# Adjunctive Brexpiprazole in Patients With Major Depressive Disorder and Irritability: An Exploratory Study

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## ABSTRACT

***Objective:*** To evaluate the effects of adjunctive brexpiprazole on symptoms of irritability in patients with major depressive disorder (MDD).

***Methods:*** Patients diagnosed with MDD according to *DSM-IV-TR* criteria who had inadequate response to antidepressant treatment continued treatment with their current antidepressant for 2 weeks. Patients still having inadequate response, and with irritability, received 6 weeks of open-label treatment with their current antidepressant at the same dose and adjunctive brexpiprazole (target dose: 3 mg/d). Brexpiprazole was discontinued at week 6, and the patients continued with their antidepressant until week 10. Changes from baseline to week 6 and week 6 to week 10 were analyzed.

***Results:*** This study was conducted between October 7, 2013, and July 30, 2014. Fifty-four patients were treated with adjunctive brexpiprazole. At week 6, clinically relevant improvements were observed in Sheehan Irritability Scale total (−21.1) and item 1 (irritable mood) (−3.5) scores, Kellner Symptom Questionnaire total (−24.4) and anger-hostility subscale (−7.7) scores, and 30-item Inventory of Depressive Symptomatology, clinician version (IDS-$C_{30}$), item 6 (irritable mood) score (−1.2). More (15 patients) stopped than developed (5 patients) anger attacks during treatment, as measured by the Anger Attacks Questionnaire. The Clinical Global Impressions-Severity of Illness score improved (−1.4), as did the depressive symptoms (IDS-$C_{30}$ total score, −17.8; Kellner Symptom Questionnaire depression subscale score, −7.7; and Montgomery-Asberg Depression Rating Scale total score, −14.2). Irritability symptoms worsened after brexpiprazole discontinuation, assessed at week 10. Adjunctive brexpiprazole was well tolerated.

***Conclusions:*** Adjunctive treatment with brexpiprazole may represent a strategy for patients with MDD and inadequate response to antidepressant treatment who have symptoms of irritability.

***Trials Registration:*** ClinicalTrials.gov identifier: NCT01942785


*J Clin Psychiatry 2016;77(12):1695–1701*
*dx.doi.org/10.4088/JCP.15m10470*



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Irritability and anger attacks are common in major depressive disorder (MDD), affecting about one-third to half of the patients.[1,2] Irritability in MDD is associated with greater severity, earlier age at onset, higher rates of comorbid anxiety and impulse-control disorders, increased incidence of suicidality, greater chronicity, fatigue and self-blame during episodes, and general disability.[1–3] Although acknowledged in children and adolescents, irritability during major depressive episodes (MDEs) is not considered standard diagnostic criteria for MDD in adults. Nevertheless, in the Sequenced Treatment Alternatives to Relieve Depression observational study in adults, 46% of the 2,307 study participants reported irritability at least half of the time during the preceding week.[2] In addition, results from a US National Comorbidity Survey Replication showed that approximately 50% of the respondents with lifetime MDD reported irritability during MDEs.[1]

MDD patients with irritable mood may or may not experience anger, which encompasses irritability. Anger attacks are common in these patients, affecting approximately one-third,[4,5] and are associated with a higher incidence of anxiety and somatic symptoms, higher rates of comorbid personality traits, greater levels of perceived stress, greater disease severity, greater likelihood of suicidality, and poorer quality of life.[4–8] Symptoms of irritability, hostility, and anger are considered to be related more to the depressive state of the patients, whereas impulsivity is considered to be more of a trait-like characteristic that is consistent and stable over time. Unfortunately, current symptomatic treatment of patients experiencing irritability in a current MDE is associated with limited success rates.[2]

Brexpiprazole (OPC-34712) is a partial agonist at serotonin 5-$HT_{1A}$ and dopamine $D_2$ receptors and an antagonist at serotonin 5-$HT_{2A}$ and norepinephrine $\alpha_{1B/2C}$ receptors, all with similar subnanomolar binding affinity.[9] Clinical studies[10,11] demonstrated that brexpiprazole was efficacious as adjunctive treatment in adult patients with MDD who had an inadequate response to antidepressant treatment. In addition, brexpiprazole was safe and well-tolerated, with low rates of sedating (eg, somnolence, sedation) and activating (eg, akathisia, restlessness, anxiety, insomnia) side effects.[10,11]

The aim of this interventional, open-label, flexible-dose, exploratory study was to evaluate changes in irritability, anger, and other impulsivity-related behaviors, as well as depressive symptoms, in patients with MDD who were treated with adjunctive brexpiprazole. In addition, the safety and tolerability of brexpiprazole were assessed.

