

A Double-Blind Placebo-Controlled Trial of levetiracetam for Global Severity in Child Autism Spectrum Disorders

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Abstract

Objectives: The effects of levetiracetam and placebo on global severity were compared in Child Autism Spectrum Disorders (ASD). **Materials and methods:** Children with ASDs were enrolled in a 12-week double-blind placebo-controlled levetiracetam trial. Fifty were randomly assigned to levetiracetam (n=50) or placebo (n=50). The mean maximum dosage for levetiracetam was 950.50±279.19 mg/day. Repetitive behaviors were measured with the Clinical Global Impression (CGI) improvement scale. **Results:** There was a significant treatment-by-time interaction indicating a significantly greater reduction in repetitive behaviors across time for levetiracetam than for placebo. With overall response defined as a CGI global improvement score of 2 or less, there were significantly more responders at week 12 in the levetiracetam group than in the placebo group. The risk ratio was 1.5 for CGI global improvement (responders: levetiracetam, 50%; placebo, 10%). Side effects were not observed. **Conclusions:** levetiracetam treatment, compared to placebo, resulted in significantly greater improvement in global severity behaviors, according to CGI rating scale. levetiracetam appeared to be well tolerated. Movement score of 2 or less, there were significantly more responders at week 12 in the levetiracetam group than in the placebo group. Side effects were not observed.

Keywords: levetiracetam, autism spectrum disorders, treatment.

Introduction

Currently, disorders of the autism spectrum are the most urgent problem of modern psychiatry. It is no accident that the SIXTY-SEVENTH WORLD HEALTH ASSEMBLY adopted a resolution called "WHA67.8 Integrated and coordinated efforts to combat autism spectrum disorders." In particular, the document indicated that autism spectrum disorders are disruptions and developmental conditions that occur in early childhood and in most cases persist throughout life and are marked by the presence of impaired development in social interaction and communication and a restricted repertoire of activity and interest, with or without accompanying intellectual and language disabilities; and that manifestations of the disorder vary greatly in terms of combinations and levels of severity of symptoms.^[1] In one hand, last several decades based on epidemiological studies conducted over the past 50 years, the prevalence of autism spectrum disorders (ASD) appears to be increasing globally. There are many possible explanations for this apparent increase, including increasing the level of confidence, expanding diagnostic criteria, improving diagnostic tools and improving reporting. It is estimated that worldwide 1 in 160 children has an ASD. Other authors indicated that autism spectrum disorder currently estimated to affect between 1 and 1.5% of children and adults worldwide.^[2,3]

In other hand, the cost of supporting an individual with an ASD and intellectual disability during his or her lifespan was \$2.4

million in the United States and £1.5 million (US \$2.2 million) in the United Kingdom. The cost of supporting an individual with an ASD without intellectual disability was \$1.4 million in the United States and £0.92 million (US \$1.4 million) in the United Kingdom.^[4]

It is known that autism spectrum disorder, previously known as the pervasive developmental disorders, is a phenotypically heterogeneous group of neurodevelopmental syndromes, with polygenic heritability, characterized by a wide range of impairments in social communication and restricted and repetitive behaviors. Prior to the development of the Fifth Edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), autism spectrum disorder was conceptualized as five discrete disorders, including: *autistic disorder*, Asperger's disorder, childhood disintegrative disorder, Rett syndrome, and pervasive developmental disorder not otherwise specified.^[5] Autistic disorder was characterized by three core symptom areas: impairments in three domains: social communication, restricted and repetitive behaviors, and aberrant language development and usage.

Medications are mainly used to treat the associated symptoms of an autism spectrum disorder, as the effectiveness of use in treating the main symptoms of autism is not established. In addition to psychosocial therapy of autism, there are data in the literature on the use of typical (haloperidol) and atypical antipsychotics

(risperidone, aripiprazole, olanzapine, lurasidone, quetiapine, ziprasidone, paliperidone), antidepressants (selective serotonin reuptake inhibitors and others), mood stabilizers, stimulants (stimulants / atomoxetine / alpha-2 agonists) and other agents for the treatment of autism spectrum disorders.^[6]

The aim of this study was examines the effects of levetiracetam and placebo on global severity were compared in child autism spectrum disorders (ASD).

