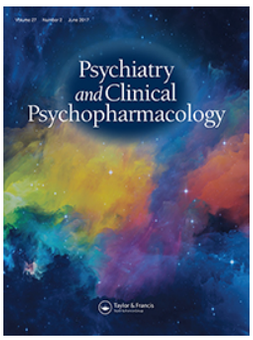

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Treatment response to valproate in case with generalized anxiety disorder resistant to antidepressants

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ABSTRACT

Objective: Pharmacological treatment of anxiety disorders is an active research field and Selective Serotonin Reuptake Inhibitors (SSRIs) are considered to be the first line of drugs in this treatment. In cases resistant to SSRI, in addition to serotonin-noradrenaline reuptake inhibitors (SNRIs), antiepileptic drugs that have anxiolytic activity by increasing the efficiency of gamma-aminobutyric acid (GABA) such as valproate can be used.
Methods: Observational case report.
Results: The author describes the use of valproic acid in the treatment of a patient who had resistant anxiety symptoms despite the treatment with SSRIs and SNRIs in appropriate doses for appropriate time.
Conclusions: The favorable response obtained with the use of valproate outside of its classical indications in our patient who was resistant to antidepressants indicates that valproate should be considered in anxiety disorders.

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KEYWORDS
Valproate; anxiety disorders; treatment response

Introduction

Favorable outcomes, which are obtained with the use of antiepileptic drugs in the treatment of mood disorders, led the development of studies on the potential use of these drugs in the treatment of psychiatric problems, notably anxiety disorders. Valproic acid is an antiepileptic whose effectiveness in various mood and anxiety disorders has been shown [1–3]. Valproic acid exerts its antiepileptic effects by increasing the activity of gamma-aminobutyric acid (GABA) in the brain [4, 5]. It has been shown that valproic acid reduces anxiety symptoms in a 12-week open-label study in patients with social anxiety disorder [6]. A meta-analysis that examined the effectiveness of valproate in the treatment of post-traumatic stress disorder reported that although the evidence was limited, valproate is an effective treatment by reducing hyperarousal and modulating tension, burst of anger, and mood [7]. The first and only double-blind, placebo-controlled randomized study that investigated the effectiveness of valproate in the treatment of anxiety disorders in 68 patients with generalized anxiety disorder reported that valproate significantly reduced anxiety symptoms compared to placebo [8].

The current case was presented to discuss the response of generalized anxiety disorder antidepressant-resistant patient, which is rarely reported in the literature, to valproate.

Case

A 45-year-old female, who was married with two children, a graduate of a 2-year higher education, and a housewife, presented to the outpatient clinic with her husband to request her medication, venlafaxine (150 mg/day), to be prescribed. At the start of the examination, the patient's irritated and tired appearance was noticeable. The patient was assured that her medication would be prescribed provided that an interview and psychiatric examination would be performed in order to understand the disease process and symptoms. She told desperately that she was tired of explaining her complaints, she believed that nothing would change even if she tells, she was given a one-year medication refill six months ago and she was applying every three months to get a new prescription for her drugs, and she did not have any other aim except that. Her psychiatric history was obtained from her and her husband with a supportive approach. Her complaints started four years ago with uneasiness, tension, forgetfulness and myalgia notable in the arms. She firstly presented with these complaints to the internal medicine clinic, which referred her to the psychiatric clinic since no organic explanations for her complaints were identified. After psychiatric evaluation, escitalopram at 10 mg/day was started but the dose of escitalopram was increased to 20 mg/day after three months since her complaints did not resolve. Her complaints partially resolved after one month with the increase in the drug dose; this