## METHODS

### Patients

This interventional, open-label, flexible dose, exploratory study was conducted at 15 sites in the United States between October

7, 2013, and July 30, 2014 (ClinicalTrials.gov identifier: NCT01942785). The study was conducted in compliance with the Declaration of Helsinki and the principles of Good Clinical Practice and was approved by the appropriate institutional review boards. All patients provided written informed consent before enrollment. At screening, eligible patients were men and women aged between 18 and 65 years. The patients were required to have been diagnosed with MDD according to *DSM-IV-TR* criteria. The current MDE had to be confirmed using the Mini International Neuropsychiatric Interview.[12] Further, the patients should have displayed an inadequate response to at least 1 antidepressant treatment (including the treatment the patient was taking at screening) in the current MDE, as documented by self-report of a less than 50% response on the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire.[13] Included patients presented a Montgomery-Asberg Depression Rating Scale (MADRS)[14] total score >18, a Clinical Global Impressions-Severity of Illness (CGI-S)[15] score ≥3, and a 30-item Inventory of Depressive Symptomatology, clinician version (IDS-$C_{30}$), item 6 (irritable mood)[16] score ≥2. The duration of the current MDE should have been more than 10 weeks. Patients were currently treated for the existing MDE with a selective serotonin reuptake inhibitor (SSRI) or a serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressant as monotherapy at the same dosage for at least 2 weeks, and for a total period of at least 6 weeks.

Between the screening and the baseline visit, eligible patients' diagnosis of MDE was confirmed and deemed "valid" using the **S**tate versus trait, **A**ssessability, **F**ace validity, **E**cological validity, and **R**ule of 3 Ps (pervasive, persistent, and pathological)—SAFER—criteria interview,[17] administered by remote, independent raters (highly trained and experienced psychiatrists or psychologists from the Massachusetts General Hospital, Boston). In addition, an *inadequate response*, defined as a <50% reduction in depressive symptom severity both currently and at any point during the current episode, as assessed by the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire,[13] as well as the presence of irritability (displayed as an IDS-$C_{30}$ item 6 [irritable mood] score>2), was confirmed at the SAFER interview. At the baseline visit, patients must have still fulfilled the *DSM-IV-TR* criteria for MDE and have received the same antidepressant treatment at an adequate dose for the entire period since screening. Any improvement in the MADRS total score at baseline had to be <25% compared to screening. Included individuals had a Clinical Global Impressions-Global Improvement (CGI-I)[15] score ≥3 relative to the screening visit and still displayed an IDS-$C_{30}$ item 6 (irritable mood) score more than 2, inclusive.

Excluded patients were those who had any current psychiatric disorder other than MDD, a current MDE with psychotic features, or a current Axis II diagnosis of antisocial, borderline, paranoid, schizoid, schizotypal, or histrionic personality disorder. Patients were excluded if they, in the opinion of the investigator, were at significant risk of suicide or if answering yes on the Columbia-Suicide Severity Rating Scale suicidal ideation items 4 or 5 or on any of the 5 suicidal behavior items.[24] Per protocol, anxiety disorders, impulse-control disorders, and nonsuicidal self-injury were considered allowed comorbidities.

**Clinical Points**

- While literature on the clinical impact of irritability grows, data on the treatment of irritability associated with major depressive disorder (MDD) are sparse. Treatment options are limited by the fact that commonly used scales in registrational studies for MDD (eg, Montgomery-Asberg Depression Rating Scale and Hamilton Depression Rating Scale) do not measure irritability or anger.
- Our study suggests that symptoms of irritability may improve in patients with MDD and inadequate response to antidepressants when treated with adjunctive brexpiprazole.

### Procedures

The study consisted of a 2-week period of open-label treatment with the current antidepressant, which remained the same in dosing for the duration of the study. Eligible patients then entered a 6-week open-label treatment period with brexpiprazole adjunctive to their antidepressant treatment followed by a 4-week follow-up period after discontinuation of brexpiprazole treatment in which patients continued taking their antidepressant. During the 6-week adjunctive brexpiprazole treatment period, the antidepressant dose remained the same, while brexpiprazole was titrated up from 1 mg once daily for 1 week, followed by 2 mg once daily for 1 week, and then increased to the target dose of 3 mg once daily for 4 weeks. If tolerability issues arose, the dose could be reduced to 2 mg once daily at any point after week 2 until visit 5 in week 4. The 2-mg once-daily dose was then kept stable.

