Title

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Journal

The International Journal of Neuropsychopharmacology, 20(8)

ISSN

1461-1457

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Publication Date

2017-08-01

DOI

10.1093/ijnp/pyx033

Peer reviewed

International Journal of Neuropsychopharmacology (2017) 20(8): 613–618

doi:10.1093/ijnp/pyx033
Advance Access Publication: June 8, 2017
Brief Report

BRIEF REPORT

Phase II Proof-of-Concept Trial of the Orexin Receptor Antagonist Filorexant (MK-6096) in Patients with Major Depressive Disorder

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Abstract

Background: We evaluated the orexin receptor antagonist filorexant (MK-6096) for treatment augmentation in patients with major depressive disorder.
Methods: We conducted a 6-week, double-blind, placebo-controlled, parallel-group, Phase II, proof-of-concept study. Patients with major depressive disorder (partial responders to ongoing antidepressant therapy) were randomized 1:1 to once-daily oral filorexant 10 mg or matching placebo.
Results: Due to enrollment challenges, the study was terminated early, resulting in insufficient statistical power to detect a prespecified treatment difference; of 326 patients planned, 129 (40%) were randomized and 128 took treatment. There was no statistically significant difference in the primary endpoint of change from baseline to week 6 in Montgomery Asberg Depression Rating Scale total score; the estimated treatment difference for filorexant-placebo was -0.7 (with negative values favoring filorexant) ($P = .679$). The most common adverse events were somnolence and suicidal ideation.
Conclusions: The interpretation of the results is limited by the enrollment, which was less than originally planned, but the available data do not suggest efficacy of orexin receptor antagonism with filorexant for the treatment of depression.
(Clinical Trial Registry: clinicaltrials.gov: NCT01554176)

Keywords: depression, filorexant, MK-6096, orexin receptor antagonist

Introduction

Insomnia shows high comorbidity with depression and is associated with a 3- to 4-fold increased risk of developing the condition (Breslau et al., 1996; Staner, 2010; Baglioni and Riemann, 2012). Despite the availability of a wide range of antidepressant drugs, more than 50% of patients with major depressive disorder (MDD) fail to demonstrate an adequate response to first-line treatment. Switching to another antidepressant or treatment augmentation (i.e., adding a second agent) are commonly used

Received: December 15, 2016; **Revised:** April 24, 2017; **Accepted:** June 1, 2017

pharmacologic options for patients demonstrating inadequate treatment response; however, although successful for some, not all individuals experience improvement in their depressive symptoms (Fleurence et al., 2009).

The orexin signaling system, which originates in the lateral hypothalamus, plays an important role in sleep-wake control and may have additional functions, for example, regulation of stress, reward, and mood (Berridge et al., 2010; Gotter et al., 2012; Kukkonen and Leonard, 2014; Winrow and Renger, 2014; Yeoh et al., 2014). Prior studies carried out in humans and animals provide a mixed picture as to what effects orexin antagonists would be expected to have when administered to patients with MDD. However, several of these studies are consistent with the possibility that orexin antagonism might improve depression. These studies include animal models of depression where elevated orexin neuron activity was found (Mikrouli et al., 2011), that treatment with the orexin receptor antagonist almorexant had antidepressant-like effects in the tail suspension test, elevated plus maze, and resident-intruder task (Nollet et al., 2011), and that in a human study, orexin A CSF levels were found to be elevated in patients with depression and were lowered by treatment with the antidepressant sertraline (Salomon et al.. 2003), although another study failed to find an elevation in CSF orexin A in depressed patients (Schmidt et al., 2011).

Filorexant (MK-6096) is an orally bioavailable potent and selective antagonist of orexin 1 and orexin 2 receptors (i.e., it is a dual orexin receptor antagonist) (Coleman et al., 2012; Winrow et al., 2012). In humans, filorexant has a short half-life of 3 to 6 hours and has been shown to promote sleep onset and maintenance in patients with insomnia (Connor et al., 2016). Given the sleep-promoting properties of filorexant and the potential involvement of the orexin pathway in depression, it was hypothesized that filorexant may have a role in the treatment of MDD.

This proof-of-concept study evaluated the safety, tolerability, and efficacy of a sleep-promoting 10-mg dose of filorexant administered each night at bedtime compared with placebo for treatment augmentation in patients with MDD. The rationale for the dose selection in the current study was based on data from a study where patients with primary insomnia showed significant improvements in sleep with filorexant 10 mg nightly without the marked next-day somnolence in most patients (Connor et al., 2016). To our knowledge, this is the first study to evaluate the orexin receptor antagonist mechanism in MDD.

