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Monthly Extended-Release Risperidone (RBP-7000) in the Treatment of Schizophrenia

Results From the Phase 3 Program

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Abstract:

Purpose/Background: The Phase 3 program for RBP-7000, a once-monthly subcutaneous (SC) extended-release risperidone formulation approved for treatment of schizophrenia, consisted of a double-blind placebo-controlled trial (previously reported) and a 52-week open-label study of monthly RBP-7000 120 mg. The primary objective of the open-label study was to evaluate the long-term safety and tolerability of RBP-7000 in adults with schizophrenia. A secondary objective was to assess long-term maintenance of effectiveness.

Methods/Procedures: The 52-week Phase 3 open-label study (NCT02203838) enrolled 92 rollover participants from the double-blind trial (NCT02109562) and 408 stable (Positive and Negative Syndrome Scale [PANSS] total score, ≤70) de novo participants. Participants received up to 13 monthly SC injections of RBP-7000 120 mg. Safety assessments included treatment-emergent adverse events, injection-site assessments, vital signs, laboratory and ECG parameters, extrapyramidal symptoms, and suicidality. Clinical outcomes included the PANSS and Clinical Global Impression—Severity.

Findings/Results: Overall, 367 participants (73.4%) reported 1 or more treatment-emergent adverse event; the most common were injection-site pain (13.0%) and weight increase (12.8%). Most participants (>80%) experienced no injection-site reactions. No clinically meaningful changes were observed in laboratory or electrocardiogram values, vital signs, extrapyramidal symptoms, or suicidality. Over 12 months of exposure, mean PANSS scores continued to improve in rollover participants and remained stable among de novo participants. Mean Clinical Global Impression—Severity scores remained stable among all participants.

Implications/Conclusions: Except for anticipated injection-site reactions, RBP-7000 demonstrated a favorable safety and tolerability profile similar to oral risperidone. Notably, PANSS scores continued to improve for participants from the pivotal study and remained stable for de novo participants.

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Schizophrenia remains a leading cause of disability worldwide.[1,2] Current first-line treatment involves the use of oral second-generation antipsychotics, including risperidone,[3] yet nonadherence with daily oral medication is common and is associated with increased risk of relapse.[4,5] Depot medications, such as long-acting injectable antipsychotics, have been developed as alternatives to oral antipsychotics and have been shown to facilitate adherence,[6,7] increase quality of life,[8,9] and decrease rehospitalizations.[10,11]

RBP-7000, a once-monthly subcutaneous (SC) extended-release injectable suspension, is a newly Food and Drug Administration–approved risperidone formulation designed to achieve clinically relevant therapeutic plasma concentrations on the first day of dosing, with no need for a loading dose or supplemental oral dosing. The efficacy and safety of RBP-7000 were previously established in an 8-week, double-blind, placebo-controlled trial conducted in adults with acute exacerbation of schizophrenia.[12] Compared with placebo, monthly SC RBP-7000 (90 and 120 mg) significantly improved Positive and Negative Syndrome Scale (PANSS)[13] total score and the Clinical Global Impression—Severity (CGI-S)[14] score. Participants treated with RBP-7000 also showed significant improvements in health-related quality of life, physical functioning, and social integration scores.[15] Treatment was generally well tolerated, with a safety profile consistent with previous reports of oral or injectable risperidone,[16,17] with the exception of expected injection-site reactions.

The primary objective of the current study was to assess the long-term safety and tolerability of SC injections of RBP-7000 in patients with schizophrenia; however, a secondary objective was to assess long-term maintenance of effectiveness.

MATERIALS AND METHODS

Study Conduct and Design

This 52-week, multicenter, Phase 3, open-label, outpatient study (NCT02203838) was conducted at 50 sites in the United States between June 2014 and September 2016 in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines, Food and Drug Administration regulations governing clinical study conduct, and the Declaration of Helsinki (2013). The study protocol, all protocol amendments, written study patient information, informed consent form, and all other appropriate study-related information were reviewed and approved by an institutional review board.

