Original Article

Does anxiety moderate the effectiveness of mirtazapine in patients with treatment-resistant depression? A secondary analysis of the MIR trial

Journal of Psychopharmacology
1–8

DOI: 10.1177/0269881120965939
journals.sagepub.com/home/jop

Raphael Rifkin-Zybutz[1], Stephanie MacNeill[1], Simon JC Davies[2], Christopher Dickens[3], John Campbell[4], Ian M Anderson[5], Carolyn A Chew-Graham[6], Tim J Peters[1], Glyn Lewis[7], Nicola Wiles[1] and David Kessler[1]

Abstract

Background: There is a lack of evidence to guide treatment of comorbid depression and anxiety. Preliminary evidence suggests mirtazapine may be effective in treating patients with both depression and anxiety symptoms.

Methods: We undertook a secondary analysis of mirtazapine (MIR): a placebo-controlled trial of the addition of mirtazapine to a selective serotonin reuptake inhibitor or serotonin–norepinephrine reuptake inhibitor in treatment-resistant depression (TRD) in primary care. We subdivided participants into three groups by baseline generalized anxiety disorder score (GAD-7): severe (GAD-7 $\geqslant$ 16), moderate (GAD-7 = 11–15), no/mild (GAD-7 $\leqslant$ 10). We used linear regression including likelihood-ratio testing of interaction terms to assess how baseline anxiety altered the response of participants to mirtazapine as measured by 12-week GAD-7 and Beck Depression Inventory II (BDI-II) scores.

Results: Baseline generalized anxiety moderated mirtazapine's effect as measured by GAD-7 (p = 0.041) and BDI-II (p = 0.088) at 12 weeks. Participants with severe generalized anxiety receiving mirtazapine had lower 12-week GAD-7 score (adjusted difference between means (ADM) –2.82, 95% confidence interval (CI) –0.69 to –4.95) and larger decreases in BDI-II score (ADM –6.36, 95% CI –1.60 to –10.84) than placebo. Conversely, there was no anxiolytic benefit (ADM 0.28, 95% CI –1.05 to 1.60) or antidepressant benefit (ADM –0.17, 95% CI –3.02 to 2.68) compared with placebo in those with no/mild generalized anxiety.

Conclusions: These findings extend the evidence for the effectiveness of mirtazapine to reduce generalized anxiety in TRD in primary care. These results may inform targeted prescribing in depression based on concurrent anxiety symptoms, although these conclusions are constrained by the post-hoc nature of this analysis.

Keywords
Depression, GAD, treatment resistance, antidepressants, clinical trials, pharmacotherapy

Background

Depression and anxiety are common conditions representing a large global health burden, with depression the largest cause of disability globally (World Health Organization, 2017). Depression and anxiety are overlapping syndromes that commonly occur together (Fava et al., 2004; Kessler et al., 1996) and the patient burden and complexity increases when both are present (McLaughlin et al., 2006). Comorbid anxiety in depression is associated with poorer chances of response to treatment, increased severity of depression (Nutt, 1999) and increased chance of suicide (Fawcett, 1988). The majority of patients with anxiety and depression are managed in a primary care setting, with antidepressants prescriptions increasingly yearly, with 67.5 million antidepressant prescriptions in the UK in 2017 (ONS, 2018).

There is evidence for the effectiveness of mirtazapine (Neuroscience based Nomenclature (NbN): Norepinephrine, Serotonin, Receptor antagonist) in several anxiety disorders such as generalized anxiety disorder (GAD) (Gambi et al., 2005), panic disorder (Ribeiro et al., 2001), obsessive compulsive disorder (Koran et al., 2005; Pallanti et al., 2004), post-traumatic stress disorder (Davidson et al., 2003) and social anxiety disorder (Muehlbacher et al., 2005; Schutters et al., 2010). Mirtazapine has also been found to have important actions on relieving anxiety

[1]Centre for Academic Mental Health, Bristol Medical School, University of Bristol, Bristol, UK
[2]Centre for Addiction and Mental Health, University of Toronto, Toronto, Canada
[3]Mental Health Research Group, University of Exeter, Exeter, UK
[4]Academic Primary Care, University of Exeter, Exeter, UK
[5]Neuroscience and Psychiatry Unit, University of Manchester, Manchester, UK
[6]School of Primary, Community and Social Care, Keele University, Keele, UK
[7]Division of Psychiatry, University College London, London, UK

Corresponding author:
Raphael Rifkin-Zybutz, Centre for Academic Mental Health, Bristol Medical School, University of Bristol, Oakfield House Bristol, Bristol, BS8 2BN, UK.
Email: jb19343@bristol.ac.uk

symptoms in patients with comorbid anxiety and depression in a meta-analysis (Fawcett and Barkin, 1998), while a small study has shown promising anti-depressant efficacy in dual-diagnosis anxiety and depression disorder (Goodnick et al., 1999).

These trials did not, however, examine the relative effect of mirtazapine on those with and without anxiety in the same patient cohort. Furthermore, they were not conducted in a primary care setting, where most patients with anxiety and depression are managed.