Materials and methods

In accordance with the Helsinki Declaration of the World Medical Association "Recommendations for doctors engaged in biomedical research involving people", adopted by the 18th World Medical Assembly (Finland, 1964, revised in Japan in 1975, Italy - 1983, Hong Kong - 1989, the South African Republic - 1996, Edinburgh - 2000); The Constitution of the Republic of Azerbaijan, the Law "On Psychiatric Assistance" (adopted on 12.06.2001, with amendments and additions - 11.11.2011, Decisions of the Cabinet of Ministers of the Republic of Azerbaijan No. 83, dated April 30, 2010 "On Approval of the Rules for Conducting Scientific, Preclinical and Clinical studies of medicines" are established:

The conditions of the conducted researches corresponded to the generally accepted norms of morality, the requirements of ethical and legal norms, as well as the rights, interests and personal dignity of the participants of the studies were observed

- Conducted research is adequate to the topic of research work
- There is no risk for the subject of research
- Participants in the study were informed about the goals, methods, expected benefits of the study and associated with risk and inconvenience in the study
- The subject's informed consent about participation in the research was received

The decision of the Ethical Committee at the Azerbaijan Psychiatric Association on the article of NA. Aliev, Z.N. Aliev "A Double-Blind Placebo-Controlled Trial of Levetiracetam for Global Severity in Child Autism Spectrum Disorders" submitted for publication in psychiatric journals: in connection with compliance with its legislative requirements and regulatory documents is to approve the article by N.A. Aliyev, Z.N. Aliev "A Double-Blind Placebo-Controlled Trial of Levetiracetam for Global Severity in Child Autism Spectrum Disorders".

We examined 100 patients with (F10.239). Patients were observed at the Mental Health Center of the Ministry of Health of the Republic of Azerbaijan (from July 2015 to July 2018 years).

Fifty subjects were children aged 5–17 years, outpatients, who met DSM-V diagnostic criteria for autistic disorder. Subjects had to be at least moderately ill (CGI-Severity score of at least - 4) to justify exposure to this medication.

We excluded sexually active subjects with active or unstable epilepsy, other genetic syndromes or congenital infections associated with autistic-like syndromes, prematurity; subjects who have been treated within the previous 30 days by any medication known to have a clearly defined potential for toxicity or with any

psychotropic drugs; Subjects with clinically significant abnormalities in laboratory tests or physical examination; subjects with a history of hypersensitivity or serious side effects associated with the use of levetiracetam (or other ineffective previous therapeutic tests of levetiracetam. The mean maximum dosage for levetiracetam was 950.50±279.19 mg/day and subjects who, during the previous 3 months, started new non-pharmacological procedures, such as diet, vitamins and psychosocial therapy. A detailed clinical interview with parents by a clinical expert, accompanied by physical examination and blood analysis, was used to ensure that subjects did not meet any exclusion criteria. The method of randomization was given by lottery. This was a 12-week randomized double-blind, placebo-controlled trial. Participants were randomized to Levetiracetam vs placebo and the dose was titrated up according to body weight (Table 1). All clinicians involved in efficacy or safety assessments were blinded to the randomization condition. Efficacy measures were administered every 2 weeks by an independent evaluator, who was an experienced clinical psychologist blinded to side effects. Side effects were monitored by study physicians, who are experienced in treating children with ASD and using levetiracetam formulations. The dose was titrated on the basis of feedback from a non blinded physician who independently monitored blood. This clinician had no contact with the participants. Levetiracetam levels and safety blood results were forwarded to him by the laboratory. He then instructed the study physicians to decrease, maintain, or increase the dose. Feedback on subjects randomized to placebo was based on a blocked schedule, so that all study clinicians remained blinded to the condition of randomization.

The dose for children is selected individually depending on the age, the severity of the disease, the therapeutic effect. The daily dose is divided into 2 doses.

Independent samples t-tests were used to determine whether there were baseline differences between treatment groups on the following potential covariates baseline severity. Also was used χ^2 analysis. Outcome measure: CGI-I (χ^2 analysis). Consistent with intent-to treat principles, for those subjects missing the week-12 ratings, we imputed their value on the CGI at week 12 using mixed regression models based on the available values from all subjects and all seven time points. The predicted scores were then used to classify the subjects as responders or nonresponders at week 12 on the basis of the following: CGI<2 (responders) or CGI>2 (nonresponders). χ^2 test was used to compare the response between groups.

