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The clinical utility of newer antidepressant agents: Understanding the role in management of MDD

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Abstract

Whereas MDD is characterized in part by changes in mood, other symptoms can also cause significant impairment, including sexual dysfunction, cognitive impairment, and fatigue. Newer antidepressants are explored with the goal of more optimally treating these non–mood-related symptoms of MDD. The 3 oral antidepressants that have been FDA-approved most recently include vortioxetine, vilazodone, and levomilnacipran. Unique features of these antidepressants are explored through 3 patient cases.

Keywords: antidepressants, major depressive disorder, psychopharmacology, treatment-emergent sexual dysfunction, cognitive impairment, depression-related fatigue

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Disclosures: At the time of this writing, the Department of Veterans Affairs and Department of Defense Clinical Practice Guidelines for Management of Major Depressive Disorder 2022 had not yet been released. This guideline includes both vortioxetine and vilazodone as first-line treatment options for MDD. Also, I am a member of the Speaker's Bureau: Janssen Pharmaceuticals. I speak about medications that are not discussed in this article. Psychopharmacology Pearls are review articles intended to highlight both the evidence base available and/or controversial areas of clinical care for psychiatric and neurologic conditions as well as strategies of clinical decision making used by expert clinicians. As pearls, articles reflect the views and practice of each author as substantiated with evidence-based facts as well as opinion and experience. Articles are edited by members of the Psychopharmacology Pearls Editorial Board as well as peer reviewed by MHC reviewers. This article was developed as part of the 2022 Psychopharmacology Pearls product for BCPP recertification credit. The course information and testing center is at https://aapp.org/503974.

Introduction

MDD is one of the most common psychiatric disorders in the United States affecting approximately 7% of adults.[1] This condition, characterized by periods of depressed mood and/or a loss of interest or pleasure, has a significant impact on morbidity and mortality and represents a high economic burden.[2-4] Other symptoms of MDD may include changes in appetite, sleep patterns, energy, and concentration. Current trends indicate that antidepressant use is increasing in the United States. The percentage of Americans treated with an antidepressant increased by approximately 65% from 1999-2002 to 2011-2014.[5] The most recently available data (2015-2018) indicates that 13.2% of adults in the United States reported taking an antidepressant medication within the past 30 days.[6]

Despite the more widespread use of antidepressants, few new agents have become available in recent decades (see Table 1 for FDA approval dates). The most commonly prescribed medications remain the SSRIs.[7] Additional first-line treatments include SNRIs, bupropion, and mirtazapine.[8-10] The 2016 Canadian Network for Mood and Anxiety Treatments (CANMAT) guideline also includes vortioxetine as a first-line treatment option.[8] Second- and third-line options include tricyclic antidepressants; monoamine oxidase inhibitors; nonpharmacologic treatments, such as electroconvulsive therapy or transcranial magnetic stimulation; and augmentation with nonantidepressant medications, such as lithium or second-generation antipsychotics.[8-10]

The focus of this article is the most recently FDA-approved oral medications for the treatment of MDD, including

TABLE 1: FDA-approved first-line and newer oral antidepressants for MDD

Generic Medication Name	Year of FDA Approval
SSRIs	
Citalopram	1998
Escitalopram	2002
Fluoxetine	1987
Paroxetine	2001
Sertraline	1991
Vilazodone[a]	2011
Vortioxetine[b]	2013
SNRIs	
Desvenlafaxine	2008
Duloxetine	2004
Levomilnacipran	2013
Venlafaxine	1997
Norepinephrine dopamine reuptake inhibitors	
Bupropion	1985
Tetracyclic antidepressants	
Mirtazapine	1997

[a]SSRI and $5HT_{1A}$ partial agonist.

[b]SSRI and $5HT_{1A}$ agonist; $5HT_{1B}$ partial agonist; $5HT_{1D}$, $5HT_{3A}$, $5HT_7$ antagonist.

vilazodone, vortioxetine, and levomilnacipran. Although these medications have been FDA-approved for approximately 10 years, clinicians may be less familiar with these agents. Unique properties, including adverse effects and potential role in therapy, are addressed in this article in 3 patient cases.

