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Double-blind, placebo-controlled trial of risperidone plus topiramate in children with autistic disorder

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ABSTRACT

Background: Autism is a complex neurodevelopmental disorder that forms part of a spectrum of related disorders referred to as Autism Spectrum Disorders. The present study assessed the effects of topiramate plus risperidone in the treatment of autistic disorder.
Method: Forty children between the ages of 4 and 12 years with a DSM IV clinical diagnosis of autism who were outpatients from a specialty clinic for children were recruited. The children presented with a chief complaint of severely disruptive symptoms related to autistic disorder. Patients were randomly allocated to topiramate + risperidone (Group A) or placebo + risperidone (Group B) for an 8-week, double-blind, placebo-controlled study. The dose of risperidone was titrated up to 2 mg/day for children between 10 and 40 kg and 3 mg/day for children weighting above 40 kg. The dose of topiramate was titrated up to 200 mg/day depending on weight (100 mg/day for <30 kg and 200 mg/day for >30 kg). Patients were assessed at baseline and after 2, 4, 6 and 8 weeks after starting medication. Measure of outcome was the Aberrant Behavior Checklist-Community (ABC-C) Rating Scale.
Results: Difference between the two protocols was significant as the group that received topiramate had a greater reduction in ABC-C subscale scores for irritability, stereotypic behavior and hyperactivity/noncompliance.
Conclusion: The results suggest that the combination of topiramate with risperidone may be superior to risperidone monotherapy for children with autistic disorder. However the results need to be further confirmed by a larger randomized controlled trial.

1. Introduction

Autism is a severe, chronic development disorder, involving marked retardation of aptitudes for social interaction, communication and play (Myers, 2007). A meta-analysis of 37 studies of autism prevalence reported from USA, UK, Europe and Japan has estimated that the prevalence of autism is 7.1 per 10,000 in individuals less than 18 years old (Williams et al., 2006). While behavioral therapies are clearly and without question the interventions of choice for those with autism there is also often the need for psychopharmacologic intervention (West et al., 2009). Psychotropic medications are used in children with autism in a predominantly off-label manner in particular for behavioral disturbance (Mohammadi and Akhondzadeh, 2007). One way to indirectly investigate the pathophysiology of autism is to study the effect of a drug that may modulate the release of glutamate or the function of excitatory receptors (Mohammadi and Akhondzadeh, 2007). Medications that prevent excitotoxicity are desirable for treatment of asphyxia, stroke, and may benefit other neurological disorders such as autism (Levy and Hyman, 2005; Leskovec et al., 2008). Recently, there has been rising interest in the use of antiepileptic drugs (AED) in the management of pervasive developmental disorder (PDD) (Tuchman, 2004). Studies examining the effectiveness of AED for the treatment of PDD show some promise (Hellings et al., 2005; Anagnostou et al., 2006).

There are several reasons for the use of antiepileptic drugs in autistic spectrum disorders, including the high incidence of epilepsy in these individuals, the anecdotal reports suggesting an improvement of communication and behavior in autistic subjects with epileptic discharges, and the increased awareness that some disruptive behaviors may be manifestations of an associated affective

Abbreviations: ABC-C, Aberrant Behavior Checklist-Community; DSM, Diagnosis and Statistical Manual of Mental Disorders; ESRS, Extrapyramidal Symptoms Rating Scale.

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disorder (Tuchman, 2004). Topiramate is a novel broad-spectrum anticonvulsant with a unique pharmacologic profile; it inhibits glutamate activity at the a-amino-3-hydroxy-5-methylisoxazole-4-propionic acid/kainate subtype of glutamate receptors, attenuates activity at Na^+ channels and high-voltage activated Ca^{2+} channels, and augments effects at gamma-aminobutyric acid (GABA) receptor subtypes ($GABA_A$) (Shank et al., 2000; Ormrod and McClellan, 2001). Topiramate is tolerated well in children and adolescents with epilepsy (Glauser, 1998) and is indicated for adjunctive treatment of epilepsy in children 2 years of age and older as well as for prevention of migraine headaches in adults (Ferraro and Di Trapani, 2008). Harden et al. in a retrospective study in fifteen patients showed that topiramate may be beneficial for treating secondary symptoms of PDD (Hardan et al., 2004). However, they mentioned that prospective open label studies or double-blind, placebo-controlled studies are needed to assess its efficacy and safety.

We assessed the effects of topiramate plus risperidone in the treatment of autistic disorder in particular for irritability symptoms. From a scientific viewpoint, the therapeutic effects of topiramate without an additional neuroleptic drug would be more interesting. However, since atypical antipsychotics are relatively effective in the treatment of autism, our ethics committees would not approve a study with topiramate as the only drug for autistic patients. To the best of our knowledge, this study is the first double-blind and placebo-controlled clinical trial assessing the adjunctive role of topiramate in the management of autism.

