schizophrenia. This insufficient evidence calls for further RCTs to establish whether, and to what extent, SGAs have favorable neurocognitive effects over placebo in schizophrenia.

ACKNOWLEDGMENTS

Dr Takeuchi is supported through the Canadian Institutes of Health Research Fellowship program. This funding source had no role in study design, interpretation of findings, or in manuscript preparation or submission for publication.

AUTHOR DISCLOSURE INFORMATION

Dr Takeuchi has received fellowship grants from the Centre for Addiction and Mental Health Foundation and manuscript fees from Sumitomo Dainippon Pharma. Ms Thiyanavadivel and Dr Fervaha have no competing interests to disclose. Dr Remington has received research support from Novartis and consultant fees from Synchroneuron.

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OPEN

Efficacy of Brexpiprazole as Adjunctive Treatment in Major Depressive Disorder With Irritability

Post Hoc Analysis of 2 Pivotal Clinical Studies

To the Editors:

Irritability in patients with major depressive disorder (MDD) has been associated with greater overall severity, previous suicide attempts, and suicidal ideations.[1] Irritability in MDD is also associated with longer duration of episodes, a more chronic course of illness, impaired functioning, and less favorable outcomes.[2–4] Irritability is a symptom often addressed with the use of an antipsychotic as adjunctive therapy to antidepressant treatment (ADT).[5] The adverse effects profile of atypical antipsychotics, however, may limit their use in clinical practice.[6] Aripiprazole is associated with activating adverse effects, including akathisia and anxiety,[7] whereas quetiapine is associated with sedation.[8] Brexpiprazole is a serotonin-dopamine activity modulator that is a partial agonist at 5-HT_{1A} and dopamine D_2 receptors, and an antagonist at 5-HT_{2A} and noradrenaline alpha$_{1B/2C}$ receptors, all at similar potencies.[9] Brexpiprazole was approved in 2015 in the United States for the treatment of schizophrenia and for use as an adjunctive therapy to antidepressants for the treatment of MDD. Here we assess the efficacy of adjunctive brexpiprazole in patients with MDD and irritability, comparing brexpiprazole to placebo as adjunctive therapy to ADT in patients with and without self-rated irritability, using pooled data from the 2 similarly designed randomized, double-blind, placebo-controlled, pivotal phase 3 studies.[10,11] Briefly, each study included a screening phase, an 8-week single-blind prospective phase, and a 6-week double-blind randomized treatment phase. Patients aged 18 to 65 years diagnosed according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* with a single or recurrent nonpsychotic episode of MDD of 8 weeks or more duration were recruited. Patients

