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Review Article

A Review of Anticonvulsants use in Psychiatric Conditions

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Abstract

Anticonvulsants which are also referred to as Antiepileptic drugs (AEDs) are increasingly being used in conditions other than epilepsy. Some AEDs are U.S. Food and Drug Administration (FDA) approved for the treatment of certain psychiatric conditions. Other AEDs are not FDA- approved for the treatment of psychiatric conditions, but are widely used by mental health and primary care providers for the treatment of multiple psychiatric conditions. The purpose of this review is to describe the mechanism of action of AEDs beyond their anticonvulsant properties, and to summarize the use of the AEDs: carbamazepine, divalproex, lamotrigine, oxcarbazepine, gabapentin, topiramate, levetiracetam, tiagabine, and zonisamide in the treatment of various psychiatric disorders. Special emphasis is also placed on the various AEDs dosing schedule, adverse effects and interactions with other medications. Despite AEDs therapeutic effects in the treatment of unapproved FDA psychiatric conditions, large, randomized controlled clinical trials are still needed to confirm their efficacy in the treatment of the multiple conditions for which they are often prescribed in clinical practice.

Keywords: *Anticonvulsants; Antiepileptic drugs (AEDs); Food and Drug Administration (FDA)*

Introduction

Over the past three decades, the number of new AEDs has increased considerably. As the number of new agents increases, so too does the reporting of their off-label use in psychiatric disorders. This review will summarize the U.S. Food and Drug Administration (FDA) approved use of carbamazepine, divalproex, and lamotrigine and the off-label use of oxcarbazepine, gabapentin, topiramate, levetiracetam, tiagabine, and zonisamide in the treatment of various psychiatric disorders.

Valproate/Divalproex/Valproic acid

Depakote is a brand name for sodium divalproex, a compound made of sodium valproate and valproic acid. It is also available both in an extended release and a delayed release formula. Valproate is FDA-approved for the treatment of acute mania and mixed states of bipolar disorder I, bipolar II disorder [1]. It has also been used as an adjunctive treatment in schizoaffective disorder, with some reports suggesting an improvement and in the negative symptoms of a schizophrenia and as a useful adjunctive agent in specifically reducing hostility among patients with schizophrenia experiencing an acute psychotic episode, a potential efficacy in the treatment of panic disorder, posttraumatic stress disorder in combat veterans and the civilian population, and childhood posttraumatic stress disorder related to physical and sexual abuse [2]. Other studies have suggested that it may possess some efficacy in preventing relapse in patients with alcohol use disorder specially in patients with co-occurring bipolar disorder and alcohol addiction [3]. It has also been reported to reduce cocaine cravings and improving mood in patients with cocaine addiction even in the absence of co-occurring bipolar disorder [4]. There are some reports about its usefulness in the management of agitation and aggressive behavior associated with dementia, impulse control disorders,

and in controlling the adverse effect of Parkinson's disease medical therapy [2]. It could also decrease impulsiveness, agitation and aggressive behavior associated with autistic spectrum disorder in children and adolescents, aged 5 to 17 years [2]. In correctional settings it has also been used in the management of impulsive aggression and mood lability in patients even in those without co- occurring bipolar disorder [5]. Valproate appears also to be of particularly efficacious in patients with borderline personality disorder especially in those with prominent impulsive aggression, rather than in patients with affective instability [2].

Mechanism of action

Although the mechanism of action is presently unknown, it is postulated that divalproex sodium effects are mediated through its function on brain gamma-aminobutyric acid specifically by increasing brain concentrations of this inhibitory transmitter with some evidence that valproic acid may inhibit the re-uptake of gamma-aminobutyric acid into the glia and nerve endings [1].

Dosing regimen

1) Usual dose (Depakote (R) ER, extended-release): 25 mg/kg/day orally once daily; increase as quickly as possible to achieve desired clinical effect; target trough plasma level range was 85 to 125 mcg/mL (590 to 867 mcmol/l) in studies; maximum recommended dose, 60 mg/kg/day.
2) Usual dose (Depakote (R), delayed-release): 750 mg orally per day in divided doses; increase as quickly as possible to achieve desired clinical effect; target trough plasma level was 50 to 125 mcg/mL (347 to 867 mcmol/L) in studies; maximum recommended dose, 60 mg/kg/day.

