Which role for brexpiprazole, a new dopamine D2 partial agonist, in the treatment of schizophrenia?

Leslie Citrome

Correspondence to New York Medical College, Valhalla, New York, USA; citrome@cnsconsultant.com

ABSTRACT FROM: Correll CU, Skuban A, Ouyang J, *et al*. Efficacy and safety of brexpiprazole for the treatment of acute schizophrenia: a 6-Week Randomized, Double-Blind, Placebo-Controlled Trial. *Am J Psychiatry* 2015;172:870–80.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Despite the availability of different antipsychotics for the treatment of schizophrenia, in clinical practice it is somewhat of a struggle to identify an antipsychotic medication for individual patients that they are willing to adhere to. Brexpiprazole is a new molecular entity that is a dopamine receptor partial agonist that differs from aripiprazole in terms of greater potency at serotonin 5-HT_{1A} receptors and less intrinsic activity at dopamine D_2 receptors.[1] Brexpiprazole received approval in the USA for the treatment of schizophrenia in July 2015, based in part on two acute phase clinical trials,[2] of which one is the subject of this commentary.

METHODS OF THE STUDY

In this international, randomised, double-blind, placebo-controlled study, participants were inpatients 18–65 years old with an acute exacerbation of schizophrenia. A total of 949 participants were assessed for eligibility; 313 were screen failures, and 636 were randomised. Interventions were brexpiprazole at a dosage of 0.25, 2, or 4 mg or placebo, daily, for 6 weeks. In the groups receiving 2 or 4 mg of brexpiprazole, dosing began at 1 mg/day and was titrated to 2 mg on day 5 and 4 mg on day 8. The primary outcome measure was change from baseline to week 6 in Positive and Negative Syndrome Scale (PANSS) total score. Rate of response at week 6, as defined by change from baseline ≥30% in PANSS total score or Clinical Global Impressions Scale improvement score of 1 or 2, was also determined. Other efficacy and tolerability measures were collected.

WHAT THIS PAPER ADD

- At week 6, compared with placebo, brexpiprazole 2 mg/day and 4 mg/day produced statistically significantly greater reductions in PANSS total score, with effect sizes of 0.41 and 0.36, respectively.
- Responder rates were 47.8%, 46.1% and 30.3%, for brexpiprazole 2 mg/day, 4 mg/day, and placebo, respectively, resulting in number needed to treat (NNT) values versus placebo of 6 and 7 for brexpiprazole 2 mg/day and 4 mg/day, respectively.
- The most common treatment emergent adverse event for brexpiprazole was akathisia, with rates of 4.4%, 7.2%, and 2.2%, for brexpiprazole 2 mg/day, 4 mg/day, and placebo, respectively.

LIMITATIONS

- Overall, 410 patients (64%) completed the study; drop-out rates ranged from 32% of participants randomised to brexpiprazole 2 mg/day to 41% for participants randomised to placebo.
- No active comparator.
- Patients with comorbidities were excluded.

WHAT NEXT IN RESEARCH

As the authors have pointed out, 'longer-term studies that include a comparator, as well as patients with common comorbid conditions, will be needed to further evaluate the efficacy, safety, and effectiveness of brexpiprazole in the treatment of patients with schizophrenia commonly encountered in clinical care and in comparison with other first-line antipsychotics.'

DO THESE RESULTS CHANGE YOUR PRACTICES AND WHY?

Possibly, for some patients. This study needs to be taken in context with the second pivotal trial,[3] so that when data are pooled, more precise estimates of efficacy and tolerability are produced.[2] Of interest are the rates of akathisia, which are 5.5% for the pooled doses of brexpiprazole 1–4 mg/day versus 4.6% for placebo, yielding a number needed to harm (NNH) of 112, and consistent with what was observed on the Barnes Akathisia Rating Scale for both studies. This is different from the rates of akathisia observed with aripiprazole, which are 8% for aripiprazole versus 4% for placebo, yielding a NNH of 25.[4] Given the NNT for response for aripiprazole 10–30 mg/day versus placebo is 8, and that for brexpiprazole 2–4 mg/day is 7, for the person with schizophrenia being treated with aripiprazole but experiencing akathisia, brexpiprazole is a potential alternative. However, aripiprazole is available in a variety of different formulations, including as a long-acting injection, limiting brexpiprazole at this time to persons who prefer an oral formulation.

Competing interests In the past 36 months LC has engaged in collaborative research with, or received consulting or speaking fees, from: Acadia, Alexza, Alkermes, Allergan, AstraZeneca, Avanir, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Forum, Genentech, Janssen, Jazz, Lundbeck, Merck, Medivation, Mylan, Neurocrine, Novartis, Noven, Otsuka, Pfizer, Reckitt Benckiser, Reviva, Shire, Sunovion, Takeda, Teva, Valeant, Vanda.

Provenance and peer review Commissioned; internally peer reviewed.

doi:10.1136/eb-2015-102143

Received 1 December 2015; Accepted 15 March 2016

REFERENCES

1. **Citrome L**, Stensbøl TB, Maeda K**.** The preclinical profile of brexpiprazole: what is its clinical relevance for the treatment of psychiatric disorders? *Expert Rev Neurother* 2015;**15**:1219–29.
2. **Citrome L.** Brexpiprazole for schizophrenia and as adjunct for major depressive disorder: a systematic review of the efficacy and safety profile for this newly approved antipsychotic—what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? *Int J Clin Pract* 2015;**69**:978–97.
3. **Kane JM**, Skuban A, Ouyang J, *et al*. A multicenter, randomized, double-blind, controlled phase 3 trial of fixed-dose brexpiprazole for the treatment of adults with acute schizophrenia. *Schizophr Res* 2015;**164**:127–35.
4. **Citrome L.** The ABC's of dopamine receptor partial agonists—aripiprazole, brexpiprazole and cariprazine: the 15-min challenge to sort these agents out. *Int J Clin Pract.* 2015;**69**:1211–20.