Case 1: MDD and Antidepressant-Related Sexual Dysfunction

A 38-year-old female patient with a past medical history of generalized anxiety disorder (GAD), type II diabetes mellitus, obesity, and MDD presents to her outpatient psychiatrist. Active home medications include escitalopram 20 mg daily and metformin 500 mg twice daily. Escitalopram was initiated approximately 4 months ago and has contributed to a significant improvement of both GAD and MDD symptoms. However, the patient is experiencing anorgasmia and decreased libido, which has been affecting the patient's relationship with her partner. The patient recalls significantly elevated levels of anxiety and insomnia in the past when trialed on bupropion XL.

Sexual dysfunction, including problems with libido, arousal, orgasm, and ejaculation, may be caused or worsened by MDD in the absence of pharmacologic treatment.[11,12] Antidepressants may contribute to treatment-emergent sexual dysfunction (TESD).[13,14] It is estimated that as many as 70% of patients treated with an SSRI experience TESD, which contributes to antidepressant nonadherence.[13,15] The mechanism by which antidepressants contribute to sexual dysfunction remains poorly understood. Activation of $5HT_{2A}$ receptors in the central serotonergic system is likely a factor.[16] Serotonergic activation may also reduce dopamine transmission in the mesolimbic area. Dopamine is known to have a positive effect on sexual functioning.[13,14,16] Pharmacologic management of TESD may include short-term interruption of dosing (*drug holidays*); changing the administration time; switching to another antidepressant with less serotonergic activity, such as bupropion or mirtazapine; decreasing the dose of the antidepressant; or initiating add-on treatment.[17] Add-on treatments may include a second antidepressant, such as bupropion, or a $5HT_{2A}$ antagonist, such as mirtazapine, although mirtazapine's adverse effect profile may limit its use for patients when sedation and appetite stimulation are not desired. In cases of erectile dysfunction in male patients, a phosphodiesterase type 5 inhibitor, such as sildenafil, may also be added. The partial $5HT_{1A}$ agonist buspirone may also be used although data are mixed in terms of its effect on sexual dysfunction caused by SSRI treatment.[16-18]

Vilazodone was first approved by the FDA in 2011 primarily based on the results of 2 phase III randomized placebo-controlled trials.[19,20] Whereas it is generally considered an SSRI, vilazodone also acts as a partial agonist of presynaptic $5HT_{1A}$ receptors.[21] This combined mechanism of action mimics the combination of an SSRI plus buspirone, another $5HT_{1A}$ partial agonist, although with different binding capacities. The combination of an SSRI/SNRI and buspirone results in 10% to 20% occupation of the $5HT_{1A}$ receptors and 80% inhibition of the serotonin transporter (SERT) compared with vilazodone's ability to occupy 50% of both $5HT_{1A}$ receptors and SERT.[22,23] Vilazodone's partial ago-

Take Home Points:

1. Non–mood-related symptoms of MDD can cause significant impairment and may not be adequately treated by standard treatment options. These symptoms can include sexual dysfunction, cognitive impairment, and depression-related fatigue.
2. The most recently FDA-approved oral antidepressants include vortioxetine, vilazodone, and levomilnacipran. It is hypothesized that these medications may be able to better target these non–mood-related symptoms of MDD.
3. Current data assessing unique features of these newer antidepressants demonstrate relatively low clinical significance compared with typical first-line treatment, including SSRIs and SNRIs.

nism of the presynaptic $5HT_{1A}$ autoreceptors may enhance the serotonergic effect, and it was hypothesized that this would contribute to a more rapid onset of symptom relief and greater efficacy. The partial agonism of these receptors was hypothesized to reduce the degree of sexual dysfunction associated with SSRIs.[21,24,25] Although animal models did demonstrate a more rapid elevation of synaptic serotonin compared with SSRIs, the anticipated rapid onset of clinical effect and greater efficacy has not been demonstrated in head-to-head human trials.[22,27] The rapid serotonin increase may also contribute to the higher prevalence of serotonin-mediated nausea and vomiting more commonly associated with vilazodone (20% to 30%) as compared with other SSRIs.[28,29]

