

Vortioxetine and Lewy Body Disorders

Charles M. Lepkowsky, Ph.D.

Independent Practice, 1143 Deer Trail Lane, Solvang, CA USA 93463

Telephone: (805) 688-1229

Email: clepkowsky@gmail.com

Abstract—

Introduction: Vortioxetine is a newer antidepressant medication with reported potential for mitigating cognitive impairment secondary to major depressive disorder. However, the current study suggests that the use of Vortioxetine for patients with Lewy Body Disorders may present complications due to its interactions with medications frequently prescribed to that population, including Bupropion and Carbidopa-Levodopa.

Methods: A case study is presented to illustrate Vortioxetine's potential interactions with Lewy pathology and other medications frequently used for patients with Lewy Body Disorders. Vortioxetine's potential for exacerbation of Lewy pathology symptoms including cognitive impairment and gastric immotility is described, and the underlying biochemical mechanisms are explained.

Results: The use of Vortioxetine exacerbated Lewy Body symptoms including cognitive impairment and gastric immotility. Discontinuation of Vortioxetine alleviated symptom exacerbation.

Discussion and Conclusions: The chemical mechanisms responsible for symptom changes consequent to Vortioxetine's interactions with serotonergic and cholinergic suppression characteristic of Lewy pathology, and other medications used for the Lewy Body patient in the case study are discussed. The use of Vortioxetine for patients with Lewy Body Disorders may present complications due to its effect on neurotransmitter pathways affected by Lewy pathology, as well as its interactions with medications frequently prescribed to that population. Recommendations are made for screening Lewy Body patients before prescribing Vortioxetine.

Keywords— Cognitive Impairment; Constipation; Drug Interactions; Lewy Body Disorders; Parkinson's Disease; Vortioxetine.

I. INTRODUCTION

Approved for use in the U.S. by the FDA in 2013 [1, 2], Vortioxetine is described as both an atypical antipsychotic and an antidepressant. Intended for the treatment of major depressive disorder (MDD) [3], it may have benefit for reduction of anxiety [4] and enhancement of memory and cognitive performance [5]. The purpose of this paper is to review the literature on Vortioxetine's efficacy for treating MDD and anxiety, potential for memory enhancement, mechanisms of action, and specific suitability for use with patients diagnosed with Lewy Body disorders.

A. Clinical Trials, Efficacy and Safety, Long-Term Use

In clinical trials, Vortioxetine has demonstrated efficacy in reducing the symptoms of depression [4, 6-18] and anxiety [4, 19, 20], comparing favorably with SNRI's including Duloxetine [17, 20-23], Venlafaxine [24], and Desvenlafaxine [25], atypical antidepressants including Agomelatine [26, 27], and SRI's including Escitalopram, Sertraline, and Vilazodone [25] for efficacy and safety. Vortioxetine appears to compare favorably with SRIs including Paroxetine for mitigation of sleep disturbance [28, 29], and may have long-term benefit in the treatment of MDD [30, 31].

B. Memory Enhancement

Animal research indicates that Vortioxetine enhances memory [32], restoring reversal learning [33], increasing hippocampal synaptic plasticity [34], and improving recognition memory [35], benefits not found with Fluoxetine [36], Escitalopram, or Duloxetine [37]. Clinical trials with human subjects diagnosed with MDD indicate that Vortioxetine not only mitigates cognitive impairment as a symptom of MDD [37-40], but may improve cognition in

other conditions wherein cognitive impairment is a prominent feature [41], prompting the FDA to update Vortioxetine labels to "include data showing improvement in processing speed, an important aspect of cognitive function in acute Major Depressive Disorder (MDD)" [5].