There is a lack of evidence to inform guidelines around treating depression with comorbid anxiety. Most evidence-informed guidelines such as National Institute for Health and Clinical Excellence (NICE) guidelines do not offer any specific advice on treating comorbid psychiatric conditions or preferred augmentation agents (NICE, 2020). This issue is recognized by a recent guideline from the French Association for Biological Psychiatry: "Although the issue of comorbidity is recognized by evidence-based guidelines, few specific recommendations are provided regarding acute treatment with antidepressant drugs". This guideline, based on expert consensus, suggests a selective serotonin reuptake inhibitor (SSRI, NbN: SERT) or serotonin norepinephrine reuptake inhibitor (SNRI, NbN: SERT and NET) as first-line therapy for depression with any comorbid anxiety disorder, with mirtazapine recommended as a possible second-line agent (Bennabi et al., 2019).

The mirtazapine (MIR) trial (Kessler et al., 2018) investigated the effectiveness of the addition of mirtazapine to an SSRI or SNRI in 480 patients with treatment-resistant depression (TRD) recruited from primary care. Treatment-resistance was defined pragmatically as failure to respond to at least six weeks of an SSRI/SNRI at an adequate dose; in the event, 90% of patients in MIR had been on antidepressants for more than six months. The MIR trial did not find evidence of a meaningful clinical difference between Beck Depression Inventory score (BDI-II) scores at 12 weeks for mirtazapine compared with placebo (adjusted difference between means (ADM) −1.83, 95% confidence interval (CI) −3.92 to 0.27, primary outcome). It did, however, find a small difference in GAD-7 scores at 12 weeks for mirtazapine compared with placebo (ADM 0.98, 95% CI 0.03 to 1.93, secondary outcome), although it is not clear whether this is clinically meaningful. GAD-7 is a questionnaire which captures the features of GAD – a syndrome with the core symptoms of excessive, difficult to control and disruptive anxiety and worry with associated features such as restlessness and lack of sleep (American Psychiatric Association, 2013). Similarly PANDA, a recent primary care trial of sertraline for depression, showed clear improvements in generalized anxiety, despite less convincing evidence of a superior antidepressant effect compared with placebo (Lewis et al., 2019).

The frequent comorbidity of depression and anxiety means targeted prescribing for this group is a potentially valuable objective. The MIR participants had high levels of generalized anxiety, with 48.6% scoring greater than 10 on GAD-7 at baseline, the normal cut-off point for screening for GAD (Spitzer et al., 2006). This is consistent with the previous research finding that 46% of those with depression have moderate to severe anxiety (Fava et al., 2004). The MIR trial thus represents an important resource to examine a possible rationale for targeted prescribing in a common and difficult to manage cohort. Using data from the MIR trial, we aimed to investigate whether there was a differential effect on generalized anxiety and depression symptoms at 12 weeks according to baseline severity of generalized anxiety. Because there is evidence of mirtazapine's effectiveness in anxiety disorders (Baldwin et al., 2014; Katzman et al., 2014) and preliminary evidence of its effectiveness in depression with anxiety symptoms (Fawcett and Barkin, 1998; Goodnick et al., 1999), we hypothesized that mirtazapine may be more effective in individuals within the MIR trial with greater generalized anxiety symptoms at baseline.

Methods

MIR study

The MIR study (Kessler et al., 2018) was a multicentre pragmatic randomized, placebo-controlled trial recruiting 480 adults aged 18 years or more from general practices within four sites in England. Participants fulfilled International Classification of Disease-10 (ICD-10) criteria for depression with an initial BDI-II score of >14, despite using an SSRI or SNRI for at least six weeks. Patients with dementia, bipolar disorder, psychosis or any substance misuse disorder were excluded. Participants were identified through interrogation of GP records for those receiving antidepressant prescriptions on repeat or recruited opportunistically during GP consultations. These patients were then screened according to inclusion and exclusion criteria and invited to join the study.

In MIR, 241 participants were randomized to mirtazapine and 239 to placebo, both given in addition to usual SSRI or SNRI treatment. Participants were stratified by centre and minimized by baseline BDI-II score (Beck et al., 1996), sex and current psychological therapy. The primary outcome was BDI-II score at 12 weeks, with the GAD-7 score at 12 weeks a secondary outcome measure.

Full details of the MIR trial methodology are available elsewhere (Kessler et al., 2018). The protocol for the original trial was pre-published (Tallon et al., 2016).

