A randomised, double-blind, placebo controlled trial of pramipexole in addition to mood stabilisers for patients with treatment resistant bipolar depression

The PAX-BD Study

Thank you very much for taking part in the PAX-BD Study. Without your help and valuable time, we would not have been able to undertake the study.

PAX-BD was carried out by a large team of people led by the Chief Investigator, Professor Hamish McAllister-Williams. The study was sponsored by Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust and funded by the National Institute for Health and Social Care Research Health Technology Assessment Programme (NIHR HTA).

Bipolar disorder is seen in about 2.5% of people worldwide. There are few treatment options for patients with bipolar disorder experiencing depressive symptoms, and their depression does not always improve with the treatments that we have.

Pramipexole is a drug that is already approved for use in the NHS for patients with Parkinson's disease or Restless Legs Syndrome. Some small research studies have shown that pramipexole improved symptoms of depression in patients with Parkinson's, and in patients with bipolar disorder when taken with mood stabilisers.

We wanted to see if pramipexole could be a good treatment option for patients with bipolar disorder and depressive symptoms, who have not benefited from current treatments.

The study took place in 21 NHS trusts across England and Scotland. Recruitment started at the end of 2019 and finished in Summer 2022. There was a pause to recruitment of around 6 months in 2020 due to the COVID-19 pandemic. The study ended earlier than planned due to the funder being concerned about slow recruitment rates.

PAX-BD included a Patient and Public Involvement group. This group included members of the public with experience of bipolar disorder/depression (either personally or through family members). The group met regularly throughout the study and helped the research significantly by reviewing study documentation to ensure it was clear and providing advice regarding any changes needed to how the study was carried out.

Who participated in the study?

The study included adults aged 18 years and over, diagnosed with bipolar depression, who had already tried at least two currently recommended treatments for their depression which had either not helped, the side effects were too bad, or the treatments were felt to not be appropriate by the patient or their doctor, for example because they had either not previously worked or there was a concern about possible side effects.

What treatments did the participants receive?

Participants were randomised (randomly placed in a group by a computer program) to either get pramipexole or a placebo ('dummy' drug).

What side effects did the participants have?

Overall people were able to manage many of the adverse effects, or side effects, from pramipexole and the number of adverse effects reported by participants was similar between people taking pramipexole and those taking the dummy drug. As expected, there were more moderate to severe adverse events reported by participants taking pramipexole related to psychiatric symptoms (such as confusion; dizziness; drowsiness; fatigue; hallucination; headache; impulse control problems such as increased gambling or using the internet) and gastrointestinal symptoms (such as abnormal appetite; nausea; vomiting; constipation; weight changes). These are already well known, common side effects of pramipexole.

Adverse effects related to hypomanic/manic symptoms were reported more often by participants taking pramipexole, usually early on in treatment. The study data suggests that these symptoms are less common the longer a participant takes pramipexole and may be less likely to occur if the person is taking an antipsychotic with pramipexole.

What happened during the study?

Participants took their study medication for a maximum of 52 weeks. During this time, they were asked to complete on-line questionnaires about their mood and behaviours. Participants also had regular telephone calls with a member of the study team (a research assistant) who gave them ongoing support during their time in the study.

Following a decision by the funders of PAX-BD to close the study early, not all participants were able to complete the full 52 weeks in the study. All participants did, however, receive a minimum of 12 weeks of medication and were followed up for as long as possible after this.

The decision to close early was related to recruitment rates and finance and not due to the safety of the study.

What were the results of the study?

Unfortunately, the study was closed early with fewer participants included than planned. We recruited 51 participants and only 39 of these were given either pramiprexole or the dummy drug. This means that getting answers from the results must be done with caution, and the study is unable to give definitive results.

The data collected during the study may give some support to the idea that pramipexole could be another possible treatment for treatment resistant bipolar depression. Positive effects were seen consistently in a number of areas, including improvements in mood, reductions in anxiety, and improvements in quality of life. The treatment was generally acceptable to participants with manageable side effects. However, as there is not enough data available from the study to provide a definite answer about the use of the medication, the findings of the PAX-BD study are not enough to recommend any changes to current clinical care of patients at this stage.

How has this study helped patients and researchers?

Pramipexole is a complex medication to use. This study has provided clinicians with some valuable information on how it can be used effectively whilst keeping patients safe and minimising side effects.

The study was run largely remotely as participants were able to complete study questionnaires online and follow up sessions with the research assistants were carried out by phone. PAX-BD therefore showed that it is possible to run a complex study largely remotely.

Details of any further research planned:

We hope to combine the data from the PAX-BD study with the two smaller, similar studies previously completed, to see if they also show that pramipexole is beneficial for bipolar depression.

Another study is being carried out in several NHS Trusts to see if pramipexole is helpful for non-bipolar depression (the PAX-D study). This will produce more information about how pramipexole can be used safely, which will be combined with the data from the PAX-BD

study to provide guidance for doctors considering using pramipexole for mood disorders in the future.

Ultimately, a further and larger study of pramipexole for people with bipolar depression which is proving difficult to treat with current treatments is needed before it could be recommended to be used regularly.

Where can I learn more about this study?

You can find out more information about the PAX-BD study by visiting the study website: https://paxbd.org