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Original Article

Topiramate for Tourette's Syndrome in Children: A Meta-Analysis

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ABSTRACT

OBJECTIVES: To assess the efficacy and safety of topiramate for children with Tourette syndrome. **METHODS:** Randomized controlled trials evaluating topiramate for children with Tourette syndrome were identified from the Cochrane library, PubMed, Cochrane Central, Embase, CBM, CNKI, VIP, WANG FANG database, and relevant reference lists. Two reviewers independently selected trials, assessed trial quality, and extracted the data. Disagreement was resolved by discussion. Quality assessment referred to the Cochrane Handbook for Systematic Reviews of Interventions (version 5.0.1.). **RESULTS:** Fourteen trials involving 1003 patients were included, of which 720 cases were male (71.8%). Ages were 2 to 17 years old. The general quality of included randomized controlled trials was poor. All trials were positive drug–controlled (12 randomized controlled trials used haloperidol as control, 2 used tiapride). The follow-up period was from 20 days to 12 months. Meta-analysis of 3 trials (n = 207), in which tics symptoms control was assessed by Yale Global Tic Severity Scale, suggested that there was significant difference in the mean change of Yale Global Tic Severity Scale score during the treatment period (mean difference = −7.74, 95% CI [−10.49, −4.99], $I^2 = 0$) between topiramate and control groups. Meta-analysis of 9 trials (n = 668) evaluating tics symptoms control ≥50% suggested that there was no significant difference in reduction of tics between topiramate and control group during the treatment period (relative ratio = 1.36, 95% CI [0.90, 2.06], $I^2 = 0$). Adverse events were reported in 13 trials. Drowsiness (3.3-16%), loss of appetite (4-16.7%), cognitive dysfunction (7.89-12.5%), and weight loss (6-10.5%) were common adverse events. **CONCLUSIONS:** The current evidence is promising but not yet sufficient to support the routine use of topiramate for Tourette syndrome in children due to low quality of the study designs. It deserves to confirm in further high-quality, placebo-controlled trials.

Introduction

Tourette syndrome (TS) is a common childhood-onset neuropsychiatric disorder, characterized by multiple motor and phonic tics[1] and associated with extensive behavioral disorders (e.g., attention deficit, obsessive-compulsive disorder, emotional problems).[2] The worldwide incidence is between 5.5 and 7.6 per 10,000.[3] A recent epidemiological study showed that TS may affect approximately 1% of pediatric population.[4] At present, the most commonly prescribed drugs are typical antipsychotics (e.g., haloperidol), benzamides (e.g., sulpiride, tiapride), and atypical antipsychotics (e.g., risperidone) for patients with TS. However, the use of these agents is limited by the frequent occurrence of adverse events (AEs). The most common AEs are tardive dyskinesia, weight gain, drowsiness, extrapyramidal reactions, and electrocardiographic alterations.

Topiramate is a novel broad-spectrum antiepileptic medication commonly used for a variety of seizures in pediatric population with good tolerance. The exact mechanism of action of topiramate is unknown, but the drug may enhance the activity of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), thereby

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increasing GABA-mediated neural inhibition. Topiramate also blocks the α-amino-3-hydroxyl-5-methylisoxazole-4-proprionic acid (AMPA)/kainate subtype of glutamate receptors without affecting the N-methyl-D-aspartate subtype.[5] These mechanisms of action might produce beneficial effects in patients with TS. In 2001, topiramate in the treatment of TS was first reported.[6] Recently, some clinical trials evaluating the safety and efficacy of topiramate for patients with TS have been published.[5,7] In 2010, A retrospective chart review of 41 patients treated with topiramate for tics for 9.43 ± 7.03 months suggested that topiramate can be used for tics in TS.[7] A multicenter randomized controlled trial (RCT) reported that topiramate had statistically significant improvements in suppressing tics.[5] In clinical practice, topiramate is one of alternative prescriptions for patients with TS. Consequently, we plan to conduct a systematic review of the literature to determine whether there are clear evidence of efficacy and safety of topiramate for TS.