Stratification

This analysis was a hypothesis-driven secondary analysis using data from the MIR trial. Participants were stratified into groups based on their initial depression and generalized anxiety scores. To ensure clinically relevant categories, BDI and GAD-7 were stratified according to the scoring criteria used in validation studies (Beck et al., 1996; Spitzer et al., 2006). We wanted to optimize power of our analysis and so aimed to minimize the number of categories to preserve the ability of interaction terms to find differences. Previous research suggested that 10 was an optimal cut-off to ensure optimal sensitivity and specificity for diagnosis of generalized anxiety (Spitzer et al., 2006). Therefore, we combined the GAD-7 categories of 0–5 and 6–10 to provide our low/no anxiety baseline group. Resulting participants were stratified into three anxiety groups: mild generalized anxiety symptoms (GAD-7 $\leqslant 10$, $n = 245$), moderate generalized anxiety symptoms (GAD-7 11–15, $n = 133$) and severe generalized anxiety symptoms (GAD-7 $\geqslant 16$, $n = 99$). Three participants had no baseline GAD-7 measure and, thus, could not be included. BDI-II was stratified according to its standard clinical groupings: mild depression (BDI-II 14–19, $n = 69$), moderate depression (BDI-II 20–28, $n = 138$) and severe depression (BDI-II >29, $n = 273$) (Beck et al., 1996).

Statistical analysis

Chi-square tests were used to examine differences in baseline characteristics between groups stratified according to GAD-7 scores as described above. Univariable regression was employed likewise for continuous measures. Three categorical baseline variables were found to differ across generalized anxiety severity strata above our threshold level for inclusion ($p < 0.05$): education level, suicidal ideation and financial situation.

We used multivariable linear regression models to compare the mirtazapine and placebo groups, adjusting for stratification and minimization variables and the corresponding baseline value. This approach was based upon the model used in MIR. In the models examining GAD-7 at follow-up, we adjusted for baseline GAD-7 using the three-level categorical measure. We used likelihood ratio tests of an interaction term between treatment group and baseline anxiety strata to model the effect that baseline generalized anxiety had on each outcome as described in the below section.

We ran the analysis with two models. The primary model was identical to the original MIR analysis to ensure comparability. The second, fully adjusted model additionally adjusted for education level, suicidal ideation and financial situation – the three baseline variables that differed by anxiety strata. All of these models adjusted for baseline depression level.

We used categorial variables in our interaction term as we decided that these would enable any findings to be easily interpretable and relevant to clinical practice.

To check if our results were specific to severe generalized anxiety rather than general symptom severity, we repeated all the linear regression models described above, substituting baseline depression group for baseline generalized anxiety group in the interaction term to see if the response to mirtazapine compared with placebo was moderated by increasingly severe baseline depression.

All analyses were performed with STATA v15.

Sensitivity analysis

As a sensitivity analysis, we ran our main models with logged values of the baseline and 12-week symptom scale scores. This enables a regression model assessing a ratio of baseline to 12-week score and, thus, the percentage change in symptoms to assess if our results still applied in this scenario. We also ran a missing imputation using chained equations (MICE) regression model on our data to check for effects of missing data as in the original MIR study. This model was run with 30 iterations, as guided by the fraction of missing information on the initial model.

Outcomes

Primary outcomes of interest were 12-week generalized anxiety and depression symptoms (GAD-7 and BDI-II) with mirtazapine compared with placebo. We also examined response as assessed by GAD-7 and BDI-II (defined as at least a 50% decrease in score relative to baseline) as although this measure is less powered this was a secondary outcome in the original MIR analysis and an easier measure to interpret clinically.

To further explore any benefits, we also assessed the effect generalized anxiety had on the other MIR secondary outcomes: PHQ-9 (Patient Health Questionairre-9), social and physical functioning (SF-12 mental subscale) and quality of life scores (EQ-5D-5L).

Results

Baseline characteristics

At baseline, 477/480 (99.4%) of participants in the MIR study had a GAD-7 measurement. For analysis purpose, these individuals were then stratified into three groups: mild generalized anxiety symptoms (GAD-7 $\leqslant$10, $n = 245$), moderate generalized anxiety symptoms (GAD-7 11–15, $n = 133$) and severe generalized anxiety symptoms (GAD-7 $\geqslant$16, $n = 99$).

There was no major differences in proportions allocated to mirtazapine and placebo across the three anxiety stratification groups. In addition, there was no evidence of such differences in terms of sex ($p = 0.66$), age ($p = 0.12$), ethnicity ($p = 0.19$) or currently being in receipt of psychological treatment ($p = 0.30$). Groups with higher generalized anxiety had poorer educational attainment ($p < 0.01$), reported worse financial well-being ($p < 0.01$) and more suicidal ideation ($p < 0.01$). The higher generalized anxiety groups also had higher baseline depression ($p < 0.01$) and lower quality of life scores ($p < 0.01$) (Table 1).

Missing data

Since 49 participants had missing end-point values and three participants were missing baseline anxiety levels, we analysed 428 out of 480 participants (89.2%). Missing data were balanced between the two randomized groups (Placebo 22/239, Mirtazapine 30/241, $\chi^2(1) = 1.31$, $p = 0.25$). There was a suggestion of slightly more missing data in the higher severity anxiety strata ($\chi^2(2) = 4.97$, $p = 0.083$). Full details of the breakdown of missing data can be found in Supplementary Table 1.

