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Vortioxetine (Brintellix®): A Review

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Major depressive disorder (MDD) is a common and prevailing mental disorder that affects an individual's overall health, quality of life and productivity. The annual and lifetime prevalence of MDD in United States is 6.7% and 16.5% of the adult population, respectively, and 50% to 80% will experience another depressive episode.[1,2] MDD also carries a significant economic burden in United States, contributing $83.1 billion in healthcare and productivity costs in 2000.[3] The exact pathophysiology is still unknown but likely multi-factorial and associated with different neurotransmitter pathways.[4]

Long term treatment with antidepressants can reduce reoccurrence up to 70%.[5] However, up to 40% of affected individuals do not receive treatment.[6] For individuals receiving treatment for MDD there are many options. Pharmacologic treatment options include serotonin-norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), serotonin modulators, atypical antidepressants, monoamine oxidase inhibitors and tricyclic antidepressants .[7] In spite of the available options, MDD continues to be difficult to treat. Major obstacles include delayed therapeutic effect, high non-response rate due to heterogeneous treatment responses, adverse effects, and consequent low compliance.[8] In response to these treatment issues and a multifactorial pathophysiology, newer antidepressants target different but complementary therapeutic mechanism of actions.

Vortioxetine (Brintellixâ) is one of the new multi-modal antidepressants. On September 30, 2013, the FDA approved vortioxetine for major depressive disorder in adults. It was jointly marketed by Lundbeck and Takeda Pharmaceuticals Incorporated. The objectives of this paper are to review the pharmacology, pharmacokinetics, pertinent clinic trials, safety and dosing of vortioxetine.

Pharmacology & Pharmacokinetics

Vortioxetine is a SSRI that binds to the presynaptic serotonin reuptake site, increasing the level of serotonin (5-HT) in the neuronal synapse, as well as selectively binding to a variety of other serotonin receptors. It selectively binds to and acts as an antagonist to 5-HT_3, 5-HT_{1D}, and 5-HT_7 receptors, partial agonist to 5-HT_{1B} receptors, and agonist to 5-HT_{1A} receptors (Table 1).[8] Although each serotonin receptor subtype is associated with different functions, the clinical effects of these receptor activity modulations in vortioxetine are still unknown (Table 2).[9,10] Its 5-HT_{1A}

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Table 1 | Receptor Profiles for the New Multi-Modal Antidepressants Compared with Commonly Used SSRIs and SNRIs[8,23]

Class	Drug	5-HT$_{1A}$	5-HT$_{1B}$	5-HT$_{2C}$	5-HT$_3$	5-HT$_7$	SERT inhibition	NET inhibition	DAT inhibition
SSRI	Citalopram						+++		
	Fluoxetine			++			+++		
SNRI	Duloxetine						+++	+++	+
	Venlafaxine						+++	++	
Multi-modal	Vilazodone	+++					+++		
	Vortioxetine	+++	+++		+++	+++	+++		

DAT: dopamine transporter; NET: norepinephrine transporter; SERT: serotonin transporter; +: weak affinity; ++ : moderate affinity ; +++: strong affinity. *Adapted from Richelson et al.*[8]

agonist activity may supplement the antidepressant activity similar to the proposed mechanism for buspirone and vilazodone. [9,11,12] In-vivo studies found vortioxetine was associated with increased levels other neurotransmitters, such as dopamine, norepinephrine, acetylcholine and histamine, in addition to serotonin.[13] Vortioxetine is currently being investigated for its anxiolytic and potential procognitive effects, which may be due to the receptor activity modulations.

In clinical trials, vortioxetine displayed a linear dose-response relationship with a half-life of 66 hours. The relatively long half-life allows once daily dosing and may possibly reduce the rebound and withdrawal effects from missing doses or stopping the drug. After oral administration, peak plasma concentrations were achieved in 7 to 11 hours and vortioxetine displayed 75% bioavailability. Since food did not have an observed effect, vortioxetine can be taken without regards to food.[9]

Vortioxetine is primarily metabolized by the cytochrome P450 (CYP) pathway in the liver. Although vortioxetine is a substrate for many CYP enzymes, CYP2D6 is the primary enzyme, which metabolizes vortioxetine to a pharmacologically inactive metabolite. Thus, dosing adjustment may be necessary for people taking strong CYP2D6 inhibitors or inducers concomitantly with vortioxetine.[9] No adjustment is needed for renal impairment or mild to moderate hepatic impairment. No dose adjustments are needed for age although vortioxetine has not been studied in the pediatric population.