The post hoc analysis of a randomized, double-blind, active-controlled phase IV clinical trial compared the impact on sexual functioning of vilazodone at doses of 20 and 40 mg/d with citalopram 40 mg/d and placebo.[15,28] The abbreviated version of the Changes in Sexual Functioning Questionnaire (CSFQ-14) was utilized to assess 1047 outpatients with MDD experiencing a current depressive episode. The CSFQ-14 is a validated, 14-item, sex-specific, self-reported scale that was developed to assess changes in sexual functioning associated with psychiatric illnesses or medications.[29] The total score ranges from 14 to 70 with lower scores indicating more sexual dysfunction.[32,33] A score of $\leq$47 and $\leq$41 represent clinically significant sexual dysfunction in males and females, respectively. In this study, patients in all groups demonstrated an improvement in CSFQ-14 scores from baseline to week 10 of treatment with a greater improvement in subjects who were considered treatment responders (based on Montomery-Åsberg Depression Rating Scale [MADRS] scores; see Table 2). Subjects with baseline sexual dysfunction (>50% of subjects) had greater improvements in CSFQ-14 scores, whereas the change in subjects with normal baseline sexual functioning was small. The mean changes in total CSFQ-14 score were relatively small in all groups. No groups showed statistically significant improvement in CSFQ-14 scores compared with placebo in the original study, and no inferential statistics were performed in the post hoc analysis. Although a minimal clinically important difference in CSFQ-14 scores has not been definitively established, it is sometimes cited as a change in 3 to 5 points.[39,40] Therefore, minimal clinical improvement was demonstrated in this analysis. The rates of decreased libido and delayed ejaculation identified are similar to those associated with bupropion, an antidepressant generally not associated with TESD.[41] Therefore, the rates of TESD identified in this comparison trial with vilazodone and citalopram identified relatively low rates of TESD in all groups. No subjects discontinued vilazodone due to TESD. Although this study showed a trend toward less TESD in the vilazodone groups, the results were not statistically significant. It should also be noted that antidepressants with high serotonin selectivity, which include citalopram along with fluoxetine, paroxetine, sertraline, and venlafaxine, are associated with higher rates of sexual dysfunction compared with other less selective antidepressants.[36] Despite the use of citalopram as a control in this study, there was still no clinically significant difference in TESD.

A phase I, randomized, double-blind, parallel-group study[37] assessed the impact of placebo, paroxetine 20 mg/d, and vilazodone 20 or 40 mg/d on sexual functioning in healthy, sexually active volunteers aged 18 to 45 years. The primary outcome was the change in CSFQ-14 scores from baseline to day 35. Whereas the CSFQ-14 scores did decrease (worsen) in all groups, there were no statistically significant differences. A post hoc analysis that excluded patients in the active treatment groups with an undetectable plasma drug concentration demonstrated that the paroxetine group experienced a more significant decrease in CSFQ-14 total of −10.5 compared with −1.14 and −0.78 in the placebo and vilazodone 20 mg/d groups, respectively ($P < .05$). Thus, neither comparative trial including vilazodone demonstrated a statistically significant difference in sexual functioning in the primary analysis despite comparison with antidepressants generally associated with a higher rate of TESD.

Vortioxetine has also been investigated for a potentially lower incidence of TESD. It was FDA-approved in 2013 based on the results of 6 short-term (6 to 8 week) randomized, double-blind, placebo-controlled clinical trials and 1 maintenance study, which demonstrated efficacy in the treatment of MDD.[38] In addition to the inhibition of SERT, it antagonizes $5HT_3$, $5HT_7$, and $5HT_{1D}$ receptors. Additional mechanisms include partial agonist activity at $5HT_{1B}$ receptors and agonist activity at $5HT_{1A}$ receptors.[39,40] These additional serotonergic mechanisms may contribute to the high rate of nausea (15% to 20%) associated with vortioxetine.[38] Early trials[37,41] suggest that vortioxetine had similar rates of sexual dysfunction as placebo. One study included patients with adequately treated MDD who experienced TESD as measured by CSFQ-14 during treatment with citalopram, paroxetine, or sertraline.[42,43] These patients were randomly assigned to switch directly to flexible doses (10 or 20 mg/d) of vortioxetine (n = 225) or escitalopram (n = 222). The primary endpoint was the change in CSFQ-14 total score from baseline to the end of 8 weeks of treatment. Patients in the vortioxetine group showed statistically significant mean improvement in CSFQ-14 scores (8.8 ± 0.64) compared with escitalopram (6.6 ± 0.64; $P = .013$). This difference was also significant at week 4. If a 3- to 5-point improvement is to be considered the minimal threshold for clinical improvement, this study demonstrates meaningful improvement in TESD in both groups. Several studies[44,45] also compared the rate of TESD associated with vortioxetine with that of duloxetine. One of these studies[45] compared the rate of TESD using the Arizona Sexual Experiences Scale (ASEX) in adult patients age 18 to 75 years with MDD over

