NIHR | National Institute for Health and Care Research

Health Technology Assessment

Check for updates

Extended Research Article

Pramipexole in addition to mood stabilisers for treatment-resistant bipolar depression: the PAX-BD randomised double-blind placebo-controlled trial

Hamish McAllister-Williams,[1,2,3*] Nicola Goudie,[4] Lumbini Azim,[3] Victoria Bartle,[3] Michael Berger,[5] Chrissie Butcher,[4] Thomas Chadwick,[4] Emily Clare,[3] Paul Courtney,[3] Lyndsey Dixon,[3] Nichola Duffelen,[3] Tony Fouweather,[4] William Gann,[6] John Geddes,[7] Sumeet Gupta,[8] Beth Hall,[3] Timea Helter,[5] Paul Hindmarch,[3] Eva-Maria Holstein,[4] Ward Lawrence,[9] Phil Mawson,[4] Iain McKinnon,[3,4] Adam Milne,[4] Aisling Molloy,[3] Abigail Moore,[4] Richard Morriss,[10] Anisha Nakulan,[3] Judit Simon,[5,7] Daniel Smith,[11] Bryony Stokes-Crossley,[3] Paul Stokes,[12] Andrew Swain,[4] Zoë Walmsley,[4] Christopher Weetman,[4] Allan H Young[12] and Stuart Watson[1,2,3]

[1]Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK
[2]Northern Centre for Mood Disorders, Newcastle University, Newcastle upon Tyne, UK
[3]Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust, Newcastle upon Tyne, UK
[4]Population Health Sciences Institute, Newcastle University, Newcastle upon Tyne, UK
[5]Medical University of Vienna, Vienna, Austria
[6]Sheffield Health and Social Care NHS Foundation Trust, Sheffield, UK
[7]University of Oxford, Oxford, UK
[8]Tees, Esk and Wear Valleys NHS Foundation Trust, Darlington, UK
[9]Surrey and Borders Partnership NHS Trust, Leatherhead, UK
[10]University of Nottingham, Nottingham, UK
[11]Edinburgh University, Edinburgh, UK
[12]King's College London, London, UK

[*]Corresponding author hamish.mcallister-williams@newcastle.ac.uk

Published May 2025
DOI: 10.3310/HBFC1953

Scientific summary

Pramipexole in addition to mood stabilisers for treatment-resistant bipolar depression: the PAX-BD randomised double-blind placebo-controlled trial

Health Technology Assessment 2025; Vol. 29: No. 21
DOI: 10.3310/HBFC1953

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Patients with bipolar disorder are symptomatic around 50% of the time, the vast majority of which relates to depressive symptoms. Current National Institute for Health and Care Excellence (NICE) guidelines for the management of bipolar depression (BD) include just three medication options: lamotrigine, quetiapine and olanzapine (with or without fluoxetine). Quetiapine and olanzapine are often poorly tolerated due to weight gain and sedation. Lamotrigine has a relatively small effect size and requires slow dose titration. British Association for Psychopharmacology (BAP) guidelines include a fourth option: lurasidone. However, BD often does not respond to these options leading patients to suffer from 'treatment-resistant bipolar depression' (TRBD). Rates of TRBD are unknown, however, around 50% of patients remain depressed at 6 months, and 30% at a year, because of treatment non-response, intolerance or non-acceptance. In addition, around 70% of currently depressed bipolar disorder patients in the UK are on at least one antidepressant despite little evidence that they are effective.

Pramipexole is currently used to treat patients with Parkinson's disease and has been shown to improve depressive symptoms in these patients, with two small pilot randomised controlled trials in BD also being positive.

Objectives

Primary objective

To evaluate the clinical effectiveness of pramipexole versus placebo alongside standard mood-stabilising medication, over 12 weeks, in the management of TRBD.