C. Mechanisms of Action

Vortioxetine's mechanism of action is novel, and more complex than that of other antidepressants [42]. Vortioxetine is metabolized by cytochrome P450 enzymes (e.g., CYP450 2D6) and subsequently by uridine diphosphate glucuronosyltransferase [43]. Although its direct mechanism of action is not fully understood, Vortioxetine is thought to act as a serotonin reuptake inhibitor (SRI), and is classified as a serotonin modulator and simulator (SMS). Acting as a partial agonist of the 5-HT_{1B} receptor, an agonist of 5-HT_{1A}, and an antagonist of the 5-HT₃, 5-HT_{1D}, and 5-HT₇ receptors, Vortioxetine is a serotonin (5-HT) transporter (SERT) inhibitor [44-48].

Achieving significant clinical effects at much lower serotonin SERT occupancy (inhibition) rates than traditional SERT inhibitors, Vortioxetine (unlike SRIs) appears to engage additional downstream and non-serotonergic mechanisms that mediate its antidepressant and domain-specific effects on cognition [49]. Its interaction with 5-HT-receptor-mediated negative feedback mechanisms controlling neuronal activity increases serotonergic, noradrenergic, dopaminergic, cholinergic, histaminergic and glutamatergic neurotransmission in brain structures associated with MDD, its specific antagonism of 5-HT₃ receptors reducing 5-HT₃ receptor-mediated excitation of GABA interneurons, consequently increasing hippocampal pyramidal activity [50]. The downstream mechanisms influencing glutamatergic and

GABAergic neurotransmission are thought to be the basis of Vortioxetine's memory- and cognition-enhancing effects [51-53].

D. Drug Interactions

Vortioxetine's numerous and complex mechanisms of action create the potential for complications. Its 5-HT₃ receptor antagonism appears to exert inhibitory effects over the release of norepinephrine (NE) and acetylcholine (ACh) [54], complicating its role in the regulation of mood and memory. Although Vortioxetine was initially thought to have a relatively low risk for pharmacodynamic drug interactions [50, 55], Vortioxetine peak plasma concentration and systemic exposure are significantly decreased when Vortioxetine is co-administered with Rifampicin, a broad cytochrome P450 inducer which accelerates that enzyme's metabolism of Vortioxetine [56].

Conversely, several CYP450 2D6 inhibitors (which limit CYP450 2D6's metabolism of Vortioxetine) significantly increase Vortioxetine peak plasma concentration and systemic exposure. These include Fluconazole, Ketoconazole, Bupropion, Cinacalcet, Fluoxetine, Paroxetine, Quinidine, Ritonavir, and Terbinafine [43, 56]. Because Fluoxetine and Paroxetine are selective serotonin reuptake inhibitors, additive serotonergic effects with Vortioxetine specifically increase the risk of serotonin syndrome [57]. Vortioxetine peak plasma concentration and systemic exposure are even greater in combination with the potent CYP450 2D6 inhibitor Bupropion [43]. When co-administered, Levodopa-Carbidopa (Sinemet) also significantly increases Vortioxetine peak plasma concentration and systemic exposure [58, 59].

E. Lewy Body Disorders: Prevalence

Lewy body disorders are gaining prominence in the research literature, as their diagnostic criteria become more defined, making more apparent their increasing prevalence [60, 61]. In 2017, 50 million people worldwide were diagnosed with neurocognitive disease, a figure expected to exceed 75 million by 2030, and 131.5 million by 2050 [62-64]. Approximately 22% of these diagnoses are assigned to Neurocognitive Disorder with Lewy Bodies (NCDLB) (previously called Lewy Body Dementia) and 9% to Parkinson's disease (PD) [65]. The prevalence of Lewy Body disorders (LBDs) is expected to increase from 15.5 million people worldwide today to over 40 million by year 2050 [64, 66-67]. These figures are likely to grow, as more accurate diagnosis decreases the frequent misdiagnosis of LBDs [68].

F. α -synucleinopathy

Both PD and NCDLB are characterized by the intraneuronal presence of Lewy bodies, pathologic aggregates of the synaptic protein α -synuclein [69, 70]. α -synucleinopathy is not confined to the central nervous system (CNS), but also affects the autonomic nervous system (ANS), the peripheral nervous system (PNS) and the enteric nervous system (ENS), spreading from one nervous system area to another over time [71, 72]. Lewy bodies aggregate not only near the nucleus of the neuron, but even more abundantly in neurites (axons and dendrites) [73].