Alternative regimens

1) A loading dose of 20 mg/kg/day achieved serum valproate concentrations of 80 mg/L (555 mcmol/L), which was effective for rapidly reaching therapeutic levels in patients with acute psychotic manic symptoms.
2) Another accelerated loading regimen used 30 mg/kg/day on days 1 and 2 followed by 20 mg/kg/day for days 3 through 10.

Adverse effects

The most common adverse effects are asthenia, somnolence, dizziness, tremor, headache, nausea, vomiting, abdominal pain, diplopia, and blurred vision [6].

Thrombocytopenia appears to be dose- or concentration-dependent, the probability increasing significantly at serum concentrations exceeding 110 mg/mL (females) or 135 mg/mL (males). It is reversible upon discontinuation.

FDA black box warning

Hepatotoxicity: Serious or fatal hepatic failure has occurred, usually during 1st 6 months of treatment. This risk increases specially in patients receiving multiple AEDs, and those patients with congenital metabolic disorder, severe seizure disorder, mental retardation, or other brain disease. Hepatotoxicity may be preceded by malaise, weakness, lethargy, facial edema, anorexia, vomiting and loss of seizure control. The risk of hepatotoxicity is markedly increased in patients with Mitochondrial disease. It is essential for clinicians to monitor for signs and symptoms of hepatotoxicity by checking liver function tests at baseline, then frequently, especially during the 1st 6 months of treatment [6].

Fetal risk: Congenital malformations including. neural tube defects and decreased IQ scores after in utero exposure [1].

Pancreatitis. Cases with rapid progression to death have been reported shortly after initial use as well as after several years of use [1,6].

Medication interactions

Serum concentrations of valproic acid can be elevated by concomitant chlorpromazine, felbamate, sertraline, and cimetidine administartion. The Serum concentrations would decrease with the concurrent use of bile acid–binding resin, such as rifampin, carbamazepine,

ethosuximide, lamotrigine, and phenytoin. Valproic acid can raise the serum concentrations of amitriptyline, nortriptyline, carbamazepine, epoxide, diazepam, lamotrigine, barbiturates, phenytoin, and zidovudine [7].

Carbamazepine

Carbamazepine is FDA-approved for the treatment Bipolar I disorder, acute manic and mixed episodes [8]. A significant decrease of manic and depressive symptoms has also been reported in patients with schizoaffective disorder who were treated with carbamazepine [2]. It has been also used in the treatment of schizophrenia [9], in psychosis with visual hallucinations. Because of its effect on over activity, aggression and poor impulse control, carbamazepine could have a clinical utility to improve these symptoms in a variety of different diagnostic conditions and possibly clinically useful to stabilize these symptoms rather than being the treatment of choice for a psychiatric condition or disease entity [10]. For instance, carbamazepine was found to be effective in the treatment of a disorder which used to be described clinically as temporal lobe syndrome that was manifested by temporal lobe dysfunction, with subtle mental changes and most prominently atypical, labile, irritable mood with agitation and potential for aggressive behaviors. It also had similar effects on decreasing aggression and agitation in certain patients with traumatic brain injury [11]. This particular effect of carbamazepine on agitation had shown some effectiveness in the management of aggressive and agitated behaviors in patients with dementia [12] on decreasing the severity and frequency of behavioral decontrol in patients with borderline personality disorder [13]. Other clinical use and of carbamazepine includes its calming effects as an adjunctive treatment of posttraumatic stress disorder [14]. Carbamazepine is also included as one of the agents that can be used in the treatment of substance use disorders including alcohol use disorder, and alcohol withdrawal [15]. Although carbamazepine was having useful adjunctive properties for assisting in easing the discontinuation of benzodiazepines, however the available data are insufficient for recommending its use in primary care settings [16].

Mechanism of action

Carbamazepine is related to the tricyclic antidepressants and is a sodium channel blocker which binds preferentially to voltage-gated sodium channels in their inactive conformation, which prevents repetitive and sustained firing of an action potential. Carbamazepine has effects on serotonin systems with some evidence that it is a serotonin releasing agent and possibly even a serotonin reuptake inhibitor [17]. It seems that long term administration of carbamazepine also increases gamma-aminobutyric acid concentrations in several brain regions, especially in the limbic areas [18].

Dosing regimen

Carbamazepine is available in 200 mg tablets, extended release ER 100 mg, 200 mg, 400 mg tablets, extended release ER 100 mg, 200 mg, 300 mg; capsules, 100 mg Chewable and Suspension liquid of 100 mg per 5 Mr.