Moderation of GAD-7 at 12 weeks by severity of generalized anxiety

The original MIR analysis found a small overall benefit in reducing generalized anxiety at 12 weeks for mirtazapine compared with placebo (ADM −0.98, 95% CI −0.03 to −1.93, $p = 0.04$). Here we found evidence that the anxiolytic benefit of mirtazapine at 12 weeks was moderated by baseline GAD-7 group (likelihood ratio test for interaction $p = 0.041$). A load-dependent effect of generalized anxiety on the benefit of mirtazapine over placebo was observed with those most anxious obtaining the highest benefit (Table 2, Figure 1). We similarly found evidence that GAD-7 response rate ($\geqslant$50% reduction in GAD-7 scores at 12 weeks) was moderated by baseline GAD-7 scores (likelihood ratio $p = 0.023$). Mirtazapine had a higher GAD-7 response rate compared with placebo in both those with moderate and severe generalized anxiety. Our fully adjusted regression models, which accounted for baseline differences in group characteristics, showed similar differences (Supplementary Table 2).

Moderation of BDI-II at 12 weeks by severity of generalized anxiety

The original MIR analysis did not find a clinically meaningful benefit in depressive symptoms for mirtazapine compared with placebo at 12 weeks (ADM −1.83, 95% CI −3.92 to 0.27). In the present research, we found weak evidence for a beneficial effect moderated by baseline GAD-7 scores by assessing the interaction

Table 1. Participant characteristics by generalized anxiety severity group.

		GAD-7 ⩽ 10 mild/ minimal generalized anxiety	GAD-7 11–15 moderate generalized anxiety	GAD-7 ⩾ 16 severe generalized anxiety	Total across all strata	*p*-value with statistical test results
Total in each stratum		245	133	99	477	-
Allocation						
Allocated to mirtazapine: *n* (%)		117 (47.8%)	69 (51.9%)	52 (52.5%)	238 (49.9%)	N/A†
Socio-demographic variables						
Sex: *n* (%)	Female	174 (71.0%)	90 (67.7%)	66 (66.7%)	330 (69.2%)	$p = 0.662$ $\chi^2(2) = 0.82$
In receipt of psychological therapy: *n* (%)	Yes	27 (11.0%)	18 (13.5%)	17 (17.2%)	62 (13.0%)	$p = 0.300$ $\chi^2(2) = 2.41$
Age (years): mean (SD)		51.2 (13.0)	48.4 (13.0)	49.6 (13.8)	50.1 (13.2)	$p = 0.124$ $F(2) = 2.10$
Ethnic group: *n* (%)	White	240 (98.0%)	131 (98.5%)	94 (94.9%)	465 (97.5%)	$p = 0.185$ $\chi^2(2) = 3.37$
	Non-White	5 (2.0%)	2 (1.5%)	5 (5.1%)	12 (2.5%)	
Financial well-being: *n* (%)	"Comfortable/ OK"	133 (54.3%)	51 (38.3%)	39 (39.4%)	223 (46.8%)	$p = 0.003$ $\chi^2(2) = 11.51$
	"Just about getting by or worse"	112 (45.7%)	82 (61.7%)	60 (60.6%)	254 (53.2%)	
Baseline severity variables						
GAD-7 score: mean (SD)		7.1 (2.2)	12.8 (1.3)	18.2 (1.8)	11.0 (4.8)	N/A
BDI-II score: mean (SD)		26.8 (7.9)	32.2 (9.3)	39.7 (9.0)	31.0 (9.9)	$p < 0.001$ $F(2) = 81.52$
SF-12 mental subscale : mean (SD)		32.5 (8.9)	26.8 (8.7)	21.5 (8.3)	28.6 (9.7)	$p < 0.001$ $F(2) = 57.92$
CIS-R score: mean (SD)		23.6 (7.1)	29.3 (6.5)	35.3 (6.9)	27.6 (8.3)	$p < 0.001$ $F(2) = 105.56$
Suicidal ideation: *n* (%)	Suicidal thoughts	62 (25.3%)	59 (44.4%)	53 (53.5%)	174 (36.5%)	$p < 0.001$ $\chi^2(4) = 2.23$

†There is no need for statistical testing across randomization groups.
SD: standard deviation.

term (likelihood ratio $p = 0.088$). The bulk of this effect was accounted for by a large increase in the antidepressant effect of mirtazapine in the most anxious (ADM −6.11, 95% CI −1.51 to −10.71) (Table 2, Figure 1). In contrast, there was no statistical evidence that baseline generalized anxiety moderated BDI-II response rate (50% decrease in BDI symptoms at 12 weeks) (likelihood ratio $p = 0.254$), although the descriptive statistics are in keeping with more improvement in those who are most anxious (OR 2.80, 95% CI 1.08 to 7.28) (Table 2).

Unadjusted change in GAD-7 and BDI scores with response rates by anxiety group are shown in full in Table 3.

Moderation of secondary outcomes by severity of generalized anxiety

We found moderating effects of anxiety group on depressive symptoms measured using the PHQ-9 (likelihood ratio: $p = 0.056$) and scores on the SF-12 mental subscale (likelihood ratio: $p = 0.065$) but not quality of life scores (EQ-5D-5L) (likelihood ratio: $p = 0.684$).

