Pramipexole augmentation for the acute phase of treatment-resistant, unipolar depression: a placebo-controlled, double-blind, randomised trial in the UK

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Summary

Background About 30% of patients with depression treated with antidepressant medication do not respond sufficiently to the first agents used. Pramipexole might usefully augment antidepressant medication in such cases of treatment-resistant depression, but data on its effects and tolerability are scarce. We aimed to assess the efficacy and tolerability of pramipexole augmentation of ongoing antidepressant treatment, over 48 weeks, in patients with treatment-resistant depression.

Methods We did a multicentre, double-blind, placebo-controlled randomised trial in which adults with resistant major depressive disorder were randomly assigned (1:1; using an online randomisation system) to 48 weeks of pramipexole (titrated to 2·5 mg) or placebo added to their ongoing antidepressant medication. The study was conducted in nine National Health Service Trusts in England. Participants, investigators, and researchers involved in recruitment and assessment were masked to group allocation, and the central pharmacy team dispensing the medication was not masked. The primary outcome was change from baseline to week 12 in the total score of the 16-item Quick Inventory of Depressive Symptomology self-report version (QIDS-SR$_{16}$). The primary analysis was performed on the intention-to-treat population that included all eligible, randomly assigned participants. People with lived experience were involved in the design, oversight, and interpretation of the study. The trial was registered with ISCTRN (ISRCTN84666271) and EudraCT (2019-001023-13) and is complete.

Findings Between Feb 16, 2021 and May 29, 2024, 217 participants attended a screening visit, of whom 66 were excluded due to ineligibility. 151 participants were randomly assigned (75 to the pramipexole group and 75 to the placebo group, after one participant was found to be ineligible after randomisation). 84 (56%) participants were female and 66 (44%) were male and the mean age of participants was 44·9 years (SD 14·0). Ethnicity data were not available. The mean QIDS-SR$_{16}$ total score at baseline was 16·4 (SD 3·4) in the pramipexole group and 16·2 (3·5) in the placebo group. The mean dose of pramipexole received at week 12 was 2·3 mg (SD 0·45). Adjusted mean decrease from baseline to week 12 of the QIDS-SR$_{16}$ total score was 6·4 (SD 4·9) for the pramipexole group and 2·4 (4·0) for the placebo group; the mean difference between groups was –3·91 (95% CI –5·37 to –2·45; p<0·0001). Termination of trial treatment due to adverse events was more frequent in the pramipexole group (15 participants [20%]) than in the placebo group (four participants [5%]), with reported adverse events consistent with known side-effects of pramipexole, in particular nausea, headache, and sleep disturbance or somnolence.

Interpretation In this trial involving participants with treatment-resistant depression, pramipexole augmentation of antidepressant treatment, at a target dose of 2·5 mg, demonstrated a reduction in symptoms relative to placebo at 12 weeks but was associated with some adverse effects. These results suggest that pramipexole is a clinically effective option for reducing symptoms in patients with treatment-resistant depression. Future trials directly comparing pramipexole with existing treatments for this disorder are needed.

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Introduction

The management of people with major depressive disorder who are not helped sufficiently by first-line antidepressant medication and psychological treatment is a pressing clinical problem. Conventionally, patients with depression who have not responded to two adequate courses of antidepressant medication are regarded as experiencing treatment- resistant depression. A US survey,

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See Online for appendix

Research in context

Evidence before this study

Current guidelines for people with depression that has not responded to initial antidepressant medications recommend augmentation strategies—adding pharmacological agents to ongoing antidepressant treatment. The most recommended augmentation agents are lithium, atypical antipsychotics, and other antidepressants such as mirtazapine or trazodone. However, the efficacy of these treatments is limited, with many patients not showing an adequate clinical response Pramipexole, a dopamine D2/3 agonist licensed for Parkinson's disease and restless legs syndrome, might be an effective option but is associated with well-documented side effects that might limit its tolerability.

Our evidence synthesis involved searching the Cochrane Central Register for Controlled Trials, Embase, MEDLINE, and PsycINFO for randomised controlled trials comparing pramipexole (as monotherapy or augmentation) to control interventions in participants with major depressive disorder. The search strategy included terms related to major depressive disorder ["major depressive disorder", "mdd", "depression"], pramipexole ["pramipexole"], and randomised controlled trials ["RCT", "randomis/zed controlled trial", "controlled trial"], with no language restrictions.

Three randomised controlled trials were identified comparing pramipexole to either placebo or selective serotonin reuptake inhibitor (SSRI) control groups in treating major depressive disorder. These studies reported short-term (6–8 weeks) effects of pramipexole at doses between 0·375 and 5 mg daily, with the largest treatment group comprising only 35 participants. Meta-analyses by Tundo and colleagues found no significant effect of pramipexole on efficacy outcomes in patients with major depressive disorder (the authors found some benefit for patients with bipolar depression). The relative risk of symptomatic response in patients with major depressive disorder was estimated as 1·47 (95% CI 0·92 to 2·36) versus placebo and 0·93 (0·44 to 1·95) versus SSRIs. The standardised mean difference in depression symptoms was –0·3 (95% CI –0·81 to 0·21) versus placebo and –0·14 (–0·91 to 0·63) versus SSRIs. Treatment discontinuation due to adverse events was not significantly higher than placebo (relative risk 1·6 [95% CI 0·73 to 3·49]) and significantly higher than SSRIs (relative risk 6·28 [95% CI 1·19 to 33]). Most studies used pramipexole doses of 1·55 mg daily or lower, except one group in Corrigan and colleagues' study that used 5 mg, which was poorly tolerated with a 52% dropout rate due to adverse events. Overall, randomised, controlled evidence on pramipexole's efficacy and tolerability was limited to small, short-term studies of low-dose treatment. Because treatment-resistant depression is frequently chronic with a high relapse probability, longer-term estimates of pramipexole's efficacy and tolerability from randomised controlled studies are needed.