Assessment used to measure changes in levels of irritability, impulsivity, anger, and hostility included the Sheehan Irritability Scale,[18] Sheehan Irritability Scale item 1 (irritable mood), and IDS-$C_{30}$ item 6 (irritable mood) to measure irritability; Monetary Choice Questionnaire[19] and Barratt Impulsiveness Scale, version 11,[20] to measure impulsivity; and patient-rated Kellner Symptom Questionnaire[21] anger-hostility subscale score and Anger Attacks Questionnaire[4] to measure anger and hostility. The Anger Attacks Questionnaire is a patient-rated scale developed to assess the presence of distinct forms of anger attacks over a period of time. Depressive symptoms were measured using the clinician-rated MADRS and IDS-$C_{30}$ as well as the patient-rated Kellner Symptom Questionnaire depression subscale. Patients' perception of their cognitive performance was assessed using the self-rated Cognitive and Physical Functioning Questionnaire.[22,23] Overall disease severity/distress was assessed using Kellner Symptom Questionnaire, CGI-I, and CGI-S.

The safety assessments included adverse events (AEs), clinical safety laboratory tests, vital signs, and electrocardiogram parameters. Risk of suicide was assessed using the Columbia-Suicide Severity Rating Scale.[24]

### Statistical Analyses

All statistics were descriptive in nature. Safety analyses were conducted on the *all patients treated set*, comprising all patients who took at least 1 dose of brexpiprazole. Efficacy analyses were conducted on the *full analysis set* comprising all patients in the *all patients treated set* with a baseline assessment and at least 1 postbaseline efficacy assessment or on the *completer analysis set* comprising all patients in the *full analysis set* with at least 1 efficacy assessment in the follow-up period after discontinuation of brexpiprazole treatment. Changes from baseline to week 6 were analyzed using a restricted maximum likelihood–based mixed-model repeated-measures (MMRM) approach, using observed cases with the site and visit as fixed effects and baseline score–by-visit interaction, on the *full analysis set*, except for CGI-S for which an analysis of covariance (ANCOVA) was used, with site as fixed factor and the baseline value as a covariate. Changes from end of treatment (week 6) to completion (week 10) were analyzed using an ANCOVA with site as fixed factor and the week 6 value as a covariate, on the *completer analysis set*. Nominal *P* values were calculated post hoc to indicate statistically significant differences (< .05) when testing the null hypothesis of no change from baseline or week 6. Number and percentage of patients were tabulated for the MADRS response and remission rates as well as the presence or absence of anger attacks.

The statistical software used was SAS, version 9.4 (SAS Institute Inc, Cary, North Carolina).

## RESULTS

### Patients

Of 117 screened patients, 55 were eligible for inclusion in the study by passing the SAFER interview, and 54 patients were treated. Of these, 4 patients were withdrawn (2 withdrew as a result of AEs, 1 patient withdrew consent, and 1 patient was considered a protocol violator), leaving 50 patients who completed 6-week brexpiprazole treatment. The full analysis set and completer analysis set comprised 54 and 48 patients, respectively. The ratio of men to women was approximately 1 to 2. The mean age was 42 years, with majority of the patients being white (61.1%).

Patients had a mean of 8 previous MDEs, with the mean duration of the current episode being 14 months. The marked difference observed between the mean values and the medians was caused by a few patients with large values affecting the mean values but not the medians (Table 1). The mean duration of the patients' last period of wellness was 12 months. A total of 14 patients suffered from comorbid psychiatric disorders, including alcohol abuse, anxiety disorders, and insomnia-related symptoms. The mean baseline patient demographics, depression history, and concurrent psychiatric disorders are summarized in Table 1, and baseline scores on all efficacy measures are summarized in Table 2. Baseline depression and irritability scale scores confirmed that the patient population had moderate-to-severe depression with symptoms of irritability. Forty-three of 54 patients (80%) were up-titrated to and stayed at 3 mg/d of brexpiprazole until the end of treatment/withdrawal visit; the mean (standard deviation) daily dose of study medication was 2.4 (0.3) mg.

**Table 1. Demographic and Baseline Clinical Characteristics in 54 Patients Treated With an Antidepressant and Adjunctive Brexpiprazole (APTS)**

| Characteristic | Value |
|---|---|
| Demographic | |
| Age, mean (SD), y | 42.4 (10.3) |
| Male, n (%) | 20 (37.0) |
| Race, n (%) | |
| White | 33 (61.1) |
| Black or African American | 17 (31.5) |
| Native Hawaiian or other Pacific Islander | 2 (3.7) |
| Other | 2 (3.7) |
| Clinical | |
| Duration of last period of wellness, mo | |
| Mean (SD)[a] | 11.9 (18.5) |
| Median (range) | 6 (0–99) |
| No. of depressive episodes | |
| Mean (SD)[a] | 8.2 (8.7) |
| Median (range) | 5 (1–40) |
| Months since onset of current episode | |
| Mean (SD) | 14.1 (24.0) |
| Median (range) | 7 (3–130) |

[a]52 patients (2 missing values).
Abbreviations: ADT = antidepressant treatment, APTS = all-patients–treated set, SD = standard deviation.