The study enrolled patients with acute exacerbations of schizophrenia who had completed a double-blind trial ("rollover" participants from study NCT02109562)[12] in which they had received

2 monthly SC injections of either placebo, RBP-7000 90 mg, or RBP-7000 120 mg. The present study also included newly enrolled (de novo) participants with stable schizophrenia (Supplemental Fig. 1, Supplemental Digital Content 1, http://links.lww.com/JCP/A583). De novo participants already receiving 3 or 4 mg/d oral risperidone began the study at day 1; those receiving oral risperidone at a dosage other than 3 or 4 mg/d entered a 7-day conversion period in which they were titrated to an oral risperidone dosage of 3 or 4 mg/d. De novo participants receiving antipsychotic medication other than oral risperidone entered a 14-day run-in period during which their current antipsychotic therapy was down-titrated and oral risperidone was up-titrated to a dosage of either 3 or 4 mg/d at the investigator's discretion.

During the open-label treatment phase, rollover participants received up to 11 monthly SC injections of RBP-7000 120 mg and de novo participants received up to 13 injections. At the investigator's discretion, participants were allowed a single dose modification to 90 mg for tolerability and a subsequent single dose modification to 120 mg if psychiatric symptoms worsened (PANSS total score >70 or a 20% increase in PANSS total score from the last 120 mg dose assessment).

Participants

Adults 18 to 65 years (inclusive) who met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, *Text Revision* criteria for schizophrenia were eligible. Rollover participants from the double-blind study had been treated for 8 weeks with 2 injections of RBP-7000 or placebo in an inpatient setting after an acute exacerbation of schizophrenia as described previously.[12] Completers from that study were allowed to enroll in the present study. De novo participants were required to have a diagnosis of schizophrenia, considered stable with a PANSS total score of less than or equal to 70 at screening and were otherwise healthy based on physical examination. De novo participants with suicidal ideation (within 6 months) or behavior (within 1 year) based on Columbia Suicide Severity Rating Scale[18] assessment, or with a significant risk of suicide in the opinion of the investigator, were excluded.

Exclusion criteria for both the double-blind and open-label studies included previous treatment with clozapine, current use of oral risperidone (≥6 mg/d), *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, *Text Revision* criteria for alcohol or substance abuse, and clinically relevant abnormalities of liver function or QTc interval. Concomitant use of CYP2D6 inhibitors or inducers or any long-acting injectable antipsychotic medication (other than the study drug) was prohibited during the treatment period; participants were discontinued if antipsychotic rescue treatment became necessary. With these exceptions, participants could continue any previously prescribed medications other than antipsychotics. The use of benzodiazepines, propranolol, and anti-parkinsonian medication was allowed during treatment except within 12 hours before PANSS, CGI-S, or extrapyramidal symptom (EPS) scale assessments.

Safety Assessments

Safety assessments included treatment-emergent adverse events (TEAEs), local injection-site tolerability, clinical laboratory values, vital signs, and electrocardiograms (ECGs), as well as measurements of body weight, height, body mass index (BMI), and abdominal fat, measured by waist-hip ratio. Extrapyramidal symptoms were assessed using Abnormal Involuntary Movement Scale,[19] Simpson-Angus Scale,[20] and Barnes Akathisia Rating Scale.[21] Suicidal ideation and behavior were monitored using Columbia Suicide Severity Rating Scale.

Local injection-site grading was performed within 10 minutes of each injection and at 3 hours (±10 minutes) postinjection for pain, tenderness, erythema/redness, and induration/swelling; each symptom was assigned a severity grade of none (grade 0) to potentially life-threatening (grade 4). Injection-site pain was also measured using the Injection-site Pain Visual Analog Scale (VAS), a 2-item, participant-reported questionnaire with responses (0–100 mm) ranging from "no injection-site pain" to "worst imaginable injection-site pain."[22] Visual Analog Scale assessments were completed by the participant after each RBP-7000 injection at 1 (±15 seconds), 5 (±2), 30 (±2), and 60 (±2) minutes postinjection.

Effectiveness Assessments

The long-term effects of RBP-7000 on schizophrenia symptoms (secondary outcomes) were evaluated in this long-term study using PANSS total score, PANSS Positive Scale, Negative Scale and General Psychopathology Scale scores, and CGI-S score collected at baseline, day 29, day 169, and at the end of study (EOS).

