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Anti-Epileptics for Non-Epileptic Indications.

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ABSTRACT

Antiepileptics are wonder drugs.They act through diverse mechanisms and affect multiple systems. Over a period of time they were tried over numerous conditions with significant impact. They have shown to be equally effective for both CNS and non-CNS conditions. Carbamazepine has been used in trigeminal, glossopharyngeal neuralgia and bipolar disorder. Valproate has worked marvelously in bipolar disorder and mania. Gamma amino butyric acid (GABA) analogs have been successful in countering the tricky neuropathic pain. Topiramate has shown significant anti-craving property in alcohol and smoking addiction. Lamotrigine in bipolar disorder, primidone in essential tremors, phenytoin as an antiarrhythmic, the list is never ending. Here is a review article of anti-epileptics in various conditions other than epilepsy.

Keywords: Neuropathic pain, fibromyalgia, migraine, bipolar disorder, obesity.

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Why Use Anti-Epileptics in Non-Epileptic Conditions?

There are two ways to look at it. One from the pharmacologists point of view i.e. anti-epileptics have multiple complex mechanisms, modulates different ion channels and neurotransmitter mechanisms which is why it has been tried in various CNS and non-CNS conditions. The other way to look at it is from the pharmaceutical company's point of view i.e. antiepileptic market is overcrowded with multiple anti-epileptics and hence not profitable. Thus anti-epileptics have been tried in various non-epileptic conditions with significant success [1].

Following is a list of conditions where anti-epileptics are approved or waiting approval.

Neuropathic Pain

Pain is usually felt when the nociceptive afferents are activated by a noxious stimuli. This type of pain is called nociceptive pain. Pain may also generate from the abnormal neuronal activity in absence of an adequate stimuli. This type of pain is termed neuropathic pain [2]. Hyperalgesia, allodynia and spontaneous pain are hallmark of neuropathic pain. Pathogenesis includes increased peripheral nociceptor firing (as a result of increased sodium channel activity causing ectopic discharge). Secondly there is decreased inhibition of neurons in central nervous system. In addition, central pain processing is altered as a result of central sensitization [3]. A phenomenon called ephaptic conduction is hypothesized according to which the damaged neuron cross talks with the neighboring intact neuron thereby transferring the electrical signal to it. So not only damaged but also intact neuron takes part in pathogenesis of neuropathic pain as per this phenomenon [4].

Diabetic neuropathy- peripheral neuropathy is one of the common complications of diabetes mellitus. It is due to nerve damage mediated by reactive oxygen species. It is characterized by pins and needle prick sensations. Clinical trial data supports use of amitriptyline, capsaicin, gabapentin, venlafaxine and desipramine. Drugs like oxcarbazepine and lamotrigine can be considered alternatively. Data assisting use of phenytoin and zonisamide are considered equivocal [5]. GABA analogs like gabapentin and pregabalin act by binding to presynaptic N type calcium channel finally reducing neurotransmitter release [6].

Post herpetic neuralgia- herpes zoster is a self-limiting condition in most of the patients. However, in some the pain might reappear years after rashes have healed. Persistence of pain 3 months after the rashes have gone is diagnostic. Drugs like opioids, anticonvulsants, lidocaine patches and tricyclic antidepressants have caused pain relief in these patients. GABA analogs like pregabalin and gabapentin have shown established efficacy in this condition and are first line drugs along with topical lidocaine. Pregabalin was approved for post herpetic neuralgia and diabetic neuropathy in 2004 both by United States and Europe [7].

Trigeminal neuralgia- Tic douloureux or trigeminal neuralgia is a paroxysmal painful condition limited to facial distribution of fifth nerve as a result of stimulation of sensory nerve endings. An episode is precipitated by activities like talking, biting, touching the face etc [8]. About 80% of cases is due to vascular compression resulting in de-myelination of the nerves. This supports the hypothesis of cross talk or ephaptic transmission [9].

From the time Blom reported improvement of symptoms in patients suffering from trigeminal neuralgia in 1962, carbamazepine is being used almost universally as a first line drug in this condition [10]. Therefore, carbamazepine is first line drug, Oxcarbazine is second line, lamatrigine and baclofen are alternate drugs. In case of refractory cases, procedures like gamma knife, microvascular decompression and gasserian ganglion techniques may be considered [11].

Phantom limb- it refers to pain in the body part that has been severed or amputated. It was initially thought to be a mental disorder. Currently it is thought to be a CNS phenomenon due to plastic changes at multiple levels in the neuraxis, particularly involving the cortex [12].

Opioids like morphine, tramadol, antidepressants like amitriptyline, memantine, ketamine have been tried with mixed results. Anticonvulsants like carbamazepine, oxcarbazepine, pregabaline and gabapentin have been tried with promising results. However, there is a need for further studies [13].