The recommended initial dose is 200 mg twice daily (tablets) or 100 mg four times daily (oral suspension), with subsequent titration in 200 mg/day increments at weekly intervals, to a maximum of 1200 (rarely, 1600) mg/day. In older individuals, a lower initial dose of 100 mg twice daily (tablets) or 50 mg four times daily (oral suspension) is prudent, with titration occurring at 7 to 14-day intervals. The dose should be gradually tapered before discontinuation.

Adverse effects

The major adverse effects of carbamazepine involve the CNS and gastrointestinal tract and include drowsiness, dizziness, confusion, headache, fatigue, nystagmus, incoordination, nausea, and vomiting. In addition, rare cases of bone marrow depression of one to all cell lines, hepatotoxicity, and dermatologic reactions have been reported [19]. Carbamazepine is one of the most frequent causes of drug-induced syndrome of inappropriate antidiuretic hormone secretion [20]. Occasional monitoring of serum sodium concentration, complete blood count with differential, and liver function tests are recommended. Since carbamazepine is used in combination with other agents for the management of treatment resistant bipolar disorder, serum carbamazepine concentration, hematological profile, and serum electrolytes should be monitored carefully to minimize the risk of toxic adverse effects.

Medication interactions

Cytochrome P-450 isozyme 3A4 inhibitors can increase plasma carbamazepine concentrations such as cimetidine, diltiazem, macrolide antimicrobials, fluoxetine, fluvoxamine, nefazodone, isoniazid, propoxyphene, systemic azole antifungals, metronidazole, verapamil,

risperidone, grapefruit juice, and protease inhibitors [21]. Valproate, felbamate, and quetiapine can increase plasma concentrations of the active 10,11-epoxide metabolite [55]. Cytochrome P-450 isozyme 3A4 inducers such as cisplatin, doxorubicin, rifampin, barbiturates, phenytoin, and primidone can reduce plasma carbamazepine concentrations and carbamazepine can increase plasma concentrations of phenytoin and primidone and decrease those of dihydropyridine calcium channel blockers, cyclosporine, corticosteroids, selected benzodiazepines, selected traditional and atypical antipsychotics , itraconazole, lamotrigine, methadone, oral contraceptives/hormone replacement therapy, phenytoin, protease inhibitors, tiagabine, topiramate, tricyclic antidepressants, valproate, and warfarin [22].

Lamotrigine

Lamotrigine is FDA-approved for maintenance treatment of bipolar disorder with effectiveness when depression is prominent [23]. It also has a role in treating acute bipolar depression and unipolar depression, and in patients presenting with mixed or depressed states [57,58]. It has also been used in treatment-resistant schizoaffective disorder, and as an adjuvant in combination with clozapine for treatment resistant schizophrenia [24]. Some beneficial use of lamotrigine has been also reported for the treatment of borderline personality disorder, anxiety disorders, depression, and posttraumatic stress disorder [24]. Reports also suggest that lamotrigine have a favorable result in alleviating the sexual side effects associated with other AEDs [25].

Mechanism of action

The action mechanisms underlying the mood-stabilizing effects of lamotrigine are unknown, it is known to modulate various ion channels, altering neuronal excitability. The use-dependent inhibition of neuronal firing by lamotrigine is potentially important because it could result in attenuating neuronal activities that are possibly associated with bipolar disorder. Lamotrigine inhibits the release of glutamate, similarly to lithium, and its possible association with mood-stabilizing or antidepressant effects needs to be further examined. Unlike lithium or valproic acid, however, lamotrigine does not down-regulate the expression of protein kinase C or MARCKS, suggesting that lamotrigine employs different intracellular mechanisms for long-term changes in neuro-biology from those of lithium or valproic acid [26].

Dosing regimen

Lamotrigine is available as 25, 100, 150, and 200 mg tablets and 2, 5, and 25 mg chewable/dispersible tablets. Patients receiving concurrent therapy with enzyme inducing drugs and valproate should receive 25 mg every other day for 14 days followed by 25 mg once daily for 14 days followed by dose escalation in 25 to 50 mg/day increments every one to two weeks to the maintenance dose. To maintain its therapeutic benefits lamotrigine's doses should be halved in individuals taking enzyme inhibitors and doubled in those on enzyme inducers [27]. Patients receiving concurrent therapy with enzyme-inducing medications may need to be treated with 50 mg once daily for 14 days followed by dose escalation in 100 mg/day increments every one to two weeks until the maintenance dose is reached [28]. So, lamotrigine initial dose may need to be increased and individualized depending on age, body weight, the presence of underlying medical conditions and the coadministration of enzyme inducers medications such as carbamazepine, ethinylestradiol, fluoxetine, lithium, phenytoin, phenobarbital, or topiramate [28].