Added value of this study

To our knowledge, this is the largest efficacy trial to date comparing pramipexole augmentation versus placebo (n=75 per group) and assesses the effect of treatment over a much longer time period (48 weeks) than previous trials.The achieved pramipexole dose (2·3 mg) was substantially higher than that of most other randomised trials. We found that pramipexole produced a larger symptom reduction at week 12 (the primary outcome) than previously reported, with a standardised mean difference between groups of d=0·87 (relative risk of response, 2·75; number-needed-to treat, 4). We assessed tolerability and the emergence of side-effects over a much longer time period than previous randomised studies.

Implications of all the available evidence

In patients with treatment-resistant depression, pramipexole titrated to a target dose of 2·5 mg produces substantial symptom reduction across 48 weeks of treatment. However, significant side effects limit its use in approximately one in five patients. Pramipexole might therefore be a useful treatment strategy for patients with depression who have not responded to initial treatments. Future research should focus on improving treatment tolerability, assessing cost effectiveness, and directly comparing pramipexole with other augmenting agents.

based on health insurance claims, estimated that treatment-resistant depression occurred in about 30% of adults treated with antidepressant medication and that these patients contributed disproportionally to the health and unemployment costs of depressive conditions.[1]

A core symptom of treatment-resistant depression, not well addressed by the serotonergic medications commonly used to treat depression, is anhedonia, which is the diminished ability to experience pleasure from rewarding activities.[2,3] Dopamine pathways have been shown to play an important role in reward processes but, with the exception of bupropion, the commonly used, conventional antidepressants have little acute effect on central dopaminergic mechanisms.[4] Dopaminergic agents might therefore represent an underutilised therapeutic option for depressive symptoms, particularly anhedonia, that have not responded to previous antidepressant treatment.

For this reason, there has been interest in the possible antidepressant effect of dopamine agonists such as pramipexole, which three small controlled trials[5–8] and several observational studies[9–11] suggest have potential value in treatment-resistant depression. The aim of the present study was to provide a rigorous test of the benefits and risks of pramipexole in relieving depressive symptoms in patients with treatment-resistant depression. Moreover, because treatment-resistant depression is associated with high relapse rates,[12] even after initially positive responses, the study was extended to identify the presence of

longer-term gains during pramipexole maintenance treatment over the course of 1 year.

Methods

Study design

We did a multicentre, double-blind, parallel-group, placebo-controlled, randomised trial evaluating the effects of the addition of pramipexole to antidepressant treatment in patients with treatment-resistant depression. Following a single-site internal pilot in Oxford, recruitment continued in five National Health Service (NHS) trusts linked to National Institute for Health and Care Research (NIHR) Biomedical Research Centres with expertise in the recruitment and study of patients with treatment-resistant depression. Other secondary care NHS sites were added as needed and nine sites in England eventually contributed to trial recruitment. Sites included both academic-linked (Oxford University, Newcastle University, Liverpool University, Kings College London, University College London, University of Bristol, Nottingham University) and non-academic-linked (Pennine Care NHS Foundation Trust, Midlands Partnership University NHS Foundation Trust) secondary-care centres in which standard care for patients with treatment-resistant depression would involve pharmacotherapy (including augmentation therapies as studied here), psychotherapy, and neurostimulatory interventions. The trial protocol has previously been published.[13] The study was funded through the Efficacy and Mechanism Evaluation Programme of the NIHR. The University of Oxford acted as the study sponsor. The trial protocol was approved by the Southwest-Central Bristol Research Ethics Committee (reference: 19/SW/0216) and by the Medicines and Healthcare Regulatory Agency (reference: CTA 21584/0419/001). All participants provided written, informed consent. The trial was registered with ISCTRN (ISRCTN84666271) and EudraCT (2019-001023-13) and is complete.

Participants

Participants were recruited through referrals from primary and secondary care services, search of primary care health system records, and online and poster advertisements. Recruitment using advertisements was included because many patients with treatment-resistant depression only intermittently access health services and it has been shown that direct recruitment methods, including advertisements, are effective.[14] All participants recruited to the study were assessed and managed in their local secondary care service for the duration of the trial. Men and women aged 18 years or older were eligible if they met diagnostic criteria for DSM-5 Major Depressive Disorder, confirmed using the Mini International Neuropsychiatric Interview (version 7.0.2),[15] and scored more than 10 on the 16-item Quick Inventory of Depressive Symptomatology self-report version (QIDS-SR$_{16}$); which is classified as moderate, severe, or very severe depression.[16] Participants were currently taking an antidepressant medication that they were willing to continue. During the present episode, there had been a lack of therapeutic response to an adequate course of at least two licensed, pharmacological antidepressant treatments, defined as at least 4 weeks of treatment (unless limited by tolerability) at the minimum dose recommended using criteria from the Maudsley Prescribing Guidelines[17] and British National Formulary.[18]

Exclusion criteria included a current diagnosis of or a history of psychosis, bipolar disorder, or clinically significant current or previous impulse control difficulties. Concomitant antipsychotic drug treatment was not permitted. A full list of inclusion and exclusion criteria is presented in the appendix (pp 3–4). People with lived experience were involved in the study design (reviewing protocol, choice of outcome measures, and reviewing patient-facing documents), were represented on study oversight committees, and provided feedback on interpretation of the results.

Randomisation and masking

Randomisation was performed centrally via an online randomisation system, Sortition, developed by the Primary Care Clinical Trials Unit of Oxford University. The randomisation schedule was designed by a trial statistician. Each participant was randomly assigned (1:1) to receive either pramipexole or placebo. A non-deterministic algorithm was used to produce treatment groups balanced for important prognostic factors by minimising separately on: trial site, age (18–50 *vs* >50 years), self-reported sex (male or female), and baseline QIDS-SR$_{16}$ severity (11–15 *vs* 16–20 *vs* >20).