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period lasted for three months and even though she was using the drug at the same dose, her complaints especially unreasonable tension related to the fear of bad things to happen any time increased more than the pretreatment symptoms, therefore escitalopram was ceased and sertraline 50 mg/day was started during the control examination. Sertraline dose was gradually increased every four weeks and a dose of 200 mg/day was reached after three months. She told that her complaints had reduced 30–40% but her complaints of tension and uneasiness had continued. She also told that her doctor had recommended psychotherapy as a support during this process, she had started to see a psychiatrist in a private center but she had stopped that after two sessions due to financial reasons and considering the therapy was not useful. Due to an increase in her complaints after six months of sertraline treatment at a dose of 200 mg/day, haloperidol 1 mg/day was added to the treatment plan to strengthen the treatment. Since akathisia, which appeared as hand tremors, was developed after two weeks of haloperidol treatment, it was ceased and the dose of sertraline was increased to 250 mg/day. Due to nausea after two days of sertraline use at this dose, she continued to use the drug at a dose of 200 mg/day. It was decided to switch to paroxetine treatment during the control examination after two weeks. In order to avoid withdrawal symptoms, the dose of sertraline was reduced 50 mg/day each week and after one-month paroxetine was started at a dose of 20 mg/day. One month later, paroxetine dose was increased to 30 mg/day due to continuing symptoms. After three days, she had palpitation and chest tightness. Tachycardia was found in the examination which was considered to be a complication of paroxetine. Therefore, paroxetine dose was reduced to 20 mg/day again. After using the drug for two months at this dose, it was switched to citalopram 20 mg/day. Drug dose had been gradually increased each month and a dose of 60 mg/day was reached. She told that her complaints were reduced 50% and used the drug for one year at that dose. Thereafter, since her complaints increased, risperidone 1 mg/day was added to strengthen her treatment. One month after the addition of risperidone, she developed a feeling of fullness in her breasts and galactorrhea and high prolactin levels were detected in her blood assays, which were considered to be the side effects of risperidone. Risperidone was ceased and after one month, her prolactin level was reduced to normal range. Since citalopram treatment response was unsatisfactory, it was decided to switch to venlafaxine. The dose of citalopram was reduced 20 mg/day each week and after three weeks venlafaxine was started at a dose of 75 mg/day. Venlafaxine dose was increased to 150 mg/day after one month. The complaints of the patient reduced 50% and venlafaxine was increased to 225 mg/day after two months. The blood pressure of the patient, who had headache at this dose, increased to 160/100 mmHg. High blood pressure was considered to be due to venlafaxine treatment and the drug dose was reduced back to 150 mg/day. The blood pressure of the patient whose headache relieved gradually in three days after the reduction of drug dose, went back to 120/80 mmHg. The patient, who had been using venlafaxine 150 mg/day for six months, was asked to describe her complaints in more detail. She told that although her complaints reduced in half compared to the start of her disorder, she still had unreasonable tension and anxiety. She did not have a history of surgery. In her family history, she told that her aunt had been treated for the panic disorder.

No neurological problems were identified in the patient, who was consulted to the neurology clinic for an underlying physiological or medical reasons considering the atypical onset age of anxiety symptoms. Her thyroid functions and other blood tests were noncontributory. The dose of her medication, venlafaxine, was reduced to 75 mg/day and valproate 1000 mg/day was started. Within one week, venlafaxine dose was reduced to 37.5 mg/day; valproic acid in the blood level was measured on the 10th day of the treatment. The patient, whose blood valproic acid level was 73 μg/mL, reported that she was feeling very good and almost free from anxiety, tension; however, she had slight dizziness. Within four days, venlafaxine was completely stopped and valproate treatment at a dose of 1000 mg/day continued. Her valproic acid level was 78 μg/mL at control examination one month later; she told that she was feeling completely relaxed, she did not have any anxiety, uneasiness, or tension and she also did not have dizziness. The patient, who was invited to follow-up visits every three months, was free of any psychiatric complaints at the sixth month of her treatment.

Discussion

In this case, despite the use of various antidepressants belonging to selective serotonin reuptake inhibitor and serotonin-noradrenaline reuptake inhibitor groups in appropriate doses for appropriate durations and occasional attempts to strengthen the antidepressant treatment with antipsychotic drugs, her treatment was either unsuccessful or partially successful. In clinical practice, valproic acid is commonly used as an antiepileptic in the treatment of epilepsy or as a mood stabilizer in the treatment of mood disorders. Besides its anticonvulsant and mood-stabilizing effects, valproic acid has anxiolytic, antimigraine and anti-nociceptive effects which are caused via GABA-mediated transmission [9].

The favorable response obtained with the use of valproate outside of its classical indications in our patient who was resistant to antidepressants indicates that valproate should be considered in similar situations. In order to understand more clearly the therapeutic effects of valproate on anxiety disorders notably generalized anxiety disorder, further placebo-controlled randomized studies are needed.

Disclosure statement

No potential conflict of interest was reported by the author.

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