Adverse effects

Monotherapy with lamotrigine is most frequently associated with dizziness, diplopia, ataxia, blurred vision, and somnolence, with skin rash as the most frequent cause of therapy withdrawal with lamotrigine occurring in 4% in clinical trials and it is typically maculopapular or erythematous and displays characteristics of a delayed type hypersensitivity reaction, appearing within the first month of therapy and resolving rapidly with treatment withdrawal [3]. In 0.3% of cases it may progress to potentially fatal forms such as erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis [29]. The latter finding mandates that lamotrigine be stopped at the first sign of rash and not restarted. The risk of rash appears to be enhanced significantly when lamotrigine dose escalation is performed rapidly while the risk is significantly reduced when dose escalation is performed slowly. Some bioequivalence studies evaluating 50 mg doses of lamotrigine suggest that such doses may minimize the risk of severe rash or Stevens-Johnson syndrome [30]. In September 2006, the

FDA issued a warning stating that taking lamotrigine during the first trimester of pregnancy may increase the risk for cleft lip and palate_malformation in newborns, however review studies have found that overall rates of congenital malformations in infants exposed to lamotrigine *in utero* are relatively low (14%) compared to the typical 3% rate in the untreated population [31]. Lamotrigine is expressed in breast milk and it is not recommended to breast feed during lamotrigine treatment [32].

Medication interaction

Carbamazepine inducing enzymes lower lamotrigine plasma levels, while valproate could double lamotrigine plasma levels [33]. Lamotrigine may increase the depressant effects of alcohol or other CNS depressants, including antihistaminic, sedatives, hypnotics, narcotics, barbiturates, muscle relaxants, and anesthetics, including some dental anesthetics and oral contraceptives can lower the plasma level of lamotrigine by as much as 50% [33].

Oxcarbazepine

Oxcarbazepine has been used for the treatment of bipolar disorder including acute mania of mild to moderate severity, depression, rapid cycling and maintenance treatment and despite it's appealing long term low risk of adverse effects, it has not shown to be more effective than carbamazepine and is rarely used in the treatment of psychiatric conditions that are not associated with epilepsy [34].

Mechanism of action

Oxcarbazepine exert its action by blocking voltage-sensitive sodium channels, thus leading to the stabilization of hyper excited neural membranes, suppression of repetitive neuronal firing and diminishment propagation of synaptic impulses in addition to enhancing potassium conductance and modulating of high-voltage activated calcium channels [34].

Dosing regimen

Oxcarbazepine is available in 150 mg, 300 mg and 600 mg tablets and 300 mg/5 mL suspension. Usually started at the dose of 300 mg twice a day to be increased by increment of 300 mg/day every 3 days or by 600 mg/day weekly. Seniors and individuals with renal impairment may require lower dosages. It is important to taper that dose gradually prior to discontinuation.

Adverse effects

Hyponatremia and the syndrome of inappropriate antidiuretic hormone secretion have been reported with oxcarbazepine in addition to other most common adverse effects of which include sedation, headache, dizziness, rash, vertigo, ataxia, nausea, and diplopia [35]. These effects appear to be dose-dependent, occurring at higher frequencies as the dose increases. Behavioral effects such as depression and mania could rarely occur, also rashes and Stevens-Johnson syndrome occur less frequently with oxcarbazepine compared to carbamazepine with approximately 30% cross-reactivity rate [36]. Oxcarbazepine is not known to cause hepatic or hematologic toxicities. Because oxcarbazepine was found to cause fetal abnormalities and infertility in animals treated at doses like recommended human doses and is also excreted in human breast milk, so as such, it should be avoided during preconception, pregnancy, and breast-feeding [37].

Medication interaction

Oxcarbazepine selectively induce cytochrome P450 isozyme 3A4/3A5, enhancing the metabolism of estrogen, progestogen, felodipine, and carbamazepine. In addition, induction of UDP-glucuronic transferase activity occurs, leading to enhanced glucuronidation and elimination of lamotrigine [38]. The inhibition of cytochrome P450 isozyme 2C19 by oxcarbazepine can produce increases in phenytoin and phenobarbital concentrations [38]. Hepatic enzyme inducers such as carbamazepine, phenobarbital, and phenytoin enhance oxcarbazepine systemic clearance while verapamil and valproate may also reduce oxcarbazepine plasma concentrations by unknown mechanisms [38].