Clinical Trials

Vortioxetine was granted approval in the United States based on six short-term trials and one maintenance study in adult patients with Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) major depressive disorder.[9,13,17-21] These trials were randomized, multi-center, double-blinded, placebo-controlled, fixed-dose trials. Approximately half of these studies were presented as abstracts at the American Psychiatric Association annual meeting and have not yet been published or peer-reviewed. The exclusion criteria varied between studies but generally excluded participants with a history of a psychiatric, neurologic, or substance abuse disorder besides depression, clinically significant medical comorbidities, considered at risk of suicidal behavior,

Table 2 | Location and Clinically Relevant Function of Selected Serotonin Subtype Receptors[10]

Receptor Subtype	Location	Function
5-HT$_{1A}$	CNS	Neuronal inhibition, behavioral effects (sleep, feeding, thermoregulation, and anxiety)
5-HT$_{1B}$	CNS	Presynaptic inhibition, behavioral effects
	Vascular	Pulmonary vasoconstriction
5-HT$_{1D}$	Unknown	Unknown
5-HT$_3$	GI tract	Sensory and enteric nerves, emesis
5-HT$_7$	CNS, blood vessels, GI tract	Unknown

5-HT: serotonin; CNS: central nervous system; GI: Gastrointestinal. *Adapted from Mohammad-Zadeh et al.*[10]

mild-to-moderate depression or treatment-resistant depression. The mean baseline MADRS or HDRS-24 score across all the six short-term trials was approximately 30, reflecting a high moderate to severe depression patient population.[14,15] The primary endpoint of all the studies was change in total score of a validated depression scale from baseline compared to placebo. All the studies used Montgomery-Asberg Depression Rating Scale (MADRS) except two studies used Hamilton Depression Scale (HDRS-24). Although HDRS-24 has been more commonly used in clinical trials, there is a high correlation between the two scales.[16] For both scales, a higher score is associated with increased severity.

Five of the short-term clinical trials were conducted in adults between the ages of 18 to 75 years diagnosed with MDD (Table 3).[17-21]These trials were approximately 6 to 8 weeks long and three of the five studies were conducted outside of the United States and mostly in Europe. Collectively, the participants were randomized to one of the treatment groups (vortioxetine 5 mg, 10 mg, 15 mg or 20 mg) or placebo once daily. Participants assigned to 15 mg or 20 mg were titrated from 10 mg within 1 week. Alvarez et al and Boulenger et al used venlafaxine XR 225 mg daily as the active control for assay sensitivity to validate their findings.[16,17] It is unknown whether the other three trials used an active control since they have not been published. In each of the five trials, at least one of the vortioxetine arms had statistically significant changes in depression scores compared to placebo (Table 3). Of note, the statistically significant differences in depression score from placebo ranged from -4.1 to -7.1 in the non-US studies and -2.8 to -3.6 in the US studies. The cause and significance of the non-US studies consistently achieving a higher reduction in severity scores have not been determined. Possible reasons are differences in compliance, reporting responses, and differences in weight between European and American populations.

Katona et al conducted an 8-week, multicenter trial in 453 elderly patients with MDD who ranged between 64 and 88 years old in seven countries, including the United States. Participants were randomly assigned to vortioxetine 5 mg, placebo, or duloxetine 60 mg, which was the active control.[13] Participants were considered responders if they had 50% or greater reduction in total HDRS-24 score at endpoint compared to their baseline score. Significantly more participants in the vortioxetine group were responders compared to placebo (53.2% versus 35.2%, $P<0.05$) (Table 3). Nausea was the sole side effect significantly more prevalent in the treatment arm compared to placebo (21.8% versus 8.3%, $P < 0.01$). In addition, cognitive effects independent of the antidepressant effect were explored by assessing changes in scores for Rey Auditory Verbal Learning Test (RAVLT) and The Digit Symbol Substitution Test (DSST). Both duloxetine and vortioxetine were associated with an improvement in verbal learning but only vortioxetine was associated with an improvement in memory and processing speed compared to placebo. The investigators concluded that vortioxetine is both safe and efficacious in elderly patients and may have pro-cognitive effects.