Methods

Study Design and Treatment

This was a 6-week, double-blind, placebo-controlled, randomized (1:1), parallel-group study conducted between June 2012 and September 2013 at 61 sites within Canada, Finland, France, Germany, Norway, Sweden, and the United States (clinicaltrials.gov: NCT01554176).

The study comprised a screening period (≤2 weeks), a 6-week double-blind treatment period, and a 2-week double-blind, run-out period for patients who completed the treatment period. During the treatment period, patients were randomized (1:1) to receive oral filorexant 10 mg once nightly (at bedtime) or matching placebo. Randomization was stratified by severity of depressive symptoms on the Hamilton Depression Rating Scale 17-item (HAMD-17) (Hamilton 1960) total score (≤20 vs. >20) and extent of insomnia (Insomnia Severity Index [ISI] total score ≤14 vs. >14) (Bastien et al. 2001). During the run-out period, patients initially randomized to filorexant received either filorexant or placebo, and patients initially randomized to placebo continued to receive placebo. Patients continued to take their prescribed pretrial antidepressant medication (selective serotonin reuptake inhibitor, serotonin norepinephrine reuptake inhibitor, or bupropion) throughout the trial.

Patients

Patients were required to have a current primary diagnosis of recurrent MDD, without psychotic features, with a current moderate or severe depressive episode, as defined by the DSM-IV-TR (American Psychiatric Association 2000) and as confirmed by the Mini International Neuropsychiatric Interview (Sheehan et al. 1998) and clinical assessment. Male and female MDD patients (aged 21 to <65 years) were eligible for inclusion if they were partial responders to antidepressant therapy, defined as persistence of moderate to severe, nonpsychotic depressive symptoms, despite an adequate trial (dose and duration of treatment) of selective serotonin reuptake inhibitor, serotonin norepinephrine reuptake inhibitor, or bupropion monotherapy. Patients were excluded if they had an inadequate response (investigator's opinion) to more than three adequate antidepressant trials for treatment of the current depressive episode. Severity of depressive symptoms was based on the investigator's clinical assessment, including the Montgomery Asberg Depression Rating Scale (MADRS) total score (Montgomery and Asberg 1979), and on patients' assessment of their depressive symptoms using HAMD criteria. The HAMD-17 was completed by patients at screening and baseline in the clinic using an interactive voice response system (Moore et al., 2006). The threshold for study entry was initially based on a HAMD Bech subscale (consisting of HAMD-17 items 1, 2, 7, 8, 10, and 13) score of ≥10 (Bent-Hansen and Bech, 2011); this was later changed to ≥9 due to enrollment difficulties and feedback from study sites and external consultants. Both patients and sites were blinded to the HAMD threshold required for study entry in an attempt to minimize assessment bias and reduce placebo response. Patients were excluded if they were at imminent risk of self-harm, based on clinical interview and responses to item number 10 of the MADRS or on the Columbia Suicidality Severity Rating Scale (C-SSRS) (Posner et al. 2011), or if they reported suicidal ideation with intent, with or without a plan (i.e., MADRS item 10 ≥ 5 and/or Type 4 or 5 on the C-SSRS), in the past 1 month or suicidal behavior in the past 6 months. Patients were also excluded if they were using anxiolytic or sedative-hypnotic agents chronically. Patients with narcolepsy were excluded.

All patients gave written informed consent to participate in the study. The study protocol (Protocol 022) was approved by the relevant Institutional Review Board/Independent Ethics Committee at each participating center. The study was conducted in accordance with good clinical practice and in compliance with all local and/or national regulations and directives.

Efficacy Endpoints

Patients were evaluated in the clinic at the end of week 3 and week 6 of the treatment period and again at the end of the run-out period (week 8). Patients also received follow-up phone call 1 and 2 weeks after the last dose of study medication.

The primary endpoint was change from baseline to week 6 in the MADRS total score. Planned secondary endpoints included: change from baseline to week 6 in the MADRS total score, excluding the sleep item; change from baseline to week 6 in the HAMD Bech subscale score; change from baseline to week 6 in the HAMD-17 total score; and HAMD-17 remission rate (i.e., HAMD-17 total score

≤7) at week 6. Exploratory endpoints were also planned, including change from baseline in HAMD-17 total score and ISI total score.

