DOWNLOAD PDF USE OF ANTICONVULSANTS IN PSYCHIATRY

Chapter 1 : Anticonvulsant - Wikipedia

The use of anticonvulsants in psychiatry has steadily increased in recent years. Two anticonvulsants in particular, carbamazepine (CBZ) and valproate (VPA), have become commonplace in psychiatric practice for the treatment of bipolar disorder. Schizoaffective dis order and aggression have also been.

Open in a separate window Although safety and tolerability are aspects of utmost importance, they will not be dealt with in this article for the sake of comprehensiveness. However, it is strongly recommended that readers educate themselves about the individual safety issues of ACs before applying them in routine practice. Recent reviews eg, refs are a comprehensive source of information for further reading. Mechanisms of action beyond antiepileptic properties A common link between the different indications where ACs are used may be an underlying state of hyperexcitability which may manifest itself as sleep disturbances, mood swings, anger, or impulsiveness. There are several hypotheses about a common underlying pathophysiology, but excessive sodium and calcium fluxes may play a role both in epilepsy and the abovementioned psychiatric conditions. Several anticonvulsants, including carbamazepine, valproate, lamotrogine, and phenytoin, have a regulating effect on these ion fluxes, 8 and this may explain part of their efficacy in some psychiatric disorders such as withdrawal states, pain, or, as a state of behavioral hyperactivity, acute mania. During the last decade, it has been demonstrated that not only lithium, but also valproate and, in part, carbamazepine, regulate numerous factors enhancing cellular plasticity and resilience, including inositol biosynthesis MIP synthase , cyclic adenosine monophosphate c-AMP response element binding protein, brain-derived neurotrophic factor BDNF , the extracellular signal-regulated kinase pathway, the arachidonic acid pathway, the cytoprotective protein bcl-2 and mitogen-activated protein kinases. The amygdala kindling model, originally developed to explain progression of epileptic seizures, 25 may also be applicable to affective episodes, panic attacks and anxiety states, or alcohol and drug relapses. A recent Cochrane meta-analysis of 48 studies involving subjects compared different ACs with placebo for alcohol withdrawal, Therapeutic success tended to be more common among the anticonvulsant-treated patients relative risk RR 1. Carbamazepine 28 and oxcarbazepine 29 alone or, especially in Germany, in combination with tiapridc, 30 are frequently used for alcohol withdrawal because they reduce the risk of convulsions and, especially in the case of carbamazepine, cause an initial sedation when titrated rapidly. For oxcarbazepine, open data also suggest anticraving effects in sober alcoholics. Myrick et al 32 reported comparable effects of lorazepam and valproate in reducing alcohol withdrawal symptoms in an open trial. In a double-blind randomized study, Tress et al 33 compared valproate with clomethiazol, observing no difference in somatic symptoms and the absence of severe delirious states with both medication. The so-far largest controlled study using valproate for alcohol withdrawal syndromes was conducted by Hillbom et al 34 comparing valproate with carbamazepine and placebo. Hie reduction of withdrawal seizures was more pronounced with valproate 2. However, there was also a higher, but not significant, rate of delirium valproate 4. The authors also report a better general tolerability of valproate compared with carbamazepine. In conclusion, there is some evidence for effectiveness not only of carbamazepine, but also of valproate in uncomplicated alcohol withdrawal, but it is obvious that better controlled studies are needed. So far, of all the anticonvulsants only carbamazepine reached such a level of confidence that it has been recommended in guidelines as suitable for the pharmacological management of alcohol withdrawal. For valproate, a significant reduction in heavy drinking days was found in a controlled study, 40 and also lamotrigine reduced alcohol intake and craving in an open study. Both valproate 44 and lamotrigine 45 demonstrated mood-stabilizing effects in openlabel trials, and some positive effects on drug abuse, such as diminished consumption valproate and less craving lamotrigine. In a small placebo-controlled pilot trial, topiramate also proved effective in attaining at least 3 weeks of continuous abstinence. Sedatives and tranquilizer abuse A potential role for GABA uptake inhibitors such as tiagabine for benzodiazepine withdrawal has been suggested, 47 but never been rigorously tested. Of the older anticonvulsants, valproate has been tested in open case series, 48 and has been compared against trazodone and placebo for benzodiazepine withdrawal. Rickels et al 49 reported that more patients were free of benzodiazepines after 5

