SYSTEMATIC REVIEW

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Efficacy and tolerability of calcium channel alpha-2-delta ligands in psychiatric disorders

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Abstract: *Matching drugs with anxiolytic properties- but without the potential of inducing dependence or abuse- with clinical manifestations of various affective disorders is a very important challenge for psychiatrists. Although the first line of pharmacologic treatment for anxiety disorders remains antidepressants with serotoninergic properties, calcium channel alpha-2-delta ligands are adjuvant agents which could be useful for augmenting antidepressant agents' clinical effects. Unfortunately, calcium channel alpha-2-delta ligands efficacy and tolerability are not very well known, due to a lack of large scale, randomized, placebo-controlled trials focused on psychiatric disorders. Data regarding pregabalin and gabapentin pharmacology and clinical effects are reviewed and conclusions with pragmatically impact based on the discovered evidence are formulated accordingly.*

Keywords: *calcium channel alpha-2-delta ligands, generalized anxiety disorder, fibromyalgia, social anxiety disorder, pregabalin, gabapentin*

PHARMACOLOGICAL PROPERTIES OF CALCIUM CHANNEL α2δ-LIGANDS

Alpha-2-delta subunits of voltage-gated calcium channels (VGCC) have an important role in modulation of the calcium currents and participate in important cellular and inter-cellular phenomena like muscular excitability, neurotransmission, re-gulation of gene expression etc. As a consequence, drugs with alpha-2-delta VGCC antagonist properties could improve symptoms of fibromyalgia and neuropatic pain, but they are also used for treatment of several psychiatric disorders, the most extensive researched being the field of anxiety disorders.

Pregabalin is a structural analog of the inhibitory neurotransmiter γ-aminobutyric acid (GABA). This drug reduces the synaptic release of several neurotransmitters through binding to the alpha2-delta type 1 protein and demonstrated anticonvulsant, analgesic, and anxiolytic properties in preclinical models [1,2].

Pregabalin is rapidly absorbed after oral administration, with a bioavailability value higher than 90%; peak plasma concentrations are reached after 1-1.5h, steady-state concentrations are achieved within 24-48h after repeated administration, and if used with food there is no clinically significant

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effect on the drug's absorption; pregabalin half-life is about 6 hours, it does not bind to plasma proteins, and 90% of a dose is eliminated unchanged in urine [3].

Gabapentin is derived from gamma-aminobutyric acid (GABA) by addition of a cyclohexyl group and crosses several lipid membrane barriers through L-amino acid transporters system [4]. Gabapentin has a bio-availability that varies inversely with dose (between 35% and 60%), a volume of distribution of 0.6-0.8 l/kg, cerebrospinal fluid concentrations are 20% of plasma concentrations and brain tissue values are 80% the plasma level; gabapentin is not metabolized in humans and is eliminated unchanged in the urine [5].

CLINICAL PHARMACOLOGY OF GABAPENTIN AND PREGABALIN

Agents from alpha-2-delta ligands class have a large number of indications in psychiatry and neurology, but this paper focused only on the first area of interest. Regarding the second domain, pregabalin and gabapentin are used for diabetic neuropathy, post-herpetic neuralgia, pain associated with spinal cord lesions, diverse types of seizures etc [6]. We also included in this paper trials focused on fibromyalgia, since this pathology usually requires an interdisciplinary approach, and psychiatrists are included in the consultation teams.

Pregabalin combined with duloxetine lead to good results in depression associated with fibromyalgia, according to a randomized, double-blind trial, which reported lower final Beck Depression Inventory–II (BDI-II) scores compared to placebo ($p<0.05$) [7]. Another randomized, placebo-controlled trial targeting fibromyalgia patients with asociated affective symptoms showed significant improvement on Hospital Anxiety and Depression Scale – Anxiety and Depression ($p<0.001$) [8].

Pregabalin used as augmentation agent to amitriptyline, venlafaxine, or paroxetine in old age patients with fibromyalgia improved overall symptoms, including depressive scores on Center for Epidemiological Studies Depression Scale (CESDS), and the highest tolerability was detected in pregabalin+ paroxetine group [9].

Pregabalin had a good therapeutic effect in anxious depression, according to a case series [10]. Adjunctive pregabalin to conventional antidepressants in partial responders with major depressive disorder and residual anxiety decreased Hamilton Depression Rating Scale overall scores and anxiety/somatization subscale scores after 8 weeks with 65% response rate and 35% remission rate [11]. Therefore, pregabalin could be recommended as add-on agent in unipolar depressed patients with significant levels of anxiety and 49.1% of overall consecutive diagnosed outpatients that received pregabalin had a diagnosis of mood disorder, followed by 21.9% generalized anxiety disorder [10,12].

A review of 3 randomized controlled trials that compared efficacy and safety of pregabalin with placebo in social anxiety disorder- generalized form revealed a good efficacy in patients who couldn't tolerate or didn't respond well enough to SSRIs or SNRIs, which recommend pregabalin as either alternative to antidepressants or add-on agent to pharmacotherapy or cognitive-behavioural therapy [13].

Pregabalin is considered by expert opinion a safe and efficacious agent for generalized anxiety disorder, with favourable properties like absence of active metabolites and no interactions with CYP450 enzymes [14]. A pooled analysis of 6 studies confirmed the efficacy of pregabalin in depressive symptoms associated with generalized anxiety disorder, and the most beneficial response was detected at 300-450 mg daily dose [15]. A recent post-hoc analysis of a multicenter, prospective, 6-month study evaluated the effectiveness of pregabalin in resistant generalized anxiety disorder and severe depressive symptoms and concluded reduced with more than 50% Hamilton Anxiety Scale total score, and Montgomery-Asberg Rating Scale score, when combined with antidepressants and/or benzodiazepines [16].