In addition to the short-term clinical trials, a 52-week relapse prevention study was conducted to assess the long term efficacy in patient with moderate to severe MDD and at least one prior depressive episode.[22] Severity was reflected in the mean baseline MADRS total score of 32.5. This study was conducted in 17 countries, but was not conducted in the United States. The study population consisted of 396 of the initial 639 participants between the ages of 18 and 75 years that were diagnosed to be in remission by end of an open-label, flexible dosing acute treatment phase. Remission was defined as a MADRS total score of 10 or less. The eligible participants were randomized to receive individualized fixed treatment dose (5 mg or 10 mg) or placebo for 24 to 46 weeks. The primary outcome was time to relapse within the first 24 weeks of the double-blind phase where relapse was defined as a MADRS score of 22 or greater. The time to relapse was twice as long with vortioxetine compared to placebo (HR = 2.01, p= 0.0035). The relapse rate of the vortioxetine group was 13% compared to 26% of the placebo group (p=0.0013). The discontinuation rate due to side effects was 8% in the open-label, flexible dosing phase that allowed either 5 mg or 10 mg treatment doses. In the double-blind phase, the discontinuation rates were

8% in the vortioxetine group and 3% in the placebo group. The investigators concluded vortioxetine significantly reduces the risk of recurrent depressive episodes compared to placebo and is well tolerated for long-term use.

There are key limitations to the data from these studies. Although having an active control increases the validity of the results, none of the studies were powered to directly compare vortioxetine to the active control. More importantly, similar to most clinical trials, generalizability of the data is limited since the trials excluded patients that are representative of the general patient population treated in clinical practice, such as treatment-resistant patients and patients with multiple comorbidities. In addition, it is unclear of the significance of the varying results between non-US population and US-population. Further studies conducted in the US assessing vortioxetine in people with treatment-resistance depression or who have other concomitant disorders are needed.

Table 3 | Summary of Primary Outcome Results of the 6 to 8 week Clinical Trials[9, 13, 17, 18, 19, 20, 21]

Clinical Trial Location	Treatment Group	Number of patients	Primary Measure Depression Rating Scale	Mean Baseline Score	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference (95% CI)
Alvarez et al[17] Non-US Study	Vortioxetine 5 mg/day	108	MADRS	34.1 (2.6)	-20.4 (1.0)	-5.9 (-8.6, -3.2)
	Vortioxetine 10 mg/day	100		34.0 (2.8)	-20.2 (1.0)	-5.7
	Placebo	105		33.9 (2.7)	-14.5 (1.0)	(-8.5, -2.9)
Henigsberg et al[18] Non-US Study	Vortioxetine 5 mg/day	139	HAMD-24	32.2 (5.0)	-15.4 (0.7)	-4.1 (-6.2, -2.1)
	Vortioxetine 10 mg/day	139		33.1 (4.8)	-16.2 (0.8)	-4.9
	Placebo	139		32.7 (4.4)	-11.3 (0.7)	(-7.0, -2.9)
Boulenger et al[19] Non-US Study	Vortioxetine 15 mg/day	149	MADRS	31.8 (3.4)	-17.2 (0.8)	-5.5 (-7.7, -3.4)
	Vortioxetine 20 mg/day	151		31.2 (3.4)	-18.8 (0.8)	-7.1
	Placebo	158		31.5 (3.6)	-11.7 (0.8)	(-9.2, -5.0)
Mahableshwarkar et al[20] US Study	Vortioxetine 15 mg/day	145	MADRS	31.9 (4.1)	-14.3 (0.9)	-1.5 (-3.9, 0.9)
	Vortioxetine 20 mg/day	147		32.0 (4.4)	-15.6 (0.9)	-2.8
	Placebo	153		31.5 (4.2)	-12.8 (0.8)	(-5.1, -0.4)
Jacobsen et al[21] US Study	Vortioxetine 10 mg/day	154	MADRS	32.2 (4.5)	-13.0 (0.8)	-2.2 (-4.5, 0.1)
	Vortioxetine 20 mg/day	148		32.5 (4.3)	-14.4 (0.9)	-3.6
	Placebo	155		32.0 (4.0)	-10.8 (0.8)	(-5.9, -1.4)
Katona et al[13] US and Non-US Study Elderly	Vortioxetine 5 mg/day	155	HAMD-24	29.2 (5.0)	-13.7 (0.7)	-3.3
	Placebo	145		29.1 (5.1)	-10.3 (0.8)	(-5.3, -1.3)

Adapted from Brintellix (vortioxetine) package insert[9]

Adverse Events and Drug Interactions

Many of vortioxetine's reported adverse effects and drug interactions are expected. Its most common side effects are gastrointestinal and neurological, such as nausea, diarrhea, constipation, dizziness and abnormal dreams. Other common side effects are listed in Table 4.[9] If patients experience intolerable side effects, lowering the initial dose may be beneficial.