The first ten participants were allocated treatment randomly without minimisation to avoid predictability. Subsequently, the minimisation algorithm was applied with an allocation ratio that was not fully deterministic: there was an 80% bias towards allocations that minimised the imbalance. Using a centralised randomisation system aided allocation concealment.

Participants, investigators, and researchers involved in trial recruitment and assessment visits were masked to allocation. The central pharmacy team dispensing trial medication were not masked. Participants wishing to remain on pramipexole treatment after the end of the treatment period might have been unmasked at the discretion of the investigator, when necessary to guide their ongoing treatment. The trial statistician remained masked to treatment allocation when performing the final analysis. Functional unmasking was assessed after participants had completed all study treatment by asking participants to guess whether they had been receiving pramipexole or placebo and to rate their certainty for this guess on a scale of 0 (not at all confident) to 4 (entirely confident).

Procedures

Before randomisation, eligible participants entered a run-in phase of 2 weeks to ensure symptom stability

and compliance with self-rating scales. Eligibility for randomisation was assessed 1–5 weeks after screening. Eligible participants were then randomly assigned to either pramipexole or identical placebo capsules on a 1:1 basis. The dosing of pramipexole was derived from the case series of Fawcett and colleagues[9] and consisted of immediate-release pramipexole given as a single dose at night. The starting dose was 0·25 mg of pramipexole which increased every 3 days, reaching a target of dose of 2·5 mg over 4 weeks if tolerance permitted. If side-effects developed, the dose could be reduced to the maximum tolerated. The administration of placebo followed an identical procedure to that used for pramipexole. The maximum duration of treatment in the study was 48 weeks. Alteration of other antidepressant medication before week 12 was not allowed in the protocol unless deemed clinically necessary by the treating team. Changes to antidepressants were permitted after 12 weeks.

Outcomes

The primary endpoint of the study was improvement (change from baseline) at week 12 on the QIDS-SR_{16}. The scale ranges from 0 to 27, with higher scores indicating a greater severity of depression, with severity thresholds of mild (score of 6–10), moderate (11–15), severe (16–20), and very severe (21–27) depression. The scale was completed digitally by participants at weekly intervals using the previously validated True Colours system.[19] After 12 weeks, QIDS-SR_{16} ratings were collected every 4 weeks up to week 48. The primary outcome was collected in the intention-to-treat population of all eligible, randomly assigned participants. The QIDS-SR_{16} was selected as the primary outcome as it is a well validated, self-report measure of depressive symptoms, with good psychometric properties,[16] is frequently used in interventional studies in mood disorders;[20,21] and has an associated clinician-rated scale. It is available to use without charge and is available in several different languages (although only the English language version was used in this study). It is a 16-item self-rating scale for depression based on the DSM-5 depressive symptom domains.

Secondary efficacy endpoints were change in QIDS-SR_{16} at 48 weeks; response and remission on the QIDS-SR_{16} at 12 weeks; the clinician-rated QIDS-C (range from 0 to 27, with higher scores indicating greater severity of depression);[16] the Snaith Hamilton Pleasure Scale for rating anhedonia (SHAPS; range from 0 to 14, with higher scores indicating a greater severity of anhedonia);[22] the General Anxiety Disorder-7 scale (GAD-7; range from 0 to 21, with higher scores indicating a greater severity of anxiety);[23] and the Work and Social Adjustment Scale (WSAS)[24] which measures functional outcome (range from 0 to 40, with higher scores indicating a greater severity of functional impairment). The Treatment Satisfaction Questionnaire for Medication (TSQM-9)[25] was used to assess treatment acceptability (range from 0 to 100, with higher scores indicating greater satisfaction). No changes to outcomes were made following commencement of the trial. Secondary outcomes were collected from the intention-to-treat sample of all eligible, randomly assigned participants.

Adverse and serious adverse events were recorded at each patient contact and classified with the Medical Dictionary for Regulatory Activities (version 27.1). Medication discontinuation rate from the study because of medication intolerance was a specified secondary outcome. Other specified safety outcomes were the development of impulse control difficulties, scores on the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS) (range 0 to 112, with a higher score indicating greater severity of impulse control difficulties),[26] development of symptoms of psychosis or mania, and scores on the Altman Self-Rating Mania Scale (ALTMAN) (range 0 to 20, with a higher score indicating a greater severity of symptoms of mania).[27] The QUIP-RS and the ALTMAN were administered with the same frequency as the QIDS-SR_{16}. Measures of suicidality were extracted from question 12 of the QIDS-SR_{16}.

Participants were prompted to complete the online scales by email and were contacted by telephone by the study team to complete safety measures (adverse events, QUIP-RS) weekly until week 12 and then monthly until week 48.

A change to the protocol was made to adjust the estimated dropout rate used in the sample size calculation. This change was made as the initial estimated dropout rate was 20%, but the actual dropout rate achieved in the study was 8%.

Statistical analysis

Analyses were conducted according to a pre-specified Statistical Analysis Plan. The sample size was determined using the assumption that a 3-point difference on the primary outcome, QIDS-SR_{16} score between pramipexole and placebo at 12 weeks, was clinically important (as a change of between 2 to 3 on the QIDS-SR_{16} has been estimated as equivalent to the previously recommended threshold of a 3-point change on the Hamilton Depression Rating Scale[16]). The SD of the score was estimated using previous data as 5·4,[20] which produced a standardised effect size of 0·56. The sample size to test differences between groups at 90% power and at a type one error rate of 5% was required to be 68 per group (136 total, without dropout). The initial estimated dropout rate at week 12 was 20%; however, the achieved dropout was lower (8%) and produced a sample size estimate of 74 participants per group (148 total). Additional mechanistic outcomes were collected (to be reported elsewhere), and incorporating these into the sample size calculation (by reducing the alpha to 0·025) resulted in a sample size estimate of 89 participants per group (178 in total).