Results adjusted for variables imbalanced between anxiety strata were very similar (data not shown).

Sensitivity analysis

Sensitivity analyses were run using logged outcomes for continuous symptom scales. These analyses showed results that were in line with our main regression models (Supplementary Table 3). Similarly, regression models run with MICE analysis to examine effects of missing data showed substantively similar results to the original model (Supplementary Table 4).

Moderation of mirtazapine effects by severity of depression

There was no evidence that baseline depression (as measured by the BDI-II) moderated the effect of mirtazapine compared with placebo in terms of its effect on GAD-7 (likelihood ratio $p = 0.86$), response on the GAD-7 response (likelihood ratio $p = 0.20$), improvement in BDI-II (likelihood ratio $p = 0.66$) or response on the BDI-II (likelihood ratio $p = 0.63$). Results adjusted for variables imbalanced between anxiety strata were very similar (data not shown).

Discussion

Our analysis found that the reduction in generalized anxiety symptoms (GAD-7) at 12 weeks after addition of mirtazapine to an SSRI or SNRI in TRD was moderated by baseline anxiety. Furthermore, there was weak evidence that baseline generalized anxiety moderated reduction in depression as assessed by BDI-II scores at 12 weeks. Additional analyses also showed some evidence that baseline generalized anxiety moderated change in depression as measured by PHQ-9, and social functioning (SF-12) but not quality of life scores (EQ-5D-5L).

The benefit of mirtazapine over placebo was the most pronounced in people with severe generalized anxiety (GAD-7

Table 2. Effectiveness by generalized anxiety group – Model 1 (original MIR model).

	Mild generalized anxiety (GAD-7 ⩽10) $n = 227$	Moderate generalized anxiety (GAD-7 11–15) $n = 114$	Severe generalized anxiety (GAD-7 ⩾16) $n = 87$	p-value from likelihood ratio test of overall interaction term
Adjusted difference in mean GAD-7 score at 12 weeks when treated with mirtazapine compared to placebo	0.20 (95% CI −1.13 to 1.53)	−1.58 (95% CI −3.46 to 0.30)	−2.81 (95% CI −4.95 to −0.67)	$p = 0.041$
Response with mirtazapine vs placebo (>50% change in GAD)	OR 0.85 (95% CI 0.49 to 1.46)	OR 2.92 (95% CI 1.34 to 6.42)	OR 2.62 (95% CI 1.00 to 6.86)	$p = 0.023$
Adjusted difference in mean BDI score at 12 weeks when treated with mirtazapine compared to placebo	−0.17 (95% CI −3.02 to 2.68)	−2.49 (95% CI −6.54 to 1.56)	−6.11 (95% CI −10.71 to −1.51)	$p = 0.088$
Response with mirtazapine vs placebo (>50% change in BDI)	1.12 (95% CI 0.66 to 1.93)	1.45 (95% CI 0.67 to 3.12)	OR 2.80 (95% CI 1.08 to 7.28)	$p = 0.254$

This table describes the effectiveness of mirtazapine compared to placebo. Lower values represent superiority of mirtazapine – e.g. the mean GAD-7 score in the high anxiety participants taking mirtazapine is 2.81 points lower than those on placebo at the 12-week time point. This original model adjusts for minimization and stratification variables only (centre, gender, current receipt of psychological service, baseline BDI score and baseline of the construct being assessed).
CI: confidence interval; OR: odds ratio.

Figure 1. Difference in depression and generalized anxiety using mirtazapine compared to placebo, by baseline generalized anxiety. Bars represent 95% confidence intervals. Lower numbers indicate lower symptom severity scores at end of treatment – that is, more benefit from use of mirtazapine.

⩾16). In this group, the benefit was apparent in BDI-II, PHQ-9 and SF-12 scores as well as GAD-7. Conversely, in the group with minimal/mild generalized anxiety (GAD-7 ⩽10), estimates of difference between adding in mirtazapine versus placebo were close to zero across all relevant outcome measures (BDI-II, GAD-7, PHQ-9, SF-12 and EQ-5D-5L) despite a larger group size of 227. This suggests that in the TRD group with mild generalized anxiety, there appears to be little benefit for adding in mirtazapine to an SSRI/SNRI. This group represents around half the study population.

There was no evidence of moderation by baseline depression severity as measured by the BDI-II. However, those with severe generalized anxiety symptoms had, on average, severe depression on the BDI-II, while those with low levels of generalized anxiety had only moderate severity depression. While our results do not support mirtazapine being more effective than placebo in those with greater severity of depressive symptoms in isolation, it is possible that its benefits are more apparent in patients experiencing a greater severity of illness expressed as a combination of depressive and anxiety symptoms.

