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Case Report

Levetiracetam Treatment of Refractory Obsessive-Compulsive Disorder

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Abstract

The antiepileptic drug levetiracetam is an approved adjunctive treatment for various types of seizure disorders. It has not been used for the treatment of obsessive-compulsive disorder. This case report describes levetiracetam favorable effects in the treatment of a patient with refractory obsessive-compulsive who was initially prescribed the medication for the treatment of co-occurring cluster headaches. The patient tolerated the medication without any adverse effects. To the author's knowledge there have been no reports on the use of Levetiracetam for the treatment of refractory obsessive-compulsive disorder. Clinicians prescribing Levetiracetam should be aware of its reported psychiatric adverse events including the precipitation of obsessive-compulsive disorder.

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Keywords

- Obsessive-compulsive disorder
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ABBREVIATIONS

AED: Antiepileptic Drug; CBT: Cognitive-Behavioral Therapy; CGI: Clinical Global Improvement And Severity Scale; DBS: Deep Brain Stimulation; DSM-5: Diagnostic And Statistical Manual Of Mental Disorders; Fifth Edition; ECG: Electrocardiogram; ECT: Electroconvulsive Therapy; FDA :United States Food And Drug Administration; FGAS: First Generation Antipsychotics; *LEV*: *Levetiracetam;*MAOIS: Mono Amino Oxidase Inhibitors; MCAT: Medical College Admission Test;*MRI: Magnetic Resonance Imaging;* NMDA: N-Methyl-D-Aspartate; OCD: Obsessive-Compulsive Disorder; P/Q:Electrophysiological P- And Q-Type Channels; PTSD: Posttraumatic Stress Disorder; SGAS: Second Generation Antipsychotics; SNRIS: Serotonin Nor Epinephrine Reuptake Inhibitors; SSRIS: Selective Serotonin Reuptake Inhibitors; TCAS: Tricyclic Antidepressants; TMS: Transcranial Magnetic Stimulation; Y-BOCS: Yale-Brown Obsessive Compulsive Scale.

INTRODUCTION

OCD is a relatively common persistent disorder characterized by intrusive and disturbing thoughts (obsessions) and repetitive behaviors (compulsions) that the person feels driven to perform which are time-consuming; causing marked distress; or significantly interfering with a person's functioning. Some patients with OCD have either obsessions or compulsions; however the majority of patients have both obsessions and compulsions. It is the 10th most common cause of disability worldwide; with a lifetime prevalence of approximately 2% [1].

In DSM-5; [2] OCD was moved from the anxiety disorders to a new category of Obsessive-Compulsive and Related Disorders. OCD has an early onset; usually in childhood or adolescence with females experiencing slightly higher rates in adulthood; while males having a slightly elevated rate in childhood and frequently the disorder become chronic and disabling if left untreated [2]. The rate of co-occurring psychiatric conditions in patients with OCD is high especially for major depressive disorder; panic disorder; social anxiety disorder; specific phobias; PTSD and substance use disorders; with some studies suggesting that 10% to 27% of OCD patients could attempt suicide during their lifetime [3]. Depression and hopelessness are major correlates of suicidal behavior in OCD thus requiring careful and constant monitoring for suicide risk [2,3]. Most patients with OCD experience symptoms throughout their lives and benefit from long-term treatment. Psychotherapy and pharmacotherapy are recommended; either alone or in combination; with CBT being the first psychotherapy of choice [4]. Although many patients with OCD will usually respond to SSRIs alone or to the combination of SSRIs and CBT; an estimated 50% of patients remain treatment refractive with little or no relief of their symptoms[5,6].

The preferential efficacy of the SSRIs in OCD led to the inception of the serotonin hypothesis despite the absence of a direct correlation of the role of serotonin as a biomarker of OCD pathophysiology in pharmacological challenge studies. Recent emerging body of evidence from neuroimaging; genetic and clinical trials and animal models supports the hypothesis that dysregulation of glutamate neurotransmission may contribute to the Pathophysiology of OCD [7,8]. In addition the neuropharmacology studies of glutamate-modulating agents have yielded support for their development and use in the

management of OCD [9]. Convergent evidence also suggests an imbalance in glutamate; in some patients with OCD [10]. Although the available literature suggest a possible role for AEDs with glutamatergic effects such as lamotrigine, topiramate, gabapentin and pregabalin as augmenting agents in refractory OCD treatment[11-13]. To this author's knowledge there have been no reports on the glutamatergic effects of LEV on reducing refractory OCD symptoms as illustrated in this case report.

