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Sodium valproate for the treatment of Tourette's syndrome in children: A systematic review and meta-analysis

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ABSTRACT

The aims are to evaluate the efficacy and safety of sodium valproate for children with Tourette's syndrome (TS). We searched PubMed, EMBASE, the Cochrane library, Cochrane Central, CBM, CNKI, VIP, WANG FANG database and relevant reference lists. Five RCTs ($N=247$) and five case series ($N=163$) studies were included. Only one RCT (93 patients) evaluated total YGTSS scores and there was significant difference in the reduction of total YGTSS scores between sodium valproate and the control group (3.50 ± 4.59 vs 7.86 ± 7.03, $P<0.01$). One RCT (30 patients) evaluated motor and vocal tics, and there was significant difference in the reduction of motor and vocal tics scores between sodium valproate and haloperidol (10.45 ± 4.15 vs 14.92 ± 3.01, $P<0.01$). Meta-analysis of three RCTs ($N=124$) showed there was no significant difference in the reduction of the number of tics between sodium valproate and the positive control group [Relative Risk (RR)=1.09, 95%CI (0.92, 1.30), $P=0.30$]. The pooled proportion in five case series studies which used tics symptom improvement self-defined by authors was 80.7% (95% CI: 73.7–86.2, $I^2=0$). No fatal side effects were reported. In conclusion, based on the limited evidence, the routine use of sodium valproate for treatment of TS in children is not recommended. Further well-conducted trials that examine long-term outcomes are required.

1. Introduction

Tourette's syndrome (TS) is a neuropsychiatric disorder characterized by multiple motor and vocal tics. The typical age of onset is between four and eight years old and TS is frequently associated with extensive behavioral disorders such as attention deficit disorder, obsessive compulsive disorder and emotional problems (Stern et al., 2005; Roessner et al., 2011). TS occurs in all populations and ethnic groups worldwide and is four times more prevalent in males than in females (Roessner et al., 2011; Robertson et al., 2009). The prevalence of TS in children is estimated at between 0.3% and 1% (Robertson et al., 2009; Scharf et al., 2012).

Currently, pharmacotherapy is the main treatment for motor and vocal tics and comorbidity symptoms (Lie et al., 2009). 82.9% of children with TS received pharmacotherapy in a survey in the US (Woods et al., 2010). Typical neuroleptics such as haloperidol and pimozide were the first drugs proven to be effective in the control of tics and have long since been used in the treatment of TS. However, because of their poor tolerability profile (mainly extrapyramidal and metabolicside effects), these agents are not recommended as a first line treatment and are only used in selected patients (Cavanna and Seri, 2013; Waldon et al., 2013). Benzamides such as sulpiride and tiapride are commonly used in Europe. Compared with typical neuroleptics they appear to have fewer or no extrapyramidal side effects but weight gain and sedation can occur and therefore their administration must be monitored (Roessner et al., 2011). In comparison with typical neuroleptics, the atypical antipsychotics such as risperidone and aripiprazole are better tolerated and have similar efficacy for tic control, but similarly weight gain and sedation have been reported as common side effects (Waldon et al., 2013; Roessner et al., 2013). Alpha-2 adrenergic agonists such as clonidine and guanfacine are used more commonly in Anglo-American countries as a first line treatment for mild to moderate tics, but their efficacy in treating patients with pure tic disorder is very low and side effects related to their hypotensive action should be monitored (Cavanna and Seri, 2013; Pringsheim et al., 2012; Weisman et al., 2013; Singer et al., 2012).

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Drugs that enhance gamma-aminobutyric acid (GABA) activity have been shown to statistically significantly improve tic suppression. A multicenter randomized controlled trial (RCT) and a retrospective study reported that topiramate could significantly improve tic suppression (Jankovic et al., 2010; Kuoand Jimenez-Shahed, 2010). However increasing data show that topiramate induces cognitive impairment (attention, memory, and language function) in adults and children (Ijff and Aldenkamp, 2013). Levetiracetam, an anticonvulsant used to treat epilepsy, has also been shown to reduce tics in some open-label TS studies (Awaad et al., 2005; Fernandez-Jaen et al., 2009). However, it did not change the mean total Yale Global Tic Severity Scale (YGTSS) and Clinical Global Impression score in two RCTs (Hedderick et al., 2009; Smith-Hicks et al., 2007). In clinical practice, sodium valproate (a GABA enhancing agent) is one of alternative prescriptions to patients with TS. Positive results from some RCTs and case series studies indicate that sodium valproate may be beneficial for children with TS, especially refractory TS (Wen and Wang, 2012; Zheng et al., 2001; Zhao et al., 1997). Although there is no exact definition of refractory TS (Sassi et al., 2011), it is widely accepted as TS in which clinical symptoms are not relieved after treatment with conventional anti-TS medications (Porta et al., 2011). Sodium valproate is recommended as one of the treatment options for TS in China (The Branch of Pediatric Neurology of Chinese Medical Association, 2013), but other professional organizations do not recommend it. Consequently, we conducted a systematic review to evaluate the efficacy and safety of sodium valproate in treating tics in children with TS.

2. Materials and methods

2.1. Inclusion and exclusion criteria

2.1.1. Types of studies

All types of clinical studies (i.e., RCTs, cohort studies, case control studies, case series studies and case reports) which evaluated sodium valproate in treating tics for children with TS were included. Trials were excluded if (1) the data for children could not be obtained (even though we attempted to contact the original study investigators) or (2) they compared different doses of drugs, i.e. the treatment group used high (or low) doses of sodium valproate and the control group used low (or high) doses.

