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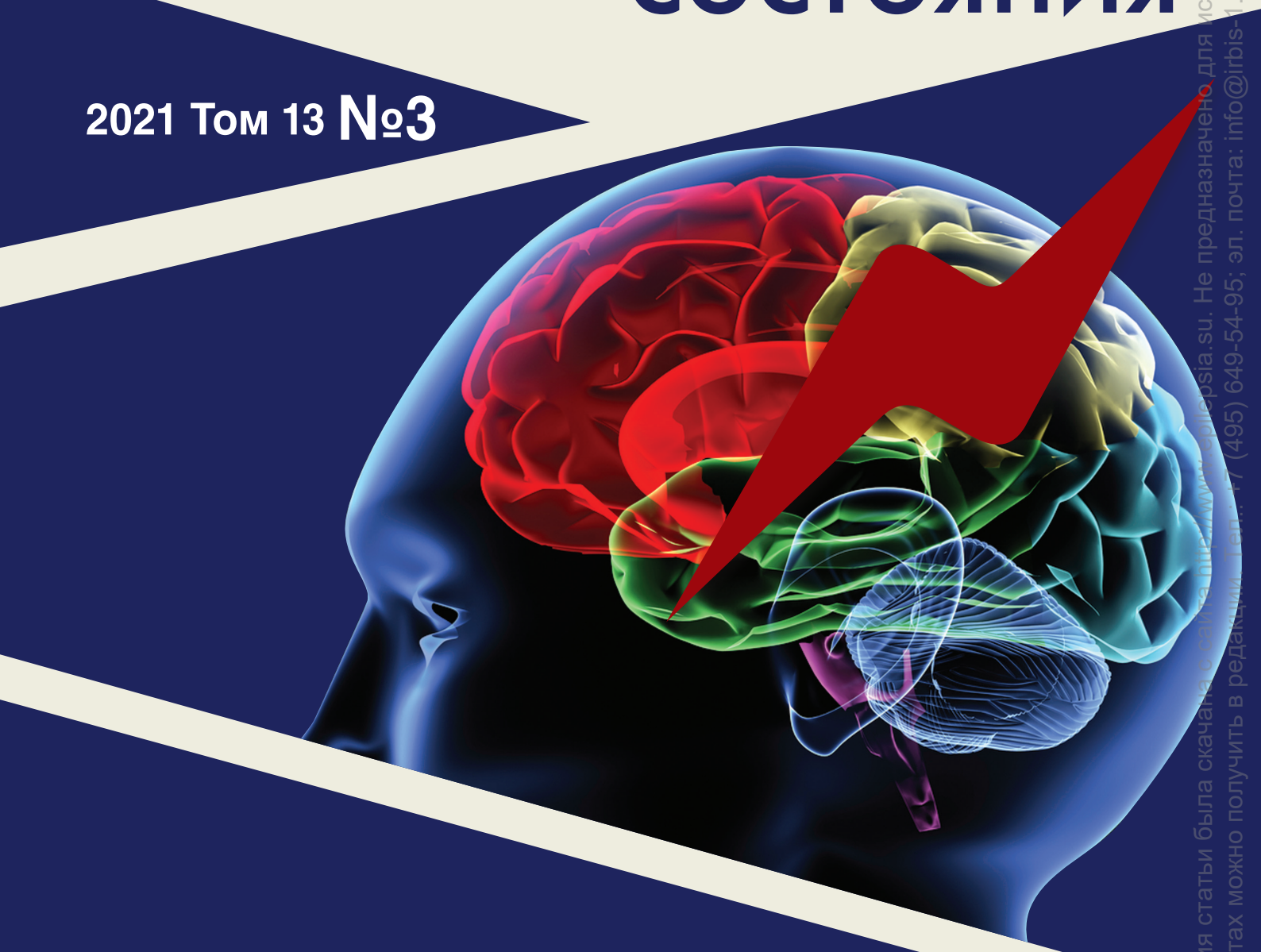

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Regulatory restrictions on the use of valproate in girls and women of childbearing potential: status update

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SUMMARY

In 2019, some restrictions for use of valproic acid in women with reproductive potential by regulatory authorities and the original drug manufacturer based on the results of studies in real clinical practice were introduced. During 2019–2021, there were a further clinical data accumulation and labeling changes. The review presents a critical analysis of the changes in prescribing information and product label. There is a long lead time from the moment when safety data become known to the moment when changes are made to the medicinal product label and patient brochures. Some of the changes, including the need for high doses of folic acid to prevent neural tube defects, are debatable. Repealing the provision for mandatory archiving of informed consent forms for valproic acid use in girls and women raises legal risks. Improvements in pregnancy prevention programs and further research on the safety of valproic acid in real-world clinical settings are needed.

