Review Article

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Guideline to the Three New Antidepressants

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Abstract

In the past six years, FDA has approved the three new Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) class of antidepressants i.e., vortioxetine, levomilnacipran and vilazodone. Extensive data is available on different aspects of their use. In this article, we will reason about the efficacy, adverse events reported and tolerability of these three antidepressants in the light of clinical trials conducted in the past 6 years.

Vortioxetine is an SNRI, proven to be well tolerated for Major Depressive Disorder (MDD) and for anxiety symptoms related to MDD as exhibited by clinical trials [1]. It has lesser sexual side effects and cognitive disturbance associated with its use[1]. Levomilnacipran is an SNRI to be used with caution in raised blood pressure, according to the available data; it can cause urinary obstruction in vulnerable population and requires dosage adjustment in renal dysfunction [2]. Similarly, vilazodone is a new SSRI with partial agonism at 5HT-1A receptors [3]. It has little effects on weight and lesser sexual side effects [4]. Each of these drugs can cause serotonin syndrome with a list of other drugs, as mentioned in this article in detail.

Full Article

The stability of a body stands in need of a stable mood and affect, and hence, a stable brain. Those who have travelled the road of clinical depression once, they say "it is a bad place to be in." One wishes to be delightful, but doesn't sense happiness anymore. The chores you used to love now become meaningless to you. Which is why, every day the medical science is paving paths to fight clinical depression. SSRIare the most extensively and widely used class of antidepressant medications for Clinical Depression [5]. Serotonin is linked with many psychiatricillnesses; these include depression, schizophrenia, panic disorder, generalized anxiety disorder and social anxiety [3]. In this article, we will discuss the newer antidepressants, approved by FDA in past 5 years, "Vortioxetine, Levomilnacipran and Vilazodone" in detail.

Major Depressive Disorder affects about 121 million people around the globe, influencing 15 million American adults [6]. MDD is a notorious cause of disability among the adult population in USA [6]. According to one survey, in 2009, antidepressants were the fourth leading prescribed medication [7].

Vortioxetine

Vortioxetine was FDA approved in January 2011. Previously, vortioxetine appeared in the market with the brand name "Brintellix", to which there were turbulences in marketplace as the name "Brintellix" sounded similar to "Brilinta" (ticagrelor), an antiplatelet agent [8]. FDA gave warnings in 2015 regarding this issue. In June 2016, Takeda pharmaceuticals U.S.A., Inc. and Lundbeck declared publicly that "Brintellix" will come with the trade name of "Trintellix". The current brand name for vortioxetine is "Trintellix" [8].

Vortioxetine is commonly prescribed for "Major Depressive Disorder" including its use in the elderly population [9]. Also, it is prescribed for generalized anxiety disorder and is useful for cognitive symptoms appearing in depression [10].

How well does vortioxetine work?

Vortioxetine has manifoldmode of action [11]. Vortioxetine is a multimodal antidepressant which upsurges many different neurotransmitters such as serotonin, dopamine, norepinephrine, glutamate, acetylcholine and histamine [11]. The drug has a number of mechanisms by which it decreases the release of GABA. These modes of action include blocking the serotonin transporter [12]. Vortioxetine also attaches to the G-protein linked receptors. It is a full agonist at serotonin 1A receptors, a partial agonist at serotonin 1B receptors and an antagonist at 1D and serotonin 7 receptors [11]. It also affixes to the ion channel linked receptors, which are the serotonin 3 receptors. It acts as an antagonist at serotonin 3 receptors inducing serotonin reuptake inhibition [11]. The unification of all these tools upsurges the serotonin levels at the multiplex nodes in the network of neuronal circuitry in brain. Vortioxetine's partial agonism at 1B receptors increases not only serotonin but also acetylcholine and histamine [11].

According to a meta-analysis featuring 12 RCTs, vortioxetine was more efficacious than placebo with a Standardized Mean Difference (SMD) of -0.217 [13]. Persons with MDD treated with

SNRIs/agomelatine showed similar effects as that of vortioxetine with regards to the SMD and Odds ratio for response and remission respectively. However, the rate of discontinuation of drug owing to its efficacy was more with placebo than vortioxetine and the rate of discontinuation of drug due to adverse effects was more for vortioxetine than with placebo in this meta-analysis [13].