weeks when treated with valproate or trazodone compared with placebo. However, they did not find a significant reduction of somatic symptoms during benzodiazepine tapering. According to a Cochrane meta-analysis of available trials, carbamazepine shows a rather modest benefit in reducing withdrawal severity, but it does significantly improve drug-free outcome. A small open study by Khazaal et al 53 supports this assumption; however, in briefly abstinent smokers topiramate may also enhance withdrawal and rewarding effects when relapsing, thus calling into question its usefulness. This area has been most recently comprehensively reviewed by Mula et al. Thus, ACs could be of potential value by limiting this excessive activation. Open studies provide some limited evidence for the usefulness of carbamazepine in PTSD, 55 - 57 whereas for other anxiety syndromes the evidence is vague or negative eg, for panic disorder For valproate, one controlled study and several open studies reported efficacy in panic disorder alone or when accompanied by mood symptoms. He observed a significant reduction in the intensity and the duration of panic attacks. Also of interest is an open study by Keck. After treatment, with valproate for 1 month, almost half of the patients were free of spontaneous panic attacks, and 10 out of 12 patients tested no longer developed panic attacks provoked by lactate infusions. For other anxiety syndromes and PTSD, evidence is again restricted to open-label trials eg, ref 62 and case series. Moderate evidence stemming from a small, but controlled study exists for the use of lamotrigine in PTSD 63 ; however, no proper-sized randomized studies have been conducted so far. This situation is different for two other antidepressants, gabapentin and pregabalin. For gabapentin, two doubleblind placebo-controlled studies showed positive results in panic disorder and social phobia. Five positive double-blind, placebo-controlled studies in GAD 69 - 73 and one positive controlled study in social phobia 74 make this compound indeed a well-proven anxiolytic medication. After several case reports showed efficacy on aggressiveness with valproate, a recent review article by Lindenmayer 76 analyzed these case reports of violent, and aggressive demented patients and found an overall response rate of Pain Many neurologists might object, to a section on pain as a psychiatric condition. However, most types of pain cannot be conceptualized as a pure neurological dysfunction, but also involve strong subjective and emotional aspects. The exact mechanisms of how ACs work in pain conditions are far from being understood; however, it is intuitive that they may be able to dampen many of the proposed causes of chronic pain, such as peripheral sensitization, central sensitization, wind-up, hyperexcitability, neuronal disinhibition, ectopic impulse formation, and finally, the subjective impression and emotional handling of pain. Not all ACs appear to be as effective as antidepressants tricyclics and noradrenalin and serotonin reuptake inhibitors in treating pain syndromes, 86 but at least gabapentin and pregablin can be recommended, among other medications, as first-line treatment for neuropathic pain 87 - 88 and related conditions. Both medications are also licensed for the treatment of neuropathic pain, based on a large portfolio of controlled studies. In addition, several of these studies described positive effects on mood and sleep quality. Pregabalin has demonstrated efficacy in seven controlled studies in PHN, DPN, or either of these conditions 99 - A randomized controlled trial in patients with spinal cord injury neuropathic pain also demonstrated greater pain relief with pregabalin than with placebo. In contrast to their established efficacy in trigeminal neuralgia, , carbamazepine and oxcarbazepinc have yielded inconsistent results in controlled studies of other types of neuropathic pain. Three positive trials of valproate in DPN or PHN were reported from a single center, but a controlled study conducted in patients with painful polyneuropathies by a different, research group was negative. However, intention-to-treat analyses were negative in three large recent, randomized controlled studies, two of which were in painful DPN and one in neuropathic pain of different, origin. Consecutively, Simhandl et al reported a significant effect in chronic schizophrenia for adjunctive carbamazepine treatment in an 8-week double-blind, placebocontrolled study. However, the use of carbamazepine may also diminish serum levels of some antipsychotics, eg, risperidone or haloperidol, and thus lead to worsening of psychosis. They may be capable of reducing excessive glutamatergic hyperactivity due to selective NMDA receptorblocka. Retrospective chart reviews eg, ref open and randomized open-label, and controlled augmentation studies , are supportive of an antidepressant effect of lamotrigine add-on in treatment-resistant major depressive disorder MDD. In a double-blind, placebo-controlled study, topiramate appeared to be an effective agent in the reduction of depressive symptoms and anger in moderately depressed women, but these results have not yet been replicated. Of the