A rare but serious side effect characteristic of all antidepressants that modulate serotonin reuptake is increased risk of suicide. Short-term trials indicate that only participants younger than 24 years old taking vortioxetine were observed to be at risk, but all patients should be closely monitored.[9] Other serious side effects that require monitoring include hypersensitivity, angioedema, and mania or hypomania. Thus, patients should be screened for risk of bipolar disorder prior to initiating voritioxetine.[9] Currently available data suggests vortioxetine is weight neutral. Only the male participants taking vortioxetine reported a higher incidence of sexual dysfunction compared to their counterparts taking placebo (Table 5).[9] Similar to other SSRIs and SNRIs, hyponatremia has been reported; patients concomitantly taking diuretics and elderly patients may be at higher risk. No other clinical important changes in laboratory tests and vital signs, including blood pressure and heart rate, have been observed.

Vortioxetine has some key drug interactions. Patients concomitantly taking NSAIDS, aspirin, or anticoagulants such as warfarin are at increased bleeding risk. Vortioxetine use is contraindicated with the following medications due to an increase risk of serotonin syndrome: MAO inhibitors, linezolid and intravenous methylene blue. Caution should be exercised in patients concomitantly taking vortioxetine and serotonergic agents; both medications should be discontinued if serotonin syndrome develops. Since vortioxetine is primarily metabolized by the CYP2D6 enzyme, its serum drug levels may change when taken with medications that induce or inhibit CYP2D6. The recommended maximum dose is reduced by 50% to 10 mg daily in known CYP2D6 poor metabolizers or patients concomitantly taking a strong CYP2D6 inhibitor, such as bupropion, fluoxetine, paroxetine, or quinidine. Of note, concomitant use of fluoxetine or paroxetine with vortioxetine may increase risk of serotonin syndrome in addition to serum vortioxetine concentration. Conversely, a dose increase may be warranted in patients taking a strong CYP2C6 inducer, such as rifampin, carbamazepine, or phenytoin, for greater than 14 days.[9]

Table 4 | Common Adverse Reactions Occurring in ≥2% of Patients Treated with any Vortioxetine Dose and at Least 2% More Frequently than Incidence in Placebo-treated Patients in the 6 to 8 Week Placebo-Controlled Studies[9]

Dose of Vortioxetine	5 mg per day	10 mg per day	15 mg per day	20 mg per day
	N=1013 (%)	N=699 (%)	N=449 (%)	N=455 (%)
Gastrointestinal disorders				
Nausea	21	26	32	32
Diarrhea	7	7	10	7
Dry mouth	7	7	6	8
Constipation	3	5	6	6
Vomiting	3	5	6	6
Flatulence	1	3	2	1
Nervous system disorders				
Dizziness	6	6	8	9
Psychiatric disorders				
Abnormal dreams	6	6	8	9
Skin and subcutaneous tissue disorders				
Pruritus	1	2	3	3

Dosing

It is recommended that patients initially start with 10 mg orally once daily without regards to food and titrate as tolerated. Patients should be titrated down to 5 mg daily if they experience intolerable side effects. The maximum recommended dose is 20 mg daily. However, for poor CYP2D6 metabolizers or patients concomitantly taking a strong CYP2C6 inhibitor, the maximum recommended dose is 10 mg daily. Dose increases up to

three times the original dose may be considered in patients taking a strong CYP2D6 inducer for greater than 14 days. No dose adjustments are recommended for geriatric patients, renal impairment and mild to moderate hepatic failure.

Summary

Vortioxetine is a new multimodal antidepressant indicated for MDD in adults. In addition to being a SSRI, vortioxetine has modulating activity of a variety of serotonin receptors. Specifically, it acts as an antagonist to 5-HT_3, 5-HT_{1D}, and 5-HT_7 receptors, partial agonist at 5-HT_{1B} receptors, and agonist at 5-HT_{1A} receptors but the clinical effects remains unknown. It is a new option for acute and long-term treatment. However, majority of the clinical trials used to support its approval were short-term, conducted outside the United States and excluded patients that are commonly seen in clinical practice. Patients should be started on 10 mg daily and can be titrated up to 20 mg daily; some patients experiencing side effects may benefit from having their initial dose reduced to 5 mg daily. Vortioxetine can be taken without regard to meals and no dose adjustments are needed for age, renal function or mild to moderate hepatic impairment. However, there is potential for drug interactions, patients taking strong CYP2D6 inhibitors or inducers may require dose adjustments.