Analyses of efficacy and safety outcomes were performed on all participants who were randomly

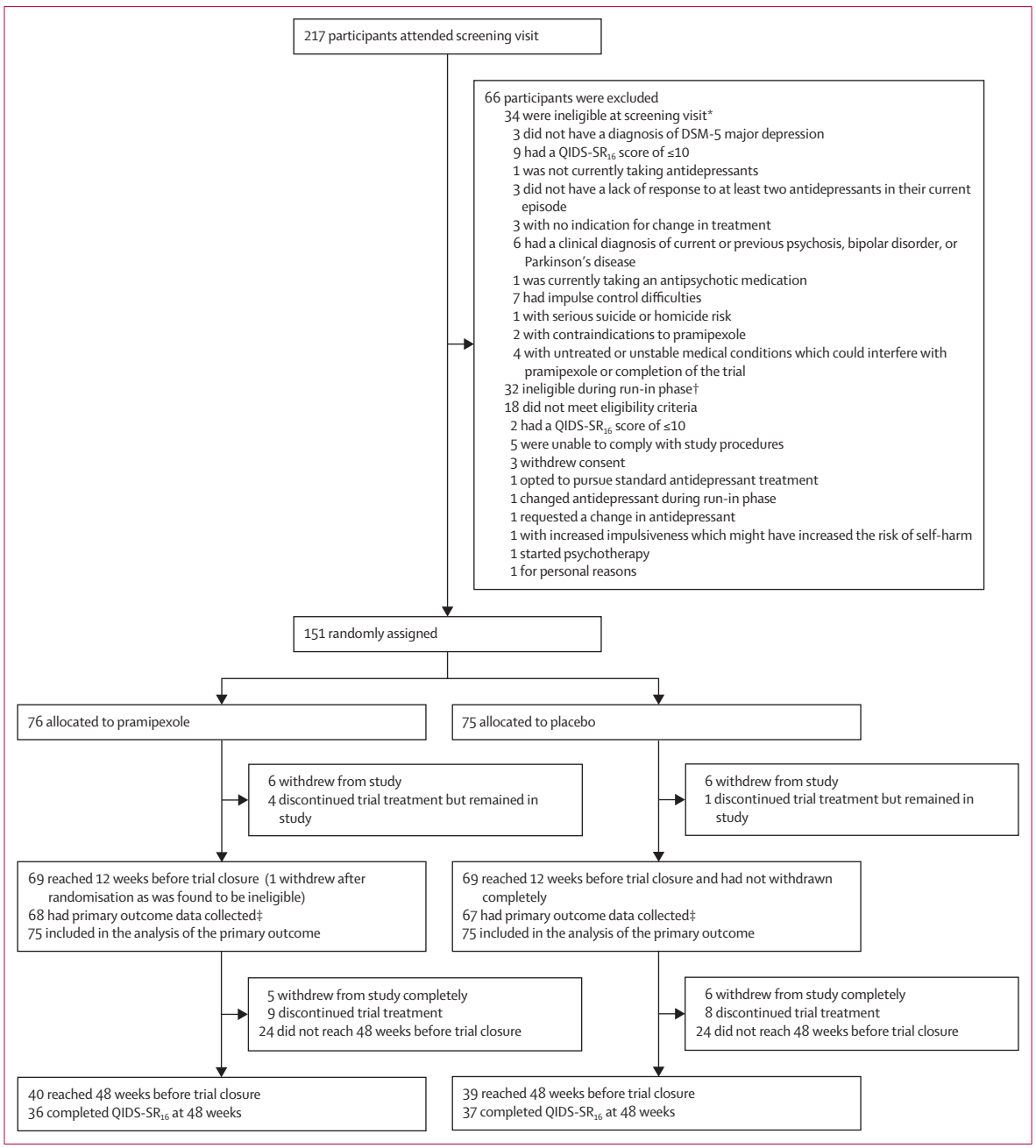

Figure 1: **Trial profile**
QIDS-SR$_{16}$=Quick Inventory of Depressive Symptomology, 16-item, self-report version *Six participants had two reasons for ineligibility at screening visit. †Two participants had two reasons for ineligibility at randomisation visit. ‡One participant in the pramipexole group and two participants in the placebo group did not provide QIDS-SR$_{16}$ data within the required time window for the 12-week analysis, they gave responses at a later date but their data was missing at week 12.

assigned to an intervention, as defined by the protocol eligibility criteria, regardless of the intervention they received, compliance with intervention, or completion of outcomes. The primary outcome was analysed using a generalised linear mixed-effects model which included all QIDS-SR$_{16}$ data collected up to week 48. The model included fixed effect terms for treatment group, timepoint, and an interaction between time and treatment group, as well as minimisation variables. Treatment site was included as a random effect and participant identification as a random intercept. Details of the analyses of other outcomes, including binary and count measures, handling of missing data, and sensitivity analyses are included in the appendix (pp 5–6). Treatment