older anticonvulsants, carbamazepine has shown limited evidence in open studies for an acute antidepressant - and prophylactic effect. Phcnytoin showed some efficacy in a comparator study against fluoxetine, but not in an augmentation study in SSRI nonresponders. Licensed in this indication or at least, used with good evidence are valproate, carbamazepine, and lamotrigine, but phenytoin, oxcarbazepine, levetiracetam, topiramate, zonisamide, and gabapentin may also be beneficial in some, yet insufficiently characterized patients. Carbamazepine has proven antimanic and prophylactic efficacy, and has been traditionally used in patients who were not sufficiently responding to lithium. Comparing the prophylactic efficacy of carbamazepine against, lithium, the two most recent studies suggest superiority of lithium treatment. Superiority over placebo has been shown in double-blind controlled monotherapy and add-on studies. Further analysis revealed that this was mainly due to a selection bias, as patients having a benign course of the illness were overrepresented in the study. Looking for secondary outcome parameters, however, clinically useful information was detected, eg, valproate was significantly better than placebo in preventing new depressive episodes. In addition, patients who were previously responsive to valproate when treated for an acute episode also performed better when randomized to valproate maintenance treatment compared with when randomized to lithium or placebo. However, reanalyzing this study together with other, smaller studies, a meta-analysis was able to support the prophylactic efficacy of valproate. However, other mechanisms, such as an as anti-glucocorticoid mechanism, are also possible. For acute bipolar depression, only one study showed a positive result, in a secondary outcome parameter, whereas three further studies failed to separate it from placebo. Two doubleblind, randomized maintenance trials over 18 months proved the efficacy of lamotrigine when compared with placebo and lithium. Looking for differential rates of relapse, lamotrigine was more effective in preventing newdepressive episodes, whereas lithium was better in preventing manic episodes. As far as bipolar depression and prophylactic treatment, are concerned, evidence from methodologically rigorous trials is also lacking. The story of gabapentin in bipolar disorder is largely similar: For levetiracetam, positive open studies in acute mania , have been reported, but controlled evidence is missing. Personality disorders Personality disorders accompanied by mood instability may be a potential target, for ACs. In a double-blind, placebo-controlled crossover trial, carbamazepine significantly decreased the severity of behavioral problems in 11 women with borderline personality disorder. Of the newer ACs, the efficacy of topiramate has been tested by one group of investigators in controlled studies, showing efficacy, especially on symptoms related to anger, - but replication of these positive results from other investigators is still lacking. Conclusion Anticonvulsants as a group are today an established part of the treatment portfolio in many psychiatric condirions, especially in bipolar disorder, anxiety, and pain disorders. In some instances, their use in psychiatric indications may even exceed their use in epilepsy. However, their individual strengths in these different indications, and the strength of recommendations, may vary considerably. The story will continue, as new anticonvulsants such as lacosamide, rufinamidc, talampancl, eslicarbazepine, hydroxy carbazepine, valrocemide, isovaleramide, brivaracetam, and seletracetam are potential future candidates for psychiatric indications, and some of them are already in the process of being tested in clinical trials. The usefulness of diphenylhydantoin in treatment of non-epileptic emotional disorders. Anti-manic and prophylactic effects of carbamazepine Tegretol on manic depressive psychosis. Folia Psychiatr Neurol Jpn. Safety and tolerability of emerging pharmacological treatments for bipolar disorder. Towards an improved risk-benefit ratio. Adverse effects of new antiepileptic drugs. Concerns with antiepileptic drug initiation: The neurobiology of antiepileptic drugs for the treatment of nonepileptic conditions. Intracellular calcium ions in affective disorders: Pharmacological comparison of anticonvulsant drugs in animal models of persistent pain and anxiety. Valproate and its major metabolite Een-valproate induce different effects on behaviour and brain monoamine metabolism in rats. Regional effects of sodium valproate on extracellular concentrations of 5-hydroxytryptamine, dopamine, and their metabolites in the rat brain: Changes of serotonin-induced field potentials by lamotrigine. Antidepressant-like effect of lamotrigine in the mouse forced swimming test: The role of anticonvulsant drugs in anxiety disorders: The extracellular signal-regulated kinase pathway: Mood stabilizers target cellular plasticity and resilience cascades: Mood stabilizers regulate cytoprotective and mRNA-binding proteins in the brain: A common mechanism of action for three mood-stabilizing drugs.

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Chapter 2 : The effectiveness of anticonvulsants in psychiatric disorders

The arrival of new anticonvulsants has seen more and more utility in a wide variety of psychiatric disorders. The clinical off-label use of these new agents is not surprising given the history of carbamazepine and valproic acid, both approved as anticonvulsants, but certainly used as mood stabilizers.

Chapter 3 : Anticonvulsant - Wikipedia

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