In the most anxious group (GAD-7 ⩾16), depression scores as assessed by BDI-II were 6.11 lower than the placebo group on average. This difference is sizeable and likely to be clinically important. Meanwhile, the improvement of 2.8 points on GAD-7 compared with placebo found in the most anxious group in our analysis compares favourably to the improvement found in PANDA of sertraline over placebo (1.3) (Lewis et al., 2019). Furthermore, recent unpublished work based on the PANDA cohort suggests that an improvement of 1.5 on the GAD-7 is a clinically meaningful change whereby patients are likely to feel better (Kounali et al., 2020), a threshold our findings exceed. However, the population in PANDA were not treatment-resistant, and a higher threshold for meaningful clinical improvement might apply to the MIR trial population (Button et al., 2015).

We found that mirtazapine appears to decrease depressive symptoms and improve mental-health-related social functioning in people with more severe generalized anxiety, but not in those without generalized anxiety, in the context of a trial that did not find overall treatment group differences (Kessler et al., 2018). A possible explanation for this is that augmentation of mirtazapine in depressed patients with comorbid generalized anxiety helps relieve anxious symptoms, which then may lead to reduction in

Table 3. Raw score changes and response rates.

	Mild generalized anxiety (GAD-7 ⩽10)		Moderate generalized anxiety (GAD-7 11–15)		Severe generalized anxiety (GAD-7 ⩾16)	
	Placebo (n = 120)	Mirtazapine (n = 107)	Placebo (n = 56)	Mirtazapine (n = 58)	Placebo (n = 41)	Mirtazapine (n = 46)
Mean change in GAD-7 from baseline to 12 weeks (SD)	1.46 (4.42)	1.37 (4.72)	4.05 (4.96)	6.02 (5.02)	4.61 (5.29)	7.70 (6.72)
GAD-7 response rate	36.7%	32.5%	32.8%	55.1%	19.1%	36.5%
Mean change in BDI-II from baseline to 12 weeks (SD)	10.71 (10.17)	10.77 (10.87)	11.39 (12.73)	13.81 (10.47)	10.65 (13.15)	16.76 (16.67)
BDI-II response rate	40.0%	42.1%	37.5%	48.3%	22.0%	43.5%

This table shows the raw mean change in GAD-7 and BDI-II scores and response rate for each sub-stratum.
SD: standard deviation.

depressive symptoms and better general functioning. This was observed in the PANDA trial where decreases in anxiety levels were seen at six weeks, while decreases in depressive symptoms took 12 weeks to occur (Salaminios et al., 2017). Unfortunately, the MIR trial did not measure GAD-7 levels at six weeks, so we were unable to test this hypothesis in this study.

Strengths and limitations

Limitations of this paper include that this was an unplanned secondary analysis of a trial, which can be susceptible to hypothesizing after results are known (Kerr, 1998) and multiple testing. However, previous literature has explored mirtazapine's effect in anxiety (Fawcett and Barkin, 1998; Kim et al., 2011) and this led to the hypothesis-driven nature of this analysis of a single moderating factor.

The post-hoc nature of the analysis means that the trial was not originally designed to examine the relationships explored in this paper and, hence, was underpowered. This explains the wide confidence intervals found in our analysis, which cover differences that may or may not be clinically relevant.

Participants were recruited based on depression diagnosis and high BDI-II scores. A sizeable proportion of the participants, therefore, had lower generalized anxiety scores as assessed by GAD-7. These participants have less scope for improving anxiety symptoms due to a floor effect. However, although this effect may contribute to the observed interaction when examining GAD-7 scores, it is not sufficient to explain the observed moderating effects of baseline generalized anxiety on PHQ-9, SF-12 or BDI-II scores, even when adjusting for baseline depression.

The strengths of this analysis are that this large, randomized controlled trial was pragmatically recruited, with a definition of TRD easy to operationalize in a primary care setting. Furthermore, this tests the treatment in the setting where it is most used: primary care. Additionally, our participants had a range of generalized anxiety symptoms representative of findings in previous research (Fava et al., 2004). These factors make our findings more generalizable.

Furthermore, our regression analyses adjusted for baseline differences including all the minimizing factors involved in randomization and baseline depression scores. Additionally, our analyses survived last observation carried forward, log transformation and further adjustment for other baseline differences across baseline anxiety stratum. This suggests a robust observed effect.

Another strength is the large size of the trial, which meant there were substantial numbers in each sub-group, allowing for direct comparison of effectiveness across anxiety groups in one trial – which has not previously been examined. Furthermore, unlike previous evidence (Fawcett and Barkin, 1998) that used subscales of depression scores to assess anxiety, MIR examined generalized anxiety with GAD-7. This is a specific, well-validated measure used widely in screening for GAD, with a cut-off score of 10 on GAD-7, having a 89% sensitivity and 82% specificity (Spitzer et al., 2006). The effects found here would be clinically important if they were to be replicated.

Implications

Clarifying effective treatment for patients with treatment-resistance in primary care is key, as these patients are a common group that suffer from poorer quality of life, are harder to manage and utilize substantial healthcare resources (Mrazek et al., 2014). When depression and anxiety symptoms co-occur, they represent a more severe end of the population of depressed people (Pandarakalam, 2018). This is reflected in the baseline characteristics of participants in our high generalized anxiety group (GAD-7 ⩾16) who had higher baseline depression, rates of suicidal ideation and rates of struggling financially in addition to lower quality of life measures.