Secondary objectives

- To examine the impact of pramipexole on mood and anxiety symptoms, psychosocial function (over 48 weeks), and pleasure (over 12 weeks).
- To examine the rate of known possible side effects of pramipexole (switching to mania and occurrence of impulse control disorders) as well as tolerability by reviewing rates of adverse events (AEs), serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs), and overall acceptability of pramipexole.
- To examine the impact of pramipexole on quality of life, well-being, health and social care and broader societal costs of participants randomised to either pramipexole or placebo, to assess cost-effectiveness.

Methods

Randomised, double-blind, placebo-controlled trial, conducted within secondary care settings in 21 NHS Trusts and Health Boards across England and Scotland.

The trial included two stages: pre-randomisation to adjust antipsychotics and commencing mood-stabilising medication (where required) and ensuring participant engagement with study procedures, prior to randomisation.

Eligibility criteria

Inclusion criteria: pre-randomisation stage

1. Under secondary care mental health services.
2. Decision made by the patient's clinical team that a change in medication is indicated.
3. Current diagnosis of bipolar disorder (type I or II).

4. Currently meeting criteria for a major depressive episode with a Quick Inventory of Depressive Symptoms, Self-Rated (QIDS-SR) score > 10.
5. Suffering from TRBD defined as the failure (non-response, intolerance and/or refused/clinically not indicated) of ≥ 2 NICE or BAP recommended mediations for BD (quetiapine, olanzapine, lamotrigine or lurasidone) in the current episode of depression.
6. Aged 18 or over.
7. Willing and able to provide written informed consent.
8. Able to follow the trial prescription instructions and manage 8 week supplies of trial medication.
9. If female and of child-bearing potential, must have a negative pregnancy test [urine beta-human chorionic gonadotropin (β-hCG)] and required to use a highly effective contraceptive method throughout the trial.

Exclusion criteria: pre-randomisation stage

1. Severe substance use disorder.
2. Current psychotic symptoms.
3. History of retinal disease.
4. Current symptoms or significant concerns around cardiovascular disease.
5. History of significant renal disease.
6. Any known sensitivity to trial drug including its excipients.
7. Current or planned pregnancy during the trial period, or breastfeeding.
8. Starting specific psychotherapy from 4 weeks before randomisation through to week 12 post randomisation.
9. Currently taking part in another clinical trial that would interfere with the outcomes of PAX-BD.
10. Confirmed diagnosis with potential confounding factors such as Parkinson's disease or restless leg syndrome.
11. Significant clinical concern regarding impulse control behaviours.

Inclusion criteria: randomisation stage

1. Been in pre-randomisation stage for a minimum of 23 calendar days.
2. Currently depressed (QIDS-SR > 10).
3. Minimum of two telephone/tele- or videoconference calls with a trial central research assistant (RA) team and two online weekly symptom ratings completed during the pre-randomisation stage.
4. On mood-stabilising medication (lithium, valproate, carbamazepine, lamotrigine).
5. Not on an antipsychotic. These criteria were amended during the trial to allow antipsychotics within specified dosing limits.
6. All regular psychotropic medication at a stable dose ≥ 4 weeks. Additionally, if taking lamotrigine, quetiapine, olanzapine or lurasidone, this must have been at the current dose or higher for ≥ 3 months.
7. If female and of child-bearing potential, a negative urine β-hCG test and using a highly effective contraceptive method.
8. Willing and able to confirm written informed consent at the point of randomisation.

Exclusion criteria: randomisation stage

As per pre-randomisation stage including.

1. Psychotic symptoms over the preceding 4 weeks.
2. Any deterioration in physical or mental health since pre-randomisation leading to a clinical concern to proceed.
3. Electroconvulsive therapy in the last 28 days.
4. Any concern regarding the patient's ability to remain engaged in the trial.

Intervention

Randomisation (1 : 1) to pramipexole or matched placebo was carried out using Sealed Envelope™, Sealed Envelope Ltd, UK (a central, secure, 24-hour web-based randomisation system with concealed allocation).

