pancreatitis (pre-existing gallstones)	Unlikely to be related
Placebo	Fall, broken rib. Had not started IMP.	Not related
Placebo	Infective gastroenteritis (norovirus)	Not related
Placebo	Fall leading to Ankle fracture	Not related

In the period following the primary outcome, between 12 and 52 weeks when participants could be voluntarily unblinded, there were 36 SAEs, 20 of which occurred in those allocated to the Mirtazapine group. None of these were attributable to the IMP.

Table A6: Comparison of results of primary analysis of complete cases with corresponding (ITT) analysis where missing data were imputed using "best" and "worst" case scenarios and multiple imputation for primary outcome of BDI-II score at 12 weeks

	N	**Difference in means***	**95% CI**	**p-value**
Complete case	431	-1.83	-3.92 to 0.27	0.087
"Best" case scenario	480	-2.22	-4.41 to -0.03	0.047
"Worst" case scenario	480	-1.11	-4.11 to 1.89	0.469
Multiple imputation	480	-1.78	-3.90 to 0.34	0.100

* *Adjusted for baseline BDI-II score, stratification and minimisation variables*