### Exploratory Efficacy Assessments

The mean changes in the exploratory end points from baseline to week 6, together with changes from week 6 to week 10, are summarized in Table 2.

At week 6, irritability symptoms had improved, as seen in the decrease from baseline in mean Sheehan Irritability Scale total score (mean change from baseline −21.1 [95% CI, −26.3 to −16.0]), mean Sheehan Irritability Scale item 1 score (−3.5 [95% CI, −4.2 to −2.7]), and mean IDS-$C_{30}$ item 6 score (−1.2 [95% CI, −1.5 to −1.0]). No further improvement in irritability symptoms was seen from week 6 to week 10 after discontinuation of adjunctive brexpiprazole as reflected in the Sheehan Irritability Scale total score (4.4 [95% CI, −0.5 to 9.4]; Figure 1) and in the mean Sheehan Irritability Scale item 1 score (0.5 [95% CI, −0.3 to 1.4]).

Analysis of the mean natural log-transformed Monetary Choice Questionnaire revealed no real change over the first 6 weeks of treatment with adjunctive brexpiprazole, while the symptoms worsened after brexpiprazole discontinuation (Table 2). Analysis of the mean change from baseline in Barratt Impulsiveness Scale total score revealed an improvement of 4.9 points (95% CI, −6.6 to −3.1) at week 6, with no further improvement when assessed at week 10 (1.2-point improvement [95% CI, −3.0 to 0.6]).

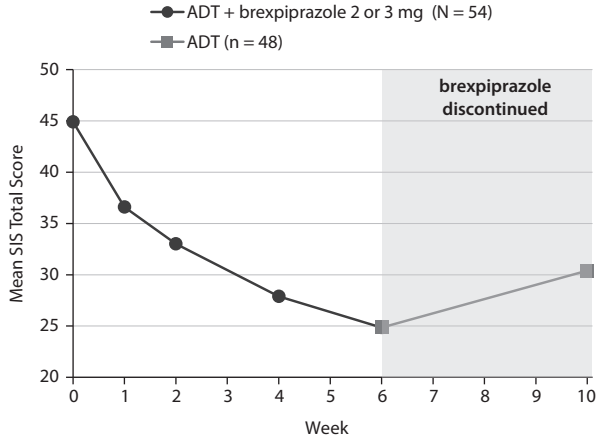
The mean Kellner Symptom Questionnaire anger-hostility subscale scores improved by 7.7 points (95% CI, −9.6 to −5.9) at week 6, with no further improvement following discontinuation of brexpiprazole, as evidenced by a mean score change of 1.2 points (95% CI, −0.8 to 3.2) when assessed at week 10. In addition, analysis of the Anger Attacks

**Table 2. Baseline Measures and Mean Change From Baseline to Week 6 and From Week 6 to Week 10**

| | ADT + Brexpiprazole (FAS[a]) | | | | ADT (CAS[a]) | |
|---|---|---|---|---|---|---|
| | Baseline | | Change From Baseline to Week 6 | | Change From Week 6 to Week 10 | |
| Measure | N | Mean (SD) | n | Mean (CI) | n | Mean (CI) |
| Irritability | | | | | | |
| SIS total score (patient-rated) | 54 | 44.9 (9.8) | 50 | −21.1 (−26.3 to −16.0)** | 48 | 4.4 (−0.5 to 9.4) |
| SIS item 1 score (patient-rated) | 54 | 7.1 (1.5) | 50 | −3.5 (−4.2 to −2.7)** | 47 | 0.5 (−0.3 to 1.4) |
| IDS-$C_{30}$ item 6 (clinician-rated) | 54 | 2.2 (0.4) | 50 | −1.2 (−1.5 to −1.0)** | … | … |
| Impulsivity-related behavior | | | | | | |
| MCQ total score[b] (patient-rated) | 54 | −3.5 (1.5) | 50 | 0.0 (−0.5 to 0.5) | 47 | 0.4 (0.0 to 0.7)* |
| BIS-11 total score (patient-rated) | 54 | 73.2 (12.8) | 50 | −4.9 (−6.6 to −3.1)** | 47 | −1.2 (−3.0 to 0.6) |
| Anger-hostility | | | | | | |
| KSQ anger-hostility subscale score (patient-rated) | 54 | 14.8 (4.8) | 50 | −7.7 (−9.6 to −5.9)** | 48 | 1.2 (−0.8 to 3.2) |
| Depression | | | | | | |
| IDS-$C_{30}$ total score (clinician-rated) | 54 | 37.4 (7.5) | 50 | −17.8 (−21.0 to −14.6)** | … | … |
| KSQ depression subscale score (patient-rated) | 54 | 15.0 (4.5) | 50 | −7.7 (−9.6 to −5.8)** | 48 | 2.1 (0.1 to 4.2)* |
| MADRS total score (clinician-rated) | 54 | 28.5 (4.5) | 50 | −14.2 (−16.7 to −11.6)** | … | … |
| Cognitive and physical functioning | | | | | | |
| CPFQ total score (patient-rated) | 54 | 28.1 (5.8) | 50 | −7.7 (−9.7 to −5.8)** | … | … |
| Overall severity/distress | | | | | | |
| CGI-S score[c] (clinician-rated) | 54 | 4.1 (0.4) | 54 | −1.4 (−1.8 to −1.1)** | 48 | 0.3 (0.0 to 0.5) |
| KSQ total score (patient-rated) | 54 | 54.9 (13.1) | 50 | −24.4 (−30.3 to −18.4)** | … | … |