KEYWORDS

Epilepsy, pregnancy, teratogenicity, serious birth defects, attention deficit and hyperactivity disorder, ADHD, autism, autism spectrum disorders, ASDs, valproic acid, valproate, hearing impairment, hearing loss, male fertility disorders, pregnancy prevention program.

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Conflict of interests

The authors declare no conflict of interest regarding this publication.

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Регуляторные ограничения использования вальпроевой кислоты у девочек и женщин с репродуктивным потенциалом: новые сведения

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РЕЗЮМЕ

В 2019 г. были введены основанные на результатах исследований в реальной клинической практике ограничительные действия со стороны регуляторных органов и производителя оригинального препарата в отношении применения вальпроевой кислоты у женщин с репродуктивным потенциалом. В течение 2019–2021 гг. происходило дальнейшее накопление данных и в инструкции по медицинскому применению периодически вносились изменения. В обзоре представлен их критический анализ. Отмечено, что проходит долгое время от момента, когда данные о безопасности становятся известны, до момента внесения изменений в инструкции по медицинскому применению и брошюры для пациентов. Часть изменений, включая необходимость применения высоких доз фолиевой кислоты для предупреждения дефектов нервной трубки, являются дискутабельными. Отмена положения об обязательном хранении форм информированного согласия на использование вальпроевой кислоты у девочек и женщин повышает юридические риски. Необходимо совершенствование программ предупреждения беременности и дальнейшие исследования безопасности вальпроевой кислоты в условиях реальной клинической практики.

КЛЮЧЕВЫЕ СЛОВА

Эпилепсия, беременность, тератогенность, серьезные врожденные пороки развития, синдром дефицита внимания с гиперактивностью, СДВГ, аутизм, расстройства аутистического спектра, РАС, вальпроевая кислота, вальпроат, нарушения слуха, нарушения фертильности у мужчин, программа предупреждения беременности.

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INTRODUCTION / ВВЕДЕНИЕ

It is a general medical advice that valproic acid can be prescribed if other antiepileptic drugs are ineffective and/or poorly tolerated [1, 2]. In real-world evidence studies related to children born to mothers using valproic acid during pregnancy, it has been proven an increased risk of neural tube defects, as well as an increased risk of impaired cognitive functions, of development of attention deficit hyperactivity disorder (ADHD), of autism and autism spectrum disorders [3–8]. Based on this, in 2018–2019, worldwide regulatory authorities have imposed restrictions on the use of valproic acid in women of childbearing potential [9–13]. Changes have been made to the instructions for the medical use of drugs containing valproic acid. A pregnancy prevention program has also been proposed for women taken valproic acid, including a physician's guide, a patient information brochure, and an informed consent form to be completed and signed where the patient (or her caregiver) confirms that she is aware of the risks of assuming the drug.

In particular, in Russia, under the auspices of the Russian League Against Epilepsy (RLAE) and the Institute for Preventive and Social Medicine, the PREVENT program was implemented, developed on similar programs in Western Europe, as well as documents were provided by the Department of State Regulation of the Circulation of Medicines of the Ministry of Health of Russia, Federal State Budgetary Institution Scientific Center for the Expertise of Funds Medical Use of the Ministry of Health of Russia and by the manufacturer of the original preparation of valproic acid Depakine® (Sanofi, France) [14].

In 2019–2021 new information was introduced in the Instructions for medical use of the original drug [15–17]. The letter from Sanofi (France) was distributed to healthcare professionals, in which the manufacturer informs about the update of the brochure for healthcare professionals and patients on the use of valproic acid [18].