Safety and Tolerability

Safety was assessed based on the incidence and severity of adverse events (AEs). Prespecified events of clinical interest (ECIs) included suicidal ideation and/or behaviors, selected AEs associated with potential for abuse, overdose, complex sleep-related behaviors, hypnagogic or hypnopompic hallucinations, excessive daytime sleepiness, sleep paralysis, sleep-onset paralysis, cataplexy, and falls. Vital signs, body weight, electrocardiogram, physical and neurological examination, and laboratory evaluations were also assessed and the C-SSRS was completed (baseline, week 3, week 6, and run-out period).

Statistical Methods

The study was originally designed to include 326 patients (163 per treatment group) to provide 80% power to detect a 3.5-point difference between treatments (based upon a 2-sided 5% level test) for the primary endpoint. This assumed a SD of 9.6 points and a 21% dropout rate and accounted for a planned interim futility analysis (not conducted due to early termination). This difference corresponds to a standardized effect size of 0.4.

Efficacy analyses were conducted using the full-analysis-set population (all randomized patients who received at least one dose of double-blind study treatment and had at least one evaluable endpoint measurement, including those patients who only had a baseline measurement). Efficacy endpoints (i.e., change from baseline in MADRS total score, MADRS score excluding sleep item, HAMD-17 total score, and HAMD Bech subscale score) were assessed using a constrained longitudinal data analysis model, including terms for treatment, time, time-by-treatment interaction, severity of disease at baseline (HAMD-17 ≤20 vs. >20), and insomnia at baseline (ISI ≤14 vs. >14) as categorical terms. This model assumes a common mean across treatment groups at baseline and a different mean for each postbaseline time point. Time is treated as a categorical variable so that no restriction is imposed on the trajectory of the means over time. An unstructured covariance matrix was used to model the correlation among repeated measurements.

The all-patients-as-treated population was used for safety analyses (all randomized patients who received at least one dose of double-blind study treatment).

Results

A total of 129 patients, 40% of the originally planned population (129/326), were randomized to treatment. Study treatment was administered to 128 of these patients and 116 patients completed the treatment period (Supplementary Figure 1). The study was terminated early because of low recruitment resulting from enrollment challenges. If the study had been designed with a sample size of 65 patients per treatment group (i.e., the approximate observed sample size), based on the assumptions already described, the study would have been underpowered (<50%) to detect a treatment difference in MADRS.

Patient characteristics were similar across treatment groups (Supplementary Table 1), with patients predominantly female (63.3%) and white (86.7%). Mean age was 48.8 years. The majority (~80%) of patients had baseline insomnia (ISI total score >14). Mean baseline HAMD-17 total scores were ~24, consistent with moderate to severe depression.

Efficacy

Results for change from baseline in depression endpoints are summarized in Table 1. There was no statistically significant difference on the primary endpoint of mean change from baseline to week 6 in MADRS total score with filorexant vs. placebo (Table 1). The estimated treatment difference (filorexant–placebo) was -0.7 (95% CI: -3.8, 2.5; $P = .679$), with a negative difference corresponding to numerical improvement compared with placebo. This difference corresponds to a standardized effect size of -0.1. In addition, no significant difference between filorexant and placebo was observed in change from baseline to week 3 in MADRS total score. There were no significant differences between treatments on other change from baseline depression endpoints (Table 1). The percentages of patients with remission (HAMD-17 total score ≤7) at week 6 were 12/56 (21.4%) for filorexant vs. 6/61 (9.8%) for placebo (estimated odds ratio = 2.5 [95% CI: 0.8, 7.3], $P = .097$).

Exploratory analyses were performed to assess whether filorexant improved insomnia severity in this study, consistent with its known sleep-promoting properties. Surprisingly, no statistically significant improvements in the change from baseline in ISI total score were observed with filorexant vs. placebo at week 3 or week 6 (mean [SD] change from baseline to week 6: -5.6 [6.2] with filorexant and -4.8 [5.5] with placebo; estimated treatment difference: -0.7 [95% CI: -2.8, 1.4], $P = .481$).

Safety and Tolerability

Twenty-seven patients (42%) in the filorexant group and 17 patients (27%) in the placebo group reported AEs during the treatment period (Table 2). One patient in each treatment group discontinued due to an AE (filorexant: sedation; placebo: fibromyalgia). One serious AE (diverticulitis, not drug related) was reported in the filorexant group and did not result in treatment discontinuation. No deaths were reported. The most commonly reported AEs with numerically greater incidence for filorexant than placebo during the treatment period were somnolence and suicidal ideation (Table 2).