Statistical Analyses

A descriptive analysis of the long-term effects of RBP-7000 on safety, tolerability, and efficacy was performed on the safety population, which comprised all participants who received 1 or more open-label RBP-7000 injections. The results are presented for all participants and also by the following study groups: rollover (by double-blind treatment group) and de novo participants. Baseline was defined as the last nonmissing measurement taken before the first injection (including unscheduled assessments). Data are as observed with no imputation of missing data and are presented as change from baseline to EOS (defined as the last visit) or to the end of treatment (EOT, defined as EOS for completers and early termination visit for participants who discontinued). For rollover participants, safety assessments performed at the EOS visit of the previous double-blind study (screening visit for open-label study) served as the preinjection assessments for the open-label study.

RESULTS

Disposition and Demographics

A total of 500 participants were eligible for study participation (Supplemental Fig. 2, Supplemental Digital Content 2, http://links.lww.com/JCP/A584); 92 had completed the previous double-blind study, placebo (30.4%, n = 28), RBP-7000 90 mg (33.7%, n = 31), or RBP-7000 120 mg (35.9%, n = 33), and 408 were de novo participants with stable schizophrenia. In this study, rollover participants received up to 11 injections of RBP-7000 120 mg, and de novo participants received up to 13 injections of RBP-7000 120 mg. Overall, 234 participants (46.8%) completed this study, with the proportion of rollover placebo participants completing being approximately half that of the other groups. The most common reasons for discontinuation were withdrawal of consent (22.4%), adverse events (11.4%), and lost to follow-up (9.0%). Demographic and baseline clinical characteristics were comparable across study groups (Supplemental Table 1, Supplemental Digital Content 3, http://links.lww.com/JCP/A585). The overall dropout rate observed in this study was 53.2%, which was consistent with published literature in clinical trials of similar duration with second-generation antipsychotics.[23–26]

Safety

Extent of Exposure

Overall, 326 participants (65.2%) were exposed to RBP-7000 for 6 months or longer including 48.0% of de novo participants

exposed for 1 year or longer. The mean duration of treatment among rollover participants (11 injections) was as follows: 161.9 days for rollover placebo, 196.6 days for rollover RBP-7000 90 mg, and 196.6 days for rollover RBP-7000 120 mg (including 58 days of active treatment during the double-blind study). For de novo participants (13 injections), mean exposure was 259.3 days.

Adverse Events

The majority of participants (367; 73.4%) reported 1 or more TEAEs (Supplemental Table 2, Supplemental Digital Content 4, http://links.lww.com/JCP/A586), most of which were mild (29.6%) to moderate (39%) with only 4.8% reporting 1 or more severe TEAEs. The most common TEAEs (≥5%) were injection-site pain (13.0%) and weight increase (12.8%), schizophrenia (7.8%), insomnia (7.0%), injection-site nodule (6.8%), akathisia (6.0%), injection-site induration (5.8%), upper respiratory tract infection (5.2%), and headache (5.0%). Fifty-eight participants (11.6%) discontinued the study owing to TEAEs, most commonly owing to schizophrenia (2.0%), akathisia (0.8%), weight increase (0.8%), tremor (0.6%), and galactorrhea (0.6%). Only 2 participants discontinued owing to injection-site reactions (tenderness and nodule). Treatment-emergent adverse events attributed to RBP-7000 were injection-site pain (12.8%), weight increase (11.4%), injection-site nodule (6.8%), injection-site induration (5.8%), and akathisia (5.8%).

Thirty-four participants (6.8%) experienced a serious adverse event (SAE), none of which was considered related to study drug. Four deaths were reported (pulmonary embolism, cardiac arrest, head trauma, and increased psychosis), none of which were considered related to study drug by either the investigator or by adjudication.

TEAEs Among Participants With a Dose Modification

Of 86 participants who had a dose modification to 90 mg (77 de novo participants [18.9%], 3 rollover placebo [10.7%], 3 rollover RBP-7000 90 mg [9.7%], and 3 rollover RBP-7000 120 mg [9.1%]), 42 (48.8%) did so owing to a TEAE. The most commonly reported TEAEs included injection-site pain (14.0%), insomnia (11.6%), schizophrenia (10.5%), akathisia (10.5%), and blood prolactin increased (10.5%). The severity was mostly mild (27.9%) or moderate (57.0%), with 5 participants (5.8%) reporting a severe TEAE (weight increase, n = 2; dry mouth, sedation, and deep vein thrombosis, n = 1 each).