HIV associated sensory neuropathy- three types of sensory neuropathies are seen. 1) DSP (Distal Sensory Polyneuropathy, 2) TNA (Toxic Neuropathy due to antiretrovirals) caused due to NRTI's like zalcitabine, stavudine, didanosine and 3) progressive radiculopathy due to cytomegalovirus which is an opportunistic infection of AIDS. DSP and TNA are phenotypically identical. It presents as distal sensory loss and neuropathic pain. Researchers now believe that TNA is probably due to unmasking of already existing DSP. Progressive radiculopathy presents as lumbosacral pain and saddle type anaesthesia [14].

Usually, amitriptyline and mexilitine provides good pain relief in neuropathic pain. But in case of HIV induced sensory neuropathy they surprisingly showed no improvement [15]. Anticonvulsants have been tried for the above indication. Lamotrigine and gabapentin have significant pain relief compared to placebo [16, 17].

Paclitaxel induced neuropathic pain- paclitaxel is a commonly used anti-tumor agent. It acts by stabilizing the tubules thereby inhibiting replication of cells. Development of peripheral neuropathy is one of the major adverse events associated with this therapy and is characterized by thermal hyperalgesia and mechanical allodynia. Gabapentin by blocking alpha 2 delta subunits of pre-synaptic calcium channels has shown to improve paclitaxel induced neuropathic pain [18]. In addition, lamotrigine has shown to improve chemotherapy induced neuropathic pain owing to sodium channel blockade thereby lowering abnormal signals generated by these channels [19].

Glossopharyngeal neuralgia- another painful condition similar to trigeminal neuralgia is characterized by pain in the ear and oro-pharyngeal area. Likely explanation to this phenomenon is vascular compression of the nerve. Other causes are para-pharyngeal space lesions and cerebello-pontine angle tumors. Even though micro vascular decompression can be considered, a trial of anticonvulsants with drugs like carbamazepine is done. Like trigeminal neuralgia, carbamazepine has also shown improvement in glossopharyngeal neuralgia. It is usually started at a low dose and slowly increased [20]. Studies have also shown that patients responded well to pregabaline. However, further studies are warranted [21].

Bipolar Disorder

Bipolar disorder is characterized by mania and depression. Mania presents as elated mood, reduced sleep, impulsivity and irritability. Bipolar depression consists of diurnal variation, anxiety, sleep disturbance and depressed mood. Although the precise mechanisms behind cyclic changes are unknown, the basis shifts towards catecholamine related activity [22].

Lithium is one of the first drugs in management of manic-depressive illness also called bipolar disorder. Lithium reduces formation of secondary messengers like IP3 (inositol phosphate 3) and DAG (diacyl glycerol). It does this by inhibiting hydrolysis of inositol mono phosphate. Also lithium is neuron-protective, thanks to inhibition of glycogen synthase kinase 3 (GSK-3) [22].

Carbamazepine, an anticonvulsant has shown anti maniac action in bipolar disorder but the mechanism behind this role is unclear as oxcarbazepine is ineffective. Carbamazepine being an enzyme inducer is a difficult drug to combine with other drugs. In addition, plasma level monitoring has to be done [22].

Valproate another anticonvulsant has shown efficacy similar to lithium in bipolar disorder. In fact, rapid cycles respond better to valproate as compared to lithium. Even the side effect profile is better than that of lithium [22]. Possible mechanism is normalization of phosphatidyl inositol cycle on chronic treatment [23].

Lamotrigine has shown improvement in bipolar depression. However it has no role in acute mania. It is approved for maintenance therapy in bipolar disorder [22]. The probable mechanism is due to inhibition of serotonin, norepinephrine and dopamine reuptake [24].

Migraine

Migraine is a commonly encountered episodic chronic illness. It is called common migraine in absence of aura and classical in presence of it. Management strategies for migraine emerged slowly as the cause of this disorder remained elusive. Therapy for migraine prevention is aimed at preventing neuronal excitation. That's

precisely the reason why neuronal depressants like beta blockers, serotonin antagonists, calcium channel blockers have shown benefit in migraine prophylaxis [25].

Sodium valproate is the first drug among the anticonvulsant, to be approved for migraine prophylaxis. Valproate suppresses migraine related events in trigeminal nucleus caudalis and cortex by increasing brain GABA levels. It also reduces neurogenic inflammation. It can directly reduce nociceptive neurotransmission. Its role in prophylaxis of migraine is probably due to combination of all these above mentioned effects [26].

Topiramate has shown efficacy in prevention of migraine. At a dose of 100mg/day it was found to be as efficacious as propranolol. Topiramate is at present approved for use in more than 40 countries as monotherapy for migraine prophylaxis. It is probably due to its actions on voltage gated ion channels are excitatory neurotransmitter receptors [27].