Table 1: Titration Schedule

From: Levetiracetam vs Placebo for the Treatment of Children with Autism Spectrum Disorders

| | <40 kg | >40 kg |
|------------------|--------------------------------|--------------------------------|
| Week | Dose | Dose |
| Week 0, days 1–4 | 125 mg | 250 mg |
| Week 1, days 5–7 | 250 mg | 500 mg |
| Weeks 2–3 | 750 mg | 1000 mg |
| Weeks 4–12 | Maintained on therapeutic dose | Maintained on therapeutic dose |

Results

We evaluated efficacy using the Clinical Global Impression-Improvement Scale (CGI-I). The CGI-I is a 7-point improvement scale. Ratings of 1 or 2 (responders) indicate a substantial reduction in symptoms, so that a treating clinician would be unlikely to readily change the treatment regimen. A rating of 3 (minimally improved) on the CGI is defined as a slight symptomatic improvement that is not deemed clinically significant; patients with such an improvement were not considered responders.

A physical examination was conducted at baseline and end visits. Blood monitoring of hematopoietic, liver, and renal function was carried out at baseline, weeks 2 and 4, and at end visit. Weight, height, and BMI were recorded at baseline and at end visit and vital signs were taken at baseline, weeks 2 and 4, and at end visit. Adverse event monitoring took place every week for the first 4 weeks and every 2 weeks thereafter. Questioning was focused on known side effects of levetiracetam, followed by open-ended questioning. Levetiracetam was well tolerated within this group. Side effects were not observed.

Table 2: Results of the Treatment (observed and expected number from the χ^2 analysis)

| Treatment Groups | Improvement | No Improvement | Total |
|------------------|-------------|----------------|-------|
| Acidipirrol | 40 (15.60) | 10 (15.60) | 50 |
| Placebo | 6 (16.43) | 44 (16.43) | 50 |
| Total | 46 | 54 | 100 |

Expected numbers indication in the brackets, χ^2 analysis = 22.68, $df = 1$. $P < 0.001$

There was a significant treatment-by-time interaction indicating a significantly greater reduction of ASD generally symptoms across time for Levetiracetam than for placebo. With overall response defined as a CGI global improvement score of 2 or less, there were significantly more responders at week 12 in the Levetiracetam group than in the placebo group. The risk ratio was 1.5 for CGI global improvement (responders: levetiracetam, 50%; placebo, 10%). Side effects were not observed.

Discussion

This study suggests that levetiracetam may be effective in the treatment of ASD. There are several reasons why this may be the case. First, the GABA-enhancing mechanism of levetiracetam may be relevant to both the pathophysiology of aggression and that of ASD. Anxiety, panic and stress disorders. Levetiracetam indirectly contributes to GABAergic function, and there is strong evidence that GABA plays a key role in the pathophysiology of mood disorders, anxiety and stress.^[7]

The safety and efficacy of levetiracetam in the treatment of children with autism have been studied. In their open-label prospective study showed that levetiracetam may reduce hyperactivity, impulsivity, mood instability, and aggression in autistic children.^[8] Wasserman et al. conducted an open-label, placebo-controlled, double-blind study to determine the safety and

efficacy of levetiracetam; this study did not show any improvement in the behavioral disturbances in patients with autism.^[9]

Mechanism of action of levetiracetam. This is a soluble ethyl analogue of the widely used nootropic agent of piracetam. LeV has anti-epileptic, anxiolytic and cognitive properties. Only the S-enantiomer of LeV has anticonvulsant activity. In vitro studies have shown that LEV has no significant affinity for gamma-aminobutyric acid (GABA) or benzodiazepine receptors. It seems that LEV acts through an unknown site of specific binding in the brain. This new binding site is a synaptic vesicle protein, SV2A, which is an integral membrane protein present on synaptic vesicles and some neuroendocrine cells.^[10]

There are reports of other LeV effects, including partial inhibition of the calcium channels Ca^{2+} with N-type and a decrease in the inhibition of α -aminobutyric acid (GABA) and glycine-gated currents induced by Zn^{2+} and β -carbolines. It is currently unclear whether these effects are mediated by the observed interaction with SV2A or alternative mechanisms. It is believed that the correlation between SV2A binding and drug activity suggests that LeV modulates one or more SV2A functions and accordingly contributes to its effectiveness in the treatment of epilepsy.^[11]