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Aptiom® (Eslicarbazepine acetate): A Review

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Epilepsy is a common neurological disorder that impacts the lives of many, with an age-adjusted incidence of 44 per 100,000 and a prevalence of 6-8 per 1000.[1, 2] Though many of the antiepileptic drugs have advanced the treatment of epilepsy, many individuals suffer from inadequate seizure control and/or undesirable side effects. Epilepsy is divided into two categories: generalized and partial seizures. Generalized seizures occur in both hemispheres of the brain and usually results in a loss of consciousness. Conversely, partial epilepsy is localized to one hemisphere of the brain, does not lead to a loss of consciousness, and accounts for nearly 60% of people with epilepsy. Partial epilepsy encompasses simple partial seizures, complex partial seizures, and secondary generalized seizures.[3, 4]

Seizures arise from a variety of complex mechanisms that are not completely understood. Alterations in ion channels, genetics, and neurotransmitter imbalances are believed to contribute to the pathophysiology of seizures.[5]Antiepileptic drugs (AEDs) are the mainstay in treatment for partial seizures. However, approximately 30% of treated patients with epilepsy have suboptimal control and will be required to take between 2-4 concomitant medications to manage this condition. With each additional medication added to the regimen, the side effect profile increases, with about a quarter of all epileptic patients experiencing unnecessary side effects.[6] Inadequate control and side effects contribute to an economic and social burden that may jeopardized the quality of life for many patients.[7] Thus, researchers continue to strive for developing AEDs that possesses both high efficacy and tolerability.

Eslicarbazepine acetate (ESL), manufactured by Sunovion Pharmaceuticals and marketed under the trademark name Aptiom®, was approved by the FDA on November 8th, 2013 as adjunctive treatment for partial-onset seizures.[8] This article will discuss the pharmacology, pharmacokinetics, efficacy, dosing, and safety of ESL.

Pharmacology and Pharmacokinetics

Eslicarbazepine acetate possesses a few unique characteristics when compared to other AEDs. Though the exact mechanism of action is unknown, ESL is believed to competitively block inactive high-frequency voltage-gated sodium channels at receptor site 2. This prolongs the inactivation period, thereby reducing the ability of neurons to fire at high frequencies. In addition, ESL is more selective for rapidly firing neurons versus resting neurons, showing a threefold lower affinity for resting sodium channels when compared to carbamazepine (CBZ). ESL is structurally similar to CBZ and oxcarbazepine (OXC) because it shares a dibenzazepine nucleus.[9] However, unlike CBZ, ESL is not metabolized to a toxic epoxide due to the molecular difference of ESL at the 10, 11-position on the molecule. Because of this molecular difference, ESL has modest enzyme inducing properties and, unlike CBZ, will not induce its own metabolism. Additionally, in contrast to OXC, ESL is a prodrug metabolized into a single enantiomer whereas OXC is metabolized to both R- and S-licarbazepine. This single enantiomer is believed to be more efficacious, possess fewer side effects, and cross the blood brain barrier more efficiently than the R-licarbazepine.[10]

Table 1 provides a summary of several important pharmacokinetic properties of ESL. The metabolite, eslicarbazepine, is responsible for the pharmacological activity of ESL. At doses of 400-1200 mg/day, ESL has linear, dose dependent

pharmacokinetics. The mean peak plasma concentrations (C_{max}) in the fed state was 12.8, while the C_{max} was 11.3 in the fasting state.[8] Peak plasma concentrations occur approximately 2-3 hours post dose and steady state concentrations are reached in 4-5 days.[9, 11] Because 90% of the ESL dose is recovered in urine, the bioavailability of ESL is considered high. ESL plasma protein binding is low (< 40%) and no clinically significant interaction has been observed when in the presence of warfarin, digoxin, phenytoin, or tolbutamide. Using population pharmacokinetic parameters, the volume of distribution was determined to be 61 L.[8]

Eslicarbazepine acetate is rapidly and significantly metabolized into the major active metabolite eslicarbazepine by hydrolytic first-pass.[8] Because of this rapid conversion, ESL plasma concentrations remain below quantification and a therapeutic plasma level has not been determined for ESL.[9, 11] This active metabolite accounts for 91% of plasma concentrations with the minor active metabolites, R-licarbazepine and OXC, accounting for 5% and 1%, respectively. ESL has no clinically relevant inhibitory effects on cytochrome (CYP) P450 enzymes such as CYP1A2, CYP2A6, CYP2B6, CYP2D6, CYP2E1, and CYP3A4, but ESL has been shown to have moderate inhibitory effect on CYP2C19. In mild-to-moderate hepatic insufficiency, no dose reduction is needed, but ESL is not recommended in patients with severe hepatic dysfunction.[8]