	Pramipexole group (n=75)	Placebo group (n=75)	Overall (n=150)
Demographic characteristics			
Age, years (mean [SD]; range)	43·9 (15·2; 20·8–72·3)	45·9 (12·7; 21·6–74·1)	44·9 (14·0; 20·8–74·1)
Sex			
Male	34 (45%)	32 (43%)	66 (44%)
Female	41 (55%)	43 (57%)	84 (56%)
BMI (mean [SD]; range)	30·6 (7·54; 19·5–53·0)	29·8 (6·4; 18·5–50·7)	30·2 (7·0; 18·5–53·0)
Study site			
University of Bristol	4 (5%)	6 (8%)	10 (7%)
University College London	4 (5%)	2 (3%)	6 (4%)
Newcastle University	11 (15%)	15 (20%)	26 (17%)
Liverpool University	7 (9%)	5 (7%)	12 (8%)
Midlands Partnership University NHS Foundation Trust	2 (3%)	1 (1%)	3 (2%)
Nottingham University	4 (5%)	2 (3%)	6 (4%)
Oxford University	35 (47%)	39 (52%)	74 (49%)
Pennine Care NHS Foundation Trust	1 (1%)	0	1 (<1%)
Kings College London	7 (9%)	5 (7%)	12 (8%)
Psychiatric history			
Duration of current episode in years (median [IQR])	8·0 (2·5–15·0)	10 (5·0–20·0)	8·5 (4·0–16·0)
Number of ineffective pharmacological treatments for current episode (mean [SD]; range)	3·2 (1·4; 2–8)	3·7 (2·1; 2–12)	3·5 (1·8; 2–12)
Antidepressant medication at randomisation, by class*			
SSRI	41 (55%)	40 (53%)	81 (54%)
SNRI	19 (25%)	21 (28%)	40 (27%)
TCA	6 (8%)	1 (1%)	7 (5%)
MAOI	2 (3%)	1 (1%)	3 (2%)
Other	21 (28%)	24 (32%)	45 (30%)
Use of augmentation strategy at randomisation†			
No	58 (77%)	60 (80%)	118 (79%)
Yes	17 (23%)	15 (20%)	32 (21%)
Family history of mood disorder			
No	22 (29%)	26 (35%)	48 (32%)
Yes	53 (71%)	49 (65%)	102 (68%)
Age at first depressive episode, years			
Mean (SD; range)	21·3 (9·7; 7·0–55·0)	21·4 (11·6; 0·0–58·0)	21·3 (10·6; 0·0–58·0)
Missing	12 (16%)	15 (20%)	27 (18%)
Depression and associated symptom scores			
$QIDS\text{-}SR_{16}$			
Mean (SD; range)	16·4 (3·4; 11–24)	16·2 (3·5; 11–25)	16·3 (3·4; 11–25)
Intermediate	32 (43%)	36 (48%)	68 (45%)
Severe	35 (47%)	30 (40%)	65 (43%)
Very severe	8 (11%)	9 (12%)	17 (11%)
QIDS-C (mean [SD]; range)	15·8 (3·4; 9–25)	15·4 (3·2; 8–24)	15·6 (3·3; 8–25)
SHAPS (mean [SD]; range)	7·8 (3·9; 0–14)	7·8 (3·7; 0–14)	7·8 (3·8; 0–14)
GAD-7 (mean [SD]; range)	11·7 (5·3; 0–21)	11·8 (5·3; 0–21)	11·7 (5·3; 0–21)
WSAS (mean [SD]; range)	25·2 (8·1; 0–40)	24·7 (7·4; 8–38)	25·0 (7·7; 0–40)

Data are n (%) unless otherwise indicated. Other antidepressant medications indicate bupropion, mirtazapine, trazadone, lithium, or lamotrigine. SSRI=selective serotonin reuptake inhibitor. SNRI=serotonin and norepinephrine reuptake inhibitor. TCA=tricyclic antidepressant; MAOI=monoamine oxidase inhibitor. $QIDS\text{-}SR_{16}$=Quick Inventory of Depressive Symptoms, self-report version. QIDS-C=Quick Inventory of Depressive Symptoms, clinician-reported version. SHAPS=Snaith Hamilton Pleasure Scale. GAD-7=General Anxiety Disorder-7. WSAS=Work and Social Adjustment Scale. *Not mutually exclusive. †An augmentation strategy is defined as taking more than one antidepressant agent at the same time.

Table 1: **Baseline characteristics**

effects for continuous outcomes are reported as adjusted mean differences, for binary outcomes (response rate, remission rate, medication discontinuation due to side effects) as relative risks (RR), and for count outcomes (number of adverse reactions) as incidence ratios, all with associated 95% CIs. Absolute values of continuous outcomes are reported as mean (SD), binary data as absolute numbers (%), and count data as median (IQR).

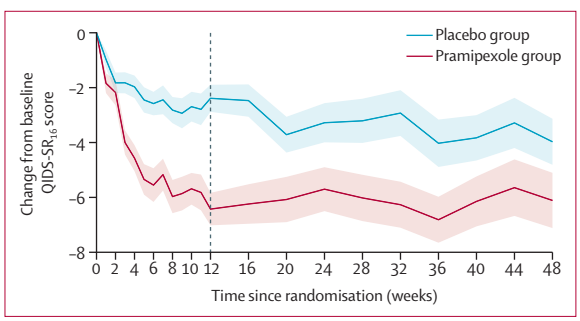

***Figure 2*: Primary efficacy assessment of change from baseline in QIDS-SR$_{16}$ total score at week 12**
Data were obtained from all randomly assigned, eligible participants. Mean change in observed score is presented, and shaded areas show SE. The dashed line is the timepoint of the primary outcome. QIDS-SR$_{16}$=Quick Inventory of Depressive Symptomology, 16-item, self-report version.

Role of the funding source
The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results
Recruitment for the study began on Feb 16, 2021, which was later than scheduled due to the COVID-19 pandemic, and ended on May 29, 2024 when the target sample size for the primary outcome was met. Participants recruited before September, 2023, were followed up for 48 weeks. Participants recruited after this date received progressively shorter follow-up but all were included in the study for sufficient time to reach the primary endpoint at 12 weeks.

