European Journal of Obstetrics & Gynecology and Reproductive Biology 202 (2016) 26–31

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Review

Reproductive and metabolic abnormalities in women taking valproate for bipolar disorder: a meta-analysis

Lin Zhang [1], Hua Li [1], Shaoping Li, Xiaoyi Zou *

Department of Neurology, West China Hospital, Sichuan University, Sichuan, China

ARTICLE INFO

Article history:
Received 21 September 2015
Received in revised form 7 April 2016
Accepted 23 April 2016

Keywords:
Polycystic ovary syndrome
Valproate
Bipolar disorder
Meta-analysis

ABSTRACT

Objective: We aimed to evaluate the relationship between valproate (VPA) and reproductive endocrine abnormalities in women with bipolar disorder.
Methods: We searched studies in electronic databases of China Biology Medicine disc, PubMed, and Embase. Two authors collected articles and extracted data independently. Meta-analysis was performed for polycystic ovary syndrome (PCOS) and its components. The mean difference (MD) and 95% confidence interval (CI) were used to compare continuous variables. The Mantel–Haenszel formula was used to calculate the odds ratio (OR).
Results: There were statistically significant differences between the VPA treated and non-VPA treated groups in PCOS (OR 6.74; 95% CI 1.66–27.32; $P = 0.00$), menstrual disorder (OR 1.81; 95% CI 1.02–3.23; $P = 0.04$), and hyperandrogenism (HA) (OR 2.02; 95% CI 1.11–3.65; $P = 0.02$). There was no statistically significant difference between the VPA treated and non-VPA treated groups in PCO (OR 1.37; 95% CI 0.71–2.66; $P = 0.35$). The overall risk of menstrual disorders, PCO, and HA in the VPA treated group was higher than in the non-VPA treated group (OR 1.75; 95% CI 1.23–2.47; $P = 0.00$). The levels of total and free testosterone in the VPA treated group were higher than in the non-VPA treated group (MD 0.12; 95% CI 0.05–0.19; $P = 0.00$; MD 0.14, 95% CI 0.07–0.21; $P = 0.00$, respectively).
Conclusions: VPA was associated with the elevated levels of testosterone and HA in women with BD.

Contents

Introduction

Bipolar disorder (BD), as a chronic mental disorder, has three primary recurring episodes: mania, depression, and mixed episodes [1]. Valproate (VPA), a broad-spectrum antiepileptic drug (AED), has been used to treat BD since the 1980s. Polycystic ovary syndrome (PCOS) is a clinical disorder of infrequent ovulation

* Corresponding author at: Department of Neurology, West China Hospital, Sichuan University, Chengdu 610041, China. Tel.: +86 18980602115; fax: +86 028 85553329.
E-mail address: xiaoyizou@163.com (X. Zou).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.ejogrb.2016.04.038
0301-2115/

and hyperandrogenism (HA). The National Institutes of Health (NIH) Conference in 1990 suggested that the "minimal" diagnostic criteria for PCOS is: menstrual irregularities (oligo/anovulation), HA (either clinical or biochemical), and exclusion of other diseases (i.e., other known causes of female HA, such as congenital adrenal hyperplasia androgen-secreting tumors and hyperprolactinemia) [2]. Some studies suggested that menstrual disorders, HA, and ultrasound manifestations of polycystic ovaries (PCO) may be more common in women treated with VPA than in those treated with lithium or other drugs [3–6]. In 1996, Isojarvi et al. [7] first proposed a hypothesis that VPA indirectly induced hyperinsulinemia. VPA induced weight gain and insulin resistance, and consequently hyperinsulinemia, which may lead to HA and PCO. VPA also may directly mediate HA, resulting from changes in chromatin modifications (histone acetylation) that augment transcription of steroidogenic genes [8], although some other studies have no repetitive results [9,10]. A number of studies have evaluated the relationship between PCOS and VPA in women with BD. A meta-analysis of their results has not been made. Our aim was to perform the meta-analysis for a better understanding of this question.

Methods

Literature-search strategy

A literature search was performed without restriction to regions, publication types within the electronic databases of CBM (China Biology Medicine disc) (1978–2015 August 14), Embase (1974–2015 August 14), and MEDLINE (Ovid) (1946–2015 Week 33) using the following search strategy: "Valproic Acid"[Mesh], valproic acid, valproate, divalpro*, valpro*, polycystic ovaries, "Polycystic Ovary Syndrome"[Mesh], polycystic ovary syndrome, menstrual disturbances, reproductive endocrine disorders and reproductive endocrine function or dysfunction, "Bipolar Disorder"[Mesh], bipolar disorder. Detailed search strategy can be obtained from Supplementary materials.