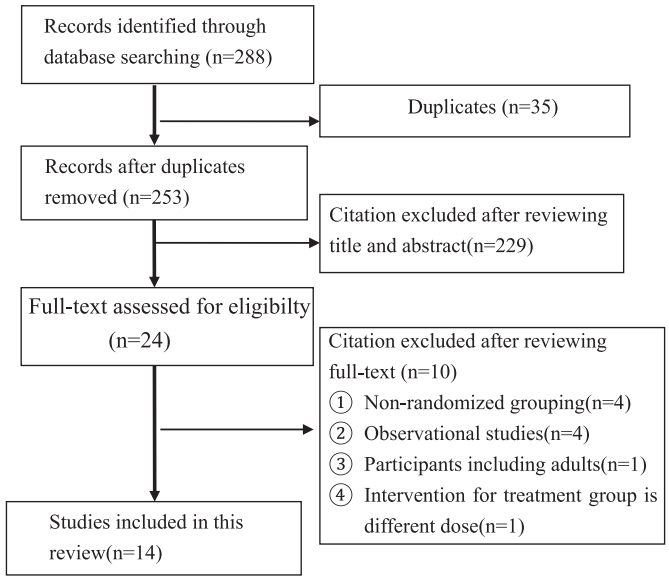

Figure 1. Flow chart of literature screening and selection process.

Materials and Methods

Inclusion and exclusion criteria

Types of studies

We included all RCTs comparing topiramate with placebo or other drugs used in the treatment of children with TS. We excluded trials if participants included children and adults or if different dosages of drugs were used.

Types of participants

Patients with a clinical diagnosis of TS were included. The widely used definitions of TS were as follows: (1) DSM-IV (Diagnostic and Statistical Manual of Mental Disorders-IV),[8] (2) ICD-10 (International Code of Diseases-10),[9] or (3) CCMD (Chinese Classification and Diagnostic Criteria of Mental Disorders).[10] Participants ≤18 years were excluded.

Types of interventions

All RCTs that examined topiramate used alone or as an add on to any approved treatments for TS were included. Comparisons included: (1) topiramate vs placebo only; (2) topiramate plus approved treatments vs placebo plus approved treatments; and (3) topiramate vs approved treatments (e.g., haloperidol, tiapride).

Types of outcome measurements

Primary outcomes. The outcomes were measured by following scales or methods: (1) Yale Global Tic Severity Scale, (2) Clinical Global Impression Scale, (3) Tourette Syndrome Global Scale, (4) Tourette Syndrome Symptom List, (5) Clinical Global Impression Tic Severity Scale, or (6) Tourette Syndrome Severity Scale or other scales.

Secondary outcomes. The secondary outcomes included tics symptom improvement assessed by author self-defined and AEs measured by following scales or methods: (1) Clinical Global Impressions Scale, Adverse Events, (2) Abnormal Involuntary Movement Scale, (3) Extrapyramidal Symptom Rating Scale, (4) weight gain, (5) electrocardiogram abnormalities or changes, or (6) other reported AEs.

Search strategy

We searched The Cochrane Library (2012, issue 11), PubMed (1966-2012.11), EMBASE (1974-2012, issue 11), Cochrane Controlled Trials databases (CENTRAL 11, 2012), Chinese Biomedical Literature Database (CBM, 1978-2012.11), China National Knowledge Infrastructure (CNKI, 1980-2012 .11), Chinese Science and Technique Journals Database (VIP, 1989-2012.11), and Wanfang Data (http://www.wanfangdata.com/) (1990-2012.11). The bibliographies of relevant articles were screened. The "topiramate," "Topamax," "Tourette syndrome," "tic disorders," and "tics" were used for searching relevant data. The search was restricted to human studies.

Selection of studies and data extraction

Two reviewers independently screened the titles and abstracts of every record. The full articles were obtained when the information given in the title or abstracts conformed to the selection criteria outlined previously. Two reviewers independently performed data extraction. The data extraction form included general characteristics of studies, general characteristics of patients, diagnostic criteria, sample size, comparisons, outcome measurements, and adverse events.

Quality assessment

Two reviewers independently evaluated the methodological quality of the included studies using the "risk of bias tool" under the domains of 6 aspects, including sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome, or other biases. The methodological criteria referred to the Cochrane Handbook for Systematic Reviews of Interventions, version 5.0.1.[11]

Statistical methods

We planed to express results for dichotomous outcomes as risk ratios (RR) with 95% confidence intervals (CI), and express results for continuous outcomes as mean difference (MD) (if the same scale for each trial is available) or standardized mean difference (if different scales are used). We evaluated heterogeneity among included studies using I^2 test. We would consider a value greater than 50% to indicate substantial heterogeneity. We would seek the potential sources of the heterogeneity (clinical heterogeneity and methodological heterogeneity). Regardless of the size of heterogeneity, a random effects model was used for statistical analysis. We conducted the meta-analysis using Cochrane RevMan 5.0 software.

Results

Results of the search

We identified 288 potentially relevant articles, of which 46 articles were English and 242 articles were Chinese. We included 14 RCTs by removing duplicate articles, reviewing the titles or abstracts and full text (Fig 1).