α -synucleinopathy most infamously impairs dopaminergic function producing Parkinsonian symptoms, but can affect all neurotransmitter pathways [60, 61]. In LBDs, the emergence of MDD is associated with impairment of multiple neurotransmitter pathways, including serotonergic and noradrenergic pathways [74-76], at a significantly higher rate than in Alzheimer's Disease [77]. NCDLB and PD are also characterized by cholinergic neural deficits and functional impairment [60, 61, 69-83], which are recognized as symptomatic features of α -synucleinopathy [73, 83-85]. These include motor symptoms, gait dysfunction, dyskinesias, cognitive deterioration, psychosis, sleep abnormalities, autonomic dysfunction, altered olfactory function [86], and gastric immotility [87, 88].

G. Gastric Immobility as a Quantifiable Indicator of α -synuclein Cholinergic Impairment

Gastric immotility in Lewy Body patients is at least three times as prevalent as it is among the general population [89], and might be as a universal feature of Lewy Body disorders [90]. In both PD and NCDLB, α -synuclein pathology is found in the enteric nervous system [91-103], specifically in the myenteric plexus (MP) [71, 72, 104-108] and the colonic submucosal plexus (CSMP) [98], which is innervated by the MP. The MP controls motility of the colon, and 95% of its innervation is cholinergic [109], indicating that constipation in NCDLB and PD is the direct consequence of Lewy pathology in the MP. The presence of α -synuclein aggregates in the MP and its symptomatic manifestation as constipation predate cognitive and motor symptoms of Lewy body diseases [101, 108] so consistently that it has been nominated as a potential biomarker for Lewy pathology [110]. Constipation is of particular interest because it is the symptom of cholinergic impairment most immediately apparent to the patient and care givers [70], and frequency of bowel movements is a quantifiable indicator of cholinergic impairment in Lewy body patients [111].

H. Medications Used to Treat Lewy Body Patients

The importance of pharmacological facilitation of serotonergic and dopaminergic systems to address motor and depressive symptoms impaired by α -synucleinopathy is well documented [112, 113]. Antidepressants with evidence-based application for treating depression in LBD patients include the tricyclics Amitriptyline, Nortriptyline, and Desipramine, which may be contraindicated due to their anticholinergic characteristics, SRIs including Citalopram, Sertraline, Paroxetine, and Fluoxetine, SNRIs including Venlafaxine, and the atypical antidepressant Bupropion [114-117].

In order to preserve gait, balance, and other basic motor functions, Lewy body patients with significant Parkinsonian features are often prescribed L-dopa agents like Carbidopa-Levodopa (branded as Sinemet or Stalevo). [70, 118, 119]. ENS α -synucleinopathy can be complicated or exacerbated by Carbidopa-Levodopa, whose potential side effects include constipation [120-123]. Anticholinergic agents including Trihexyphenidyl (branded as Artane or Trihex) and Bzotropine mesylate (branded as Cogentin) prescribed to

reduce resting tremor in Lewy body patients can also exacerbate gastric immotility through cholinergic suppression in the ENS. [119, 124-126].

I. Medications Used to Treat Cholinergic Impairments in Lewy Body Patients

Cholinergic agonists like acetylcholinesterase inhibitors (AChEIs) are often used for symptomatic relief of cholinergic impairment attributable to α -synuclein pathology [74, 86, 127-129]. For the treatment of LBD cognitive impairment, the cholinergic agonist Donepezil (Aricept) compares favorably with other AChEIs including Galantamine and Rivastigmine, improving cognition [130], but with fewer side effects [131]. Significant improvements in cognition and behavior following administration of Donepezil disappear when Donepezil is withdrawn, and return when Donepezil is readministered [132]. In a 52-week study, long-term cognitive improvement was maintained in LBD patients with regular use of Donepezil, with no increase in Parkinsonian features or other clinically significant events. [133, 134].

