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Review Article

The Application of Salt Valproate in Psychiatry Based on Drug Gender Selection: Narrative Review

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Abstract

"Gender selection" is an important characteristic of drugs and is one of the important principles that doctors must follow when prescribing drugs. As an anti-epileptic drug, valproic acid is a classic mood stabilizer in psychiatry, and its use is widespread in addition to the treatment of bipolar disorder. However, many psychiatrists do not pay enough attention to the sex choice of valproate, for example, when adolescent girls are given too much valproate for a long time, which can cause serious problems, which is also called drug-borne illness. In order to achieve both treatment, and reasonable to avoid side effects is the highest level of treatment, especially when the drug has a gender-selective properties, more attention should be paid.

Keywords: Valproic acid, Psychiatry, Female, PCOS, Teratogenicity

Background

Gender selection refers to the selection of drugs suitable for different sexes based on differences in physiology, metabolism and efficacy between men and women. This choice is based on differences in the following areas [1,2,3].

Biological differences: Differences in organ physiology and body structure between men and women, such as height, weight, hormone secretion, fat distribution, etc., lead to different pharmacokinetic and pharmacodynamic characteristics of drugs, which alter drug efficacy and adverse reactions.

Drug metabolism: The difference of drug metabelism between male and female is mainly due to the difference of CYP450 enzymes in liver and the difference of steroidal hormones. For example, the antiepileptic drug phenytoin premenstrual clearance is faster in women than in women with a slower clearance rate in the kidneys, leading to gender differences in Drug metabelism.

Differences in Adverse Effects: Adverse effects of drugs are different for men and women due to differences in organ physiology and body structure between men and women. For example, some young women taking the antihistamine tifampin on a regular basis may cause arrhythmia and, in severe cases, even accidental death.

Retrieving of Related Articles

Because salt valproate are both central conception and key words, we retrieved related article by valproate as one of key words. But we also retrieved other anticonvulsant (carbamazepine, oxcarbazepine, and lamotrigine) in relative side effects to compared to valproate. Other explanation is that the review limited in psychiatry, especially their usage in treatment of mood disorder. So the retrieve was made as following. The key words conclude valproate, carbamazepine, oxcarbazepine, lamotrigine, PCOS (polycystic ovary syn-

drome), PCO (polycystic ovary), teratogenicity, psychiatry, mood disorder, bipolar disorder. The retrieving relationship was following: [(valproate) or (carbamazepine) or (oxcarbazepine) or (lamotrigine)] and [(PCOS) or (PCO) or (teratogenicity)] and[(psychiatry) or (mood disorder) or (bipolar disorder)].

Side Effect of Salt Valproate on Female

Although valproate is classified as an antiepileptic drug, its application in psychiatry is particularly widespread, especially for the treatment of bipolar disorder, such as manic episodes, mixed episodes, or rapid cycling, which have satisfactory effects. However, a phenomenon must draw our attention, that is, valproate is not prescribed for girls, female adolescents, and women with reproductive functions.

PCOS (polycystic ovary syndrome)

It has been suggested that the higher incidence of PCOS in women with bipolar disorder may have nothing to do with valproate, and that the incidence of PCOS in women with bipolar disorder who are naked is itself higher. Bipolar disorder (BD) is frequently accompanied by endocrine disturbances. A study compared the prevalence of polycystic ovary syndrome (PCOS) and related reproductive disorders between drug-naïve BD patients and matched healthy controls (HCs) and between drug-naïve BD patients and BD patients with long-term medication, as well as the clinical metabolic correlates among BD patients [4].

72 drug-naïve BD patients, 98 HCs, and 72 BD patients with long-term medication were recruited in the study. After controlling for demographic variables, drug-naïve BD patients presented higher rates of PCOS than the HCs (OR: 3.02, 95 % CI: 1.09-8.36). Regression analysis showed that long-term treatment with valproate (OR: 3.89, 95 % CI: 1.13-13.37), age (OR: 0.37, 95 % CI: 0.14-0.95), and insulin resistance index (OR: 1.73, 95 % CI: 1.10-12.71) were correlated with PCOS in BD patients. Drug-naïve BD patients are susceptible to developing PCOS, and valproate is correlated with increased occurrence and development of PCOS. Therefore, PCOS in BD patients, especially those who use valproate, needs to be investigated and monitored closely by medical personnel.

In general, prevenlance of PCOS in women with bipolar disorder was one quarters. To evaluate the comorbidities of polycystic ovary syndrome in patients with bipolar disorder and study the risk factors associated with such comorbidities. Endocrinologists evaluated 200 female patients aged between 15 and 45 who were diagnosed with bipolar disorder, in accordance with the diagnosis in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition. Among 200 patients, 46 (23%) were diagnosed with polycystic ovary syndrome. 45% (n=90) of people reported menstrual disorders, while 27% (n=54) of people had polycystic ovary syndrome on ultrasound examination. 19.2% of patients diagnosed with polycystic ovary syndrome have a history of taking sodium valproate, while 27.90% of patients do not have such a history (P=0.15).