Gabapentin

Gabapentin was initially reported to be effective in treating behavioral decontrol in intermittent explosive disorder with mental retardation and has also been used in the treatment of acute mania in bipolar disorder and in anecdotal cases of treating patients with anxiety,

panic disorder, social phobia, aggressive behavior, posttraumatic stress disorder, and obsessive-compulsive disorder [2]. However, there is not enough evidence to confirm its efficacy in treating these conditions. Gabapentin has clearer efficacy for decreasing alcohol craving and withdrawal symptoms and may have a role as an adjunctive treatment of opioid dependence [39]. Other areas of clinical use have been in the treatment of agitation and disruptive behavior in patients with dementia [39].

Mechanism of action

Gabapentin mechanism of action is not well understood, it is thought to regulate glutamate decarboxylase and branched chain aminotransferase with both the glutamate decarboxylase and the branched chain aminotransferase enzymes aiding in the synthesis of gamma-aminobutyric acid but, it does not bind to gamma-aminobutyric acid (A) or gamma-aminobutyric acid (B) receptors and it does not appear to influence synthesis or uptake of gamma-aminobutyric acid. High affinity gabapentin binding sites have been located throughout the brain; these sites correspond to the presence of voltage-gated calcium channels specifically possessing the alpha-2-delta-1 subunit [40]. This channel appears to be located in the presynaptic ally and may modulate the release of excitatory neurotransmitters, which may explain some of its effects on the treatment of certain psychiatric conditions [2].

Dosing regimen

Gabapentin is an attractive agent due to its wide range flexible doses, its high therapeutic index, its favorable side effect profile, its minimal interactions with other agents, in addition to not needing serum levels monitoring. It is usually initiated with 300 mg once a day, usually in the evening. The dose is increased every 3 to 5 days. Depending on its tolerability, the dose could be increased by 600 mg/day up to 4,800 mg/day [41].

Adverse effects

Dizziness, double vision, fatigue, nystagmus, sleepiness, tremors, unsteadiness, nausea and/or vomiting. Most side effects developed during the first few days following an increase in the dose. They usually subside over time [42]. Side effects of agitation decreased, or increased libido, depersonalization, mania, paranoia, misuse and abuse have also occurred with gabapentin [42].

Medication interaction

Antacids could decrease gabapentin absorption, as well as lower its blood level and gabapentin could also increase the level of concentration of some oral contraceptives [43].

Topiramate

Topiramate has been used in the treatment of binge eating disorder, bulimia nervosa, alcohol use disorders and to treat the depressive phase bipolar disorders, rapid cycling bipolar disorders, as an adjunctive treatment in refractory bipolar disorder, schizophrenia, posttraumatic of stress disorder, depression, borderline personality disorder and Gilles de la Tourette's syndrome [44-46].

Mechanism of action

Although topiramate mechanism of action is not well known some pharmacological evidence indicates that topiramate may act via several mechanisms including: modulation of voltage-dependent, sodium channels, potentiation of gamma-aminobutyric acid inhibition, block of excitatory neurotransmission, and possibly modulation of voltage- and receptor-gated calcium ion channels [47].

Dosing regimen

Topiramate is available as 25, 100, and 200 mg oral tablets and 15 and 25 mg sprinkle capsules. The recommended starting dose in adults is 25 to 50 mg/day, followed by dose titration in increments of 25 to 50 mg/day every one to two weeks based on response to a usual maintenance dose of 200 to 400 mg/day (maximum 600 mg/day). Doses should be given twice daily. The sprinkle capsules may be swallowed whole or the contents can be sprinkled on a small amount of soft food. This sprinkle/food mixture should not be chewed.