Other symptoms of α -synuclein cholinergic impairment including hallucinations, delusions, and psychotic symptoms in PD patients have been reduced using Donepezil, without the emergence of other side effects or exacerbation of Parkinsonian features [135, 136]. Donepezil's efficacy for consistent reduction of neurocognitive symptoms in PD & NCDLB without exacerbation of Parkinsonian features or other side effects has been confirmed by a Cochrane database systematic review of previous research [137] and reproduced in subsequent research [138, 139]. Donepezil's support of cholinergic neurotransmitter pathways to counter alpha-synuclein cholinergic impairment in the MP and the CSMP reduces constipation in LBD patients, without exacerbation or instigation of other symptoms [111]. Longitudinal case studies indicate that these benefits endure over 6, 12, and 18 month periods [140, 141, 142].

J. Vortioxetine and LBD Patients

Frequently prescribed to LBD patient for containment of Parkinsonian features, Levodopa-Carbidopa (Sinemet) significantly increases Vortioxetine peak plasma concentration and systemic exposure, requiring significant reductions of Vortioxetine dosages and close monitoring [58, 59]. Often prescribed to LBD patients for management of MDD symptoms, the SRI's Fluoxetine and Paroxetine are CYP450 2D6 inhibitors, which co-administered with Vortioxetine can produce additive serotonergic effects with the risk of serotonin syndrome [43, 56]. Also used to treat depression in LCDs, Bupropion is a potent CYP450 2D6 inhibitor, and co-administered with Vortioxetine can more than double its peak plasma concentration and systemic exposure [56, 57]. Frequently used to address sleep impairment in LBD patients, tricyclic antidepressants multiply Vortioxetine's anticholinergic effects [53], demonstrated with Amitriptyline, Nortriptyline, and Desipramine [73].

In LBD patients, amplified cholinergic suppression consequent to the use of Vortioxetine in combination with tricyclics or Bupropion can exacerbate α -synuclein cholinergic

suppression, whose symptomatic expression paradoxically includes cognitive deterioration, as well as motor and gait dysfunction, dyskinesias, psychosis, sleep abnormalities, altered olfactory function [86], and autonomic dysfunction, including gastric immotility [87, 88]. Gastric immotility's advancement from constipation to obstipation and impaction complicate treatment by interfering with mobility, sleep, cognition, and mood, increase the cost of care, and can debilitate and/or dramatically reduce the quality of life for the patient [143-149]. Exacerbation of α -synuclein cholinergic suppression consequent to the use of Vortioxetine in combination with Bupropion is illustrated in the following case study, for which an Institutional Review Board has granted a waiver.

II. METHODS

For the purpose of illustrating potential interactions between Vortioxetine and other medications frequently used to treat patients diagnosed with Lewy Body disorders, a case study was selected using pre-existing deidentified records originally collected for clinical purposes.

A. Case Study

Mr. C. was a white male between 65 and 70 years of age diagnosed with Neurocognitive Disorder with Lewy Bodies (NCDLB). His symptoms were characteristic of Lewy Body α -synucleinopathy, including late-life onset major depressive disorder (MDD), anxiety, motor abnormalities (tremor, weakness), gait dysfunction, dyskinesias, cognitive deterioration including short-term memory loss and difficulty word-finding, sleep abnormalities including REM Sleep Behavior Disorder (RSBD) and REM Sleep without Atonia (RSWA), and autonomic dysfunction including appetite suppression and gastric immotility, which had progressed over the preceding two years from constipation to obstipation to impaction. His frequency of bowel movements was about once a week, with periodic decreases infrequency. He had been hospitalized three times during the previous year for treatment of impaction. Screening using the Mini-Mental State Exam (MMSE) [150], the Quick Dementia Rating Scale (QDRS) [151], and the Lewy Body Composite Risk Score (LBCRS) [152] indicated mild cognitive impairment (MCI) and neurocognitive impairment consistent with Lewy body diseases.