Injection-Site Tolerability

The maximum reported intensity for injection-site assessments made by site staff for pain, tenderness, erythema/redness, and induration/swelling, was none (grade 0) for 81.8% and 97.4% of participants immediately and at 3 hours postdose, respectively. A total of 18.0% of participants reported a mild (grade 1) injection-site reaction immediately after injection. One rollover RBP-7000 120 mg participant and 1 de novo participant each reported a single instance of severe injection-site tenderness immediately after injection. Injection-site tolerability symptoms were mostly resolved within 3 hours postinjection, with only 2.5% of participants experiencing mild pain, 4.3% tenderness, 3.9% induration/swelling, and 0.8% erythema/redness at 3 hours.

Fewer participants reported burning/stinging at 1 minute after injection on day 337 as compared with day 1, decreasing from 43.4% on day 1 to 35.7% on day 337. Supplemental Figure 3 (Supplemental Digital Content 5, http://links.lww.com/JCP/A587) displays the participant-reported injection-site pain VAS scores at 1, 5, 30, and 60 minutes after the first injection for the de novo and rollover subgroups. For all subgroups, there was a notable decrease in pain between 1 and 5 minutes postinjection, with median pain intensity VAS scores ranging from 3.5 to 14 at 1 minute postinjection, dropping to between 1 and 3 at the 5 minutes postinjection time point.

The median/mean injection-site pain VAS score for the total population decreased from 13.0/24.9 one minute after the first injection to 2.5/15.8 one minute after the 11th injection (day 281), suggesting pain intensity decreased with subsequent injections.

Body Weight, BMI, and Abdominal Fat

During the initial 3 months of treatment, mean body weight increased modestly in treatment-naive participants (de novo [1.9 kg], rollover placebo [1.6 kg]) and then stabilized for the remainder of the study. Mean body weight remained stable for participants in the rollover RBP-7000 120 mg group and decreased modestly for those in the rollover RBP-7000 90 mg group, with mean (SD) changes from baseline in body weight of 0.7 (5.0) kg and −1.5 (5.8) kg, respectively, by EOT. Box plots of the mean and median change from baseline for weight, although showing wide variability, show a normal distribution, which should be generalizable (Supplemental Fig. 4, Supplemental Digital Content 6, http://links.lww.com/JCP/A588).

At EOT, 22.1% (94/426) of all participants had a ≥7% increase in body weight from baseline, with a higher incidence in de novo participants (24.6%) than rollover placebo (9.5%), rollover RBP-7000 90 mg (13.8%) or rollover RBP-7000 120 mg (10.0%). Treatment-emergent adverse events of weight increase were reported for 12.8% of participants; however, only 4 participants (0.8%) withdrew because of this adverse event. Mean differences from baseline to EOT in BMI and abdominal fat were small and similar across study groups (Supplemental Table 3, Supplemental Digital Content 7, http://links.lww.com/JCP/A589).

Metabolic Parameters and Prolactin Levels

Small mean changes from baseline to EOT of unknown clinical significance were observed in glucose, HbA1c, and cholesterol levels (Supplemental Table 3, Supplemental Digital Content 7, http://links.lww.com/JCP/A589). A post hoc shift analysis of serum glucose showed a total of 20 de novo participants (9.2%) and 4 rollover participants (4.3%) had a shift in fasting glucose levels from less than 100 mg/dL to greater than 126 mg/dL at any time during the study. Treatment-emergent adverse events associated with metabolic changes occurring in more than 1% of all participants were type 2 diabetes mellitus (2.0%) and diabetes mellitus (1.4%). Box plots of mean and median change from baseline for total cholesterol and glucose also show a normal distribution, confirming the previous data (data not shown).

The overall incidence of markedly abnormal postbaseline prolactin values (≥3 times the upper limit of normal [ULN]) was 28.8% for females and 3.8% for males. Most females with prolactin values less than or equal to 3 times the ULN at baseline remained in that range throughout the study (62.1%) or shifted to greater than 3 times the ULN to less than or equal to 6 times the ULN (16.3%). The majority (94.9%) of males with prolactin values less than or equal to 3 times the ULN at baseline remained within that range. Few participants had TEAEs pertaining to elevated prolactin, including blood prolactin increased (3.0%), galactorrhea (2.8%), hyperprolactinemia (1.4%), and blood prolactin abnormal (0.2%).