Another 8 week, double blind, randomized controlled trial published in September 2012 regarding the desirability and competence of vortioxetine is vital to discuss in this context. 5 mg of vortioxetine compared with placebo showed no significant differences in the diminution of the symptoms of Major Depressive Disorder [14]. However, the subgroup of population which demonstrated more baseline anxiety i.e. HAMA (Hamilton anxiety rating scale) more than 19, exhibited a convincing cutoff in HAMD-24 (Hamilton scale for depression) total score beginning at 3rd week. Thus, it worked wonders in MDD patients with more baseline anxiety. Generally, suspension of treatment due to tolerability is a common issue. In this study, minor complaints like nausea and diarrhea were more common. However, less than only 5 percent of subjects reported sexual side effects, somnolence, weight gain and insomnia overall [14].

The downsides and advantages of using vortioxetine

The chemical structure of any drug, no matter how efficient it might be, reciprocates to the body's innate composition. Vortioxetine also produces a number of common side effects like nausea, diarrhea, constipation, vomiting, sexual dysfunction, dry mouth, flatulence, dizziness, nightmares and rash [15]. However, it also comes with certain speculations such as suicidal thoughts, serotonin syndrome, and activation of mania/hypomania, hyponatremia, abnormal bleeding and hypersensitivity [16]. The suicidal behavior is most common in the children, young adults and in the first few months of use. It is imperative to inform your care provider if any change in mood, impulsiveness, anger,talkativeness, andsuicidal thoughts is witnessed [16]. In multiple studies, the most common side effects seen with vortioxetine are nausea, diarrhea, dry mouth, hyperhidrosis and headache [17]. The probable perks with vortioxetine use include less weight gain, less sexual side effects and less somnolence/insomnia [17].

In a double-blind, placebo controlled, three-way crossover design study, vortioxetine 10 mg was given to 24 healthy subjects. The aim of the study was to discuss the drug's effects on cognition, driving and psychomotor performance [18]. Mirtazapine 30 mg was compared with it. According to the results of this clinical trial, vortioxetine did nott show any disturbance in cognition or psychomotor performance after multiple doses were given. But for mirtazapine the results were otherwise as it impaired cognition and psychomotor performance. The results were derived from driving tests, critical tracking task, divided attention task, word learning task; psychomotor vigilance task and Groningen sleep [18]. Mirtazapine's effects on alpha 2 and histamine receptors predispose it to the effects on cognition. However, vortioxetine has effects on serotonin receptors only [18]. In another clinical trial, vortioxetine has proven beneficial and the only adverse events noted were nausea, headache and diarrhea [17].

Sometimes, patients may not respond fully to the treatment of vortioxetine and some symptoms improve while other remains there. Or there might be chances that patients do not respond at all to the treatment, called as "non-responders", "treatment refractory" or "treatment resistant" [19]. In these circumstances, adding another drug/therapy or switching to another treatment would be appropriate. Some doctors also consider psychotherapy. Occasionally, a doctor can also re-consider the diagnosis and search for any co-morbid illness or a drug abuse history. If the patient has an underlying Bipolar Disorder, stopping the antidepressant and switching to a mood stabilizer would be an appropriate option [20].

Who should not receive vortioxetine?

All the serotonergic medications should be avoided or used with caution when usingvortioxetine, these include meperidine, lithium, SSRIs, SNRIs, MAO inhibitors, TCAs, fentanyl, triptans, pentazocine, methylene blue, tramadol etc [21]. Additionally, aspirin, warfarin and all anticoagulant drugs, which increase the risk of bleeding, should be watchfully usedwhen taking vortioxetine [22]. Any signs of bleeding like hemorrhage, black stools, dizziness etc., should be monitored. Also, vortioxetine has Cytochrome P450 isozyme metabolizing pathways. The main enzyme is CYP2D6. All the inducers and inhibitors at this enzyme affect the drug's quantity in body. Thus, dose should be reduced or increased accordingly [23].