CASE PRESENTATION

Mr. S is a 32-year-old single Caucasian gentleman with 12-year history of treatment-refractory chronic OCD characterized by multiple obsessions and compulsions. His obsessions were related to excessive fears of being contaminated by unseen environmental germs and of being an agent of contaminating other. His compulsions included excessive hand washing and showering; using cleansing lotions rubbing alcohol; and ingesting various antibiotics that he purchased on line from pharmacies in Mexico; India and South Korea. He could not handle any objects or get in close proximity of any person; without wearing a face mask and silk white glove. His face masks and white silk gloves were specially tailored and were immediately discarded. Due to the severity of his OCD he was unable to be gainfully employed and was on the verge of depleting all of his inheritance. He had stopped OCD treatment two years earlier due to lack of response to many pharmacological interventions in combination with CBT. Mr. S was first diagnosed with OCD at age 16; at that time he demanded that his parents should wear face masks and white silk gloves to be protected from infection by unseen killer germs. His parents assumed that he was influenced by the many video games that depicted aliens infeteing the atmosphere and by his unshaken conviction that his baby sister whom he dearly loved unexpectedly died during her sleep was contaminated by a mysterious out of space germ that he had passed on to her after conducting a science experience at the local county fair. As their only child his parents concentrated their efforts on distracting him by allowing him to get all the latest models of X-box and video games; and because of his excessive fears of contaminating himself and others he was home schooled and was allowed to spent enormous amount of time in tiding his room and even placing an area of artificially made quarantine wall around his own bedroom. He was also allowed to paint all of his furniture; his bedroom walls and his closet with a shinny white color to identify any dust particles. The parents were hoping that he will grow out of these extreme rituals and fortunately their wishes were fulfilled and his OCD remitted spontaneously 2 years later and he was able to obtain high school diploma and completed 2 years of college without recurrence of any OCD symptoms. Then tragically his parents died in a head on car collision by a drunken person who fell asleep on the wheel. Almost instantly during the preparation of his parents' funeral which coincided with his 20th birthday his OCD symptoms reemerged and persisted.

Mr. S had no family history of psychiatric; medical or substance use disorders and did not use any alcohol; tobacco; caffeine or illicit drugs; he also did not have any co-occurring psychiatric or medical conditions except for cluster headaches which did not respond to multiple pharmacological interventions. He constantly refused treatment for the cluster headaches despite their severity and intensity.

Mr. S cousin who was a pharmacist and was working in Japan heard about his pending financial ruin and came to the US and was able to schedule him an appointment to reassess his cluster headaches and OCD. His physical examination; and neurological examinations were all normal and despite his excessive intake of antibiotics he had no laboratory abnormalities. Based on his past lack of response to various cluster headaches treatment; he agreed to take LEV based on published case reports [14].

Mr. S signed informed consent for the off-label use of LEV and also completed the Y-BOCS scale a total score of 40;showing a fair insight on item 11; and an avoidance and had score of 4;suggesting extensive and pervasive avoidance; with circumscribed activities reaching housebound proportion [15]. In addition he had a CGI - severity score of 7 reflecting a level of most extremely ill [16,17]. To rule out possible medical conditions for cluster headaches an ECG and a brain MRI with gadolinium and angiography sequences were ordered and they were normal. The treatment was started with LEV at the dose of 500 mg once day; which was increased to 500 mg twice a day after three days. Mr. S was surprised to notice that he remained free from cluster headache attacks after 12 days of initiating LEV and he also did not develop any side effects to this agent. On day 15 of LEV treatment the Y-BOCS severity score decreased to 10 for each obsession and compulsion [15]. After receiving LEV for 28 days; he remained free of cluster headaches and the Y-BOCS severity score dropped to 4 for each obsession and compulsion showing an avoidance score of 1 suggesting mild; minimal and infrequent avoidance [15]. A follow-up CGI showed score severity of 2 which suggesting a mildly ill condition; and CGI improvement score of 2 which is indicative of a much improved status [16,17].