A recent study was conducted to investigate the efficacy of levetiracetam for the treatment of tics in children with TC. This double-blind, randomized, placebo-controlled, crossover study was performed in children with moderately severe tics. This study did not reveal any significant differences between treatment groups and placebo. Thus, levetiracetam therapy is not beneficial in children with autism following the results of this study. Currently, there are no large-scale, double-blind studies on the use of levetiracetam in mood disorders.^[12]

We would also like to make note of our findings suggesting that therapeutic blood levels of Levetiracetam are associated with better response. The safety profile of levetiracetam in this study was very good. One should not assume though that the safety profile of a medication in a short-term study would be reflective of a long-term safety with this medication. The mechanism of action of levetiracetam has not been yet established.^[13]

These activities appear to be mediated, at least in part, by its effects on GABA - mediated neurotransmission. Levetiracetam increases CNS concentrations of GABA, possibly by increasing its synthesis and/or inhibiting its catabolism. Levetiracetam has also been reported to decrease neurotransmission by the excitatory amino acids (hydroxybutyric, aspartic and glutamic acids), to inhibit cell firing induced by Af-methyl-D-aspartate, and to exert a direct neuronal membrane depressant effect via modulation of sodium and potassium conductance. Levetiracetam is generally well tolerated, does not induce hepatic drug metabolism and has a low propensity for interactions with psychotropic agents.

Limitations of our study include the relatively small sample size, which did not allow for a complete analysis of EEG and levetiracetam blood level data. In addition, the absence of an EEG record at the end of the study makes it impossible for investigators to determine whether an improvement in EEG patterns correlated with treatment response. The choice of the ABC-Irritability subscale, although a validated measure in ASD, precludes us from

making recommendations regarding specific types of aggression that may be responsive to Levetiracetam.

To our knowledge, this is the first report of a randomized, double-blind, placebo-controlled study of a levetiracetamin the acute Treatment of outpatients with generalized anxiety disorder without of psychiatric comorbidity. Our data suggest that levetiracetam is efficacious in the management of acute anxiety disorders, as the participants had a clinically and statistically significant improvement in anxiety symptoms over 6 weeks of treatment.

Mechanisms underlying the pathological characteristics of the ASD have yet to be fully elucidated. One of the most widely accepted mediators known to play a central role in the pathophysiology of anxiety disorders is the g-aminobutyric acid (GABA) system. Data confirming the role of the dysfunctional GABA system are the result of clinical experience with benzodiazepines, as well as the subsequent determination of the mechanism of action, genetic engineering and neuroimaging studies of the GABA receptor.

Levetiracetam has demonstrated anxiolytic, mood-stabilizing, antimigraine and antinociceptive effects and has been evaluated in the management of various other disorders, particularly psychiatric conditions. These activities appear to be mediated, at least in part, by its effects on GABA - mediated neurotransmission. Levetiracetam increases CNS concentrations of GABA, possibly by increasing its synthesis and/or inhibiting its catabolism. Levetiracetam has also been reported to decrease neurotransmission by the excitatory amino acids (hydroxybutyric, aspartic and glutamic acids), to inhibit cell firing induced by Af-methyl-D-aspartate, and to exert a direct neuronal membrane depressant effect via modulation of sodium and potassium conductance. Levetiracetam is generally well tolerated, does not induce hepatic drug metabolism and has a low propensity for interactions with psychotropic agents. However, as has been observed with several other antiepileptic drugs, it is teratogenic and can cause elevated hepatic enzyme levels and rare, fatal hepatotoxicity.^[14] But some authors suggest that levetiracetam does not improve symptoms of autism.^[15,16,17]

Two limitations should be noted. First, our small study group and we recommend that these results be replicated in a larger group so that effect sizes can be more precisely estimated. Second, it is necessary study of possibility generalizability these data to girls. Notwithstanding these limitations, this study suggests that, levetiracetam are efficacious and well tolerated in the treatment ASD.

In any event, pending a further understanding of levetiracetam's mechanisms of action, the present data suggest that this drug is a useful new agent for the treatment of ASD.

Author Disclosure Information

The authors declare that the article is submitted on behalf of all authors. None of the material in the article has been published previously in any form and none of the material is currently under consideration for publication elsewhere other than noted in the cover letter to the editor. Authors declare no financial and personal relationship with other people or organizations that could inappropriately influence this work. All authors contributed to and

have approved the final article. The authors declare no conflicts of interest.

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