As it is described by FDA, vortioxetine's dose should be decreased to half the dose which the patient is already taking if a strong CYP2D6 inhibitor such as fluoxetine, paroxetine, bupropion or quinidine is used. Similarly, with a strong CYP inducer like rifampin, carbamazepine etc. The dose of vortioxetine should be increased. However, the maximum dose should not increase three times the original dose [23].

Can the pregnant and nursing mothers use vortioxetine?

There is no data available on human subjects regarding the use of vortioxetine in pregnancy. However, there have been clinical studies on rats and rabbits. When vortioxetine is administered at oral doses of 160 and 60 mg/kg/day, which is 77 and 58 times the maximum recommended human dose, no teratogenic effects were seen during the periods of organogenesis. At dosages 10 to 15 times of maximum recommended human doses (MRHD) i.e., equal to or greater than 30 and 10 mg/kg, rats and rabbits showed developmental delays in the form of delayed ossification and decreased fetal body weight. The number of live born pups was reduced when vortioxetine was administered at doses 58 times the MRHD to pregnant rats [24].

Similarly, there are no data available on the presence of vortioxetine in human milk [23]. However, vortioxetine is present in the milk of lactating rats. Thus, vortioxetine is the category C in pregnancy risk and should be administered to pregnant or lactating females only if the advantages are more than the potential adverse events [25].

Conclusion

In sum, vortioxetine is a new SSRI, has shown minor adverse events in clinical trials and is well tolerated. It has shown substantially promising effects in the treatment of Major Depressive Disorder, also has shown to be effective in elderly persons (as no dose adjustment is required on the basis of age) and for anxiety symptoms in depression. However, it has not exhibited any superiority over active comparators [26]. The prevalence of sexual adverse events is lesser than others. According to clinical

trials, it has not shown any cognitive disturbances with its use [18].

Levomilnacipran

Levomilnacipran with the brand name "Fetzima", by the Forest laboratories, was first approved in July 2013 by FDA. It belongs to the class Serotonin Norepinephrine Reuptake Inhibitors, SNRIs. It was approved by FDA for Major Depressive Disorder, but is occasionally also prescribed for Fibromyalgia and Neuropathic pain/chronic pain [27]. However, its effectiveness and safety for the treatment of fibromyalgia has not been well-established [28].

Does levomilnacipran require dosage adjustment in special population?

The initiating dose of levomilnacipran is 20 mg/day for the first 2 days. Based on tolerability, it is increased by 40 mg every two days until 120 mg/day. The dosage range is 40 to 120 mg/day. When discontinuingthe treatment, decreasing the dose slowly is recommended [29].

No dosage modification is required in hepatic impairment. However, dosage should not exceed 80 mg/day with use of CYP3A4 inhibitors [27]. In renal impairment, dose is adjusted according to mild, moderate and severe renal impairment. In mild renal impairment, no dosage adjustment is required. In moderate renal impairment, dosage should not exceed 80 mg/day and similarly it might not exceed 40 mg/day in severe renal impairment [30].

When levomilnacipran is administered in a 40 mg dose to persons with mild, moderate and severe hepatic impairment in a parallel group study, it does not show any dangerous side effects, deaths or treatment discontinuation due to hepatic impairment. It demonstrates that the drug does not require any adjustment of dose in hepatic impairment [31].

How does levomilnacipran perform its action?

Levomilnacipranaugments the neurotransmitters serotonin, norepinephrine and dopamine. It implements this by hindering the norepinephrine reuptake pump, the norepinephrine transporter. Additionally, it executes its function by knocking off serotonin reuptake pump, the serotonin transporter, increasing serotonergic neurotransmission [27]. It also desensitizes serotonin 1A receptors and beta-adrenergic receptors. On the reuptake of norepinephrine in the frontal cortex, dopamine is inactivated as this part of the brain lacks dopamine transporters. Thus, levomilnacipran will upsurge the neurotransmission of dopamine in this part of the brain. Like other SNRIs, its onset of action takes 2-4 weeks. Levomilnacipran is different from other SNRIs in that it has two times the potency than other SNRIs for norepinephrine as compared to serotonin reuptake inhibition [32].