These results add support to existing evidence that mirtazapine is a useful treatment in managing generalized anxiety in those with depression (Fawcett and Barkin, 1998). Additionally, this analysis suggests the possibility that this use of mirtazapine in those with severe generalized anxiety may improve both depressive symptoms and social functioning. This result was achieved by the addition of mirtazapine to an SSRI or SNRI, a strategy previous trials did not examine. These findings suggest a possible path to selectively targeting the addition of mirtazapine based on comorbid generalized anxiety symptoms when first-line treatment fails. This is in line with existing expert-consensus-based guidance on the use of mirtazapine in those with anxiety-predominant depression (Bennabi et al., 2019).

Conversely, these findings did not find any evidence for adding in mirtazapine in those without generalized anxiety symptoms, who have failed to respond to first-line antidepressant therapy. This is important, given the increase in prescriptions of antidepressants, to identify groups where antidepressants fail to work, in addition to those in whom they might be effective (ONS, 2018).

Further research

The results found here should be further explored. Obtaining individual-patient-level data in previous trials for mirtazapine in TRD would help determine if the effects found here can be replicated. A formal study to assess the benefits of mirtazapine in treating TRD with severe symptoms of generalized anxiety might then be warranted.

Conclusion

In this secondary analysis, the addition of mirtazapine was more effective at treating generalized anxiety than placebo in patients with TRD and severe anxiety symptoms. Mirtazapine may also be more effective at treating depressive symptoms and improving social functioning in those who have higher levels of anxiety. Conversely, there appears to be little clinical utility in adding mirtazapine in those without any concurrent anxiety. This should be formally assessed in trials in the future but may represent a strategy for stratifying treatment of resistant depression depending on symptom subtype.

Declaration of conflicting interests

RRZ, CD, JC, SJCD and SM report no conflict of interest. CACG, TP and DK report grants from NIHR, during the conduct of the study. NW reports grants from University of Bristol, during the conduct of the study. GL reports grants from UCL, during the conduct of the study; personal fees from Fortitude Law, outside the submitted work. IMA reports grants from Efficacy and Mechanism Evaluation (NIHR and MRC) funding, during the conduct of the study; personal fees from Lundbeck, personal fees from Takeda, personal fees from Otsuka, outside the submitted work.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The MIR trial was funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (project 11/129/76) and supported by the NIHR Biomedical Research Centre at University Hospitals Bristol NHS Foundation Trust and the University of Bristol. The views expressed in this publication are those of the authors and do not necessarily reflect those of the HTA programme, NIHR, NHS, or Department of Health. 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.

ORCID iDs

Raphael Rifkin-Zybutz https://orcid.org/0000-0003-1230-0847
Ian M Anderson https://orcid.org/0000-0003-2205-9209

Supplemental material

Supplemental material for this article is available online.

References

American Psychiatric Association (2013) *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. 5th ed. Washington, DC: American Psychiatric Association.

Baldwin DS, Anderson IM, Nutt DJ, et al. (2014). Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: A revision of the 2005 guidelines from the British Association for Psychopharmacology. *J Psychopharmacol* 28: 403–439.

Beck AT, Steer RA and Brown GK (1996) *Manual for the Beck Depression Inventory-II*. 2nd ed. San Antonio: Psychological Corporation.

Bennabi D, Yrondi A, Charpeaud T, et al. (2019) Clinical guidelines for the management of depression with specific comorbid psychiatric conditions French recommendations from experts (the French Association for Biological Psychiatry and Neuropsychopharmacology and the fondation FondaMental). *BMC Psychiatry* 19: 50.

Button KS, Kounali D, Thomas L, et al. (2015) Minimal clinically important difference on the Beck Depression Inventory–II according to the patient's perspective. *Psychol Med* 45: 3269–3279.

Davidson JR, Weisler RH, Butterfield MI, et al. (2003) Mirtazapine vs. placebo in posttraumatic stress disorder: A pilot trial. *Biol Psychiatry* 53: 188–191.

Fava M, Alpert JE, Carmin CN, et al. (2004) Clinical correlates and symptom patterns of anxious depression among patients with major depressive disorder in STAR*D. *Psychol Med* 34: 1299–1308.

Fawcett J (1988) Predictors of early suicide: Identification and appropriate intervention. *J Clin Psychiatry* 49: 7–8.

Fawcett J and Barkin RL (1998) A meta-analysis of eight randomized, double-blind, controlled clinical trials of mirtazapine for the treatment of patients with major depression and symptoms of anxiety. *J Clin Psychiatry* 59: 123–127.

Gambi F, De Berardis D, Campanella D, et al. (2005). Mirtazapine treatment of generalized anxiety disorder: A fixed dose, open label study. *J Psychopharmacol* 19: 483–487.