A total of 217 participants attended a screening visit, of whom 66 were excluded (34 for ineligibility during the screening visit and 32 for ineligibility during the run-in phase) with the remaining 151 participants being randomly assigned to either pramipexole or placebo (figure 1). One participant randomly assigned to the pramipexole group was found to be ineligible after randomisation, and was withdrawn from the study, leaving 75 participants in each group. Primary outcome data at 12 weeks were collected from 68 pramipexole-treated and 67 placebo-treated participants. 40 pramipexole-treated

	Pramipexole group (n=75)	Placebo group (n=75)	Treatment effect (95% CI)	Standardised mean difference (95% CI)	p value
Outcomes at week 12					
Primary efficacy endpoint					
Change from baseline to week 12 in QIDS-SR$_{16}$ total score (mean [SD])	−6·4 (4·9)	−2·4 (4·0)	−3·91 (−5·37 to −2·45)*	−0·87 (−1·20 to −0·55)	<0·0001
Secondary efficacy endpoint					
QIDS-SR$_{16}$ response rate at week 12†	30/68 (44%)	11/67 (16%)	2·72 (1·49 to 4·95)‡	0·62 (0·28 to 0·96)	0·0011
QIDS-SR$_{16}$ remission rate at week 12§	19/68 (28%)	5/67 (8%)	3·94 (1·61 to 9·64)‡	0·56 (0·22 to 0·90)	0·0026
Change from baseline to week 12 in QIDS-C total score (mean [SD])	−6·1 (4·5)	−3·0 (4·9)	−3·26 (−4·67 to −1·86)*	−0·70 (−1·00 to −0·40)	<0·0001
Change from baseline to week 12 in SHAPS total score (mean [SD])	−3·8 (4·0)	−1·5 (3·6)	−2·20 (−3·41 to −1·00)*	−0·58 (−0·89 to −0·26)	0·0003
Change from baseline to week 12 in GAD-7 total score (mean [SD])	−4·1 (5·5)	−1·5 (4·7)	−2·51 (−3·97 to −1·06)*	−0·49 (−0·78 to −0·21)	0·0007
Outcomes at week 48					
Number of patients in study by week 48	40	39	..	..	..
Change from baseline to week 48 in QIDS-SR$_{16}$ total score (mean [SD])	−6·1 (6·0)	−4·0 (5·1)	−2·02 (−3·73 to −0·31)*	−0·36 (−0·67 to −0·06)	0·021
Change from baseline to week 48 in WSAS total score (mean [SD])	−6·8 (11·4)	−3·3 (6·9)	−3·23 (−6·18 to −0·27)*	−0·34 (−0·66 to −0·03)	0·03

The standardised mean difference is showing Cohen's d values for the continuous outcomes and Cohen's h values for the binary outcomes. QIDS-SR$_{16}$=Quick Inventory of Depressive Symptoms, 16-item self-report version. QIDS-C=Quick Inventory of Depressive Symptoms, clinician-reported version. SHAPS=Snaith Hamilton Pleasure Scale. GAD-7=General Anxiety Disorder-7. WSAS=Work and Social Adjustment Scale. *Linear mixed effects regression model adjusted for randomised group, timepoint, age, sex, baseline QIDS-SR$_{16}$ score, an interaction between randomised group and timepoint, and baseline value of outcome, as fixed effects; site as a random effect, and participant as a random intercept. A negative mean difference indicates improvement in favour of pramipexole. †A response was defined as a greater than 50% reduction in the baseline QIDS-SR$_{16}$ total score; missing data were not imputed for this analysis, and data were available for 68 participants in the pramipexole group and 67 participants in the placebo group. ‡Mixed effects logistic regression model adjusted for randomised group, age, sex , and baseline QIDS-SR$_{16}$ score as fixed effects, and site as a random effect. A marginal relative risk greater than 1 indicates improvement in favour of pramipexole. §Remission was defined as a QIDS-SR$_{16}$ total score ≤5. Missing data were not imputed for this analysis and data were available for 68 participants in the pramipexole group and 67 participants in the placebo group.

***Table 2*: Primary and secondary efficacy endpoints and treatment exposure**

	Pramipexole group (n=75)	Placebo group (n=75)
Overall		
Any adverse event	74 (99%; 41 females, 33 males)	73 (97%; 42 females, 31 males)
Any serious adverse event	4 (5%; 3 females, 1 male)	2 (3%; 1 female, 1 male)
Adverse events of special interest		
Impulse control disorder	2 (3%; 1 female, 1 male)	0
Substance-induced psychotic symptoms*	1 (1%; 1 female)	0
Adverse events occurring in ≥10% of either group		
Nausea	50 (67%; 31 females, 19 males)	31 (41%; 18 females, 13 males)
Headache	47 (63%; 29 females, 18 males)	37 (49%; 24 females, 13 males)
Dizziness	42 (56%; 24 females, 18 males)	27 (36%; 17 females, 10 males)
Nasopharyngitis	27 (36%; 17 females, 10 males)	23 (31%; 16 females, 7 males)
Fatigue	25 (33%; 14 females, 11 males)	27 (36%; 18 females, 9 males)
Insomnia	24 (32%; 11 females, 13 males)	17 (23%; 13 females, 4 males)
Vomiting	22 (29%; 15 females, 7 males)	9 (12%; 4 females, 5 males)
Sleep disorder	21 (28%; 13 females, 8 males)	14 (19%; 7 females, 7 males)
Somnolence	18 (24%; 9 females, 9 males)	6 (8%; 2 females, 4 males)
Cough	15 (20%; 8 females, 7 males)	8 (11%; 5 females, 3 males)
Malaise	14 (19%; 10 females, 4 males)	7 (9%; 3 females, 4 males)
Diarrhoea	13 (17%; 7 females, 6 males)	7 (9%; 4 females, 3 males)
Oropharyngeal pain	12 (16%; 6 females, 6 males)	8 (11%; 2 females, 6 males)
Asthenia	12 (16%; 5 females, 7 males)	5 (7%; 2 females, 3 males)
Back pain	11 (15%; 8 females, 3 males)	11 (15%; 7 females, 4 males)
Anxiety	11 (15%; 5 females, 6 males)	10 (13%; 5 females, 5 males)
COVID-19	10 (13%; 7 females, 3 males)	9 (12%; 7 females, 2 males)
Middle insomnia	10 (13%; 6 females, 4 males)	1 (1%; 1 female)
Arthralgia	9 (12%; 4 females, 5 males)	3 (4%; 1 female, 2 males)
Rhinorrhoea	8 (11%; 5 females, 3 males)	9 (12%; 6 females, 3 males)
Seasonal allergy	8 (11%; 3 females, 5 males)	7 (9%; 7 females)
Dry mouth	8 (11%; 5 females, 3 males)	5 (7%; 5 females)
Terminal insomnia	8 (11%; 2 females, 6 males)	3 (4%; 2 females, 1 male)
Abdominal pain	8 (11%; 4 females, 4 males)	1 (1%; 1 male)
Migraine	4 (5%; 2 females, 2 males)	13 (17%; 11 females, 2 males)