Short term and long term adverse events when taking levomilnaciporan

The mechanism by which levomilnacipran exhibits adverse events is similar as of its therapeutic effects. When the serotonin in the brain upsurges, it causes side effects such as insomnia. Similarly, as the norepinephrine increases, it causes urinary retention. Or constipation by decreasing the amount of acetylcholine.The most common adverse events reported with the use of levomilnacipran are nausea, vomiting, decreased bowel movements, hyperhidrosis, increased heart rate, erectile dysfunction, urinary retention [33]. A few dangerous adverse events are seizures and induction of mania. The warning associated with the use of levomilnacipran is suicidal ideation [34].

Referring to the randomized double blind, placebo controlled study of flexible doses of Levomilnacipran ER (40-120mg) in patients with Major depressive disorder in which levomilnacipran exhibited exponential improvements in the treatment measures. But the results were not statistically significant. Thus, improvement in the levomilnacipran versus placebo groups i.e., Montgomery-Asberg Depression Rating Scale (MADRS) scores (-15.7 vs -14.2) and Sheehan Disability Scale (SDS) scores (-8.8 vs -8.2) were observed. No difference in the Arizona Sexual Experiences Scale (ASEX) scores was observed between the two groups. 14 patients in the levomilnacipran group discontinued participation due to side effects and 4 patients in the placebo group discontinued due to adverse events. However, the only adverse events reported were nausea and headache which shows that levomilnacipran was well-tolerated [35].

In the longterm trial conducted to weigh the continual effectiveness and tolerability of levomilnacipran, prevailing adverse effects noted were nausea and headache. An upsurge in mean heart rate, systolic and diastolic blood pressure was observed. QT prolongation noticed was due to increase in heart rate only. No significant differences were found in the LFT, hematologic values, urine analysis or serum values. In sum, no changes in vulnerability and tolerability were seen during the continual assessment [36].

How does levomilnacipran interact with other medications?

When using MAO inhibitors with levomilnacipran caution is advisable. At least a gap of 14 days is solicited when levomilnacipran is started after the use of MAO inhibitor. And when using MAO inhibitor after levomilnacipran, a break of a week should be given [37].

What to watch when using levomilnacipran?

Levomilnacipran upsurges the risk of suicidal thoughtsand actions in children, adolescents, and young adults aged less than 24 years of age. In elderly population, this risk has not shown to be increased. All ages of populations should be overseen for any change in behavior or impulsiveness [36].

Levomilnacipran can cause an upturn in the bleeding risk in patient population receiving anticoagulants or NSAIDS [38]. It can also increase the risk of angle closure glaucoma by virtue of the drug's noradrenergic mechanism; additionally it can cause an increased risk of urinary obstruction symptoms or urinary hesitance [36]. Additionally, it should be used with caution in patients with seizure disorder. If any symptoms of hyponatremia are observed, the drug should be discontinued as SSRIs and SNRIs have been previously established to cause SIADH [36].

One notable aftermath with the use of levomilnacipran is the increment of blood pressure levels, as described in the above section of this article. Thus, it should be used with caution in the hypertensive patients. Also, it can cause an increase in the heart rate. However, the drug has not been tested in the cardiac rhythm disorders separately [39]. When prescribed with levomilnacipran, an underlying bipolar disorder should be screened as it is not advisable in population suffering from bipolar depression [40]. All the medications which predispose to serotonin syndrome, as

described in the above section of this article, should be avoided when using levomilnacipran [41].

Conclusion

To conclude, levomilnacipran or "Fetzima" is an SNRI which has shown substantial efficacy in clinical trials but should be used cautiously in hypertensive population. It has exhibited minor side effects of nausea and headache in clinical trials. However, there is a risk of urinary obstruction in high risk individuals, due to its effects on norepinephrine. In renal dysfunction, dosage adjustment is required.

Vilazodone

How efficacious is vilazodone?