Two patients in the filorexant group reported ECIs of excessive daytime sleepiness during the double-blind treatment period. Three ECIs were reported during the run-out period, one event of a fall in the placebo group, and 2 events of accidental overdose (i.e., accidentally taking study medication) that occurred in one patient in the filorexant group. No AEs were reported in conjunction with the accidental overdose, which involved 2 occasions of accidentally taking more study medication than the prescribed dose.

In total, 13 unique patients reported suicidal ideation during the trial (based on AE/ECI reports and/or positive responses to the C-SSRS), including 10 patients during the treatment period (filorexant, n/N = 7/64; placebo, n/N = 3/64) and 9 patients during the run-out period (filorexant [treatment]/filorexant [run-out], n/N = 5/29; filorexant/placebo, n/N = 1/28; placebo/placebo, n/N = 3/59). None of the AEs of suicidal ideation (nine patients in total) were considered by the investigator to be related to the study drug. No suicidal behaviors or ideation with a plan or intent were reported. All but one patient had a prior history of suicidal ideation. Two patients reported the same level of ideation at each visit throughout the study (filorexant, n = 1; placebo, n = 1), and 2 patients reported suicidal ideation at the randomization visit only, before taking the first dose of study medication (filorexant, n = 1; placebo, n = 1).

No clinically relevant mean changes in laboratory parameters or vital signs were observed during the study.

Table 1. Summary of Change from Baseline Depression Scores at Week 3 and Week 6 (Full Analysis Set)

		Baseline	Timepoint	Change from Baseline		Difference (Filorexant vs. Placebo)	
Assessment	N	Mean (SD)	Mean (SD)	Mean (SD)	LS mean (95% CI)	LS mean (95% CI)	*P* value
MADRS total score (primary endpoint)							
Week 3							
Filorexant 10 mg	61	30.2 (4.6)	23.2 (8.0)	-7.0 (6.2)	-7.0 (-8.7, -5.3)	-0.3	0.770
Placebo	62	30.9 (4.4)	24.3 (8.1)	-6.6 (6.9)	-6.6 (-8.3, -5.0)	(-2.7, 2.0)	
Week 6							
Filorexant 10 mg	58	30.3 (4.6)	19.3 (9.7)	-11.0 (9.5)	-10.9 (-13.2, -8.7)	-0.7	0.679
Placebo	61	31.0 (4.3)	20.7 (8.7)	-10.3 (8.2)	-10.3 (-12.5, -8.0)	(-3.8, 2.5)	
MADRS score excluding sleep item							
Week 3							
Filorexant 10 mg	61	26.4 (4.2)	20.4 (7.6)	-6.0 (5.8)	-6.0 (-7.5, -4.4)	-0.2	0.831
Placebo	62	27.1 (4.2)	21.4 (7.5)	-5.7 (6.3)	-5.7 (-7.2, -4.2)	(-2.4, 1.9)	
Week 6							
Filorexant 10 mg	58	26.5 (4.1)	17.0 (8.7)	-9.5 (8.5)	-9.4 (-11.5, -7.4)	-0.3	0.820
Placebo	61	27.2 (4.1)	18.0 (8.0)	-9.1 (7.4)	-9.1 (-11.1, -7.1)	(-3.2, 2.5)	
HAMD-17 total score							
Week 3							
Filorexant 10 mg	59	24.0 (5.3)	17.5 (6.0)	-6.5 (6.3)	-6.6 (-8.1, -5.0)	-0.9	0.412
Placebo	63	24.4 (4.9)	18.7 (6.7)	-5.7 (6.1)	-5.7 (-7.2, -4.2)	(-3.0, 1.3)	
Week 6							
Filorexant 10 mg	56	23.9 (5.4)	15.7 (7.5)	-8.2 (8.7)	-8.1 (-10.1, -6.2)	-0.5	0.697
Placebo	61	24.4 (4.9)	16.6 (7.0)	-7.8 (6.5)	-7.6 (-9.5, -5.7)	(-3.2, 2.1)	
HAMD Bech subscale score							
Week 3							
Filorexant 10 mg	59	13.1 (2.3)	9.3 (4.0)	-3.8 (3.5)	-3.8 (-4.8, -2.9)	-0.7	0.250
Placebo	63	13.0 (2.1)	9.9 (3.7)	-3.0 (3.6)	-3.1 (-4.0, -2.2)	(-2.0, 0.5)	
Week 6							
Filorexant 10 mg	56	13.1 (2.4)	8.4 (4.9)	-4.7 (4.8)	-4.6 (-5.7, -3.4)	-0.3	0.701
Placebo	61	13.0 (2.1)	8.7 (4.0)	-4.2 (4.0)	-4.3 (-5.4, -3.2)	(-1.9, 1.3)	