[a]Statistical analyses were performed on the FAS using MMRM, or on the CAS using ANCOVA.
[b]Natural log-transformed values.
[c]FAS, ANCOVA.
*$P < .05$.
**$P < .0001$.
Symbol: … = not assessed in the follow-up period.
Abbreviations: ADT = antidepressant treatment; ANCOVA = analysis of covariance; BIS-11 = Barratt Impulsiveness Scale, version 11; CAS = completer analysis set; CGI-S = Clinical Global Impressions-Severity of Illness; CI = confidence interval; CPFQ = Cognitive and Physical Functioning Questionnaire; FAS = full analysis set; IDS-$C_{30}$ = 30-item Inventory of Depressive Symptomatology, clinician version; KSQ = Kellner Symptom Questionnaire; MADRS = Montgomery-Asberg Depression Rating Scale; MCQ = Monetary Choice Questionnaire; MMRM = mixed-model repeated-measures; SD = standard deviation; SIS = Sheehan Irritability Scale.

**Figure 1. Sheehan Irritability Scale Total Score: Change From Baseline to Week 6 (FAS) and Week 6 to Week 10 (CAS)[a]**




[a]Observed cases.
Abbreviations: ADT = antidepressant treatment, CAS= completer analysis set, FAS = full analysis set, SIS = Sheehan Irritability Scale.

Questionnaire showed that among the 17 patients who had anger attacks at baseline, a total of 15 patients (88.2%) shifted to not having anger attacks at week 6. Among the 37 patients who did not have anger attacks at baseline, 5 patients (13.5%) reported anger attacks during the 6-week treatment period.

Several assessments were employed to measure the severity of depressive symptoms, and they all showed a consistent improvement. At week 6, the depressive symptoms had improved, as seen in the decrease from baseline in mean IDS-$C_{30}$ total score (mean change from baseline −17.8 [95% CI, −21.0 to −14.6]), mean Kellner Symptom Questionnaire depression subscale score (−7.7 [95% CI, −9.6 to −5.8]), and mean MADRS total score (−14.2 [95% CI, −16.7 to −11.6]). Further analysis of the mean change in Kellner Symptom Questionnaire depression subscale score revealed a worsening of the depressive symptoms from week 6 to week 10, as demonstrated by a mean change of 2.1 points (95% CI, 0.1 to 4.2).

The proportion of *responders*, defined as patients with a reduction from baseline ≥ 50% in MADRS total score, was 24 of 50 (48%) at week 6. Furthermore, the proportion of *remitters*, defined as patients with a MADRS total score ≤ 10 and a reduction from baseline ≥ 50% in MADRS total score, was 17 of 50 (34%) at week 6.

CGI-S improved from baseline to week 6 by 1.4 points (95% CI, −1.8 to −1.1) and worsened by 0.3 points (95% CI, 0.0 to 0.5) following discontinuation of brexpiprazole treatment; the mean (standard error) CGI-I score at week 6 was 2.2 (0.2). Assessment of the mean Kellner Symptom Questionnaire total score at week 6 showed an improvement of 24.4 points (95% CI, −30.3 to −18.4).

Cognitive and physical functioning, assessed using the self-rated scale Cognitive and Physical Functioning Questionnaire, improved by 7.7 points (95% CI, −9.7 to −5.8) from baseline to week 6.