Trial medication taken orally once daily. Dose up-titrated 0.25 mg every 3 days to a maximum of 2.5 mg (salt weights) depending on acceptability and tolerability over 4 weeks. The achieved dose then fixed through to week 12 and subsequently flexibly adjusted based on response and tolerability for up to 48 weeks. Medication down-titrated 0.25 mg every 3 days at the end-of-trial involvement, unless participant switched to open-label pramipexole prescribed by their local clinical team, or they were known to have been taking placebo.

Outcome measures

Primary outcome measure

Quick Inventory of Depressive Symptoms, Self-Rated score at 12 weeks post randomisation.

Secondary outcome measures

- Weekly QIDS-SR and Generalised Anxiety Disorder-7 scores.
- Snaith–Hamilton Pleasure Scale at baseline and weeks 6 and 12.
- Work and Social Adjustment Scale at weeks 6, 12, 24, 36 and 48.
- Risk of mania (assessed weekly using the Altman Self-rating Scale of Mania), psychosis or impulse control disorders (using the Questionnaire for Impulsive–Compulsive Disorders in Parkinson's Disease – Rating Scale at baseline and weeks 6, 12 and 4 weekly thereafter).
- Gold-standard observer-rated scales (Montgomery–Åsberg Depression Rating Scale, Quick Inventory of Depressive Symptoms, Clinician-Rated and Young Mania Self-Rating Scale) at baseline and week 12 to facilitate comparison with other studies.
- Side effects and overall acceptability using the Treatment Satisfaction Questionnaire for Medication at weeks 6, 12 and then 4 weekly thereafter.
- Tolerability examined by reporting rates of AEs, SEAs and SUSARs.
- Adherence to medication examined using dose taken as reported during RA contacts.
- Quality of life, well-being, health and social care and broader societal costs of participants were examined (see health economic analysis below).

Sample size

A 30% dropout during pre-randomisation stage was predicted based on the BALANCE study (Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder), and post randomisation a 20% dropout by 12 weeks based on the CEQUEL study (Comparative economic evaluation of quetiapine plus lamotrigine combination vs quetiapine monotherapy (and folic acid vs placebo) in patients with bipolar depression). Power calculation based on a two-sample *t*-test at 12 weeks detecting a 3-point difference in QIDS-SR between drug and placebo (at $p < 0.05$) with a standard deviation (SD) of 7 (based CEQUEL study data). For 90% power, 232 (116 per arm) participants were required to complete the trial meaning a sample size of 290 at randomisation and an initial population of 414 recruited to the pre-randomisation stage.

Subsequently, a revised calculation was done based on recent data suggesting a more appropriate minimal clinical important difference of 4 QIDS-SR points, rather than 3, and early observations of dropout rates in both pre-randomisation and randomisation stages around 10%. This produced estimated required sample sizes of 126 participants to recruit, 112 to randomise and 100 to reach the 12-week primary outcome time point for 80% power.

Statistical methods

Primary outcome: QIDS-SR at week 12 used analysis of covariance (ANCOVA) to compare treatment arms covarying for baseline score. A two-sided significance level of $p < 0.05$ was used throughout. Unadjusted analysis, including the use of the *t*-test, or further related regression or ANCOVA methods were also undertaken. Secondary outcomes were analysed in a manner analogous to the primary outcome. As a result of the early closure of the trial and hence reduced sample size and not all participants followed up to 48 weeks, additional analysis was limited.

Health economic analysis

The incremental cost-effectiveness of pramipexole in comparison to placebo was assessed over 12 and 48 weeks from health and social care, and broader societal perspectives. The Health Economics Questionnaire (HEQ) captured health and social services utilisation and broader societal costs (in GBP, year 2020–1). The EuroQol-5 Dimensions, five-level version captured health-related quality of life (HRQoL) and was used to calculate quality-adjusted life-years gained as the primary outcome measure. The ICEpop CAPability measure for Adults and Oxford CAPabilities questionnaire-Mental Health (OxCAP-MH) capability well-being measures were used to calculate capability-weighted life-years gained as secondary outcome measures. Health economic data were collected at pre-randomisation, randomisation (baseline), and at weeks 12, 24, 36 and 48 for those who reached these time points. Any baseline imbalance between groups was adjusted statistically, data missingness was handled using multiple imputation, and uncertainty in the results estimated using bootstrapping and sensitivity analyses.