Based on a constrained longitudinal data analysis model with terms for treatment, time, the interaction of time by treatment, severity of disease measured by the Hamilton Depression Rating Scale 17-item (HAMD-17) total score (≤20, >20) and insomnia severity index total score (ISI ≤14, >14).

Table 2. Summary of Adverse Events during the Treatment Period (All Patients as Treated)

	Filorexant 10 mg (n = 64)	Placebo (n = 64)
Number (%) of patients		
With ≥1 AE	27 (42.2)	17 (26.6)
With drug-related AEs	16 (25.0)	6 (9.4)
With SAEs	1 (1.6)	0 (0)
With drug-related SAEs	0 (0)	0 (0)
Discontinued due to AEs	1 (1.6)	1 (1.6)
Discontinued due to drug-related AE	1 (1.6)	0 (0)
Discontinued due to a SAE	0 (0)	0 (0)
Common AEs (incidence ≥4 patients in either treatment group)		
Somnolence	5 (7.8)	0 (0)
Suicidal ideation[a]	5 (7.8)	1 (1.6)
Dizziness	0 (0)	4 (6.3)
Headache	4 (6.3)	5 (7.8)

Abbreviations: AE, adverse event; SAE, serious adverse event.
[a]A total of 10 patients reported suicidal ideation during the treatment period based on AE/ECI reports and/or positive responses to the C-SSRS: filorexant =7/64 (10.9%), placebo, 3/64 (4.7%). See main text for further details.

Discussion

The study hypothesis, that filorexant would be superior to placebo as augmentation therapy in patients with MDD, could not be adequately tested because of low enrollment (40% of planned). The size of the observed, nonsignificant difference on the MADRS primary endpoint (0.7-point reduction/-0.1 standardized effect size) was considerably smaller than the difference the study was powered to detect (3.5-point reduction/-0.4 standardized effect size), suggesting that even if the study had run to completion a significant effect would not have been found.

Our results argue against a direct antidepressant effect of orexin receptor antagonism in this population. As noted in the Introduction, the prior evidence supporting a direct antidepressant effect of orexin receptor antagonism is limited. It is interesting to consider whether an orexin receptor antagonist could indirectly help relieve depression through improving sleep. Although the majority (80%) of patients in our study had some degree of insomnia at baseline, improvements in insomnia symptoms were not observed with a dose of filorexant known to improve sleep in insomnia patients (Connor et al., 2016). It is unclear whether this lack of effect was due to underpowering or would have been impacted by features of the study population. As baseline insomnia was not required for inclusion, it is possible that effects of filorexant might differ in a cohort of depressed patients specifically selected based on insomnia symptoms. Had a significant effect on depression been demonstrated, it would have been important to distinguish whether the treatment effect was primarily due to an improvement in depression or attributable to an improvement in insomnia with secondary improvement in depression. However, this was not explored

due to the limited sample size and the observed results. Future studies might consider evaluating the effects of orexin receptor antagonists in patients with comorbid insomnia.

The low enrollment in our study suggests that the inclusion/exclusion criteria were too "restrictive." However, our intent was to exclude treatment-refractory patients. To be less restrictive would have resulted in a more heterogeneous population, which would have led to difficulties in interpreting the results.

Another factor that complicates interpretation of the results was the need to administer filorexant at bedtime to avoid daytime sedation resulting from its known hypnotic effect (Connor et al., 2016). It is unknown whether pharmacological activity during wakefulness would be required for the orexin receptor antagonist to provide a benefit on symptoms of depression. It is also possible that a higher dose of an orexin receptor antagonist is necessary to treat depression than insomnia, although administering a higher dose would likely not be clinically tenable due to the potential for increased next-day somnolence.

The observed safety profile of filorexant in depressed patients was generally similar to that reported with compounds in the same class, such as suvorexant and almorexant, in healthy subjects and insomnia patients (Bettica et al., 2012; Herring et al., 2012, 2016; Hoever et al., 2012; Cruz et al., 2014; Michelson et al., 2014), with somnolence being the most common adverse event. Not surprisingly, given the depressed population, suicidal ideation was reported more commonly in this study than in studies of primary insomnia patients (Michelson et al., 2014; Herring et al., 2016).