PCOS is a common heterogeneous endocrine disorder characterized by irregular menses, hyperandrogenism, and polycystic ovaries. The prevalence of PCOS varies depending on which criteria are used to make the diagnosis, but is as high as 15%-20% [6]. PCOS is in the criteria of hyperandrogenism and/or hyperandrogenemia, oligoovulation and the PCO criteria is two of the three following fulfilled: appearance of polycystic ovary (PCO) on the ultrasonogram, elevated serum testosterone levels and irregular (oligo-/amenorrhea) menstrual cycles [7]. A meta-analysis was conducted to evaluate the relationship between sodium valproate (VPA) and reproductive endocrine abnormalities in women with bipolar disorder [8]. There were statistically significant differences between the VPA treatment group and the non VPA treatment group in terms of PCOS (OR 6.74; 95% CI 1.66-27.32; P=0.00), menstrual disorders (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). In PCO, there was no statistically significant difference between the VPA treatment group and the untreated group (OR 1.37; 95% CI 0.71-2.66; P=0.35). The overall risk of menstrual disorders, PCO, and HA in the VPA treatment group was higher than that in the non VPA treatment group (OR 1.75; 95% CI 1.23-2.47; P=0.00). The total testosterone and free testosterone levels in the VPA treatment group were higher than those in the untreated 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). See Figure1

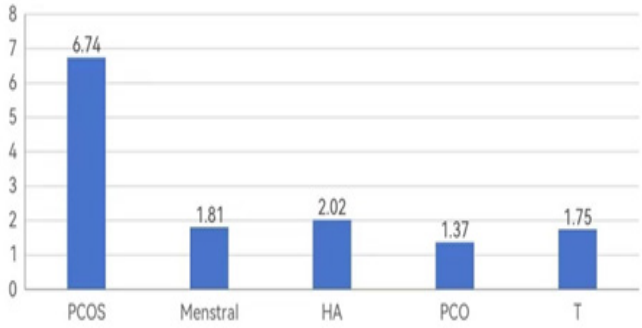

Figure1: OR of Valproate in inducing PCOS and related clinical problem (drug/Naive drug). The figure are regenerated from Zhang's data.

PCOS: polycystic ovary syndrome, Menstrual: Irregular menstrual; HA: hyperandrogenism, PCO: polycystic ovary, T: testosterone

In clinical practices, it's possible that different anticonvuldants have different side effects on PCOS and related disorder [9]. Twenty studies with a total of 1,524 patients were included in a single-arm analysis, which showed a combined effect

size (95% CI) of 0.21 (0.15-0.28) for PCOS in patients taking anticonvulsant mood stabilizers. The meta-analysis included 9 controlled studies, including 500 patients taking medication and 457 healthy controls. The results showed that women taking anticonvulsant mood stabilizers had an OR of 3.23 and a 95% CI of 2.19-4.76 for PCOS. The network meta-analysis included 16 studies with a total of 1416 patients, involving four drugs: sodium valproate (VPA), carbamazepine (CBZ), oxcarbazepine (OXC), and lamotrigine (LTG). The results of the network meta-analysis showed that, VPA (OR=6.86, 95%CI=2.92-24.07), CBZ (OR=3.28, 95%CI=0.99-12.64), OXC (OR=4.30, 95%CI=4.40-49.49) The cumulative probability ranking of LTG (OR=1.99, 95% CI=0.16-10.30) is VPA (90.1%), C (63.9%), CBZ (50.1%), and LTG (44.0%). They believe that the incidence rate of PCOS in female patients receiving anti convulsive mood stabilizer treatment is higher than that in healthy people, and VPA is the most likely to cause PCOS. When considering PCOS factors, the most recommended medication is LTG. See Figure 2.

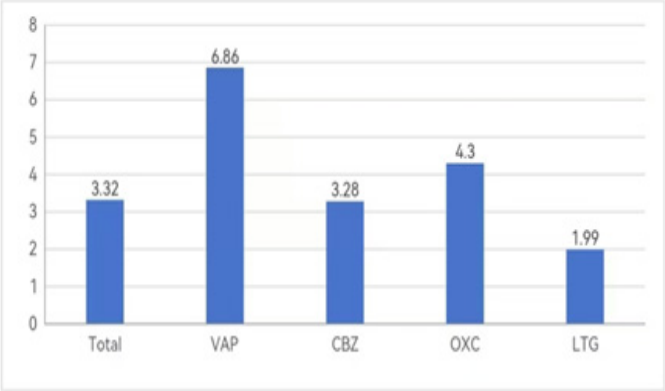

Figure2: OR of PCOS prevalence compared to different anticonvulsant mood stabilizers (drug/Naive drug). The figure are regenerated from Guo's data.