Adverse effects

The main side effects that lead to the discontinuation of topiramate are psychomotor slowing with sedation or drowsiness, fatigue, cognitive impairment with memory difficulties, confusion, and somnolence in addition to nausea, vomiting, headache, dizziness, decreased appetite, frequent peristalsis, and blurred vision [48]. Delirium could also develop especially when combined with sedatives and hypnotics or when taken with alcohol [48]. Some patients develop kidney stones, hematuria and increased risk of nephrolithiasis [49]. Acute angle glaucoma could develop in very few patients [50]. Rare but serious adverse events have been also reported with topiramate including metabolic acidosis, acute myopia, oligohidrosis and hyperthermia [51]. These adverse effects usually occurred with high dose titration and frequently resolved or lessened with time and/or dosage reduction and conversely, slow dose titration was associated with a lower rate of side effects. Studies have also suggested an increased risk of oral clefts in infants exposed to topiramate during the first trimester of pregnancy [52]. Side effects or harmful effects in breast fed babies are rarely reported with topiramate [53].

Medication interaction

Interactions between topiramate, valproate, and carbamazepine have been reported and topiramate appears to raise the blood-plasma level of phenytoin, while phenytoin decreases the level of topiramate by 50% [54]. There have been some reports that topiramate reduces the effectiveness of oral contraceptive pills, since as a mild enzyme inducer of the oral contraceptive ethinylestradiol, topiramate could increase its oral clearance at high dosages exceeding 200 mg/day, due to this dose-dependency, possible interactions between topiramate and oral contraceptives should be assessed according to the topiramate dosage utilized [55]. Some mild interactions have been reported to occur between topiramate and lithium, haloperidol, amitriptyline, risperidone, sumatriptan, propranolol and dihydroergotamine at high dosages exceeding 200 mg/day [54].

Levetiracetam

Little is known about the psychiatric effects of levetiracetam in the nonepileptic population. Some studies suggest that it can be used as a mood stabilizer or as an adjunctive therapy for patients with bipolar spectrum disorders, leading to reduction and remission of manic and rapid cycling symptoms in bipolar illness [56]. It may exert some symptoms reduction in social anxiety disorder (social phobia), panic disorder and posttraumatic stress disorder [57] and obsessive-compulsive disorder [58]. It has have also shown to reduce hyperactivity, impulsivity, mood instability, and aggression in autistic spectrum disorder [59].

Mechanism of action

The precise mechanism of action of levetiracetam is not precisely known. It binds to synaptic vesicle glycoprotein 2A5(SV2A), and inhibits presynaptic calcium channels, thus reducing neurotransmitter release and acting as a neuromodulator and that is believed to impede impulse conduction across the synapses [60].

Dosing regimen

Levetiracetam is available as 250, 500, and 750 mg oral tablets. The recommended adult starting dose is 500 to 1000 mg/day, followed by dose titration every two weeks based on response to a usual maintenance dose of 1000 to 3000 mg/day. It is usually dosed twice, with a target dose of 500 to 1500 mg twice daily. The respective target doses in mild, moderate, severe, and end-stage renal disease are as follows: 500 to 1000 mg twice daily, 250 to 750 mg twice daily, 250 to 500 mg twice daily, and 500 to 1000 mg once daily, with a 250 to 500 mg supplemental dose after each hemodialysis session.

Adverse effects

The most frequent adverse effects of levetiracetam include dizziness, headache, fatigue, somnolence and a wide spectrum of behavioral adverse effects including hallucinations, apathy, emotional lability, agitation, irritability, hostility, new onset of obsessive-compulsive symptoms which are more common in children and in patients with a history of behavioral problems, anxiety or depression [61].

Medication interaction

No clinically significant medication interactions have been identified with levetiracetam with the possibility of increased effects of other agents that cause drowsiness, including antidepressants, alcohol, antihistaminic, and sedatives hypnotics.

Tiagabine

Tiagabine has been used in the treatment of acute manic episodes in bipolar disorder, rapid cycling and schizoaffective disorder and as an adjunctive agent in the treatment of refractory bipolar I or II disorder in addition to being touted as a treatment for generalized anxiety disorder, posttraumatic stress disorder, insomnia, cocaine use disorder, and as an augmentation agent in obsessive compulsive disorder, social anxiety disorder and in reducing the symptoms of rage, aggression, and impulse control disorder [62,63].

Mechanism of action

Although tiagabine exact mechanism of action is unknown, it is a potent and selective inhibitor of the gamma-aminobutyric acid transporter, GAT-1 and may enhance inhibition via an increase in gamma-aminobutyric acid (A) receptor-mediated tonic inhibition, by increasing synaptic gamma-aminobutyric acid (A) receptor-mediated currents, and by increasing activation of gamma-aminobutyric acid (B) receptors [64].