TABLE 2: Changes in sexual functioning from post hoc analysis (baseline to week 10)

	Results							
	Female				Male			
	n (mean change in total CSFQ-14 score)	Libido decreased, %	Erectile dysfunction, %	Delayed ejaculation, %	n (mean change in total CSFQ-14 score)	Libido decreased, %	Erectile dysfunction, %	Delayed ejaculation, %
Placebo (n = 264)								
All females	147 (2.0)	0.6	0	0	117 (3.5)	0.6	2.4	0
MADRS responders	58 (3.84)				49 (4.35)			
MADRS nonresponders	60 (0.27)				45 (2.6)			
Normal sexual function at baseline	46 (–1.09)				48 (0.71)			
Sexual dysfunction at baseline	72 (4.01)				46 (6.43)			
Vilazodone 20 mg/d (n = 267)								
All females	152 (1.9)	1.8	0	0	115 (2.4)	2.5	0	0.8
MADRS responders	73 (3.82)				56 (3.21)			
MADRS nonresponders	41 (–1.41)				31 (0.97)			
Normal sexual function at baseline	44 (–1.48)				37 (0.41)			
Sexual dysfunction at baseline	70 (4.09)				50 (3.90)			
Vilazodone 40 mg/d (n = 259)								
All	148 (3.0)	0.6	0	0	111 (1.2)	3.3	2.4	1.6
MADRS responders	70 (5.06)				54 (2.26)			
MADRS nonresponders	38 (–0.87)				30 (–0.80)			
Normal sexual function at baseline	33 (–0.55)				37 (–0.95)			
Sexual dysfunction at baseline	75 (4.52)				47 (2.83)			
Citalopram 40 mg/d (n = 257)								
All	148 (1.2)	1.2	0	0	109 (2.1)	1.7	2.6	1.7
MADRS responders	72 (2.33)				57 (2.67)			
MADRS nonresponders	50 (–0.42)				26 (0.77)			
Normal sexual function at baseline	41 (–1.05)				37 (0.32)			
Sexual dysfunction at baseline	81 (2.35)				46 (3.48)			

CSFQ-14 = Changes in Sexual Functioning Questionnaire; MADRS = Montomery-Åsberg Depression Rating Scale.

an 8-week period. The ASEX is a validated 5-item rating scale that quantifies sex drive, arousal, vaginal lubrication/penile erection, and ability to reach orgasm. Possible total scores range from 5 to 30. Sexual dysfunction is considered a total score ≥19, a single item score of 5 or 6, or any 3 items having a score of ≥4.[46] Although the results show a trend toward a lower rate of TESD in the vortioxetine 15 mg/d, vortioxetine 20 mg/d, and placebo groups (35.6%, 35.6%, 36.2%, respectively) compared with the duloxetine 60 mg/d group (53.2%), these results were not statistically significant. A second study, which included adults 18 to 75 years of age with MDD, conducted an exploratory analysis of sexual function utilizing the ASEX. Participants in this study had a high rate (65% to 71.2%) of sexual dysfunction at baseline. The rate of TESD among subjects without baseline sexual dysfunction was highest in the vortioxetine 2.5 mg/d group (51%) compared with vortioxetine 5 mg/d (37.5%), duloxetine 60 mg/d (46.9%), and placebo (33.3%).[44] None of the changes in ASEX score from baseline were significant compared with placebo in any group after 6 or 8 weeks.