Gabapentin is another anticonvulsant used for migraine prophylaxis. The mechanism of action of this drug and its link to pathogenesis of migraine remains unclear. The ability of Gabapentin to elevate GABA levels in the CNS is a possible explanation. Most of drugs used for migraine prevention come at the cost of significant side effects. Gabapentin, owing to its good efficacy and tolerability profile, should be considered in migraine prophylaxis [28].

Acute Traumatic Brain Injury

Acute brain injury poses two major challenges in intensive care management, post traumatic agitation and post traumatic seizures. Epilepsy is recurrent and unprovoked, unlike post traumatic seizures. Benzodiazepines and dopamine antagonists are the commonly used drugs in this condition but the problem is that it is believed to delay the neuronal recovery as shown in animal models using haloperidol. Antiepileptics have been tried in these patients. Carbamazepine, valproate and phenytoin have shown promise in reducing post traumatic seizures. Unlike Carbamazepine and valproate which showed no cognitive impairment, phenytoin was associated with cognitive impairment. In addition, studies have shown that Gabapentin caused increased psychomotor agitation and anxiety [29].

Alcohol Withdrawal

Longterm alcohol consumption lead stone uro-adaptation. Alcoholbeinga CNS depressantincreases GABA andreduces glutamate levels. On long term exposure there is down regulation of GABA and upregulation of glutamate receptors. As a result, at the time of withdrawal there is CNS excitation. In order to explain the worsening of symptoms related to withdrawal, kindling phenomenon has been considered. This phenomenon explains worsening of symptoms of withdrawal due to related cycles of ethanol exposure and withdrawal. Benzodiazepines are currently the go to drugs in alcohol withdrawal. It has proven efficacy is reducing risk of delirium and seizures in these individuals. However, it comes at a cost as it itself can cause sedation, cognitive impairment, abuse and respiratory compromise.

Carbamazepine is one of the oldest anticonvulsant tried for this indication. It is approved for use in alcohol withdrawal syndrome in Germany. It is attributed to inhibition of voltage gated sodium channels and also due to activation of voltage gated potassium channels. Valproate though not approved has shown promise owing to GABA potentiation and glutamate suppression. Alcohol withdrawal syndrome patients treated with Phenobarbital showed reduced admissions to ICU and reduced requirement of lorazepam. This is attributed to GABA potentiation and AMPA blocking property of Phenobarbital.

Evidence from case series and reports points towards a potential role of Gabapentin in alcohol withdrawal syndrome [29].

Essential Tremors

A neurological disorder characterized initially by contraction of agonist muscles followed by contraction of antagonist muscles. The first line drugs include propranolol and primidone. Alternatively newer anticonvulsant like topiramate and Gabapentin may be considered.

Primidone has Phenobarbital and phenylethylmalonamide as active metabolites. But both these metabolites show no efficacy as tremerolytics. So the mechanism how primidoneacts as a tremerolytic is unclear.studies have shown that high dose of topiramate showed significant improvement both as adjunct and monotherapy but at the cost of reduced weight, decreased appetite and parasthesias [30].

Smoking Cessation

At a dose of 50mg/day topiramte has shown significant benefit in smoking cessation. Around 50% subjects stopped smoking and 20% reduced the number of consumed cigarettes according to a study done by Yasir et al. This anti craving effect is attributed to AMPA and Kainate antagonism [31].

But unlike topiramate, carbamazepine increases craving. Carbamazepine induces cytochrome 2A6 thereby increasing nicotine metabolism. Nicotine is cleared off faster leading to increased craving [32].

Fibromyalgia

Fibromyalgia is a common and chronic painful condition. It consists of pain, sleep disturbance, anxiety and various non-specific complaints. Pathogenesis includes interplay between genetic, environmental, psychological factors, altered sleep physiology and serotonin metabolism alterations [33]. Among the anticonvulsants, pregabalin has shown significant pain relief compared to placebo. Other anticonvulsants have not shown any benefit [34].

Obesity

Binge eating disorder is classically characterized by binge eating episodes. Binge eating disorder can be differentiated from bulimia nervosa as binge eating disorder is associated with obesity. SSRIs, desipramine, amitriptyline, cognitive behavior therapy and behavior dietary therapy have shown weight loss.

The mechanism how topiramate helps in binge eating disorder in not clearly understood. It may act as appetite suppressant or satiety enhancer. It may also be due to glutamate antagonism [35]. Qsymia a combination of phentermine and topiramate has been approved. This combination has shown robust weight loss [36]. Zonisamide is the other carbonic anhydrase inhibitor like topiramate which has shown significant weight loss compared to placebo in binge eating disorder. But the doses that produced weight loss were not well tolerated [37].