Suicidality

Mean suicidal ideation scores and suicidal intensity ratings through EOS were generally comparable with or lower than those at baseline. No participant committed suicide during the study; 1

de novo participant (0.2%) had an SAE of suicide attempt. There were 6 participants (1.2%) with TEAEs of suicidal ideation, none considered related to study drug: 2 participants with treatment-emergent SAEs that led to study discontinuation, 2 with treatment-emergent SAEs that did not lead to discontinuation, and 2 with TEAEs not considered serious.

Additional Safety Measures and EPS

No clinically meaningful differences were noted in mean changes from baseline to EOT for any laboratory test results, blood pressure, heart rate, or ECG parameters (Supplemental Table 3, Supplemental Digital Content 7, http://links.lww.com/JCP/A589). The only ECG-associated TEAE occurring in more than 1 participant was mild or moderate electrocardiogram QT prolonged (n = 4); none were serious nor resulted in discontinuation. No clinically meaningful changes from baseline to EOT were observed in Barnes Akathisia Rating Scale, Abnormal Involuntary Movement Scale, or Simpson-Angus Scale scores (Supplemental Table 3, Supplemental Digital Content 7, http://links.lww.com/JCP/A589). Treatment-emergent adverse events potentially pertaining to EPS in more than 1% of participants were akathisia (6.0%), tremor (2.0%), extrapyramidal disorder (1.8%), and muscle spasms (1.2%); none were serious.

Effectiveness Assessments

Mean PANSS total scores at baseline were 58.0 for the de novo group and ranged from 71.0 to 76.4 for the 3 rollover groups (Supplemental Fig. 5A, Supplemental Digital Content 8, http://links.lww.com/JCP/A590 [double-blind results also presented to illustrate overall clinical course]). Notably, mean (SD) change from baseline to EOS for rollover participants was −20.2 (15.6) for placebo, −12.5 (15.5) for RBP-7000 90 mg, and −10.9 (13.2) for RBP-7000 120 mg; however, the number of evaluable participants in the placebo group was small. Among de novo participants, PANSS total scores remained stable throughout the study (mean [SD] change from baseline to EOS −0.4 [8.7]).

Evaluating the rollover participants for each PANSS subscale, a decrease from baseline to EOS was observed in each group, including those who had received placebo in the double-blind study. Mean (SD) changes from baseline to EOS on the PANSS Positive Scale score were −7.8 (5.5), −3.7 (4.1), and −3.7 (3.5) among rollover participants previously treated with placebo, RBP-7000 90 mg, or RBP-7000 120 mg, respectively. For the PANSS Negative Scale score, mean (SD) changes from baseline to EOS were −4.0 (5.9) for placebo, −4.1 (4.6) for RBP-7000 90 mg, and −0.9 (3.8) for RBP-7000 120 mg. For the PANSS General Psychopathology Scale score, mean (SD) changes from baseline to EOS were −8.3 (7.0), −4.7 (9.0), and −6.4 (7.9) for placebo, RBP-7000 90 mg, and RBP-7000 120 mg, respectively.

Among de novo participants, PANSS subscale scores remained generally stable throughout the study, with mean (SD) changes from baseline to EOS of −1.3 (3.3) for PANSS Positive Scale, 1.3 (3.6) for PANSS Negative Scale, and −0.4 (5.0) for PANSS General Psychopathology Scale. For all participants, CGI-S scores also remained stable throughout the study (Supplemental Fig. 5B, Supplemental Digital Content 8, http://links.lww.com/JCP/A590).