*The event involved steroid treatment.

Table 3: **Adverse events**

and 39 placebo-treated participants reached the 48-week follow-up.

The mean age of participants was 44·9 years (SD 14·0) and 84 (56%) participants were female and 66 (44%) were male (table 1). Data on participant ethnicity were not collected. Scores on the QIDS-SR_{16} indicated a mean level of depression in the severe range (overall, 16·3 [SD 3·4]) while ratings on the WSAS were consistent with substantial functional impairment (overall, 25·0 [SD 7·7]). The SHAPS indicated a substantial level of anhedonia (overall, 7·8 [SD 3·8]). In many patients, the depressive illness was chronic in nature; the median duration of the current episode for the overall cohort was 8·5 years (IQR 4·0–16·0). There was a substantial degree of treatment resistance to conventional pharmacotherapies with an average of 3–4 antidepressants that were not deemed beneficial for the participants' current episodes. About 21% of participants were being treated using a pharmacological augmentation strategy.

At the 12-week primary endpoint, the mean decrease in QIDS-SR_{16} score from baseline in the patients in the pramipexole group was 6·4 (SD 4·9) compared with 2·4 (4·0) in the placebo group (figure 2). The difference in mean change was –3·91 (95% CI –5·37 to –2·45; p<0·0001). The QIDS-SR_{16} response rate at week 12 was 44·1% (30 of 68) in the pramipexole group and 16·4% (11 of 67) in the placebo group (RR 2·72 [95% CI 1·49 to 4·95; p=0·0011]). Remission at week 12 occurred in 27·9% (19 of 68) of participants in the pramipexole group compared with 7·5% (five of 67) in the placebo group (RR 3·94 [95% CI 1·61 to 9·64; p=0·0026]). The mean dose at week 12 of pramipexole was 2·3 mg (SD 0·45) and of placebo was 2·4 mg (0·26). The therapeutic advantage for pramipexole was apparent on all secondary outcome efficacy measures at week 12 (table 2; appendix (pp 7–9, 17–36).

At study completion, week 48, the mean decrease in QIDS-SR_{16} score from baseline was maintained in the pramipexole group (6·1 [SD 6·0]), but scores in the placebo group had improved compared with their mean 12-week rating (4·0 [5·1]). The difference in mean change between groups at 48 weeks was –2·02 (95% CI –3·73 to 0·31; p=0·021). Satisfaction with treatment at 48 weeks, measured by the TSQM-9 (global score), was substantially higher in patients in the pramipexole group than in those receiving placebo (mean difference 26·41 [95% CI 14·94 to 37·88]; p<0·0001; appendix p 9). Across the 48 weeks of the trial, adjustments to antidepressant medication were made on an average (SD) of 0·57 (SD 1·23) occasions for participants in the pramipexole group and 1·77 (2·54) occasions for participants in the placebo group (appendix p 12).

There were four serious adverse events in the pramipexole group and two in the placebo group. None of these were judged to be related to the study medication (appendix p 11). Two participants taking pramipexole developed impulse control difficulties; these remitted when the dose of trial medication was lowered. The QUIP-RS scores, which measure symptoms of impulsivity, decreased in both participant groups over the course of the study, with no differences between pramipexole and placebo at any time point (appendix pp 11, 24–27]).

Suicidal ideation measured by item 12 of the QIDS-SR_{16} was lower in the pramipexole group than in the placebo group by the third week of treatment (appendix pp 10, 27–30). There were three cases of self-injury (two in the pramipexole group and one in the placebo group), none of which required hospital admission.

Scores on the Altman Self-Rating Mania scale were raised in the pramipexole group by the second week of treatment (appendix pp 10, 22–24). Two cases of hypomania were reported (one in the pramipexole group and one in the placebo group), and one case of drug-induced psychosis (in the pramipexole group, following treatment with steroids), none of which required hospital admission.

The most common adverse effects reported in the pramipexole group were consistent with its known clinical profile and included nausea, headache, dizziness, and sleep disturbance or somnolence (table 3). Dropout of the study, at any timepoint, due to intolerance was significantly greater in the pramipexole group (15 patients [20%] overall, 11 [27%] female participants, four [12%] male participants) than in those receiving placebo (four [5%] overall, three [7%] female participants, one [3%] male participant; RR 3·95 [95% CI 1·35 to 11·57; p=0·012]), with the median number of adverse reactions being higher in the pramipexole group (six [IQR 3 to 10]) than in the placebo group (two [0 to 4]; adjusted incidence rate ratio 2·24 [95% CI 1·75 to 2·85]; p<0·0001; appendix p 20).

Functional unmasking occurred in the study, with 50 (77%) of the 65 participants in the placebo group who provided this information correctly guessing their allocation and 45 (71%) of the 63 participants in the pramipexole group guessing theirs (exploratory analysis: Chi-squared test, p<0·001, appendix pp 13–14).