An additional randomized, double-blind, parallel group, phase IV study used the CSFQ-14 as a primary endpoint when comparing TESD rates in healthy adults (age 18 to 40 years) treated with paroxetine 20 mg/d, vortioxetine 10 mg/d, vortioxetine 20 mg/d, or placebo.[47] In this study (n = 361), paroxetine was associated with significantly more TESD than vortioxetine 10 mg/d (mean difference of 2.74 points, $P = .009$) after 5 weeks of treatment in all 5 dimensions of the CSFQ-14. Vortioxetine 20 mg/d showed numerical improvements in TESD compared with placebo, but the difference was not statistically significant. Neither dose of vortioxetine was statistically significantly worse than

placebo in terms of TESD, whereas paroxetine did cause significantly more TESD.

This case demonstrates the importance of considering sexual dysfunction a constellation of symptoms that may affect patients with MDD regardless of medication status. TESD may have a profound impact on antidepressant adherence rates. For this particular patient, a medication change should be considered in an attempt to alleviate the reported TESD. While switching to or adding bupropion may be a reasonable intervention for some patients, this patient has previously experienced an increase in GAD symptoms following bupropion initiation. Because the patient is a biological female, it would also not be appropriate to recommend a phosphodiesterase type 5 inhibitor. Mirtazapine, although also less likely to induce TESD, may also not be the best option due to the patient's type II diabetes mellitus and obesity. Vortioxetine is not associated with any known weight gain, whereas the rate associated with vilazodone is low at 1% to 2%.[29,38] Therefore, it may be reasonable to consider either vilazodone or vortioxetine. Because vortioxetine is considered a first-line treatment option per the CANMAT guidelines and because it was directly compared to escitalopram (this patient's current mediation), it may be a better initial choice.

Case 2: Depression-Related Cognitive Impairment

A 45-year-old patient with MDD has achieved partial remission from treatment with venlafaxine XR 300 mg daily for 6 months. Previous trials include citalopram, sertraline, mirtazapine, and duloxetine. Although noting a significant improvement in mood, appetite, and sleep, the patient reports extreme difficulty concentrating at work. In addition, tasks that were once simple and routine are taking much more time and mental effort. The patient is worried about being demoted or terminated if quality of work does not improve.

The cognitive dysfunction often associated with MDD plays a significant role in a patient's ability to maintain activities of daily living and full-time employment.[38,48] A post hoc analysis[49] of the STAR*D trial shows that negative mood and concentration problems were the most debilitating depressive symptoms for all domains of functioning. Additional data[50,51] support this and identify that people with MDD experienced the most prominent impairment in domains of executive functioning, processing speed, concentration and attention, learning, and memory. While notable during an acute episode, these deficiencies are also found to persist during remission from mood symptoms.[51-53]

Vortioxetine, in addition to the mechanisms previously discussed, demonstrates the ability to increase extracellular acetylcholine and histamine levels while selectively increasing dopamine levels in the frontal cortex and nucleus accumbens.[39,54,55] Glutaminergic, noradrenergic, and GABAergic systems are also modulated by vortioxetine.[56,57] Although the exact mechanisms are not clear, the actions on these neurotransmitter systems may account for the potential improvements in cognition and anxiolytic effects seemingly unique to vortioxetine.[56]

Vortioxetine's impact on cognitive functioning and/or functional recovery from MDD has been an area of study as the goal of treatment has shifted to include improvement of cognitive symptoms and return to functional productivity. The CONNECT study was a multicenter, double-blind, parallel-group, placebo-controlled trial that compared the effect of vortioxetine or placebo on cognitive functioning for patients with acute recurrent MDD. This was measured via the Digit Symbol Substitution Test (DSST), which assesses processing speed, executive function, and attention.[58] This scale ranges from 0 to 133 points with a lower score indicating worse cognitive functioning. The degree of change in the DSST score is typically represented using a standard effect size statistic. The clinical significance of changes in DSST score in MDD is typically measured by how far the SD score is below the norm; however, DSST scores do not always correlate with patient-reported depression score in patients with MDD.[63,64] The primary endpoint of this study was the change in DSST from baseline to week 8 for patients receiving flexible-dose vortioxetine (10 or 20 mg/d), duloxetine (60 mg/d), or placebo. Compared with placebo, vortioxetine demonstrated a significant improvement of 1.75 points in the DSST score with a standardized effect size of 0.254 indicating small-to-moderate improvement. The change in DSST was not significantly different in the duloxetine group compared with placebo (change of 1.21). However, the small numerical difference in change in DSST score between the groups suggests there may be no clinically significant difference. A post hoc analysis was also designed to measure depressive symptoms (measured via MADRS) along with patient function as evaluated by the University of California San Diego Performance-based Skills Assessment (UPSA).[48,58] This test involves role-playing tasks in 5 functional areas, including communication, finance, and transportation. It is validated as a test of functioning in MDD and is correlated with cognitive function and work ability but may change independently of depressive symptoms.[59] An increase of 6 to 7 points after 8 weeks of antidepressant treatment is considered the threshold for clinical relevance.[60,61] This analysis identified patients who were considered dual responders, meaning that they had achieved $\geq$50% reduction in baseline MADRS score plus a change in the UPSA composite score of $\geq$7 points by the end of 8 weeks. The vortioxetine group had a significantly greater number of