The patient's medication regimen included Bupropion 75 mg HS, 50 mg QHS, Clonazepam 0.325 mg QHS, Aripiprazole 5 mg QHS, Melatonin 6 mg QHS PRN, Mirtazapine 30 mg QHS, Carbidopa-Levodopa 25/100 mg TID, Memantine 10 mg BID. Bupropion and Aripiprazole had been prescribed to address the MDD; Clonazepam for anxiety; Melatonin and Mirtazapine for sleep assistance, with the intention that Mirtazapine might also mitigate the MDD; Memantine for cognitive impairment; and Carbidopa-Levodopa for gait disturbance and other motor symptoms.

The prescriptions appeared to improve mood, motor function, and cognitive function, but there was no change in RSBD/RSWA or the frequency of bowel movements. To address the symptom of constipation and possibly further

improve cognitive functioning, the patient was prescribed Donepezil 2.5 mg daily. Within two weeks, the frequency of bowel movements had increased to every other day. The patient stated dissatisfaction with his bowel production and appetite, so the dosage of Donepezil was increased to 5 mg daily, and four weeks later to 10 mg daily, with subsequent improvements in appetite, intake, and bowel output volume. The patient's frequency of bowel movements increased to once a day, without increasing Parkinsonian features or other clinically significant symptoms. The patient and his spouse reported concurrent significant improvement in short-term memory, word finding, and general cognitive functioning. Retesting with the MMSE, the QDRS and the LBCRS verified these reports. These results remained stable when reassessed at intervals of 6, 12, and 18 months [140, 141, 142].

18 months after initiation of treatment with Donepezil, the patient stated increased depression, and (in addition to other medications reported above) was prescribed Vortioxetine 10 mg daily. Within two weeks, the patient reported that the frequency of bowel movements had dropped to once a week or less. He was taken to the Emergency Room at the hospital and was treated for impaction after 10 days without a bowel movement. The patient also complained of increased cognitive impairment (confusion, difficulty with calculations, task completion, and word-finding). Discussion with the prescribers led to a consensus that the dramatic reductions in cognitive function and gastric motility manifested as reduction in frequency of bowel movements were likely the result, respectively, of serotonergic inhibition, and exacerbation of α -synuclein cholinergic suppression consequent to the use of Vortioxetine in combination with Bupropion and Levodopa-Carbidopa. The use of Vortioxetine was discontinued, although the use of Bupropion and other medications continued.

III. RESULTS

The patient reported that about 24 following discontinuation of Vortioxetine, gastric motility had resumed, with a bowel movement. Within 48 hours, the frequency of bowel movements returned to once daily, and the patient and his spouse reported a return to pre-Vortioxetine levels of cognitive functioning. There were no other changes in the patient's symptoms. The patient's symptom picture has remained constant during the six months since the discontinuation of Vortioxetine.

IV. DISCUSSION AND CONCLUSIONS

The case study serves as a quantifiable demonstration of Vortioxetine's potential for serotonergic and cholinergic inhibition, and importantly, its reversibility. As a potent CYP450 2D6 inhibitor, Bupropion interferes with the metabolism of Vortioxetine, resulting in significant increases in Vortioxetine peak plasma concentration and systemic exposure [43]. Levodopa-Carbidopa also significantly increases Vortioxetine peak plasma concentration and systemic exposure [58, 59]. As illustrated by the case study, the combined interaction of Bupropion and Levodopa-Carbidopa with Vortioxetine can be dramatic, in this instance

apparently exacerbating Lewy Body α -synuclein cholinergic suppression in the ENS.