Vilazodone potently inhibits the reuptake of serotonin. Additionally, it is a partial agonist at the 5HT-1A receptors. However, how this partial agonism at 5HT-1A receptor affects its efficacy is not completely understood. Vilazodone's partial agonism at the 5HT-1A receptors is what makes it distinctive from otherwise SSRIs [6]. The SSRIs therapeutically benefit depression by increasing serotonin in the neurochemical pathways. Therefore, the combination of SSRI and partial agonism at 5HT-1A receptor site should profoundly boom the proficiency in treatment of depression [42]. The structure of vilazodone makes it unique in performance, when single agent SSRI or SNRI does not work, it can still be effective. Also, it exhibits lesser sexual adverse effects and weight gain [43].

According to a double blind randomized clinical trial, vilazodone has shown efficacy with improvement in the Major Depressive Disorder symptoms after use. An interesting fact is that the symptom relief begins within a week. Population at 18 to 65 years were followed up closely for 8 weeks, there was significant improvement in the Montgomery-Asberg Depression Rating Scale and Hamilton Rating Scale of Depression from baseline to 8 weeks. Additionally, it showed only mild to moderate side effects. However, fewer minor adverse events like nausea, diarrhea and somnolence did require urgent management [44].

Another 10-week, fixed dose, multi center, double blindedtrial on vilazodone 20mg, vilazodone 40 mg, citalopram 20 mg and placebo was conducted. It demonstrated efficacy of vilazodone 20 mg, 40 mg, and citalopram 20 mg as more than the placebo on Clinical Global Impressions Scale and Montgomery-Asberg Depression Rating Scale. The feedback from all the drug groups was numerically surpassing[45].

Are there anyDangers/Risksassociated with taking vilazodone?

In patients 24 years or younger, vilazodone might increase the incidence of self-harm in form of suicidality. It should be instructed to the patient before prescribing vilazodone, if they experience an increase in suicidal thoughts, they must inform their healthcare provider [36].

One might experience an exceptional change in behavior or a clinical deterioration with the use of this drug. If this happens, drug should be discontinued and prescriber should be notified immediately of the change in symptoms. These could include irritability, agitation, aggressiveness, worsening of depression, talkativeness (mania) etc [36].

SSRIs and other antidepressants may increase the risk of bleeding. This effect is amenable with the use of Warfarin, NSAIDS or Aspirin [46].

SSRIs rarely cause seizures, associated with high doses and severe symptoms associated with side effects of the drug, for example, Serotonin syndrome. One case has been reported where a patient developed seizures with the use of vilazodone. This particular patient had no seizures in the past but after starting vilazodone, she experiences two breakthrough seizures. In this case, one thing was noticeable in the history; her dosage had been recently titrated to 40 mg per day [47].

SSRIs might cause serotonin syndrome in higher doses. This syndrome comprises of symptoms manifested by the increased quantities of serotonin in the body. It expresses in form of fever, palpitations, agitation, restlessness, increased muscle rigidity, myoclonus, sweating, hypertension, twitching of muscles etc [48].

If you are on vilazodone and experience any of these symptoms in presence of high doses of drug usage, call your doctor immediately, and in case of increasingly bothersome manifestation of symptoms, visit an emergency immediately. It might be a medical emergency. Other drugs causing these symptoms include SSRIs, SNRIs, MAO Inhibitors, Triptans, Bupropion, TCAs, Opioids such as Fentanyl, Meperidine, codeine etc. Lithium, LSD, Amphetamine, St. John Wort, Nutmeg, Granisetron, Ondansetron, Metoclopramide. If you are taking more than one of these drugs, or an increased dosage of any of these drugs, you might be at an increased risk of developing Serotonin syndrome [34].

Vilazodone can cause an increase in the symptoms of glaucoma. Before starting this drug, you should inform your doctor if you have any history of glaucoma. Symptoms such as swelling, pain, redness in eye could be alarming [49]. Vilazodone can cause a decrease in the levels of sodium in blood. If any headache, confusion, dizziness, hallucinations develop with this drug, you should contact your prescriber immediately. Elderly might be at an increased risk of hyponatremia [6]. Manic symptoms might occur with the use of vilazodone and other SSRIs. These include talkativeness, pressured speech, decreased need for sleep, flight of ideas, grandiosity, and increased activity [50].