After multiple doses of ESL (800 mg/day), 92% of ESL was excreted in urine as eslicarbazepine, in which 67% was unchanged, 33% as glucuronide conjugates, and the other 8% was excreted in urine as (R)-licarbazepine, OXC, and glucuronide conjugates. Clearance of ESL relies on renal function and a creatinine clearance (CrCl) < 50 mL/min will warrant sound clinical judgment and appropriate dose adjustments that are discussed in the dosing and administration section. The half-life ($t_{1/2}$) is approximately 13-20 hours.[8]

Table 1 | Pharmacokinetic Information for Eslicarbazepine acetate (ESL)[8, 10]

Parameter	Measurement
Peak Plasma Concentration (C_{max})	2-3h
Elimination $t_{1/2}$	13-20h
Bioavailability	High
Plasma Clearance	20-30 mL/min
Metabolism	Hydrolysis (Cytochrome P450 enzymes and UDP-glucuronyl transferases)
Volume of Distribution	61 L
Excretion	>90% in urine as ESL and inactive glucuronide conjugates
Protein Binding	<40%

C_{max}= maximum concentration ESL: Eslicarbazepine

Clinical Trials

In three phase III trials performed in 23 countries, the efficacy and safety of ESL was assessed as an adjunctive therapy in patients with partial-onset seizures. All three studies were multicentered, randomized, placebo-controlled, and double-blinded. The chief enrollment criteria included patients treated with one to three AEDs and with at least four simple or complex partial-onset seizures over a 28 day period. Each of the three studies required an eight week baseline period, a two week titration period, and a 12 week treatment period.[12] Ben-Menachem et al and Elger et al used three ESL dose groups to assess the efficacy and safety (400 mg, 800 mg, and 1200 mg), while Gil-Nagel et al only addressed two ESL doses of 800 mg and 1200 mg.[6, 13, 14] In these trials, 69% of patients were using two concomitant AEDs and 28% of the patients were using one concomitant AED. Carbamazepine (50%), lamotrigine (24%), valproic acid (21%), and levetiracetam (18%) were the most commonly used AEDs in these trials. Because OXC shares common metabolites with ESL, OXC was not allowed as a concomitant AED. In all three phase III studies, ESL at doses of 800 mg and 1200 mg once a day, demonstrated effectiveness and was well tolerated by patients. The inclusion and exclusion criteria varied between the three studies, but the differences were not significant. Additionally, base-

Table 2 | Summary of ESL phase III Trials

Author/ Year	Study Design	ESL dose (mg/ day)	Responder Rate (%)	Median Relative Risk Reduction in seizure frequency (%)	Authors Conclusion
Elger et al. (2009)[6]	MC, DB, R, PC	Placebo 400 800 1200	20.0 23.0 34.0 43.0	16.0 26.0 36.0 45.0	ESL 800 and 1200 mg/day well tolerated and effective
Gil-Nagel et al. (2009)[13]	MC, DB, R, PC	Placebo 800 1200	22.6 34.5 37.7	17.0 37.9 41.9	800 and 1200 mg/ day of ESL effective and well tolerated
Ben-Menachem et al. (2010)[14]	MC, DB, R, PC	Placebo 400 800 1200	13.0 17.0 40.0 37.1	0.8 18.7 32.6 32.8	ESL 800 and 1200 mg/day well tolerated and effective

DB: Double-blind; MC: Multicenter; R: Randomized; PC: Placebo controlled; ESL: Eslicarbazepine acetate; Responder rate: percentage of patients with ≥ 50% decrease in seizure frequency;

line characteristics did not differ significantly between the trials.[12]

The primary efficacy endpoint for all three trials was seizure frequency during the 12 week maintenance period, while relative reduction in seizure frequency, and responder rate (≥ 50% reduction in seizure frequency) were analyzed as secondary endpoints. Efficacy endpoints were analyzed using an intention to treat analysis, which included all patients randomized and that received at least one dose of ESL. All three trials assessed the impact of ESL on reducing the number of seizures, while controlling for other variables such as concomitant AEDs and baseline seizure frequency. Secondary endpoints were performed per protocol and included all patients that completed the study.[12]