Acknowledgments

The authors acknowledge the contributions of Jeanne Lasorda, Heather Liebensberger, and Samar Froman from Merck & Co., Inc., to the study, and Sheila Erespe from Merck & Co., Inc., for assistance with submission. Editorial assistance was provided by Julie Adkins for Complete Medical Communications and Erin Bekes, PhD of Complete Medical Communications, Inc., Hackensack, NJ.

This assistance was funded by Merck & Co., Inc., Kenilworth, NJ. The authors are entirely responsible for the scientific content of the paper.

Statement of Interest

K. M. Connor, P. Ceesay, J. Hutzelmann, D. Snavely, C. Lines, W. J. Herring, and D. Michelson are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, and own stock/stock options in Merck. A.D. Krystal has received grants/research support from NIH, Teva, Sunovion, Astellas, Abbott, Neosync, Brainsway, Janssen, ANS St. Jude, Novartis. He has served as a consultant to: Abbott, Astellas, AstraZeneca, Attentiv, BMS, Teva, Eisai, Eli Lilly, GlaxoSmithKline, Jazz, Janssen, Merck, Neurocrine, Novartis, Otsuka, Lundbeck, Roche, Sanofi-Aventis, Somnus, Sunovion, Somaxon, Takeda, Transcept, and Vantia. M. H. Trivedi is or has been an advisor/consultant and received fees from: Abbott Laboratories, Inc., Abdi Ibrahim, Akzo (Organon Pharmaceuticals Inc.), Allergan, Alkermes, Arcadia Pharmaceuticals, AstraZeneca, Axon Advisors, Brintellix, Bristol-Myers Squibb Company, Cephalon, Inc., Cerecor, CME Institute of Physicians, Concert Pharmaceuticals, Inc., Eli Lilly & Company, Evotec, Fabre Kramer Pharmaceuticals, Inc., Forest Pharmaceuticals, GlaxoSmithKline, Health Research Associates, Janssen Global Services, LLC, Janssen Pharmaceutica Products, LP, Johnson & Johnson PRD, Libby, Lundbeck, Meade Johnson, MedAvante, Medtronic, Medscape, Merck, Mitsubishi Tanabe Pharma Development America, Inc., MSI Methylation Sciences Inc., Naurex, Neuronetics, Nestle Health Science-Pamlab Inc., One Carbon Therapeutics Ltd., Otsuka Pharmaceuticals, Pamlab, Parke-Davis Pharmaceuticals, Inc., Pfizer Inc., PgxHealth, Phoenix Marketing Solutions, Rexahn Pharmaceuticals, Ridge Diagnostics, Roche Products Ltd., Sepracor, SHIRE Development, Sierra, SK Life and Science, Sunovion, Takeda, Tal Medical/Puretech Venture, Targacept, Transcept, VantagePoint, Vivus, and Wyeth-Ayerst Laboratories. In addition, he has received grants/research support from: Agency for Healthcare Research and Quality (AHRQ), Cyberonics, Inc., National Alliance for Research in Schizophrenia and Depression, National Institute of Mental Health and National Institute on Drug Abuse, National Institute of Diabetes and Digestive Disorders, Johnson & Johnson, Janssen Research and Development. M. Thase has, during the last 3 years, received earning fees as a consultant to Acadia, Alkermes, Allergan (Forest, Naurex), AstraZeneca, Avenir, Cerecor, Eli Lilly & Co, Fabre-Kramer Pharmaceuticals, Inc., Gerson Lehman Group, Guidepoint Global, Johnson & Johnson (Janssen, Ortho-McNeil), H. Lundbeck A/S, MedAvante, Inc, Merck, Moksha8, Nestle (PamLab), Novartis, Otsuka, Pfizer, Shire, Sunovion, and Takeda. During the same timeframe, he has received research grants from Agency for Healthcare Research and Quality, Alkermes, Assurex, Avanir, Forest Pharmaceuticals, Janssen (Johnson & Johnson), Intracellular, the National Institute of Mental Health, Otsuka Pharmaceuticals, and Takeda. He has equity holdings in MedAvante. He receives royalties from the American Psychiatric Foundation, Guilford Publications, Herald House, and W.W. Norton & Company, Inc. His spouse is an employee of Peloton Advantage, which does business with several pharmaceutical companies.

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