Pharmaco-economic analysis of augmentation SSRIs treatment with pregabalin versus switch to

pregabalin in treatment resistant generalized anxiety disorder reported significantly health-care costs reductions at 6 months in both treatment algorithms [17]. Pregabalin was associated with significantly higher QALY gain in refractory generalized anxiety disorder when compared to usual care in a cost-effectiveness model based on data derived from a large scale trial [18]. Also, pregabalin was superior to SSRI and SNRI in benzodiazepine-refractory generalized anxiety disorder in terms of QALY gain, but increased health-care costs and drug costs [19].

Treatment augmentation with pregabalin in patients with combat-related chronic posttraumatic stress disorder (PTSD) was efficient in a 6-week placebo-controlled trial as it improved PTSD Check List-Military Version scores ($p<0.05$), although severity of depression, anxiety and quality of life parameters didn't differ significantly between the two groups [20]. An open label pilot study with accident-related posttraumatic stress disorder showed pregabalin augmentation to antidepressant treatment as an effective and well tolerated option [21]. However, a retrospective analysis of US service members who suffered burns didn't detect differences in posttraumatic stress disorder onset rate in patients that received pregabalin or gabapentin after trauma for pain, compared to patients who didn't receive this kind of drugs [22].

Pregabalin proved itself efficacious and well tolerated in a single-blind randomized trial with active control (clonidine) that targeted opioid withdrawal symptoms [23]. In alcohol dependence, pregabalin was efficacious, by decreasing of the craving and withdrawal symptomatology [24]. A review showed positive results for pregabalin in both treatment of alcohol dependence and benzodiazepine dependence [25].

Although the use of pregabalin as add-on agent in bipolar disorder maintenance treatment has not been extensively investigated, some authors suggest its potential use for this indication [26]. Pregabalin could increase the response to quetiapine in acute mania [27], and also could help in decreasing affective symptoms in treatment-resistant manic episodes [28]. An open trial of pregabalin as adjunctive treatment in acute and maintenance phase of resistant bipolar disorder showed mood-stabilizing effect, antidepressant effect or antimanic effect in the acute phase, and also with good efficacy on long term [29].

Data extracted from a metaanalysis focused on dopaminergic and non-dopaminergic medications in restless legs syndrome found 11 studies with α2δ-ligands supporting good efficacy for gabapentin, gabapentin enacarbil, and pregabalin [30].

Use of pregabalin, as well as buspirone, added to antipsychotics in cases of schizophrenia with anxiety (almost 65% of patients with schizophrenia have anxiety symptoms), could be considered as an efficient therapeutic option [31]. Case reports suggest efficacy of pregabalin in treatment-resistant insomnia (in a patient who didn't respond to benzodiazepines, antidepressants with sedative properties, or antipsychotics) [32], and Charles Bonnet syndrome associated visual hallucinations [33], but also an enhancement of sexual desire in overdose [34].

Gabapentin significantly improved abstinence rates and heavy drinking in patients with current alcohol dependence, during a 12-week, double-blind, placebo-controlled trial, with linear dose-effects relation in mood, sleep, and craving domains [35]. Abstinence rates in this trial corresponded to a NNT value of 8 for 1800 mg daily, while lack of heavy drinking corresponded to a NNT value of 5 for the same dose [35]. Gabapentin reduced the stress-induced GABA activation in amygdala that is associated with alcohol dependence and therefore could be useful in this addiction [36].

Patients with opioid withdrawal that received adjunctive treatment with gabapentin in addition to methadone for 3 weeks reported significant improvement of general status as reflected by Subjective Opiate Withdrawal Scale (SOWS) and doses of 1600 mg/day were significantly superior to medium doses of 900 mg/day in decreasing symptoms' severity [37].

A Cochrane analysis of gabapentin efficacy in fibromyalgia associated pain didn't found good evidence to support or contradict the

recommendation of this drug in daily doses of 1200-2400 mg [38]. However, the quality of evidence was rated as very low due to the fact that only one trial corresponded to the inclusion/exclusion criteria established by authors [38].

Gabapentin proved itself efficient in reducing symptoms of social anxiety disorder and it was also well tolerated [39].

Gabapentin wasn't efficient in bipolar depression, according to a large randomized controlled trial which compared standard mood stabilizers versus gabapentin 600-3600 mg/day [40].

A cross-over, double-blind study, showed gabapentin is efficient in treatment of sensory and motor symptoms in restless legs syndrome, improving also sleep architecture in periodic leg movements during sleep [41].

CONCLUSION

Pregabalin and gabapentin are efficient anxiolytics, pregabalin being more supported by evidence in social anxiety disorder, generalized anxiety disorder, depression with significant anxiety, and also in posttraumatic stress disorder, including cases of combat-related PTSD.

Pregabalin is a well supported indication for fibromyalgia treatment, with a high efficacy-to-adverse-effects ratio. Pregabalin had a significant impact not only over pain, as the core fibromyalgia symptom, but also over affective symptoms associated with this disorder.

Gabapentin recommendation is more supported by evidence than pregabalin in alcohol dependence and opioid withdrawal, but pregabalin has some support in the treatment of benzodiazepine dependence.

None of the alpha-2-delta ligands were associated with high quality positive evidence in bipolar disorder.

In restless legs syndrome pregabalin and gabapentin are efficient for primary symptoms and associated clinical manifestations, and gabapentin improved sleep architecture in sleep related periodic leg movements.

Occasional reports of pregabalin efficacy in schizophrenia associated anxiety, treatment resistant insomnia or Charles-Bonnet syndrome need further exploration in randomized clinical trials.

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