2.1.2. Types of participants

Patients with a clinical diagnosis of TS were included. The followings were used to define TS: (1) DSM-III (Diagnostic and Statistical manual of Mental disorder), DSM-IV or DSM-IV-TR (Yan, 1981; Freeman et al., 1995; American Psychiatric Association, 2000), (2) ICD-10 (International code of diseases-10) (World Health Organization, 1993), (3) CCMD (Chinese Classification and Diagnostic Criteria of Mental Disorders) (The Branch of Psychiatry of Chinese Medical Association, 2001). The age of participants was under the age of 18 years.

2.1.3. Types of interventions

All studies that administered sodium valproate used either alone or as an add-on to an approved treatment for TS were included. The comparisons were:

1. Sodium valproate vs placebo only.
2. Sodium valproate plus approved treatments vs placebo plus approved treatments.
3. Sodium valproate vs approved treatments (i.e., haloperidol, tiapride).
4. Sodium valproate alone or added to approved treatment.

2.1.4. Types of outcome measurements

2.1.4.1. Primary outcomes. Study investigators and/or caregivers evaluated improvement of individual tics at the end of treatment or follow-up period. We included studies that measured outcomes using one of the following scales or methods: (1) Yale Global Tic Severity Scale (YGTSS) (Leckman et al., 1989); (2) Clinical Global Impression Scale (Walkup et al., 1992); (3) Tourette Syndrome Global Scale (Pringsheim and Marras, 2009); (4) Tourette Syndrome Symptom List (Pringsheim and Marras, 2009); (5) Clinical Global Impression Tic Severity Scale (Leckman et al., 1988); and (6) Tourette Syndrome Severity Scale (Walkup et al., 1992).

2.1.4.2. Secondary outcomes. The secondary outcomes included tic symptom improvement assessed by author self-defined and adverse events (AEs) measured using the following scales or methods: (1) Clinical Global Impressions Scale, Adverse Events (Walkup et al., 1992), (2) Abnormal Involuntary Movement Scale, (3) Extrapyramidal Symptom Rating Scale, (4) Weight gain, (5) electrocardiogram (ECG) abnormalities or changes (Pringsheim and Marras, 2009), and (6) other reported AEs.

2.2. Search strategy

We performed literature searches using: PubMed (1966-2013.11), EMBASE (1974-2013, Issue 11), the Cochrane Library (2013, Issue 11), Cochrane Controlled Trials databases (CENTRAL 11, 2013), Chinese Biomedical Literature Database (CBM, 1978–2013.11), China National Knowledge Infrastructure (CNKI, 1980-2013.11), Chinese Science and Technique Journals Database (VIP, 1989-2013.11), Wanfang Database (http://www.wanfangdata.com/) (1990-2013.11). We also searched the reference lists of relevant articles. The following search terms were used: 'sodium valproate', 'depakine', 'Tourette syndrome', 'tic disorders', and 'tics'. The language of publications was restricted to English or Chinese.

2.3. Selection of studies and data extraction

Two reviewers (Yang and Zhang) independently screened the titles and abstracts of every record. Full articles were obtained when either information given in the title or abstracts conformed to the selection criteria outlined previously, or could not be ascertained due to limited information. To include studies, data were extracted independently by each reviewer and entered into a standardized form. Discrepancies were resolved by consensus.

2.4. Quality assessment

Two reviewers (Yang and Zhang) independently evaluated the methodological quality of identified studies. For RCTs we used the 'risk of bias tool' referred to the Cochrane Handbook for Systematic Reviews of Interventions version 5.0.1 to assess their methodological quality (Higgins and Green, 2008). For cohort studies and case control studies, we used the Newcastle-Ottawa Scale (NOS) to assess their methodological quality (Stang, 2010). For case series studies, quality assessment was based on the checklists developed for assessment of case series by UK national institute for clinical excellence (NICE) (NICE website, 2011)).

2.5. Statistical methods

Results for dichotomous outcomes were expressed as risk ratios (RR) with 95% confidence intervals (CI), and results for continuous outcomes were expressed as mean difference (MD) (if the same scale for each trial was available) or standardized mean difference (SMD) (if different scales were used). We also obtained the pooled proportions for outcomes in case series studies. We evaluated heterogeneity among the included studies using the I^2 test. We considered a value greater than 50% to indicate substantial heterogeneity and sought the potential sources of heterogeneity (clinical heterogeneity and methodological heterogeneity). Regardless of the size of heterogeneity, the random effects model was used for statistical analysis. We conducted the meta-analysis using Cochrane RevMan 5.1 software and Meta Analyst (version 3.13beta; Tufts Medical Center) (Wallace et al., 2009). If we could not combine the results of the studies using meta-analysis (because of significant clinical heterogeneity and unconventional methods used in the analysis of studies), results of each study were presented individually.

3. Results

3.1. Results of the literature search (Fig. 1)

A total of 341 articles were retrieved from searching electronic databases and reference lists. After removing duplicate articles and screening titles, abstracts and full-text, 11 studies were eligible. One study that included children and adults was excluded because we could not obtain data of the children from the investigators of the original study. Thus, a total of ten studies were included in this review.

3.2. The characteristics of included studies (Tables 1 and 2)

We included 10 studies involving 410 participants, of which 50% were RCTs ($n=5$) and 50% were case-series studies ($n=5$). No cohort study or case control studies were identified. Participants were aged between four and 18 years. Sample size ranged from 12 to 93 cases. All studies were conducted in mainland China. Two RCTs (Wu et al., 2010; Zheng et al., 2001) were 'open control',