dual responders (27.4%) compared with the placebo group (14.5%, $P = .004$). The calculated number needed to treat (NNT) is 8. The duloxetine group (n = 210) did not have a statistically significantly different percentage of dual responders (22.5%, NNT of 13) than the placebo group. The vortioxetine group also showed statistically significant improvement (23.4%, NNT of 11) compared with placebo (13.9%, $P = .025$) when the UPSA composite score threshold was increased to ≥ 9, whereas the duloxetine group did not. The authors concluded that vortioxetine treatment resulted in a greater probability of achieving a combined symptomatic/functional outcome.

The ReMind SWITCH study was a randomized, active-comparator, parallel-group trial[62] that included patients with MDD with an inadequate response to ≥6 weeks of SSRI or SNRI monotherapy. This study compared the effects of vortioxetine (n = 51) and escitalopram (n = 50), both flexibly dosed at 10 to 20 mg/d, on cognitive dysfunction and MDD symptoms over 8 weeks of treatment on the DSST. All cognitive performance tests conducted in this study (including secondary efficacy assessments) were also combined into a composite score to measure overall cognitive performance. The DSST score improved by 8.46 and 6.46 in the vortioxetine and escitalopram groups, respectively, with a mean difference of 2.0 points in favor of vortioxetine. The standardized effect size was 0.25 for vortioxetine versus escitalopram, indicating a small-to-moderate improvement. However, none of these results was statistically significant. Secondary outcome measures tended to favor vortioxetine regarding impact on cognitive functioning, but again, no statistically significant differences were noted. This relatively small study suggests that both vortioxetine and escitalopram improve cognitive function in patients with MDD who failed to respond to previous treatment.

The ReMind WORK study was a small (N = 152), exploratory, multisite, randomized, parallel-group, placebo-controlled trial that included patients aged 18 to 65 years with MDD (MADRS score ≥26) who were actively working.[65] Patients were randomized to 8 weeks of treatment with either vortioxetine 10 mg/d, paroxetine 20 mg/d, or placebo. The DSST score (primary outcome) increased in all treatment groups (7.37, 7.59, 6.61 in the placebo, vortioxetine, and paroxetine groups, respectively) but with no statistical differences noted. One of the secondary measures in this study was the Perceived Deficits Questionnaire-Depression (PDQ-D) score. The PDQ-D is a subjective measure and is measured on a scale from 0 to 80 with higher scores indicating more severe symptoms. Both vortioxetine, with a difference of -6.81 ($P = .012$) and paroxetine with a difference of –6.91 ($P = .010$) showed statistically significant improvement in this measure compared with placebo. A limitation of the PDQ-D score is that cutoff values are not definitely established although a change of approximately 7 points out of a potential score of 80 may not constitute a clinically significant change.[66]

Vortioxetine is also studied as a potential adjunctive treatment to standard SSRI therapy to improve cognitive impairment in MDD.[67] One randomized, double-blind, placebo-controlled trial included patients in remission or partial remission from MDD following ≥12 weeks of treatment with SSRI monotherapy (escitalopram, citalopram, or sertraline) at a stable dose for ≥ 8 weeks before screening. Subjects were then randomized to current SSRI plus placebo (SSRI monotherapy), current SSRI plus vortioxetine (vortioxetine adjunctive treatment), or vortioxetine plus placebo (vortioxetine monotherapy). The DSST score was the primary efficacy measure. Several other cognitive function assessments were included as secondary endpoints, including the Rey Auditory Verbal Learning Test, Sheehan Disability Scale (SDS), Trail Making Test A and B, and the Stroop Color Naming Test. By the end of 8 weeks, the DSST core had improved similarly in all treatment groups with no differences identified. Similar results were seen in secondary endpoint measures although numerically greater improvements were seen in some endpoints, such as SDS scores, in both vortioxetine groups compared with the SSRI monotherapy group.