2. Methods

This was a 8-week, parallel group, placebo-controlled trial undertaken in the children's outpatient clinic of Hafez Hospital, Shiraz University of Medical Sciences, Shiraz, Iran during April 2008–January 2010.

2.1. Participants

Children were considered for participation in the project if they were between 3 and 12 years of age and met DSM IV-TR criteria for diagnosis of autism. Criteria for the diagnosis of autism as defined by the Diagnostic and Statistical Manual of the American Psychiatric Association were assessed for each child in order to provide documentation of the diagnosis before study entry (American Psychiatric Association, 2000). The participants were outpatients from a specialty clinic for children at Hafez Hospital. Patients were referred by pediatricians, family physicians and parents from different parts of Shiraz. Patients presented with a chief complaint of severely disruptive symptoms related to autistic disorder. The diagnosis of autism was confirmed by a child psychiatrist (A. Ghanizadeh) based on the behavioral observation of the child and semistructured interview with the parent. A score of ≥ 6 on the DSM IV-TR diagnosis criteria for autism, an Aberrant Behavior Checklist-Community (ABC-C) Irritability subscale score of 12 or higher at screening and baseline and clinical judgment was used. In addition, diagnosis was corroborated by the Autism Diagnostic Interview-Revised, which was administered by an experienced child psychiatrist (Lord et al., 1994). Children with concomitant schizophrenia, psychotic disorders and epilepsy were excluded. Children were also excluded if they had a history of drug or alcohol abuse or tardive dyskinesia. Children were excluded if they had previously received neuroleptics or any psychotropic drug treatment 6 months prior to recruitment or had significant active medical problem. Children with severe or profound mental retardation in whom a definitive diagnosis of autism could not be made were excluded. The protocol was approved by the Institutional Review Board (IRB) of Tehran University of Medical Sciences (Grant no: 6550). The trial was performed in accordance with the Declaration of Helsinki and subsequent revisions and approved by the ethics committee at Tehran University of Medical Sciences. Written informed consents were obtained from the parents of patients before entering into the study. This trial is registered with the Iranian Clinical Trials Registry (IRCT138901141556N9).

2.2. Study design

Forty patients were randomly assigned to two groups of equal size of either topiramate + risperidone or placebo + risperidone for an 8-week, double-blind, placebo-controlled study. The dose of risperidone was titrated up to 2 mg/day (0.5 mg starting dose with subsequent dose increase in 0.5 mg increments in the weekly dosage for the first 3 weeks) for children between 10 and 40 kg and 3 mg/day for children weighting above 40 kg. The dose of topiramate was titrated up to 200 mg/day over 5 days depending on age and weight (100 mg/day for <30 kg or ages 3–6; 200 mg/day for >30 kg or ages 7–12). Placebo was identical in appearance (shape, size, color, and taste) and was dispensed by the investigational drug pharmacist. The patients did not receive any psychosocial therapies during the trial.

2.3. Outcome

The outcome measure was the ABC-C which has five subscales (Aman et al., 1985). ABC-C is an empirically-derived psychometric instrument designed to rate the presence and severity of maladaptive behaviors within the population with learning disabilities, based on an earlier version of the ABC. The checklist was developed from problem behaviors known to occur with some frequency in moderate to severe learning disabled individuals (Irritability, Lethargy/Social Withdrawal, Stereotypic Behavior, Hyperactivity/Noncompliance and Inappropriate Speech). The ABC-C rating scale has been used in several studies in Iranian populations (Akhondzadeh et al., 2004, 2008, 2010). The rater followed standardized instructions when using ABC-C rating scale. The mean decrease in the ABC-C irritability subscale score from baseline was used as the main outcome measure for response to autism treatment. Extrapyramidal symptoms were assessed using the Extrapyramidal Symptoms Rating Scale (ESRS) (Chouinard et al., 1980). Patients were randomized to receive topiramate or placebo in a 1:1 ratio using a computer-generated code. The assignments were kept in sealed, opaque envelopes until data analysis. Each child was rated at baseline and at weeks 2, 4, 6 and 8 (endpoint) by ABC-C rating scale. Throughout the study, the person who administered the medications, the rater and the patients were blind to assignments. Patients were assessed by a trainee psychiatry resident (V. R.) with input from the patients' parents (behavior was rated by V. R. and their parents every 2 weeks). V. R. was trained by a child psychiatrist in the use of the translated versions of ABC-C rating scales.

2.4. Side effects

Side effects were systematically recorded throughout the study and were assessed using a checklist administered by a resident of psychiatry during weeks 1, 2, 4, 6 and 8. This was done through questioning. The behavior ratings and the side effects were performed by independent raters.

2.5. Statistical analysis

Results are presented as mean ± SD differences and were considered significant at $P \leq 0.05$. A two-way repeated measures analysis of variance was used. The two groups were considered as a between subjects factor (group) and the five measurements during treatment were considered as a within-subjects factor (time) in the analyses. To compare the baseline data, differences in the frequency of side effects and frequency of extrapyramidal symptoms with the two