had to have inadequate response, defined as less than 50% reduction in Massachusetts General Hospital Antidepressant Treatment Response Questionnaire score to an adequate treatment course of 1 to 3 ADTs administered for 6 weeks or more. Eligible patients also had Hamilton Depression Rating Scale ($HAM\text{-}D_{17}$)[12] total scores 18 or higher at screening and at start of the prospective treatment phase. Patients were randomized to treatment if they had an inadequate response throughout the prospective treatment phase defined as a $HAM\text{-}D_{17}$ score 14 or higher, less than 50% reduction from start of prospective phase in $HAM\text{-}D_{17}$, as well as less than 50% reduction in Montgomery-Åsberg Depression Rating Scale (MADRS)[13] total score between start of prospective phase and each visit, and a Clinical Global Impression–Improvement (CGI-I) score 3 or higher at each visit. Based on their self-assessment of irritability during the preceding week on Inventory of Depressive Symptomatology–Self-Report (IDS-SR) item 6 at randomization, patients were categorized as "with irritability" (IDS item 6 score ≥ 1) or "without irritability" (IDS item 6 score = 0) with IDS-SR scores being defined as follows[14]: 0, does not feel irritable; 1, feels irritable less than half the time; 2, feels irritable more than half the time; and 3, feels extremely irritable virtually all of the time. High level of irritability was defined as IDS-SR item 6 scores of 2 or higher. Patients were randomized to 2 mg brexpiprazole + ADT or placebo + ADT (1:1 ratio) or 1 mg brexpiprazole + ADT, 3 mg brexpiprazole + ADT, or placebo + ADT (1:1:1 ratio) in the 2 studies, respectively. The primary efficacy end point was change in MADRS total score from baseline, and efficacy analyses with pooled placebo groups in patients with and without irritability were conducted with a mixed model for repeated measures methodology as previously reported.[10,11] Of the 987 patients who were randomized and fulfilled inadequate response criteria throughout the prospective ADT treatment phase, 811 (82.2%) reported irritability at baseline. At baseline, patients with and without irritability showed similar characteristics (mean age, 44.7 vs 47 years; 70% vs 61% female; mean number of lifetime depressive episodes, 3.6 vs 3.6), although patients with irritability appeared more severely ill than patients without irritability as reflected by higher baseline MADRS total scores (Fig 1). In patients with irritability, all doses of adjunctive brexpiprazole showed greater improvement than adjunctive placebo in MADRS total scores at week 6: least squares (LS) mean differences (95% confidence interval) versus adjunctive placebo were −2.18 (−3.58 to −0.78), $P = 0.0023$ for the 1 mg brexpiprazole, −2.09 (−3.62 to −0.56), $P = 0.0074$ for the 2 mg brexpiprazole, and −2.55 (−3.97 to −1.14), $P = 0.004$ for the 3 mg brexpiprazole groups (Fig. 1A). In patients without irritability, adjunctive brexpiprazole 2 mg/d showed greater improvement than adjunctive placebo in MADRS total score with LS mean differences versus placebo of −3.04 (−6.07 to −0.01), $P = 0.0496$, and numerical improvements of −1.55 (−4.65 to 1.55), $P = 0.32$ for 1 mg brexpiprazole, and −2.60 (−5.63 to 0.42), $P = 0.09$ for 3 mg brexpiprazole (Fig. 1B). Brexpiprazole 3 mg/d demonstrated efficacy on MADRS total score also in patients with higher levels of irritability (IDR-SR item 6 score ≥ 2; n = 63; LS mean difference vs placebo −3.18 [−5.46 to −0.90], $P = 0.0064$), whereas the lower doses did not (1 mg: n = 69, −1.71 [−3.97 to 0.54], $P = 0.14$; 2 mg: n = 69, −1.75 [−3.99 to 0.49], $P = 0.12$). The most common (incidence ≥5%) treatment-emergent adverse events in patients with irritability receiving brexpiprazole were akathisia (7.8%), weight increase (7.2%), and headache (7.0%). There were dose-dependent increases in the incidence of akathisia in patients with irritability, with no apparent difference in the overall incidence of akathisia between patients with and without irritability (7.8% vs 9.9%). Similarly, there were no clinically relevant differences in the incidence of other activating treatment-emergent adverse events (ie, agitation [0.8% vs 0%], anxiety [2.6% vs 2.0%], and insomnia [2.2% vs 1.0%]) between patients with and without irritability.

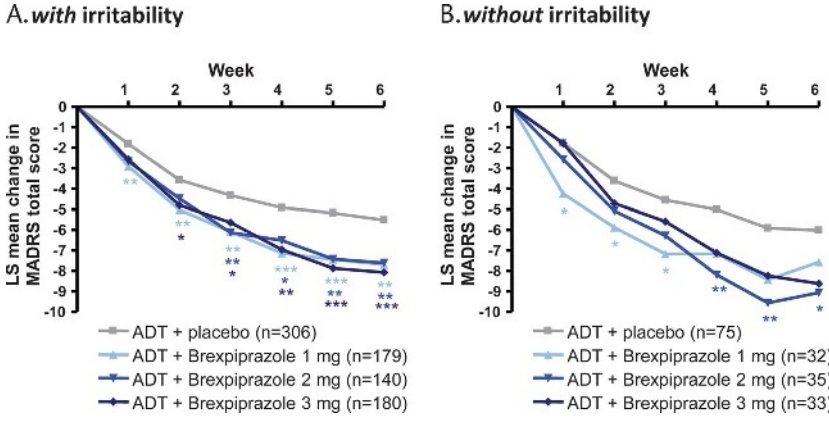

FIGURE 1. Least squares mean change from baseline in MADRS score in patients with (A) and without (B) irritability. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ versus placebo in mixed model repeated measures analyses in the efficacy sample with patients fulfilling inadequate response criteria and pooled placebo. MADRS baseline: ADT + placebo, 27.5; ADT + brexpiprazole 1 mg, 27.4; ADT + brexpiprazole 2 mg, 26.9; ADT + brexpiprazole 3 mg, 26.7 (in patients with irritability); ADT + placebo, 24.4; ADT + brexpiprazole 1 mg, 23.8; ADT + brexpiprazole 2 mg, 26.9; ADT + brexpiprazole 3 mg, 25.6 (in patients without irritability).