Discussion

The results of this study have shown that pramipexole can be a useful adjunctive medication in patients with major depressive disorder whose episodes of illness are characterised by long duration and lack of response to conventional treatments. Relative to placebo, the standardised antidepressant effect size of pramipexole in this study (d=0·87) compares favourably with those estimated by meta-analysis for other commonly used augmentation treatments in treatment-resistant depression; for example, atypical antipsychotics (d=0·27 to 0·43)[28] or esketamine (d=0·36).[29] Furthermore, the placebo response, particularly remission rates in the present study, are lower than those usually seen in treatment-resistant depression augmentation trials,[30] suggesting that the patients with depression who were recruited had relatively refractory conditions. The secondary outcome measures also favoured pramipexole, including those related more directly to patient experience of overall functioning (WSAS), anhedonia (SHAPS), anxiety (GAD-7), clinician-reported symptoms of depression (QIDS-C), and satisfaction with treatment (TSQM-9).

High relapse rates are common in patients with treatment-resistant depression who have initially responded to antidepressant treatment. For this reason, we extended the study into a maintenance phase during which pramipexole continued to exert significant benefit on key outcome measures in patients who were able to be followed up for 48 weeks. During this time, the placebo group also improved to some extent, perhaps because of the additional antidepressant treatments they received, or the passage of time leading to an enhanced placebo effect or waning of symptoms.

Tolerability is an important concern in the prescription of pramipexole. In the present study, pramipexole's well-characterised adverse effect profile was generally similar to that reported in patients with Parkinson's disease[31] and led to 20% of participants in the pramipexole group discontinuing the medication due to side effects (compared with 5% in the placebo group). This equates to a number-needed-to-harm (ie, the number of patients treated for one extra person to stop the medication due to side-effects across 48 weeks of treatment) of seven (95% CI 4–21). For comparison, the number-needed-to-treat to produce an extra treatment response by week 12 was four (95% CI 2–7). The most problematic adverse effects of pramipexole are behavioural, particularly impulse control disorders such as pathological gambling and compulsive shopping, which occur in about 15% of people receiving dopamine receptor agonist treatment for Parkinson's disease.[32] The current data suggest that the prevalence of impulse control difficulties might be less in patients with depression receiving pramipexole (about 3%), as previously reported in observational work.[11] This raises the possibility of a differential susceptibility to these symptoms in the two patient groups. However, participants with evidence of previous impulse control difficulties were excluded from the current study, which might have reduced the observed rates, and thus careful monitoring for the development of impulse control problems will be needed in clinical practice. There was an increase in scores on the Altman Self-Rating Mania scale in the pramipexole group, although there were only two cases of hypomania (one in each group), suggesting that this increase might have captured a reduction in the anhedonic and anergic symptoms of depression rather than clinical elevation of mood.

Our study has limitations, particularly the subjective effects of pramipexole which resulted in functional unmasking of treatment by the end of the study, perhaps producing so-called expectancy effects. However, such a mechanism seems less likely to explain the sustained benefits of pramipexole in the maintenance phase of treatment. We did not collect data on participant ethnicity and so are unable to determine this aspect of the representativeness of the study population.

Although our participants were broadly recruited from NHS services in the UK, it will be necessary to establish the efficacy of pramipexole in other populations, with larger future studies needed to identify patient subgroups.

In future studies, it will be important to find means of improving the tolerability of pramipexole treatment for patients with treatment-resistant depression.

Observational work[11] suggests that a slower titration of drug might be better tolerated and modified release preparations might have benefits, as well as routine initial prescription of adjunctive antiemetic medication during dose titration. Direct comparison of pramipexole with other commonly used augmentation treatments, such as quetiapine, and assessment of its cost effectiveness, will help clarify its position in the treatment pathway for those patients with depression who have prolonged and refractory illness.

Overall, this study demonstrates the potential benefits of repurposing medications for use in psychiatry. Repurposing is a particularly cost-effective approach to treatment development as it can capitalise on early phase and safety data from extant studies. Furthermore, important effects of drugs on psychiatric symptoms are often not measured, or are overlooked during initial development for other indications, increasing the possibility that such effects can be detected in future psychiatric-focused trials.

In conclusion, pramipexole was found to exert a substantial benefit on symptoms of depression over the course of 1 year, in patients with treatment-resistant, unipolar depression. This suggests that pramipexole, and possibly other dopaminergic agents, are likely to be a clinically useful option for this patient group, particularly if strategies to improve tolerability are implemented.

Contributors

MB, PJC and JRG conceptualised the study; acquired resources and study funding; and were involved in the methodology, study supervision, data acquisition and writing, and reviewing and editing of the manuscript. UG, L-MY, and SM completed formal analysis and were involved in the methodology, writing, and reviewing and editing of the manuscript. AJC, DK, and SW acquired resources, supervised the study, and were involved in data acquisition and writing, reviewing and editing of the manuscript. AB, JE, QJMH, MK, NN and AR supervised the study, were involved in data acquisition and writing, reviewing, and editing of the manuscript. JS acquired resources and together with AL was involved in the methodology, writing, and reviewing and editing of the manuscript. ACL, SMR, VF, LMF, CM, BRG, HTR, DCH, LAW, BS, AP, MW, KST, JK-G, DS, CZ, and KAS were involved in data acquisition, project administration, writing, and reviewing and editing of the manuscript. CJH acquired resources and was involved in writing and reviewing and editing of the manuscript. UG, L-MY and SM directly accessed and verified the data reported in this manuscript. All authors had full access to the data and accept final responsibility for the decision to submit for publication.

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Data sharing

De-identified individual clinical trial participant-level data will be made available for sharing in ethically approved individual patient data synthesis and meta-analyses on receipt of an appropriate application and subject to approval by the chief investigator (michael.browning@psych.ox.ac.uk).

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