DISCUSSION

Depot medications have been useful in maximizing treatment adherence and ameliorating the negative consequences of nonadherence in the long-term treatment of schizophrenia. Participants switching from shorter-acting oral medications to long-acting injectable formulations have shown greater adherence,[6,27] fewer hospitalizations,[8,9] less inpatient health care resource utilization, and decreased medical costs.[7] RBP-7000 is the first once-monthly SC risperidone injectable that demonstrated efficacy without requiring loading doses or supplemental oral dosing. In this 52-week study of participants enrolled from a recent acute inpatient study and from outpatient settings, treatment with RBP-7000 SC injections administered monthly was well tolerated and resulted in improved (rollover) or stable (de novo) clinical outcomes. No new safety signals were reported, and the safety results were consistent with the known safety profile of oral risperidone.[16]

The most commonly reported TEAEs were injection-site pain and weight increase. Pain assessments were mild or moderate in severity and expected for SC injections. For most participants (>80%), the maximum reported intensity for injection-site assessments (pain, tenderness, erythema/redness, induration/swelling) immediately or 3 hours postdose was none (grade 0). Because self-reported injection-site pain median VAS scores were low, and pain typically resolved within minutes after the injection, results from this long-term study suggest that injection-site reactions or discomfort are unlikely a major obstacle to long-term adherence with RBP-7000.

Exposure to antipsychotics can be associated with a significant increase in body weight,[28,29] making risk of significant weight gain a concern among patients with schizophrenia, caregivers, and clinicians. During the previous double-blind study, participants in all treatment groups experienced an increase in body weight,[12] with mean gains of 2.8 kg in those receiving placebo and 5.1 kg and 4.7 kg in participants receiving RBP-7000 90 mg and RBP-7000 120 mg, respectively. In the current long-term open-label trial, participants who had not received RBP-7000 previously experienced a modest increase in mean weight (1.6–1.9 kg) during the first 3 months of treatment, whereas body weight remained stable in rollover participants who had received RBP-7000 in the double-blind study. Weight remained stable or declined to some degree in all study groups during open-label months 3 to 12. Therefore, prolonged exposure to RBP-7000 may not worsen the initial weight gain that may be observed upon initiation of treatment.

Although hyperprolactinemia is commonly observed with atypical antipsychotic use,[30] no consistent trends in prolactin levels were noted in this study. A low percentage of participants had TEAEs associated with elevated prolactin levels; however, abnormal prolactin levels (≥3 times the ULN) occurred in a higher percentage of females than males.

Importantly, there were no clinically meaningful changes in EPS scales or measures of suicidality over the course of the study.

As previously reported,[12] 8 weeks of treatment with either RBP-7000 90 mg or RBP-7000 120 mg significantly improved PANSS total scores, PANSS Positive Scale and General Pathology Scale, and CGI-S scores versus placebo, whereas PANSS Negative Scale scores were significantly improved with the 120 mg dose in acutely ill participants. We now show that with 12 months of treatment, the mean PANSS total and subscale scores continued to decrease from baseline to EOS in these participants who enrolled in the longer-term study. This finding suggests continued improvement in acute schizophrenia symptoms after several months of exposure to RBP-7000.

Among de novo participants, who had been outpatients, mean PANSS total and subscale scores remained stable throughout the study.

The main limitations of this study are the open-label nature of the treatment and that participants in the rollover group had already shown the ability to tolerate chronic treatment with atypical antipsychotics, therefore creating some degree of recruitment bias. Another limitation was an overall discontinuation of 53%, which might affect the generalization of these results.

In summary, the overall frequency and severity of TEAEs, including injection-site reactions, reduced over time, and no new safety signals were observed with 12 months of RBP-7000 treatment. Except for injection-site reactions of minor severity that are expected with SC medications, the safety profile was consistent with that of oral risperidone. Clinical outcome measures improved (rollover) or remained stable (de novo) over the course of the study. RBP-7000, a once-monthly SC extended-release form of risperidone, provides additional treatment options for patients with schizophrenia.

AUTHOR DISCLOSURE INFORMATION

A.A., J.G., S.S., and C.H. are employees of Indivior Inc. G.M. was an employee of Indivior Inc. when the study was conducted and during preparation of the article. J.C. has served as a DSMB member for Eli Lilly and Sanofi-Aventis. 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, and 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 Pharmaceuticals, 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, and VistaGen; has received speaking honoraria from American Society of Clinical Psychopharmacology, Belvoir Media Group, CME Institute/Physicians Postgraduate Press, and MGH Psychiatry Academy; and holds equity in Compellis and PsyBrain. J.W.N. has received research support from National Institutes of Health and Otsuka American Pharmaceutical, Inc; has consulted for Alkermes, Sunovion, Otsuka, and Reviva Pharmaceuticals, Inc; and serves on a Data Safety Monitoring Board for Amgen.

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