Qualitative study

Semistructured interviews with participants and healthcare professionals (HCPs) were conducted by central researchers via telephone to investigate barriers and facilitators to recruitment and retention of participants. Interviews were audio-recorded and outsourced to UK Transcription for transcribing. Fifteen HCPs and 11 randomised participants were interviewed. Interpretation of the transcripts was guided by an a priori framework of subthemes from a meta-analysis of studies in depression. Transcripts were independently coded by researchers using NVivo Release 1.6.1 (QSR International, Warrington, UK), reviewed by the wider qualitative team and modified on an ongoing basis. Subthemes were inductively revised, and emergent themes added per recurring discussions. Finally, 120 codes and 11 subthemes were attributed to 3 key themes: Barriers, Facilitators and Suggestions for Future Improvement.

Results

Fifty-one participants were recruited to pre-randomisation of whom 39 progressed to randomisation (dropout rate = 24%). Completion rates for self-rated online scales were around 80%. Thirty-six participants provided primary outcome data at 12 weeks and comprised the analysis population (drop-out rate = 7.7%), 16 in the pramipexole [2.18 mg/day (0.58) mean (SD)] and 20 in the placebo arms [2.25 mg/day (0.55)]. Despite the small sample size, the two arms were well matched on demographics, illness characteristics and current medication except that the pramipexole arm had a lower QIDS-SR baseline score at randomisation [pramipexole = 15.1 (5.2) vs. placebo = 17.3 (4.7): mean (SD)].

At 12 weeks, the reduction in QIDS-SR score from baseline was twice as high in the pramipexole arm compared with the placebo arm [4.4 (4.8) vs. 2.1 (5.1)]. However, ANCOVA adjusting for baseline differences in QIDS-SR was not significant [95% confidence interval (CI) −0.4 to 6.3; $p = 0.0865$]. Observation of the data suggested that the peak effect of the drug may have occurred beyond 12 weeks. ANCOVA demonstrated a significant advantage of 6.28 points lower for pramipexole at 36 weeks post randomisation. Similarly, while there was no significant difference in response (QIDS-SR reduction from baseline > 50%) and remission (QIDS-SR score ≤ 5) at 12 weeks, there was an advantage of pramipexole for response (46% vs. 6%; $p = 0.026$) and remission (31% vs. 0%; $p = 0.030$) rates at exit from the trial.

Secondary analysis indicated significant improvements in psychosocial function at 36 and 48 weeks. There were decreases in anxiety symptoms at 36 weeks ($p = 0.087$) and an increase in the ability to experience pleasure at 6 weeks ($p = 0.062$) for participants in the pramipexole arm was not significant.

Pramipexole was associated with a significant increase in manic/hypomanic symptoms at 12 weeks, but there was no significant increase in impulse control symptoms (though a higher proportion of participants in the pramipexole vs. placebo arm experienced at least one AE related to impulse control problems). There was one SAE in the pramipexole arm assessed as related to the study medication: mania that led to hospitalisation. Of 290 AEs occurring across both treatment arms, 265 (91%) required no action, 22 (8%) had treatment interrupted/dose reduced and 3 (1%) had Investigative Medicinal Product withdrawn. There were more mild and moderate AEs in the pramipexole arm, mostly of known psychiatric, nervous system and gastrointestinal side effects. Overall, tolerability and acceptability of study medication were similar between treatment arms.

Around half of the randomised participants were taking an antipsychotic. Comparing those who were and were not taking one in combination with pramipexole, it appears that the reduction in depressive symptoms was similar, but the severity of hypomanic symptoms may have been less.