**Table 3. Summary of TEAEs in 54 Patients Treated With an Antidepressant and Adjunctive Brexpiprazole**

| TEAE | n (%) |
|---|---|
| Patients with TEAEs | 43 (79.6) |
| Patients with SAEs | 0 (0.0) |
| Patients with TEAEs leading to withdrawal[a] | 2 (3.7) |
| TEAEs occurring in ≥ 5% of patients | |
| Akathisia | 11 (20.4) |
| Headache | 6 (11.1) |
| Dry mouth | 4 (7.4) |
| Fatigue | 4 (7.4) |
| Increased appetite | 4 (7.4) |
| Insomnia | 4 (7.4) |
| Diarrhea | 3 (5.6) |
| Dizziness | 3 (5.6) |
| Fall | 3 (5.6) |
| Somnolence | 3 (5.6) |
| Weight increase | 3 (5.6) |
| Other relevant TEAEs | |
| Restlessness | 1 (1.9) |
| Sedation | 1 (1.9) |
| Anxiety | 0 (0.0) |

[a]Panic attack and somnolence.
Abbreviations: SAE = serious adverse event, TEAE = treatment-emergent adverse event.

### Safety Assessments

Of the 54 patients, 43 patients (79.6%) reported 1 or more treatment-emergent AEs (TEAEs). The 2 most commonly reported TEAEs (≥ 10% of patients) were akathisia (20.4%) and headache (11.1%). A summary of TEAEs with an incidence of > 5% is listed in Table 3. All of these TEAEs (with the exception of 1 event of insomnia) were considered mild or moderate by investigators. The overall incidence of severe TEAEs was 7.4% (4 events: insomnia, middle insomnia, panic attack, and asthma). Two patients withdrew due to TEAEs: 1 patient due to panic attack and 1 due to somnolence. No patient had a serious AE.

Dose reduction to 2 mg/d was allowed if medication was tolerated poorly according to investigator's judgment. Five of 54 patients (9.3%) had a dose reduction to 2 mg/d, and 6 of 54 patients (11.1%) were never up-titrated to 3 mg but stayed at 2 mg/d until the end of treatment/withdrawal visit).

Two of the 5 patients with AEs leading to dose reduction had akathisia, 1 had psychomotor hyperactivity, and the remaining 2 patients had apathy, disturbance in attention, increased appetite, dizziness, headache, and asthenia.

Columbia-Suicide Severity Rating Scale data collected at each visit and mapped into the Columbia Classification Algorithm for Suicide Assessment categories showed that 4 patients (7.4%) had suicidal ideation at baseline. During the treatment and follow-up period, 5 patients (9.3%) had suicidal ideation, and none of the patients had suicidal behavior.

There were no clinically meaningful changes from baseline at the last visit in mean fasting metabolic parameters (Supplementary eTable 1, available at PSYCHIATRIST.COM).

## DISCUSSION

In this exploratory, 6-week, open-label study, a total of 54 patients with inadequate response to antidepressant monotherapy were treated with brexpiprazole adjunctive to their current antidepressant.

The patient-rated end points for irritability, hostility, and anger, namely the Kellner Symptom Questionnaire, Kellner Symptom Questionnaire anger-hostility subscale, Sheehan Irritability Scale, and Sheehan Irritability Scale item 1, all indicated an improvement of distress, irritability, and anger-hostility symptoms during treatment with adjunctive brexpiprazole. These results were supported by an improvement in the clinician-rated IDS-$C_{30}$ item 6, assessing the irritable mood in the patients. In addition, nearly all patients (15 of 17) having anger attacks prior to treatment stopped having anger attacks after 6 weeks of brexpiprazole treatment. The depressive symptoms of the patients were also assessed using both patient-rated and clinician-rated end points (Kellner Symptom Questionnaire depression subscale and MADRS, CGI-S, CGI-I, respectively). The results of this study therefore indicated an improvement of irritability, anger-hostility, and other residual depressive symptoms during treatment with adjunctive brexpiprazole. Addressing the whole spectrum of residual symptoms is very important clinically, as the ultimate goal of antidepressant therapy is euthymia.[25]

Symptoms of the irritability, anger-hostility, and depressive symptoms reemerged after discontinuation of brexpiprazole, although not to same severity level observed at baseline, suggesting a direct effect of treatment on the broad cluster of symptoms. The overall improvement in the Barratt Impulsiveness Scale during brexpiprazole treatment is difficult to interpret, and the continued modest improvement after discontinuation of brexpiprazole perhaps reflects more the impulsive traits of personality rather than the severity of current symptoms or direct effects of the drug.