DISCUSSION

The efficacy of brexpiprazole at all tested doses was retained in depressive patients with irritability, demonstrating consistent improvements versus placebo on symptoms of depression; the highest dose of brexpiprazole demonstrated efficacy on MADRS total score also in patients with higher levels of irritability. The 2 mg dose of brexpiprazole demonstrated efficacy on MADRS total score in patients without irritability, reaching significance despite modest sample sizes in this subpopulation. These results did not seem to stem from a difference in tolerability profile of brexpiprazole in patients with and without irritability. The pharmacological profile of brexpiprazole, with partial agonism and lower intrinsic activity at the D_2 receptor in combination with antagonism at the $5\text{-}HT_{2A}$ receptor, suggests lower potential to induce D_2 receptor-mediated adverse effects, such as akathisia, as compared with other antipsychotics commonly used as adjunctive treatment in MDD.[15,16] The present results suggest that the efficacy of brexpiprazole in patients with MDD and irritability are achieved independently of activating or sedating adverse effects. Limitations of this analysis include that irritability was relying on a single item from a self-rated measurement and defined post hoc, and that the studies did not obtain clinician-rated or objective measures of irritability. Further, the post hoc definition of irritability (IDS item 6 score ≥ 1) resulted in an unbalanced number of patients with and without irritability. Consequently, the analyses in patients without irritability (and also in patients with higher levels of irritability) have a limited statistical power to detect

significant differences and the results here should be interpreted cautiously due to the small sample size. In conclusion, these post hoc analyses suggest that adjunctive brexpiprazole has comparable efficacy in reducing depressive symptoms in patients with MDD with irritability compared with the patients with MDD without irritability.

AUTHOR DISCLOSURE INFORMATION

This research and presentations was funded by H. Lundbeck A/S and Otsuka Pharmaceutical Development & Commercialization, Inc. The authors thank Anders Ettrup, PhD, and Johan Hellsten, PhD (employees of H. Lundbeck A/S), for the medical writing assistance with the manuscript.M.F. has received research support from AstraZeneca, Avanir Pharmaceuticals, Cerecor, Eli Lilly and Company, EnVivo Pharmaceuticals, Euthymics Bioscience, Forest Pharmaceuticals, FORUM Pharmaceuticals, Janssen R&D, Johnson & Johnson Pharmaceutical Research & Development, Lundbeck, Methylation Sciences, National Center for Complementary and Alternative Medicine, National Coordinating Center for Integrative Medicine, National Institute of Drug Abuse, National Institute of Mental Health, Neuralstem, Novartis AG, PamLab, Pfizer, PharmoRx Therapeutics, Photothera, Reckitt Benckiser, Roche Pharmaceuticals, RCT Logic (formerly Clinical Trials Solutions), Stanley Medical Research Institute, Takeda, Tal Medical; consults on behalf of his institution for Acadia, Alkermes, AstraZeneca, Auspex, Avanir Pharmaceuticals, AXSOME Therapeutics, Biogen, Bristol-Myers Squibb, Cerecor, Dainippon Sumitomo Pharma Co, Eli Lilly and Company, Euthymics Bioscience, Forest Pharmaceuticals, FORUM Pharmaceuticals, GenOmind, GlaxoSmithKline, Intracellular, Janssen Pharmaceutica, Johnson & Johnson Pharmaceutical Research & Development, Lundbeck, Merck & Co, MSI Methylation Sciences, Naurex, Nestle Health Sciences, Neuralstem, Novartis AG, Nutrition 21, Osmotica, Otsuka Pharmaceuticals, Pamlab, Pfizer, PharmoRx Therapeutics, Puretech Ventures, PsychoGenics, RCT Logic (formerly Clinical Trials Solutions, LLC), Ridge Diagnostics, Roche, Sanofi-Aventis US, Servier Laboratories, Sunovion Pharmaceuticals, Taisho Pharmaceutical, Takeda Pharmaceutical Company Limited, Tal Medical, VistaGen; has received speaking honoraria from American Society of Clinical Psychopharmacology, Belvoir Media Group, CME Institute/Physicians Postgraduate Press, MGH Psychiatry Academy; and holds equity in Compellis and PsyBrain. E.W. is a full-time employee of H. Lundbeck A/S. P.Z. and C.W. are full-time employees of Otsuka Pharmaceutical Development & Commercialization, Inc.

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Affective Recurrences in Bipolar Disorder After Switching From Lithium to Valproate or Vice Versa
A Series of 57 Cases

To the Editors:

For many years lithium was the only mood stabilizer (MS) in common use, and it is still the first choice in the preventive treatment for bipolar disorder (BD).[1] However, there are many safety and tolerability concerns such as cognitive impairment, weight gain, dermatological reactions, and renal or thyroid dysfunction that can lead to the use of lithium being stopped.[2] A higher risk of recurrences even after many years of clinical stability is associated with the discontinuation of