Elger et al randomized 402 patients, of which 102 patients were assigned to the placebo group, 100 patients were assigned to ESL 400 mg/day, 98 patients were assigned to ESL 800 mg/day, and 102 patients were assigned to ESL 1200 mg/day.[6] Of the 402 patients that entered the treatment phase, 330 (82%) completed the study. Of the 72 (18%) patients that were lost to follow-up, the most common reason was due to adverse events (AEs). Over the 12 week treatment phase, the seizure frequency was found to be significantly lower in the ESL 800 mg/day arm (Least Square (LS) Mean 5.66, p=0.0028) and in the ESL 1200 mg/day arm (LS Mean 5.35, p=0.0003), compared to the placebo group (LS Mean 7.64). The ESL 400 mg/day arm and placebo did not have a statistically significant different LS Mean. The LS Mean seizure frequency was adjusted per four week time period. The responder rate (patients with ≥50% decrease in seizure frequencies) was significantly higher in the ESL 800 mg/day (34%, p=0.0359) and in the ESL 1200 mg/day arm (43%, p=0.009) than in the placebo group (20%). The incidences of mild-to-moderate AEs increased with increasing doses, and the frequency of serious AEs was similar across all groups in the trial. The authors concluded that both the ESL 800 mg/day and 1200 mg/ day are well tolerated and effective in patients that have refractory partial-onset seizures.[6]

Gil-Nagel et al studied the efficacy and safety of daily doses of ESL 800 mg and 1200 mg as adjunctive treatment in patients with partial-onset seizures.[13] After an 8-week baseline period, 253 patients were randomized into three arms. The placebo group contained 88 patients, the ESL 800 mg/day arm had 85 participants, and the ESL 1200 mg/day group had 80 patients. After a two week titration period, patients entered a 12 week maintenance period. The population was analyzed using an intention-to-treat method. The

Table 3 | Drug interactions with ESL and dose adjustments [8, 15]

Drug	Effects of ESL on drug	Effect of drug on ESL	Dose adjustment
Carbamazepine	None	21-33% decrease in AUC	May need an increase ESL dose
Phenytoin	Increase 30-35% in AUC	21-33% decrease in AUC	Monitor phenytoin levels and may need an increase in ESL dose
Phenobarbital	None	Decrease AUC	May need an increase in ESL dose
Simvastatin	Decrease 41-61% in AUC	None	Increase in simvastatin dose may be required
Rosuvastatin	Decrease in AUC	None	Increase in rosuvastatin dose may be required
Ethinylestradiol	Decrease of 37% in AUC	None	Additional contraception should be used
Levonorgestrel	Decrease of 42% in AUC	None	Additional contraception should be used
Warfarin	Decrease of 23% in (S)-Warfarin AUC	None	Monitor INR closely

AUC : Area under the curve

standardized (per 4 week) seizure frequency was significantly lower for the 800 mg/day (LS Mean 5.7, p=0.048) and 1200 mg/day (LS Mean 5.5, p=0.021) arms when compared to placebo (LS Mean 7.3). The responder rate was 22.6% for the placebo arm, 34.5% (p=0.106) for the 800 mg/day arm, and 37.7% (p=0.020) in the 1200 mg/day arm. The authors concluded that 800 mg/day and 1200 mg/day of ESL are effective and well tolerated.[13]

Ben-Menachem et al carried out a trial similar to that of Elger et al.[6, 14] After an 8-week baseline observational period, 395 of the 503 patients that entered the study were randomized to placebo (n=100), ESL 400 mg/day (n=96), ESL 800 mg/day (n=101), or 1200 mg/day (n=98). After a two week titration period, the patients entered a 12-week treatment period followed by a two week discontinuation phase. The data collected was analyzed after the 14 week treatment period and the standardized seizure frequency (per 4 weeks) was significantly lower in the ESL 800 mg/day (LS Mean 7.1, p<0.001) and in the ESL 1200 mg/day (LS Mean 7.4, p<0.001), compared to the placebo arm. There was no statistically significant difference in the placebo and ESL 400 mg/day groups. In addition, the responder rate in the ESL 800 mg/day group (40.0%, p<0.001) and in the ESL 1200 mg/day (37.1, p<0.01) was significantly higher than the placebo group. Like previ-

Table 4 | Combined adverse reactions from three clinical trials (Events ≥ 2% of patients in ESL 800 mg and 1200 mg arms)[8]

Adverse reaction	Placebo (%)	ESL 800 mg	ESL 1200 mg
Dizziness	9	20	28
Nausea	5	10	16
Somnolence	8	11	18
Headache	9	13	15
Diplopia	2	9	11
Vomiting	3	6	10
Fatigue	4	4	7
Ataxia	2	4	6
Blurred vision	1	6	5
Tremor	1	2	4
Vertigo	1	2	6
Rash	1	1	3
Hypertension	1	1	2
Hyponatremia	1	2	2

ous findings, AEs increased with increasing doses and the discontinuation rates due to AEs were 3.0% (placebo), 12.5% (400 mg), 18.8% (800 mg), and 26.5% (1200 mg). The most common AEs were dizziness, somnolence, headache, nausea, and diplopia. The authors concluded that treatment with once daily ESL 800 mg and 1200 mg are both efficacious and well tolerated.[14] Table 2 summarizes the aforementioned trials.