Dosing regimen

It is recommended that tiagabine be taken with food, and to be initiated at the dose of 4 mg once daily. The daily dose may be increased by 4 to 8 mg at weekly intervals until clinical response is achieved or, up to 56 mg/day. The total daily dose should be given in divided doses two to four times daily. Experience is limited in patients taking total daily doses above 32 mg/day using twice daily dosing and doses above 56 mg/day have not been systematically evaluated in adequate and well-controlled clinical trials.

Adverse effects

In addition to dizziness, which is the most commonly reported side effect of tiagabine, asthenia, somnolence, nervousness, memory impairment, tremor, headache, diarrhea, and depression have been also reported. Confusion, aphasia, stuttering, and paresthesia may occur at higher dosages. and inconclusive reports have suggested the possibility of increased risk of psychosis and interferences with visual color perception. There is a paucity of data on tiagabine effects on pregnancy, fetal development and lactation.

Medication interaction

The combination of tiagabine with other central nervous system (CNS) depressants may potentiate further CNS depression. Tiagabine levels could be reduced by enzyme inducers such as phenytoin, carbamazepine, primidone, phenobarbital, St. John's wort and may interact with valproate in addition to being affected by highly protein bound drugs [65].

Zonisamide

Zonisamide may be used as an adjunctive therapy, for the management of acute phases of depression and mania and lower weight gain in bipolar disorder and for prevention of alcohol use with some preliminary finding suggesting beneficial effects in the treatment of binge eating disorder [66].

Mechanism of action

Studies with cultured neurons indicate that zonisamide blocks repetitive firing of voltage-sensitive sodium channels and reduces voltage-sensitive T-type calcium currents without affecting L-type calcium currents. Its dual mechanism of action may explain its efficacy in patients resistant to other AEDs [67].

Dosing regimen

Zonisamide is usually initiated at the dose of 100 mg/day; and then may be increased by 100 mg/day every 2 weeks up to the range of 100 to 600 mg/day in 1 to 2 divided doses, however no additional benefits have been demonstrated with dosages exceeding 400 mg/day.

Adverse effects

Zonisamide seems to be well tolerated with mild-to-moderate adverse events, which include somnolence dizziness and a very low incidence of nephrolithiasis and dermatologic reactions [66]. High incidence of weight loss, headache and psychiatric adverse effects, including mania, psychosis, and suicidal ideation, have been also been associated with zonisamide use [66].

Medication interaction

Zonisamide does not induce its own metabolism and does not induce liver enzymes. However, since zonisamide is metabolized by cytochrome P450, liver enzyme-inducing AEDs will increase zonisamide clearance, and dosage adjustments may be necessary when it is used in combination with certain AEDs [67]. It is essentially devoid of clinically significant interactions with carbamazepine, phenytoin, sodium valproate, or lamotrigine and oral contraceptives, however carbamazepine, phenytoin, and phenobarbital all increase its clearance, an interaction that may necessitate a dosage increase, and thus allowing a rapid attainment of steady-state zonisamide concentrations [68].

Summary and Conclusion

Over the past three decades, the number of new AEDs has increased considerably. As the number of new agents increases, so too does the reporting of off-label use in psychiatric disorders. Of all the available AEDs in the United States, carbamazepine and divalproex, are FDA approved for treating acute manic or mixed episodes associated with bipolar I disorder in adults and may be beneficial for bipolar disorder maintenance treatment. Lamotrigine is FDA approved for maintenance treatment of bipolar I disorder in adults [3]. In addition to reviewing the use of carbamazepine, divalproex and lamotrigine, in the treatment of various psychiatric disorders. This review summarized the off-label use of oxcarbazepine, gabapentin, topiramate, levetiracetam, tiagabine, and zonisamide in the treatment of various psychiatric disorders. Although the off-label use of several AEDs is not evidence based and, in some respects, have gone beyond the systematic evidence for efficacy; it underscores the difficulty and urgency of providing alternative treatment to many psychiatric patients who have not responded to the available approved psychiatric medications. It is also anticipated that AEDs use is likely to increase and therefore mental health and primary care providers would need to acquire knowledge about their differential efficacy, mechanism of action, dosing regimen, adverse effects and their interactions with other medications.

Conflicts of Interests

No conflicts of interests. The materials described in this review are those of the author and do not reflects the view of the Department of Veterans Affairs or the Sacramento VA Medical Center or UC Davis, School of Medicine, Sacramento, California.

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