Although believed to bind in the same binding site, Vortioxetine's serotonergic inhibitory mechanism varies from classical 5-HT₃ receptor competitive antagonists. After partial agonist activity, Vortioxetine demonstrates what has been described as "a persistent and insurmountable inhibition" [153]. The molecular mechanisms underlying Vortioxetine's site binding appear to be different from currently known 5-HT₃A orthosteric ligands. In addition to binding in a manner that resemble the setron class of competitive antagonists and 5-HT, interacting with residues of the aromatic box motif in the orthosteric binding site, Vortioxetine additionally interacts with residues not previously described to be important for the binding of either setrons or 5-HT, including Thr176 on loop B and Val202 on loop F [153]. As Vortioxetine's peak plasma concentration and systemic exposure can be more than doubled by its combined interactions with Bupropion and Levodopa-Carbidopa [43, 58, 59], its serotonergic inhibitory potential is also significantly increased. In the case study, it appears that the combination of Vortioxetine's serotonergic and cholinergic inhibition significantly interfered with cognition.

Vortioxetine also has potential for interaction with other antidepressants with evidence-based application for treating depression in LBD patients. These include the tricyclics Amitriptyline, Nortriptyline, and Desipramine, SRIs including Citalopram, Sertraline, Paroxetine, and Fluoxetine, SNRIs including Venlafaxine, and the atypical antidepressant Bupropion [114-117]. Fluoxetine and Paroxetine are potent CYP450 2D6 inhibitors, and Fluoxetine's inhibitory effects on CYP-activity can persist for several weeks after fluoxetine discontinuation because of the long half-life of fluoxetine and its metabolite Norfluoxetine, which similar to Sertraline is a moderate CYP2D6 inhibitor [154]. CYP450 2D6 inhibition lends these medications potential for increasing the peak plasma concentration and systemic exposure of Vortioxetine, increasing not only Vortioxetine's potential for cholinergic suppression, but also increasing the risk of serotonin syndrome when it is co-administered with SRI's and SNRI's. The tricyclics Amitriptyline, Nortriptyline, and Desipramine have anticholinergic side effects, which can also potentiate Vortioxetine's potential for cholinergic suppression when co-administered with Vortioxetine.

The drug interactions described above and illustrated in the case study suggest that the use of Vortioxetine with LBD patients might present complications, if not risks. There are numerous other prescriptive and over the counter (OTC) medications with anticholinergic effects frequently used by this population, including but not limited to Alimemazine (Theralen), Amantadine (Symmetrel), Alverine (Spasmonal), Belladonna (Multiple), Amoxapine (Asendin), Alprazolam (Xanax), Aripiprazole (Abilify), Asenapine (Saphris), Carbamazepine (Tegretol), Atropine (Sal-Tropine), Atenolol (Tenormin), Cyclobenzaprine (Flexeril), Benzotropine (Cogentin), Brompheniramine maleate (Bromax), Cyproheptadine (Periactin), Brompheniramine (Dimetapp), Carbinoxamine (Histex, Carbihist), Captopril (Capoten),