Health economic analysis showed significant increase in HRQoL and capability well-being, and tendency towards reduced health and social care costs with high probability (70–90%) of cost-effectiveness for all health economic outcome measures over 48 weeks from the health and social care perspective. Sensitivity analyses confirmed the main findings.

Qualitative analysis identified barriers to recruitment and retention including the complexity of BD, difficulty accessing eligible participants, inadequate research prioritisation and the COVID-19 pandemic. Participants' concerns included receiving placebo, side effects of pramipexole, the burden of managing trial medication, using technology and/or engaging with safety monitoring for 48 weeks. Facilitators included positive relationships with care teams, central team support, responsive protocol amendments, and a strong desire for effective treatment. Lessons for future trials using semiremote methodology include using mass trial promotion strategies, reducing patient burden and fostering greater collaboration between trial staff and clinicians.

The trial was conducted during the COVID-19 pandemic and was terminated early due to funding reasons. Therefore, the sample size was much more limited, and the follow-up of some participants was shorter than planned.

Conclusions

No change in clinical practice can be recommended as there was not a significant difference between pramipexole and placebo on the primary efficacy outcome measure. This may have resulted from the early closure of the study and hence small sample size. Despite this, there were suggestions of positive effects of pramipexole on mood, psychosocial function and quality of life. However, use of the medication was complicated by the need for complex dose titration and high rates of hypomanic and impulse control symptoms, which would make implementation in routine practice challenging.

Further research is required to definitively address whether pramipexole is an effective safe and cost-effective treatment for TRBD. In addition, further studies should explore the impact of coadministration of an antipsychotic alongside pramipexole.

Trial registration

This trial is registered as ISRCTN72151939 and EudraCT 2018-2869-18.

Funding

This award was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme (NIHR award ref: 16/154/01) and is published in full in *Health Technology Assessment*; Vol. 29, No. 21. See the NIHR Funding and Awards website for further award information.

Health Technology Assessment

ISSN 2046-4924 (Online)

Impact factor: 3.5

A list of Journals Library editors can be found on the NIHR Journals Library website

Launched in 1997, *Health Technology Assessment* (HTA) has an impact factor of 3.5 and is ranked 30th (out of 174 titles) in the 'Health Care Sciences & Services' category of the Clarivate 2022 Journal Citation Reports (Science Edition). It is also indexed by MEDLINE, CINAHL (EBSCO Information Services, Ipswich, MA, USA), EMBASE (Elsevier, Amsterdam, the Netherlands), NCBI Bookshelf, DOAJ, Europe PMC, the Cochrane Library (John Wiley & Sons, Inc., Hoboken, NJ, USA), INAHTA, the British Nursing Index (ProQuest LLC, Ann Arbor, MI, USA), Ulrichsweb™ (ProQuest LLC, Ann Arbor, MI, USA) and the Science Citation Index Expanded™ (Clarivate™, Philadelphia, PA, USA).

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta.

Criteria for inclusion in the *Health Technology Assessment* journal
Manuscripts are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

Health Technology Assessment (HTA) research is undertaken where some evidence already exists to show that a technology can be effective and this needs to be compared to the current standard intervention to see which works best. Research can evaluate any intervention used in the treatment, prevention or diagnosis of disease, provided the study outcomes lead to findings that have the potential to be of direct benefit to NHS patients. Technologies in this context mean any method used to promote health; prevent and treat disease; and improve rehabilitation or long-term care. They are not confined to new drugs and include any intervention used in the treatment, prevention or diagnosis of disease.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

This article

The research reported in this issue of the journal was funded by the HTA programme as award number 16/154/01. The contractual start date was in April 2018. The draft manuscript began editorial review in June 2023 and was accepted for publication in August 2024. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' manuscript and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this article.

This article presents independent research funded by the National Institute for Health and Care Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, the HTA programme or the Department of Health and Social Care.

This article was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Newgen Digitalworks Pvt Ltd, Chennai, India (www.newgen.co).