Goodnick PJ, Puig A, Devane CL, et al. (1999) Mirtazapine in major depression with comorbid generalized anxiety disorder. *J Clin Psychiatry* 60: 446–448.

Katzman MA, Bleau P, Blier P, et al. (2014) Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. *BMC Psychiatry* 14: S1.

Kerr NL (1998) HARKing: Hypothesizing after the results are known. *Pers Soc Psychol Rev* 2: 196–217.

Kessler DS, Macneill SJ, Tallon D, et al. (2018) Mirtazapine added to SSRIs or SNRIs for treatment resistant depression in primary care: Phase III randomised placebo controlled trial (MIR). *BMJ* 363: k4218.

Kessler RC, Nelson CB, Mcgonagle KA, et al. (1996) Comorbidity of DSM-III-R major depressive disorder in the general population: Results from the US National Comorbidity Survey. *Br J Psychiatry Suppl* 30: 17–30.

Kim JE, Yoon SJ, Kim J, et al. (2011) Efficacy and tolerability of mirtazapine in treating major depressive disorder with anxiety symptoms: An 8-week open-label randomised paroxetine-controlled trial. *Int J Clin Pract* 65: 323–329.

Koran LM, Gamel NN, Choung HW, et al. (2005) Mirtazapine for obsessive-compulsive disorder: An open trial followed by double-blind discontinuation. *J Clin Psychiatry* 66: 515–520.

Kounali D, Button KS, Lewis G, et al. (2020) *How Much Change is Enough? Evidence from a longitudinal study on depression in UK Primary Care*. Psychological Medicine.

Lewis G, Duffy L, Ades A, et al. (2019) The clinical effectiveness of sertraline in primary care and the role of depression severity and duration (PANDA): A pragmatic, double-blind, placebo-controlled randomised trial. *Lancet Psychiatry* 6: 903–914.

Mclaughlin TP, Khandker RK, Kruzikas DT, et al. (2006) Overlap of anxiety and depression in a managed care population: Prevalence

and association with resource utilization. *J Clin Psychiatry* 67: 1187–1193.

Mrazek DA, Hornberger JC, Altar CA, et al. (2014) A review of the clinical, economic, and societal burden of treatment-resistant depression: 1996-2013. *Psychiatr Serv* 65: 977–987.

Muehlbacher M, Nickel MK, Nickel C, et al. (2005) Mirtazapine treatment of social phobia in women: a randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol* 25: 580–583.

National Institute for Health and Care Excellence (NICE) (2020) *Depression, Scenario: New or Initial Management from Age 18 Years Onwards*. Available at: https://cks.nice.org.uk/depression#!scenario (accessed 10 October 2020).

Nutt DJ (1999) Care of depressed patients with anxiety symptoms. *J Clin Psychiatry* 60: 23–27; discussion 46–28.

Office for National Statistics (ONS) (2018) *Prescriptions Dispensed in the Community - Statistics for England, 2007-2017*. Available at: https://digital.nhs.uk/data-and-information/publications/statistical/prescriptions-dispensed-in-the-community/prescriptions-dispensed-in-the-community-england---2007---2017#resources (accessed 10 October 2020).

Pallanti S, Quercioli L and Bruscoli M (2004) Response acceleration with mirtazapine augmentation of citalopram in obsessive-compulsive disorder patients without comorbid depression: A pilot study. *J Clin Psychiatry* 65: 1394–1399.

Pandarakalam JP (2018) Challenges of treatment-resistant depression. *Psychiatria Danubina* 30: 273–284.

Ribeiro L, Busnello JV, Kauer-Sant'anna M, et al. (2001) Mirtazapine versus fluoxetine in the treatment of panic disorder. *Braz J Med Biol Res* 34: 1303–1307.

Salaminios G, Duffy L, Ades A, et al. (2017) A randomised controlled trial assessing the severity and duration of depressive symptoms associated with a clinically significant response to sertraline versus placebo, in people presenting to primary care with depression (PANDA trial): Study protocol for a randomised controlled trial. *Trials* 18: 496.

Schutters SI, Van Megen HJ, Van Veen JF, et al. (2010) Mirtazapine in generalized social anxiety disorder: A randomized, double-blind, placebo-controlled study. *Int Clin Psychopharmacol* 25: 302–304.

Spitzer RL, Kroenke K, Williams JBW, et al. (2006) A brief measure for assessing generalized anxiety disorder: The GAD-7. *Arch Intern Med* 166: 1092–1097.

Tallon D, Wiles N, Campbell J, et al. (2016) Mirtazapine added to selective serotonin reuptake inhibitors for treatment-resistant depression in primary care (MIR trial): Study protocol for a randomised controlled trial. *Trials* 17: 66.

World Health Organization (2017) *Depression and Other Common Mental Disorders: Global Health Estimate*. Geneva: World Health Organization. Available at: https://apps.who.int/iris/bitstream/handle/10665/254610/WHO-MSD-MER-2017.2-eng.pdf%3Bjsessionid=2F7D0C3E4E45C2553E7BD648B0BED548?sequence=1 (accessed 10 October 2020).