Although irritability and anger were reduced during adjunctive treatment with brexpiprazole in this study, whether these effects are reproducible in a placebo-controlled study needs to be confirmed. The hypothesis that brexpiprazole may be effective in treating irritability and anger is based on its serotonin, dopamine, and noradrenergic effects. Brexpiprazole acts as a partial agonist at serotonin 5-$HT_{1A}$ receptors, a mechanism involved in anti-aggressive effects in animal models.[26] Brexpiprazole is also a partial agonist at $D_2$ receptors. Partial agonism at the $D_2$ receptor reduces aggression in rodents.[27,28] Finally, the $\alpha_1$ receptor antagonist prazosin is currently used to treat agitation and aggression in Alzheimer's disease[29] and for the treatment of hyperarousal, trauma nightmares, and other sleep disturbances in posttraumatic stress disorder,[30] recognizing the potential of noradrenergic antagonism in the treatment of agitation/aggression and hyperarousal.

The antidepressant effects observed in the current study are also consistent with the results of previous clinical studies,[10,11] which have shown that brexpiprazole is efficacious as adjunctive treatment in adult patients with MDD who had an inadequate response to antidepressant treatment. The tolerability of the compound in this study

is also consistent with previous clinical studies, which have revealed that the compound is safe and well tolerated, with low rates of sedating (eg, somnolence, sedation) and activating (eg, akathisia, restlessness, anxiety, insomnia) side effects,[10,11] although the incidence of akathisia observed here (20.4%) was higher than those previously reported from the pivotal studies (1 mg: 4.4%; 2 mg: 7.4%; and 3 mg: 13.5%).[10,11] These differences in the incidences of akathisia might be due to differences in the populations studied but are, at the same time, difficult to interpret given the lack of a placebo group in the current study.

Mean changes in metabolic parameters were not considered clinically meaningful, supporting previous reports that brexpiprazole has a good metabolic profile.[10,11]

### Limitations of the Study

Limitations of this study must be taken into account when interpreting its results. First, because of the small sample size, the results should be considered as preliminary and they need to be replicated in a large sample. Second, given the small sample size, subgroup analyses exploring, for example, gender and racial/ethnic differences in efficacy and safety are not feasible. Third, the open-label design does not allow us to exclude a placebo response in the irritability and depression ratings.

## CONCLUSION

In this exploratory study, irritability symptoms improved together with depressive symptoms in patients with MDD treated with adjunctive brexpiprazole. These findings are consistent with the brexpiprazole pharmacologic profile. Adjunctive treatment with brexpiprazole may represent a strategy for the treatment of irritability symptoms in patients with MDD and inadequate response to antidepressant treatment.