Side Effects

Where vilazodone plays wonders in the treatment of depression, it comes with a number of side effects. Some of these are minor and tolerable, whereas others are major and require extensive management. MINOR / TRIVIAL effects includenausea, vomiting, flatulence, dyspepsia, dry mouth, diarrhea, insomnia, dizziness, somnolence, decrease appetite, fatigue, palpitations, muscle pain, restlessness, arthralgias, nightmares. MAJOR / SIZABLE effects include tremors, blurry vision, blindness, delayed ejaculation, erectile dysfunction, decreased libido, paresthesias, angle closure glaucoma, serotonin syndrome, loss of impulse control, anxiousness, chest discomfort and increased bleeding [51].

How will vilazodone intercommunicate with other class of medications?

No matter how well a drug functions independently, equally significant is the fact that we know how it will interact with the other class of medications. Vilazodone has a plenty of drug

interactions reported. Vilazodone use along with the use of dextromethorphan, chlorpheniramine, pseudoephedrine, fentanyl, codeine, guafenesin, phenylpropanolamine, sumatriptan and other drugs of this class, pentazocine, tramadol, doxepin, amphetamine, dextroamphetamine, phentermine, rasagiline and other MAO inhibitors, nortriptyline and other TCAs, lorcaserin, bupropion, buspirone,ergot derivatives, other SSRIs and SNRIs. Lithium might increase the risk of serotonin syndrome. Vilazodone can increase the risk of bleeding if taken with aspirin. If any symptoms of headache, lightheadedness, black stools, palpitations etc. develop, patient should inform the doctor immediately. Tramadol may increase the risk of seizures when given along with vilazodone. All the conditions which predispose a person to seizures like a history of seizures, trauma to head, head tumor etc. can put a person at an increased risk of seizures with this drug. Vilazodone might increase the incidence of side effects seen with amphetamine and dextroamphetamine. These effects include jitteriness, nervousness, anxiety, tremulousness, uncontrolled repeated body movements, palpitations etc. If you are taking phentermine alongwith vilazodone, the side effects of phentermine might increase like jitteriness, nervousness, anxiety, palpitations etc. Rasagiline belongs to the class of MAO inhibitors. One of the established side effects of bupropion is seizures [52].

Less serious drug interactions with vilazodone

Vilazodone engages in a menu of less serious drug interactions, as discussed below.

Urokinase, *Abciximab, Ibuprofen, Aspirin*, *Naproxen* aggravates the incidence of bleeding when taken together with vilazodone. It can present with black or tarry stools, dizziness, drop in blood pressure, increase or decrease in heartbeat, vomiting etc. Persons with age more than 65, having a liver or kidney disease are more predisposed to it. Drug levels of vilazodone decreases in the body when sumatriptan is administered along with it. Owing to this interaction, one can feel more depressed or an augmentation of symptoms of the disease can occur, which should be notified to the prescriber. The use of HCTZ and vilazodone puts the patient at a danger of hyponatremiia. It manifests as nausea, vomiting, decreased consciousness, dizziness, memory impairment, confusion, muscle spasms etc. Phenobarbital may decrease the blood levels of vilazodone, decreasing the effect of the antidepressant. It might result in aggravation of symptoms of depression or a change in behavior. If so happens, the prescriber should be informed immediately. Vilazodone can upsurge the blood levels of Amiodarone when taken with it. Amiodaronetoxicity can present with blurry vision, dry and puffy skin, skin discoloration, rash, vomiting etc. Drug levels should be checked frequently and continuous monitoring of the dosage is required. Amobarbital may mark down the effect of vilazodone when administered with it. It can worsen the depression or the effects of the drug, in such a situation, doctor should manage accordingly. Clarithromycin may burgeon the effects of vilazodone. Insulin glulisine's hypoglycemic effects may hike with the use of vilazodone. It can present with lightheadedness, nausea, vomiting, confusion, loss of consciousness, tremulousness, etc. Bosentan might weaken the effects of vilazodone by decreasing its levels in the blood [53, 54].

Conclusion

Vilazodone's little effects on the weight gain exhibit its benefits [55]. Also, it has demonstrated lesser sexualdysfunction as a side effect but some spontaneous sexual adverse events have been narrated in clinical trials. More data is required on its long term efficacy [55].

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