Cetirizine (Zyrtec), Chlorpheniramine (Chlor-Trimeton), Chlorthalidone (Diuril, Hygroton), Chlorpromazine (Thorazine), Cimetidine (Tagamet), Clemastine (Tavist), Clidinium (Librax), Clomipramine (Anafranil), Clorazepate (Tranxene), Clozapine (Clozaril), Codeine (Contin), Colchicine (Colcrys), Darifenacin (Enablex), Desloratadine (Clarinex), Dicyclomine (Bentyl), Diazepam (Valium), Dimenhydrinate (Dramamine), Digoxin (Lanoxin), Diphenhydramine (Benadryl), Dipyrindamole (Persantine), Doxepin (Sinequan), Doxylamine (Unisom), Disopyramide phosphate (Norpace), Fentanyl (Duragesic, Actiq), Fesoterodine (Toviaz), Flavoxate (Urispas), Fluvoxamine (Luvox), Furosemide (Lasix), Haloperidol (Haldol), Hydralazine (Apresoline), Hydrocortisone (Cortef, Cortaid), Hydroxyzine (Atarax, Vistaril), Hyoscyamine (Anaspaz, Levsin), Iloperidone (Fanapt), Imipramine (Tofranil), Isosorbide (Isordil, Ismo), Loperamide (Immodium), Loratadine (Claritin), Loxapine (Loxitane), Meclizine (Antivert), Meperidine (Demerol), Methocarbamol (Robaxin), Methotrimeprazine (Levoprome), Metoprolol (Lopressor, Toprol), Molindone (Moban), Morphine (Contin, Avinza), Nefopam (Nefogestic), Nifedipine (Procardia, Adalat), Oxcarbazepine (Trileptal), Olanzapine (Zyprexa), Orphenadrine (Norflex), Oxybutynin (Ditropan), Perphenazine (Trilafon), Pimozide (Orap), Prednisone (Deltasone, Sterapred), Procyclidine (Kemadrin), Promazine (Sparine), Promethazine (Phenergan), Propentheline (Pro-Banthine), Propiverine (Detrunorm), Quetiapine (Seroquel), Quinidine (Quinaglute), Ranitidine (Zantac), Risperidone (Risperdal), Scopolamine (Transderm Scop), Solifenacin (Vesicare), Theophylline (Theodur, Uniphyl), Thioridazine (Mellaril), Tolterodine (Detrol), Trazodone (Desyrel), Triamterene (Dyrenium), Trifluoperazine (Stelazine), Trihexyphenidyl (Artane), Trimipramine (Surmontil), Tropicium (Sactura), and Warfarin (Coumadin) [119]. By no means exhaustive, this list gives some idea of the broad range of prescriptive and non-prescriptive medications with potential to interact with Vortioxetine to suppress cholinergic function. Because many of these medications are non-prescriptive, the possibility that prescribers might be unaware of their use increases the risk of potential interaction with Vortioxetine.

Complicating the prescription picture, LBD patients are often simultaneously medicated by an internist, a psychiatrist, a neurologist, a movement specialist, and possibly other specialists (e.g., gastroenterologist, urologist). [70]. Difficulty coordinating ongoing communication between prescribers in siloed care settings creates greater potential risk for dangerous drug interactions [155, 156]. At this time, it appears that the use of Vortioxetine for patients diagnosed with Lewy Body disorders might present numerous risks. However, Vortioxetine is a relatively new medication, and as indicated above, research to date has produced results that are not entirely consistent. Risks can be mitigated by ongoing close communication between prescribers, which is recommended for the use of Vortioxetine, as well as any other medication for LBD patients. Further research with larger data sets matching groups for diagnosis, age, gender, and other variables will be

necessary before stronger conclusions can be drawn about the appropriateness of Vortioxetine for specific populations.

LIST OF ABBREVIATIONS

Major depressive disorder (MDD)
Serotonin Reuptake inhibitor (SRI)
Serotonin and Norepinephrine Reuptake inhibitor (SNRI)
Food and Drug Administration (FDA)
Cytochrome P450 enzymes (e.g., CYP450)
Serotonin modulator and simulator (SMS)
Five Hydroxy-Tryptophan (5-HT)
Serotonin (5-HT) transporter (SERT)
Gamma Amino Butyric Acid (GABA)
Norepinephrine (NE)
Acetylcholine (ACh)
Acetylcholinesterase (AChE)
Acetylcholinesterase inhibitor (AChEI)
Neurocognitive Disorder with Lewy Bodies (NCDLB)
Parkinson's disease (PD)
Lewy Body disorders (LBDs)
Central nervous system (CNS)
Autonomic nervous system (ANS)
Peripheral nervous system (PNS)
Enteric nervous system (ENS)
Myenteric plexus (MP)
Colonic submucosal plexus (CSMP)
Rapid Eye Movement (REM)
REM Sleep Behavior Disorder (RSBD)
REM Sleep without Atonia (RSWA)
Mini-Mental State Exam (MMSE)
Quick Dementia Rating Scale (QDRS)
Lewy Body Composite Risk Score (LBCRS)

DECLARATIONS

Ethics approval and consent to participate: The Santa Barbara Cottage Hospital Institutional Review Board granted a waiver (##18-81ix) for this case study.

Consent for publication: A completed consent for publication form for the case study is on file with the author.

Availability of data and materials: Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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