***Submitted:*** October 19, 2015; accepted May 11, 2016.

***Online first:*** July 5, 2016.

***Drug names:*** brexpiprazole (Rexulti), prazosin (Minipress and others).

***Potential conflicts of interest:*** **Dr Fava** has received research support from Abbott, Alkermes, American Cyanamid, Aspect Medical Systems, AstraZeneca, Avanir, BioResearch, BrainCells, Bristol-Myers Squibb, CeNeRx BioPharma, Cephalon, Clintara, Covance, Covidien, Eli Lilly, EnVivo, Euthymics Bioscience, Forest, Ganeden Biotech, GlaxoSmithKline, Harvard Clinical Research Institute, Hoffman-LaRoche, Icon Clinical Research, i3 Innovus/Ingenix, Janssen R&D, Jed Foundation, J & J; Lichtwer Pharma GmbH, Lorex, Lundbeck, MedAvante, Methylation Sciences, National Alliance for Research on Schizophrenia & Depression, National Center for Complementary and Alternative Medicine, National Institute on Drug Abuse, National Institute of Mental Health, Neuralstem, Novartis, Organon, PamLab, Pfizer, Pharmacia-Upjohn, Pharmaceutical Research Associates, Pharmavite, PharmoRx Therapeutics, Photothera, Reckitt Benckiser, Roche, RCT Logic, Sanofi-Aventis, Shire, Solvay Pharmaceuticals, Stanley Medical Research Institute, Synthelabo, and Wyeth-Ayerst; served as a consultant to or on the advisory boards of Abbott, Affectis, Alkermes, Amarin, Aspect Medical Systems, AstraZeneca, Auspex, Avanir, AXSOME Therapeutics, Bayer, Best Practice Project Management, BioMarin, Biovail, BrainCells, Bristol-Myers Squibb, CeNeRx BioPharma; Cephalon, Cerecor, CNS Response, Compellis, Cypress, DiagnoSearch Life Sciences, Dinippon Sumitomo, Dov, Edgemont, Eisai, Eli Lilly, EnVivo, ePharmaSolutions, EPIX, Euthymics Bioscience, Fabre-Kramer, Forest, Forum, GenOmind, GlaxoSmithKline, Grunenthal GmbH, i3 Innovus/Ingenis, Janssen, Jazz, J & J, Knoll, Labopharm, Lorex, Lundbeck, MedAvante, Merck, MSI Methylation Sciences, Naurex, Nestle Health Sciences, Neuralstem, Neuronetics, NextWave, Novartis, Nutrition 21, Orexigen Therapeutics, Organon, Otsuka, PamLab, Pfizer, PharmaStar, Pharmavite, PharmoRx Therapeutics, Precision Human Biolaboratory, Prexa, PPD, Puretech Ventures, PsychoGenics, Psylin Neurosciences, RCT Logic, Rexahn, Ridge Diagnostics, Roche, Sanofi-Aventis, Sepracor, Servier Laboratories, Schering-Plough, Solvay, Somaxon, Somerset, Sunovion, Supernus, Synthelabo, Takeda, Tal Medical, Tetragenex, TransForm, Transcept, and Vanda; has had speaking/publishing affiliations with Adamed, Advanced Meeting Partners, American Psychiatric Association, American Society of Clinical Psychopharmacology, AstraZeneca, Belvoir Media Group, Boehringer Ingelheim, Bristol-Myers Squibb, Cephalon, CME Institute/Physicians Postgraduate Press, Eli Lilly, Forest, GlaxoSmithKline, Imedex, MGH Psychiatry Academy/Primedia, MGH Psychiatry Academy/Reed Elsevier, Novartis, Organon, Pfizer, PharmaStar, United BioSource, and Wyeth-Ayerst; and has equity holdings in Compellis and PsyBrain; receives copyright royalties for the MGH Cognitive and Physical Functioning Questionnaire (CPFQ), the Sexual Functioning Inventory (SFI) scale, the Antidepressant Treatment Response Questionnaire (ATRQ), the Discontinuation-Emergent Signs & Symptoms (DESS) scale, the Symptoms of Depression Questionnaire (SDQ), and the SAFER criteria interview and has patents for SPCD and for a combination of ketamine and scopolamine in major depressive disorder. **Dr Ménard** and **Ms Davidsen** are full-time employees of H. Lundbeck A/S, Valby, Denmark. **Dr Baker** is a full-time employee of Otsuka Pharmaceutical Development & Commercialization, Inc, Princeton, NJ.

***Funding/support:*** This work was supported by H. Lundbeck A/S (Valby, Denmark) and Otsuka Pharmaceutical Development & Commercialization, Inc (Princeton, New Jersey).

***Role of the sponsor:*** H. Lundbeck A/S and Otsuka Pharmaceutical Development & Commercialization, Inc, were involved in the study design; in the collection, analysis and interpretation of data; in the writing of the paper; and in the decision to submit the paper for publication.

***Previous presentation:*** This research was presented at the Society of Biological Psychiatry (SOBP) 70th Annual Scientific Convention (via poster), May 14–16, 2015, Toronto, Ontario, Canada, and at the American Society of Clinical Psychopharmacology (ASCP) Annual Meeting (via poster), June 22–25, 2015, Miami, Florida.

***Acknowledgments:*** Paul Redrobe, PhD, and Stine Meehan, PhD, full-time employees of H. Lundbeck A/S, for providing medical writing assistance in the manuscript preparation, revision, and editing.

***Supplementary material:*** Available at PSYCHIATRIST.COM.

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THE JOURNAL OF CLINICAL PSYCHIATRY
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# Supplementary Material

**Article Title:** Adjunctive Brexpiprazole in Patients With Major Depressive Disorder and Irritability: An Exploratory Study

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**DOI Number:** 10.4088/JCP.15m10470

## List of Supplementary Material for the article

1. **eTable 1** Mean Change From Baseline to Last Visit in Fasting Metabolic Parameters (APTS)

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This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

**Supplementary eTable 1:** Mean change from baseline to last visit in fasting metabolic parameters (APTS)

| Parameter | Baseline | | Change from baseline at last visit | |
|---|---|---|---|---|
| | **n** | **Mean (SD)** | **n** | **Mean (SD)** |
| Cholesterol, mg/ml | 50 | 206.18 (36.29) | 41 | 4.63 (23.55) |
| HDL cholesterol, mg/ml | 50 | 56.76 (18.53) | 41 | -0.39 (8.11) |
| LDL cholesterol, mg/ml | 50 | 121.24 (31.66) | 41 | -6.56 (19.31) |
| Triglycerides, mg/ml | 50 | 142.48 (71.68) | 41 | 13.27 (61.95) |
| Glucose, mg/ml | 50 | 93.69 (12.61) | 41 | 3.60 (14.41) |

Abbreviations:

APTS=all-patients-treated set; HDL=high-density lipoprotein; LDL=low-density lipoprotein; SD=standard deviation