Overall, whereas it appears that vortioxetine is efficacious in the treatment of MDD, the evidence supporting its ability to target cognitive dysfunction is mixed. For the patient in this case, it may be reasonable to trial vortioxetine monotherapy given the multiple previous trials of both SSRIs and SNRIs and persistent cognitive symptoms. Furthermore, the patient is only experiencing a partial response, so a medication change may be warranted regardless of cognitive status.

Case 3: Depression-Related Fatigue

A 32-year-old patient with MDD presents to the outpatient clinic due to a new depressive episode. This is the third total lifetime episode. Previous episodes have been successfully treated with venlafaxine XR 225 mg/d. The patient notes that this episode feels different because the most prominent symptoms are fatigue and a significant lack of motivation to succeed at work and to socialize with friends. The patient states that, if given the chance, the patient would lay on the couch all day.

Some symptoms of MDD may be more specifically related to a deficiency in norepinephrine (NE). These symptoms include fatigue, amotivation, anhedonia, and apathy.[68,69] Fatigue may be one of the most common factors impacting daily functioning in MDD, affecting more than 90% of patients. Fatigue may also significantly reduce the likelihood of remission from a depressive episode.[70-72] In a secondary

analysis of the STAR*D trial, 60.8% of patients demonstrated residual fatigue after up to 14 weeks of treatment with an SSRI. Patients with residual fatigue also had worse mental and physical functioning outcomes compared with patients with remission of fatigue symptoms.[71]

Levomilnacipran extended-release (ER) was FDA-approved for MDD in 2013.[73,74] Unlike more commonly utilized SNRIs, levomilnacipran shows significant selectivity for inhibition of NE reuptake compared with serotonin (2:1 inhibition ratio). Levomilnacipran's selectivity for NE as opposed to serotonin is 17 times higher than venlafaxine and 27 times higher than duloxetine. This is a dose-related phenomenon, and at higher doses, levomilnacipran inhibits NE and serotonin transporters equally.[68,75] Levomilnacipran does not appear to have activity at other receptor types, such as dopaminergic, muscarinic, or adrenergic receptors.[73,76] Similar to the other antidepressants discussed previously, levomilnacipran has a higher rate of nausea (17%) as compared with other common antidepressants.[74]

Because of levomilnacipran's high affinity for NE receptors, the possibility that this medication could have more efficacy in NE deficiency-related symptoms of MDD has been explored. Although studies of levomilnacipran ER were not specifically designed to assess its impact on fatigue-related symptoms, several post hoc analyses[77-81] have been conducted using the results of the same 5 randomized, double-blind, placebo-controlled trials of levomilnacipran ER 40 to 120 mg daily for MDD. One post hoc analysis[70] included 2598 subjects and focused on the effect of levomilnacipran on fatigue symptoms as measured by the change in least squares mean (LSM) from baseline to the end of double-blind treatment of several fatigue-related scales. These included item 7 of the MADRS scale (lassitude, described as difficulty or slowness in initiating and/or performing daily activities) and items 7, 8, and 13 of the Hamilton Depression Rating Scale ($HAMD_{17}$), which measure work/activities, psychomotor retardation, and general somatic symptoms respectively. Patients were categorized based on whether they had high (MADRS item 7 score $\geq$4) or low (MADRS item 7 score $\geq$4) levels of fatigue prior to treatment. The majority of patients (73.8%) met criteria for high levels of fatigue. Mean baseline MADRS total scores were also higher in this group. The results of this post hoc analysis showed statistically significant improvements in the levomilnacipran ER group in all 4 fatigue-related scales compared with placebo in both the high and low fatigue level groups ($P < .05$). However, the effect sizes were small, ranging from 0.09 (psychomotor retardation) to 0.21 (work/activities). The percentage of patients in the overall study population with remission of fatigue symptoms was also greater for patients receiving levomilnacipran for all MADRS and $HAMD_{17}$ items ($P < .05$). Treatment effect sizes differed across some subgroups. Male patients and older patients had a greater effect size than female and younger patients, respectively. Premenopausal females (<50 years of age) also had a greater effect size compared with women older than 50 years. Obese patients with a BMI $\geq$30 kg/m^2 did not have a detectable difference in fatigue symptoms compared with placebo.