Mr. S believed that he was finally cured and abruptly stopped taking LEV and within 15 days the cluster headaches and the OCD symptoms reemerged which then remitted with the resumption of LEV . It has been now 3 months since the resumption of LEV treatment at the dose of 500mg twice a day without adverse effects. Incidentally he took the MCAT examination which he passed with an exceptionally high score and was accepted in a medical school. He has future plans to ultimately specialize in infection diseases.

DISCUSSION

Despite findings from family and twin studies that have shown a moderate pattern of heritability the exact etiology of OCD remains uncertain [18,19]. There are also inconsistent findings with respect to polymorphisms in the genes responsible for the serotonin transporter; dopamine transporter; and serotonin and dopamine receptor subtypes in OCD suggesting the possibility that multiple genes; each with small effects; could be contributing to the disorder [19-21]. The role of the glutamatergic system in OCD has been gaining research interests based on data from neuroimaging; genetic and clinical trials and animal models [7-10]. Although a substantial portion of OCD genetic risk architecture remains unknown; the SLC1A1 gene; which encodes the neuronal glutamate transporter; EAAC1; has consistently been implicated in OCD [22]. Environmental and familial factors including parental modeling; expressed emotion; parenting style; and family accommodation of the child's symptoms as well as the

family's involvement in the treatment of the disorder are also risk factor in the development and maintenance of OCD [23]. Like most other psychiatric disorders; OCD is suspected of being influenced by an interaction between life events and genes; both with regard to onset and course of illness.

Based on Mr. S history there were no identified familial or environmental risk factors that could have predisposed him to develop OCD. A strong link related to the death of his loved ones seems to have triggered the emergence of his severe OCD symptoms. As illustrated by his personal history; his symptoms first emerged after the sudden death of his baby sister; then followed by a period of spontaneous remission; then another bout of severe OCD symptoms reemerged due to the tragic accidental death of his parents. This is consistent with studies that are generally supportive of a relationship between traumatic life events and the development of OCD symptoms [24]. The death of loved ones could trigger the development of OCD [25]. It is appropriate to clinically conclude that Mr. S had dormant genetic predisposition for OCD; which was then fully triggered into an active illness phase by the death of his loved family members.

To quantify the severity of symptoms and impairment before and during treatment; standardized rating scales such as the Y-BOCS; which is a reliable item observer-rated 10- measure tool for measuring OCD symptom severity [15]. It is also important to monitor the effect of OCD symptoms on interpersonal relationships; employment; self-care; and leisure activities based on patients' estimate of the time they spent each day engaging in obsessive-compulsive thoughts or behaviors.

Although the SSRIs are considered first-line treatments for OCD; about 40-60% of patients do not respond to appropriate courses of treatment with SSRIs and even with the combination of various pharmacological and augmenting agents in addition to CBT a substantial number of patients remain dramatically symptomatic[5;6]. The various medications which could include SNRIs; FGAs; SGAs TCAs; MAOIs and other agents; that can be used for refractory OCD treatment are summarized in Table 1**;** **[**5,6, 26-37]. Patients with treatment resistant OCD who do not respond to the pharmacological interventions may need other treatment such as ECT [38,39]; TMS [38,39]; DBS [38-41] or for severe cases cingulotomy neurosurgery [38-42].

Despite the wide range of animal models of OCD aimed at developing new treatments for OCD based on a better understanding of the basic mechanisms that contribute to the disorder; these developments have not yielded to novel findings in human clinical studies;however there has been increasing interest in investigating glutamatergic dysfunction in OCD [7-9]. Multiple lines of evidence point toward glutamatergic dysfunction being related to the pathphysiology of OCD; with glutamate modulating agents being an alternative pharmacological strategy for treating OCD [43,44].