Inclusion and exclusion criteria

The inclusion criteria: (1) published in English and full text could be obtained; (2) patients taking VPA and/or other drugs for bipolar disorder and controls were included; (3) patients were not recruited if they had primary reproductive endocrine disorder (e.g. prior history of PCOS or infertility), contraceptive medication, or antipsychotics, gynecological or endocrine illnesses, pregnancy, and lactation; (4) at least one of the Rotterdam criteria of PCOS was reported. The exclusion criteria were as follows: (1) not writing in English, meeting abstracts or reviews; (2) author(s) did not report VPA group and/or other drug group, respectively; (3) control group or bipolar disorder group were mixed with other illness; (4) data were unavailable after corresponding with the author(s); (5) data were repeated.

Data extraction

Two authors searched and screened the titles, abstracts, and full-text articles independently. The same two reviewers independently extracted relevant information from each eligible study using a standardized form. We first determined whether the authors excluded the patients if their PCOS diagnosis preceded initiation of mood stabilizers, contraceptive medication, or antipsychotics, gynecological or endocrine illnesses, pregnancy, and lactation. For each of the included studies, the first author, date of publication, number of participants, study design, age of patients, number of patients, body mass index (BMI), duration (months), and dose (mg/day) of VPA were recorded if they were presented. According to the diagnosis of PCOS based on the Rotterdam criteria [11], we recorded the definition, the number of patients of menstrual disorders, clinical and/or biochemical signs of HA, and presence of PCO (by ultrasound) if they were presented for each of the included studies. If there was any divergence, it would be resolved through discussion by all authors.

Statistical analysis

All meta-analyses were performed using Review Manager 5.3 (Cochrane Collaboration). The mean difference (MD) and 95% confidence interval (CI) were used to compare continuous variables. The Mantel–Haenszel formula was used to calculate a summary OR. The I^2 was used to examine the between-study heterogeneity. If $I^2 > 50\%$, heterogenicity was unacceptable and the data were analyzed with random-effect model. If $I^2 < 50\%$, heterogenicity was acceptable and the data were analyzed with fixed-effect model. Sensitivity analysis was performed to test the reliability of the results of significant findings in a cyclical way that removed a single different study and repeated the analysis once. If the results did not change significantly before and after removing this study each time, they had a high stability. Publication bias was assessed qualitatively by visual inspection of funnel plots.

Results

Our search initially retrieved 197 reports. Among the 197 citations, 42 were duplications. After reading the titles and abstracts, a total of 12 studies were assessed for eligibility. However, one study did not have the data of VPA [12]. Two articles reported repetitive data [13,14]. One study failed to obtain the full text [15]. Finally, 5 studies were included for this meta-analysis [3–6,9]. Two studies had some of the same authors [6,9], but their subjects were recruited from different clinical centers. Therefore, we considered that they were not repetitive. A flow diagram of the identification and attrition of studies are shown in Fig. 1.

The detailed information of recruited studies is presented in Table 1. Data on population, valproate, other drugs, PCOS, and its components are presented in Table 2. Each study did not fully

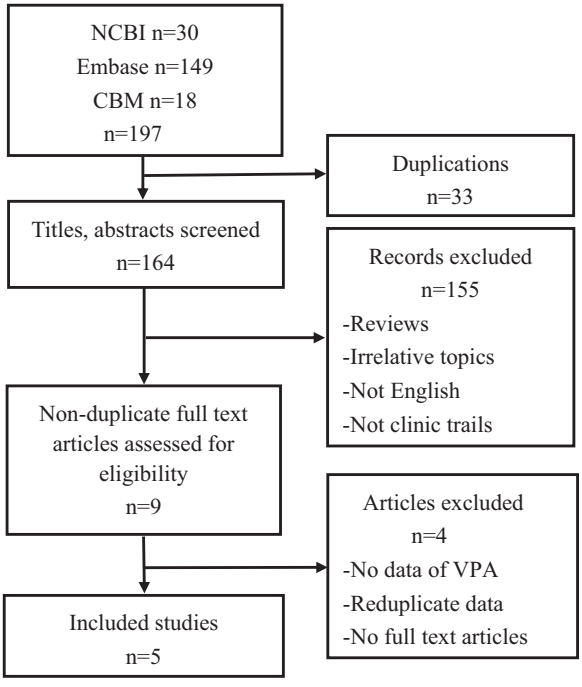

Fig. 1. Flow chart of article selection.