Drug Interactions

Many of the drug interactions noted have been with concomitant use of other AEDs. When phenytoin (PHT) and ESL are given concomitantly, a 30-35% increase in PHT and a 21-33% decrease in ESL exposure is seen. Similarly, concomitantly taking CBZ and ESL leads to an increase in CBZ plasma concentrations and a decrease in ESL plasma concentrations. Therefore, the dose of PHT, CBZ, and ESL may need to be adjusted accordingly. When used concomitantly with enzyme inducing AEDs, such as phenobarbital and primidone, higher doses of ESL may be needed. Interactions with other AEDs, such as levetiracetam, valproic acid, and gabapentin, do not appear to be clinically relevant, not requiring dose adjustments. ESL can inhibit CYP2C19, which can cause increased plasma concentrations of drugs, such as omeprazole, clobazam, and phenytoin. ESL can induce CYP3A4, decreasing plasma concentrations of agents metabolized by this CYP enzyme. Administration of ethyinyl estradiol/levonorgestrel with ESL leads to a decrease of 42% in ethyinyl estradiol and a 37% decrease in levonorgestrel. This interaction appears to occur in a dose dependent fashion. The clinically relevant interactions, along with appropriate dosing recommendations, are summarized in Table 4.[15]

Adverse Events

ESL appears to have a favorable side effect profile. In phase III studies, most of the mild to moderate AEs occurred mainly during the initiation phase of ESL. After six weeks of treatment, no significant differences in the occurrence of AEs were evident between ESL 800 mg, 1200 mg, and placebo groups. AEs leading to attrition during the trials were 4.5% in the placebo arm, 8.7% in the ESL 400 mg arm, 11.6% in the ESL 800 mg arm, and 19.3% in the ESL 1200 mg arm.[4] Gil-Nagel et al, from pooled data, concluded that 45.3% treated with ESL reported treatment related AEs, compared to 24.4% treated with placebo.[12] The occurrence of severe AEs, such as Stevens-Johnson Syndrome, Toxic epidermal necrolysis, and DRESS/Multiorgan Hypersensitivity, was low and similar in each of the ESL treatment arms. The incidence of rash was 0.3% in placebo, 0.5% with ESL 400 mg, 1.1% with ESL 800 mg, and 3.2% with ESL 1200 mg. Hyponatremia, defined by $Na^+ < 125$ mmol/L, was reported in four patients and <1% of the treatment arms experienced behavioral or psychiatric AEs.[4] The most common AEs, such as dizziness, nausea, somnolence, and headache, are summarized in Table 4.[14]

Dosing and Administration

Eslicarbazepine acetate will be available in 200 mg, 400 mg, 600 mg, and 800 mg tablets. ESL can be taken without regard to food and crushed if needed.[8] Initial doses should be 400 mg by mouth daily for one week and titrated to the recommended maintenance dose of 800 mg daily. The dose can be further titrated to 1200 mg daily based on tolerability and clinical response.[9, 11] If the desired dose is 1200 mg daily, the manufacturer recommends starting with 400 mg daily for one week, then increasing to 800 mg daily for at least a week.[8] Though this has shown to decrease seizure frequency, clinicians should be aware the AEs seen with ESL are dose dependent.[11] Therefore, clinical response and patient tolerability will be the most valuable method for assessing the efficacy of ESL in each patient. In patients with compromised renal function CrCl < 50 mL/min, the dose should be half of the recommended maintenance dose. The manufacturer recommends starting with 200 mg daily for two weeks and then initiate ESL 400 mg daily thereafter.[8] Dose adjustments are not available for CrCl <30 mL/min due to inadequate data.[15] If discontinuation of ESL is warranted, abrupt withdrawal should be avoided and the dose should be gradually tapered over several weeks to minimize the risk of seizures.[8]

Summary

Eslicarbazepine acetate is indicated as an adjuvant for the treatment of partial-onset seizures. ESL was efficacious in several phase III clinical trials and has shown good tolerability in adults, with the most common side effects including dizziness, somnolence, headache, nausea, and vomiting. Though structurally similar to carbamazepine, ESL has a much lower potential for drug-drug interactions and no autoinduction. With less drug-drug interactions, once a day dosing, and good tolerability, ESL has the potential to positively impact the lives of many patients suffering from seizures and contribute to increased quality of life.

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