Another post hoc analysis of the same 5 trials divided patients into subgroups according to baseline symptom clusters if present.[82] The noradrenaline cluster (NA Cluster) included patients with higher baseline scores in items from the MADRS and $HAMD_{17}$ scales related to concentration difficulties (High NA Subgroup). The Anxiety Cluster included subjects with higher baseline scores in items pertaining to inner tension, agitation, psychic anxiety, and somatic anxiety (High Anxiety Subgroup). A third subgroup contained patients who met criteria for both clusters (High NA + Anxiety Subgroup). The LSM changes from baseline were significantly greater in both the NA and Anxiety Cluster scores in the levomilnacipran ER group compared with placebo. These results were significant for all 6 of the items making up the NA Cluster score (effect size 0.15 to 0.24) and 3 of the 4 items making up the Anxiety Cluster score (effect size 0.10 to 0.16); there was no significant difference in $HAMD_{17}$ item 11, which assesses somatic anxiety. All 3 subgroups demonstrated a statistically significant decrease in the NA Cluster score with a greater effect in the High NA and High NA + Anxiety groups (effect size 0.31 and 0.24, respectively). The Anxiety Cluster score decreased significantly for the High Anxiety and High NA + Anxiety Subgroups but not for the High NA subgroup. The response rate, defined as $\geq$ 50% improvement in cluster score, was significantly higher in the NA Cluster (44% vs 34%) and Anxiety Cluster (39% vs 36%) compared with placebo. Compared with the pooled study population, subjects in the 3 subgroups of this post hoc analysis demonstrated more functional improvement and a higher degree of improvement in NA and Anxiety Cluster scores.

Whereas the results of these post hoc analyses are promising, it would be difficult to select levomilnacipran solely based on fatigue or other NE-related symptoms, especially given the lack of any head-to-head comparisons of levomilnacipran with other antidepressants. Because this patient had a previous good response to venlafaxine XR, it would be reasonable to trial this medication again for the current depressive episode. Similar results may be expected in relation to NE-related symptoms because venlafaxine XR also inhibits the reuptake of NE in a dose-dependent manner.[83] Although not always the case, the majority of patients also do respond to reinstatement of an antidepressant that was previously effective.[84]

With the exception of the 2016 CANMAT guidelines, which include vortioxetine as a first-line treatment option and levomilnacipran and vilazodone as second-line options,

current guidelines do not explicitly recommend the 3 new antidepressants. Multiple meta-analyses[85,86] demonstrate minimal differences in overall efficacy between vilazodone, vortioxetine, levomilnacipran, and the other commonly utilized antidepressants. Whereas generally well-tolerated, vilazodone, vortioxetine, and levomilnacipran are all associated with an increased incidence of nausea compared with other antidepressants. None of the agents discussed are currently available generically in the United States, and they are generally considered "nonpreferred" treatment options on state Medicaid formularies. This may contribute to cost concerns for patients if the prescription is not covered by the insurance provider. Costs for these agents range from approximately $400 to $500 for a 30-day supply although savings programs are available.

Conclusion

Patients with MDD may have significant variations in symptom presentation. Symptoms that are less commonly assessed, such as sexual dysfunction, cognitive impairment, and NE-related symptoms, such as fatigue, may have the most significant impact on a patient's quality of life and functional abilities. As discussed in these patient cases, the more recently FDA-approved oral antidepressants may have unique features that are able to better target these symptoms of MDD. However, at this time, the data demonstrate relatively low clinical significance (vilazodone or vortioxetine for TESD), mixed results (vortioxetine for cognitive impairment), or are based on indirect comparisons (levomilnacipran for NE-related symptoms). Although these symptoms are important to consider when initiating an antidepressant for MDD, the 3 medications discussed in this article likely do not have enough compelling evidence to make a selection solely based on the unique features discussed.

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