VAP: Valproate; CBZ: Carbamazepine; OXC: Oxcarbazepine; LTM: Lamotrigine

In addition, there are two valuable things to share with everyone. First is that rate of PCOS increased markedly in female patients with epilepsy who chose valproate (VPA), to 1.95 times higher than that of other drugs [1], which reflect the effect size of VAP on PCOS in patients with epilepsy. Seconomy is that 28% of subjects had either a previous bipolar diagnosis or met MDQ threshold criteria for bipolar screen positivity. 97% of previously diagnosed or MDQ screen-positive subjects had no valproate exposure before PCOS diagnosis [10]. These preliminary findings suggest a higher rate of bipolar screen positivity among women with PCOS than is expected in the general population, independent of an association with valproate. This observed link between PCOS and bipolar screen-positivity is consistent with a possible shared hypothalamic-pituitary-gonadal axis abnormality.

Reproductive Toxicity

In fact, valproic acid also affects male reproduction [11], but we will only discuss the effects of valproic acid on the oosperm and embryonic development, and it is not inappropriate to call it "gender selection".

However, in pregnancy, it seems to be the most teratogenic antiepileptic drug. Among the proven effects are congenital malformations in about 10% The more common congenital malformations are neural tube defects, cardiac abnormalities, and urogenital system malformations, including hypospadias, skeletal malformations, and facial and oral fissures. These effects are dose-dependent; The teratogenic potential of daily doses below 600mg is limited. When added to other antiepileptic drugs, VPA increases the deformity rate. VPA increases the incidence of neurodevelopmental problems, leading to cognitive decline and language disorders. It also increases the prevalence of specific neurodevelopmental syndromes such as autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD). VPA has several teratogenic mechanisms, but the most important mechanism seems to be its impact on folate, SAMe, and histone metabolism, thereby affecting DNA methylation [12].

A study asked 108 individuals (from 90 families) who developed complications due to exposure to sodium valproate in the uterus and were also parents themselves (85 females and 23 males) whether their children had deformities and neurodevelopmental disorders. Among their 187 children, they reported 43 (23%) children with deformities (26 with hand or foot deformities; 15 with facial deformities; 10 with kidney/urinary system deformities; 6 with spina bifida; 4 with heart deformities; 2 with craniosynostosis; 2 with cleft lip and palate) and 82 (44%) children with neurodevelopmental disorders (63 with behavioral problems and autism; 41 with psychomotor disorders; 16 with language problems; 16 with attention deficit; 5 with intellectual disability). Only 88 children (47%) had neither deformities nor developmental disorders [13]. Individual risks of exposure to valproate in the uterus must be communicated so that they can consider fertility options, prenatal diagnosis, and adequate early monitoring.

The "sodium valproate syndrome" of intrauterine growth retardation is also a symptom of infants being exposed to sodium valproate during pregnancy. Prospective and retrospective studies have demonstrated this. In addition, the incidence of developmental problems is significantly increased in children with sodium valproate syndrome, manifested as decreased speech intelligence and often accompanied by communication problems with autism spectrum disorder (ASD). Exposure during pregnancy is associated with an approximately threefold increase in the rate of major abnormalities, primarily spina bifida, with few cases of anencephaly (NTD), heart, craniofacial, skeletal, and limb defects, as well as a range of possible malformation features

The difficulties in sensory processing commonly occur in ASD. Sensory abnormalities include heightened or reduced sensitivity to pain. The findings suggest that prenatal VPA treatment causes allodynia and that spinal microglia contribute to the increased nociceptive responses [15].

Conclusion

In neurology, valproic acid is called an antiepileptic drug, in psychiatry, valproic acid is called a mood stabilizer, and in obstetrics, valproic acid is called teratogenic.

When using valproic acid in psychiatry, it should be avoided to give it to women, especially girls, adolescent women, and women with reproductive functions, because valproic acid can trigger the risk of PCOS and its related endocrine disorders, and may also lead to miscarriage or infertility. Lamotrigine can be chosen; the side effects of lamotrigine are much smaller [8,9].

When a fertile woman is treated with a mood stabilizer, valproic acid should not be prescribed, because valproic acid has a significant teratogenic effect, and lamotrigine can be selected. Because the teratogenic effect of lamotrigine is much smaller than that of valproic acid [16].

when valproate cannot be avoided in pregnancy, the lowest possible effective dose should be prescribed in 2-3 divided doses, preferably as monotherapy. Women exposed to valproate in pregnancy should be given periconceptional folic acid and followed up in a high risk pregnancy clinic. Appropriate ultrasonographic and other examinations, focusing on the possible different anomalies described with this agent, should be carried out. The specific inhibition by VPA of histone deacetylase and changes in gene expression may explain the teratogenicity of this drug [14].

Declaration

Ethics approval and consent to participate
N/A

Consent to publication
All authors agree to publish the manuscript.

Availability of data and material.
N/A

Competing interests
There were not any financial and non-financial competing interests.

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Author's contribution
Our authors have different contributions to this article and study.Dr.Chen Zhehao and Dr Letian Di participated in collection of references and write draft.Dr.Jin WD participated in references review work.Prof.SFL and Prof.JWD participated in design and final review of article.

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