Post-Traumatic Stress Disorder

It is an abnormal response to an experienced or witnessed traumatic event. It consists of three major symptoms: re-experiencing, numbing/ avoiding and hyper arousal. SSRIs are first line drugs in management of PTSD. Infact, this is the only class of drugs approved by FDA. Placebo controlled double blind trials have shown antiepileptics like topiramate, lamotrigine and tiagabine to be quite effective. Open label trials using phenytoin, valproate, carbamazepine, levatiracetam and vigabatrine have been promising but further studies are warranted [38].

Restless Leg Syndrome

Restless leg syndrome(RLS) is a condition characterized by an urge to move the limbs. It is a sensory motor disorder usually accompanied with pain and discomfort in the limbs. It is associated with day time fatigue and sleep disturbances. It is usually seen in patients suffering from anemia, dialysis patients and pregnant women. Treatment of RLS includes dopamine agonists, levodopa, benzodiazepines and opioids [39]. Studies have shown carbamazepine to be better than placebo in RLS. But efficacy is low [40]. Gabapentin has shown to improve motor and sensory symptoms of RLS and also to improve sleep architecture [41].

Spasticity

Vigabatrin acts by increasing levels of GABA in the CNS thereby reducing transfer of hypersynchronous discharge. It does this by reducing degradation of GABA. It has been found to be as efficacious as baclofen in managing spasticity of patients with multiple sclerosis and spinal cord lesions [42].

Fragile X Syndrome

It is an x linked inherited intellectual disorder. There is a characteristic presence of polymorphic CGG sequence at 5′ UTR of FMR1gene. Diagnosis is made in children around 3 years of age who have absent or delayed speech. They are anxious, impulsive and more often present as ADHD (attention deficit hyperactivity disorder) [43].

Valproate was tried in this indication as it is an HDACi (Histone De-actylator Inhibitor) and DNA de-methylating agent. Individuals on valproate showed improved adaptive behavior. Valproate has an orphan drug status in fragile X syndrome [44].

Familial Adenomatous Polyposis

These individuals are characterized by absence of APC gene which is a tumor suppressor gene. They have elevated HDAC levels. HDAC prevents apoptosis of the colonic cancer cells leading to multiple intestinal polyps [45]. Valproate is a histone deacetylase inhibitor. Therefore it blocks HDAC mediated gene silencing. Apoptosis of tumor cells are unaffected. Therefore valproate enjoys orphan drug status for this indication [46].

Central Diabetes Insipidus

Diabetes insipidus is a condition characterized by excretion large volumes of dilute urine.it can either be due to underproduction of antidiuretic hormone (central diabetes insipidus) or due to reduced renal response (nephrogenic diabetes insipidus). Differentiation between these two causes for diabetes insipidus is essential for effective management [47].

Drugs like desmopressin, chlorpropamide, thiazide and carbamazepine are effective in management of central diabetes insipidus [48]. Carbamazepine acts by increasing endogenous antidiuretic hormone release causing antidiuresis. Carbamazepine also plays a similar role in patients with polyuria secondary to compulsive water consumption, but risk of water intoxication is high among these individuals [49].

Ventricular Tachycardia

Phenytoin, a commonly used anti-epileptic has anti-arrhythmic property. It behaves as a class 1b drug. Even though it is uncommonly used for this indication, it is a drug to be considered in case of refractory ventricular tachycardias especially when other antiarrhythmic drugs are unavailable or contraindicated. In case of ventricular arrhythmia refractory to amiodaronemonotherapy, combination of phenytoin with amiodarone can be effective. Its antiarrhythmic property is attributed to its effect on sodium channels on purkinje fibers and cardiac myocytes. In case of patients on a pacemaker, phenytoin is to be used with caution. This is due to elevation of threshold of the pacemaker by phenytoin thereby affecting pacemaker capture. One more drawback of phenytoin as antiarrhythmic is that it has multiple drug to drug interactions and a narrow therapeutic index [50].

Unconjugated Hyperbilirubinia

Phenobarbitone, a barbiturate has been tried in infants with unconjugated hyperbilirubinemia. The decrease in bilirubin levels was not due to decreased bilirubin formation. Phenobarbitone an enzyme inducer induces enzyme that metabolizes bilirubin presumably UDP glucuronyl transferase [51]. Owing to the presence of better therapeutic measures like phototherapy and exchange transfusion, use of phenobarbitone has reduced [52].

CONCLUSION

There is no doubt that anti-epileptics have multiple mechanisms and also multiple uses in various disease processes involving multiple systems. However, the uses of these wonder drugs are still understated and underestimated. There is much more to it. This is just the beginning.

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