LEV is an AED that is FDA approved as an adjunctive therapy for various seizure disorders [45,46]. There is preliminary evidence about the efficacy of LEV in the treatment of different psychiatric disorders; including anxiety; panic; bipolar disorder; autistic spectrum disorder; alcohol use disorder and movement disorders including Tourette's syndrome and tardive dyskinesia [47,48]. Although it has a mild and relatively benign side effects profile; the use of LEV has been associated with neuropsychiatric adverse events; such as somnolence; fatigue; coordination difficulties; psychosis; delirium and behavioral abnormalities such as agitation aggression; hostility irritability and emotional liability [49,50]. There have also been reports of LEV inducing

Table 1: Various Medications that have used for obsessive-compulsive disorder treatment.

	Suggested intervention	Medications
1.	First-line pharmacological treatment	Initiate an SSRI such as: fluoxetine; paroxetine; sertraline; fluvoxamine; citalopram or escitalopram. To be administrated at a medium to high doses for acute treatment of at least 3 months. If efficacious; maintenance treatment is recommended for at least 1 year.
2.	No response to SSRI'S	Consider clomipramine and maintained if well tolerated at a medium to high doses for acute treatment of at least 3 months. If efficacious; maintenance treatment is recommended for at least 1 year.
3.	Partial response to either SSRI'S or Clomipramine	Augmentation strategies can be attempted by combining an SSRI or clomipramine; with FGAs or SGAs.
4.	Inadequate or no response to FGA or SGA augmentation	Consider SNRIs such as venlafaxine or duloxetine.
5.	Inadequate or no response to SNRIs	Consider an anxiolytic such as :buspirone; A mood stabilizer such as:lithium; TCA : such as desipramine; Glutamatergic agents such as: riluzole; glycine; memantine; or ketamine; Inositol Beta adrenergic blockers such as atenolol or pinodol; Stimulants such as:D-amphetamines MAOIs; AEDs
6.	Refractory /Treatment resistant to Step 1-5	Consider morphine sulfate; tramadol; ondansetron or weekly intravenous clomipramine.

Abbreviations: AEDs: Antiepileptic Drugs; FGAs: First generation Antipsychotics; MAOIs: Mono Amino Oxidase Inhibitors; SGAs: Second Generation Antipsychotics; SNRIs: neither Serotonin nor epinephrine reuptake Inhibitors; SSRIs: Selective Serotonin Reuptake Inhibitors; TCAs: Tricyclic Antidepressants.

OCD [51]. Although the available literature suggest a possible role for AEDs with glutamatergic effects such as lamotrigine; topiramate; gabapentin and pregabalin as augmenting agents in refractory OCD treatment [11-13]. To this author's knowledge there have been no reports on the effects of LEV on reducing refractory OCD symptoms. Despite the absence of a study investigating OCD and LEV; studies are available about "body dimorphic disorder"; which is a disorder that may be related to the OCD spectrum disorder [52].

The exact mechanism of LEV action is not fully known; it is unique among the AEDs because its effectiveness starts with the initial dose with favorable tolerability and pharmacokinetics with [51,52]. Specific modulating effects on the presynaptic P/Q-type voltage-dependent calcium channel leading to the reduction of glutamate release [50,53].

In summary this report illustrates that there is a need to reevaluate the role of LEV and other AEDs which reduce glutaminergic neurotransmission in the treatment of patients with refractory OCD. The association of OCD and cluster headache with the beneficial effect of LEV is noteworthy in view of a pertinence of glutamatergic dysfunction in both conditions; but controlled studies are needed to substantiate this observation. Although Mr. ZS did not consider several of the alternative pharmacological and somatic treatments for the refractory OCD symptoms; his response to LEV suggests that his OCD symptoms were related to glutamatergic dysfunction because of this agent effects on inhibiting glutamate neurotransmission [50,53]. Clinicians should be aware of the many potential psychiatric adverse effects associated with LEV including the precipitation of OCD [51]. Given the need for more efficacious treatments in OCD; and given emergent findings on the role of the glutamatergic system in this disorder; there is a need for additional pharmacotherapy trials on glutamatergic agents in OCD. Possible research designs for such trials might include randomized double blind controlled studies; stand-alone approaches; pharmacotherapy augmentation; or psychotherapy augmentation.

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