Use beyond Approval

Off-label Use of Valproate in Anxiety Disorders

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Abstract

Some evidence from preclinical and clinical studies suggests that valproate may have therapeutic effects in the treatment of anxiety disorders. We reviewed the existing literature on the efficacy of valproate in the treatment of these psychiatric disorders.

Keywords: Anxiety disorders; Biological psychiatry; off-label; Psychopharmacology; Treatment resistance

Anxiety disorders represent the most common category among mental illnesses, with a lifetime prevalence of approximately 31% in the United States of America. However, only 60–85% of patients show an adequate clinical response to pharmaco-psychotherapy, with only about 50% achieving a full recovery [1]. Selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) are considered the mainstays of evidence-based pharmacological treatment for anxiety disorders, with efficacy rates ranging from 50 to 60%. For non-responders, several strategies are suggested, including increasing maximum tolerated doses, switching to other first-line standard treatments, and using pharmacological and psychotherapeutic combinations. Even so, alternative medication treatments for anxiety disorders, such as monotherapy or augmenting agents, remain promising. Glutamatergic transmission has been linked to anxiety disorders, and anticonvulsants that modulate and restore homeostasis between glutamate and GABA have been studied as potential novel treatments [1, 2].

In this work, we reviewed the current evidence for pharmacotherapies involving valproate in anxiety disorders. A comprehensive search on PubMed from inception to October 2023, using the search input "(valproic or valproate or divalproex) AND (anxiety)", retrieved 1476 results. Criteria for inclusion were the following: anxiety disorder diagnosis, age ≥18 years, valproate as the intervention, none, placebo, or other active treatments as comparators, and quantitative or qualitative evaluation of overall or specific symptoms of anxiety. We implied no restrictions for study design. We excluded studies that reported patients with psychiatric comorbidities and studies published in a language other than English. Furthermore, the reference list of each relevant study was checked for additional information. Seven studies were included: two open-label studies and one randomized controlled trial (RCT) on Panic Disorder, one RCT and one case report on Generalized Anxiety Disorder, and

two open-label studies on Social Anxiety Disorder (table 1) [3–9]. All but two studies used clinician-rated scales for the assessment of anxiety [7, 8]. Valproate was found to be effective in all considered studies except one [8], and the dosage was generally consistent. The most common side effects reported were sedation, nausea, and dizziness.

The existing literature, although scant and dated, supports the efficacy of valproate in ameliorating anxiety symptoms as well as its general safety. The anxiolytic properties of valproate have been widely reported in rodent tests, translational human models of anxiety behavior, and investigations involving experimentally induced panic attacks. These effects may be mediated by: i) blocking voltage-dependent sodium and T-type calcium channels; ii) strong GABAergic potency due to direct action at GABA-B receptors, causing an increase in brain GABA; and iii) inhibiting the GABA-degrading enzyme GABA transaminase [10–12]. Of interest, valproate, rather than lithium, appears to have a better response in the presence of a comorbidity of bipolar and anxiety symptoms/disorders [13].

Since anxiety disorders can precede the onset of a mood disorder and anxiety is one of the most important predictors of a new-onset bipolar spectrum [14], this could explain why patients with subthreshold hypomanic symptoms and anxiety disorders may respond to valproate. However, there is currently no evidence to support the use of valproate as a first-line treatment because studies rely primarily on open-label trials. Valproate, as a monotherapy or augmenting agent, should be reserved for cases where previous and evidence-based treatments have failed to achieve a satisfactory clinical response. Further research is needed to establish the potential efficacy of valproate in anxiety disorders and the most responsive clinical phenotypes.

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Table 1: Descriptive comparison between included studies

Source	Study Design	Sample	Duration	Daily Average Dose (mg)	Outcome	Tolerability
Primeau et al. 1990 [3]	Open-label VPA in PD	10	7 weeks	up to 2250 mg	VPA was associated with significant improvements in CGI-S, SCL-90 and HAM-A scores.	Common side effects: nausea, dizziness, drowsiness, tremor, diarrhea, constipation, dry mouth and headaches. One patient withdrew.
Lum et al. 1991 [4]	Double-blind placebo-controlled VPA in PD	12	6 weeks	Dose adjusted until satisfactory response.	VPA was associated with significant improvements in CGI-S, CGI-I and HAM-A scores.	No data available.
Woodman and Noyes 1994 [5]	Open label VPA in PD	12	6 weeks	500–2000 mg	VPA was associated with significant improvements in CGI-S, CGI-I, BSI, HAM-A scores.	Common side effects: sedation and dry mouth. One patient withdrew due to safety issues.
Aliyev et al. 2008 [6]	Double-blind placebo-controlled VPA in GAD	74	6 weeks	1500 mg	VPA was associated with significant improvements in HAM-A scores.	Most common side effects: dizziness and nausea. Four patients withdrew due to safety issues
Vayısoğlu 2017 [7]	Case report VPA in GAD	1	3-months follow-up visits	1000 mg	Improvement in clinician-observed anxiety symptoms	No side effects reported.
Nardi et al. 1997 [8]	Open label VPA in SAD	16	1–9 months	500–1500 mg	VPA was not considered effective by patients.	Most common side effects: sedation, headache, tremor, gastrointestinal discomfort and weight gain.
Kinrys et al. 2003 [9]	Open label VPA in SAD	17	12 weeks	500–2500 mg	VPA was associated with significant improvements in CGI-S, HAM-A and LSAS scores	Common side effects: nausea, headache, somnolence, dizziness and fatigue. One patient withdrew due to safety issues.

BSI: Brief Symptom Inventory; CGI-I: Clinical Global Impression Scale-Improvement; CGI-S: Clinical Global Impression Scale-Severity; GAD: Generalized anxiety disorder; HAM-A: Hamilton Anxiety Rating Scale; LSAS: Liebowitz Social Anxiety Scale; PD: Panic Disorder; SAD: Social Anxiety Disorder; SCL-90: Symptom Checklist-90; VPA: Valproate

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