In this regard, it seems wise to make a brief overview of these changes and additions, as well as to familiarize epileptologists, neurologists, obstetricians-gynecologists and doctors of other specialties, all those involved in the management of women in reproductive age using valproate and of children born to mothers which used valproic acid during pregnancy.

CHANGES IN THE INSTRUCTION FOR MEDICAL USE / ИЗМЕНЕНИЯ В ИНСТРУКЦИИ ПО МЕДИЦИНСКОМУ ПРИМЕНЕНИЮ

Although in the Cover Letter to healthcare professionals [18], the manufacturing company refers to the update of the Instructions for the Medical Use of valproic acid preparations Depakine® Chronosphere and Depakine® Chrono, approved by the Ministry of Health of the Russian Federation on July 5, 2021, but there is no any information on whether the Patient Brochures have been previously updated to comply with these changes.

The product labels for both extended-release forms of the original valproic acid products placed on the official website of the State Register of Medicines contain four Amendments each with different dates of changes.

In Amendment No. 1 (August 28, 2019), in the section "Pharmacological properties" of Depakine® Chronosphera Instruction for the Medical Use it was added the information about features pharmacokinetics of the drug during pregnancy: valproic acid crosses the placental barrier. Several publications have assessed the concentration of valproate in the umbilical cord of newborns after birth. The serum concentration of valproate in the umbilical cord, reflecting the concentration of valproate in the fetal blood, was the same or slightly higher than in the blood of the mother. The information that valproic acid crosses the placental barrier in animals and humans was also added to the section "Use during pregnancy and during breastfeeding" [19]. In addition, the section "Teratogenicity and congenital malformations" has been significantly expanded. It was updated with information that the available data support an increase in the incidence of malformations. The most common malformations include neural tube defects, facial dysmorphism, cleft palate, craniostenosis, heart, kidneys, and genitourinary system malformations, limb defects (including bilateral radius aplasia and multiple abnormalities of various systems). Finally, crucial information was added: "If taken during pregnancy, valproic

acid can also lead to fetal hearing impairment or loss due to malformations of the ears and/or nose (secondary effect) and/or direct toxic effects on the hearing organs" [19]. Although indications of frequent (≥1/100 and <1/10) hearing disorders and labyrinth disorders in offspring's of patients using valproic acid were given in earlier versions of the Instruction [15], details about intrauterine exposure were given only in this Amendment of the Instruction.

In Amendment No. 2 (June 30, 2020), information on hearing impairment was expanded again with the addition of many details and recommendations: it is indicated that cases of development of unilateral and bilateral deafness or hearing impairment have been reported [20]. Outcomes are not known for all cases. The status of most cases with a known outcome is no recovery. Monitoring for signs of symptoms associated with ototoxicity is recommended. Also, while the previous version reported limited data on the greater likelihood of developing ADHD in children exposed to intrauterine exposure to valproic acid, the June 30, 2020 version clarifies that, based on data from a study using Danish patient registries, such children are approximately 1.5 times more likely to develop ADHD compared to the population of patients who have not been exposed to valproic acid [20].

Previously, the Instruction for Medical Use indicated the reversibility of fertility disorders in men after stopping treatment with valproic acid, then in Amendment No. 3 (June 4, 2021), additions were made with following sentence: "In most of those few cases (but not in all cases) when valproic acid was replaced by another antiepileptic drug or withdrawn, or the daily dose was reduced, reversibility of the decreased male fertility has been observed; successful conceptions were also reported" [21]. This sentence seems a little confusing, and also refers to the well-known fact: "For a pessimist, the glass is half empty, for an optimist, it is half full." It seems therefore justified to conclude: if earlier the Instruction for Medical Use stated that fertility disorders in men using valproic acid are reversible, then the new version claims that they are irreversible in some cases. This could lead to a debate among healthcare professionals and regulators about the need for restrictions on the use of valproate in men of reproductive age, similarly for women.

In Amendment No. 4 (July 5, 2021), the section "Pharmacological properties" is supplemented with information about an increase in the clearance of valproic acid in some patients taking estrogen-containing drugs, which can lead to a decrease in its concentration in the blood, as well as lower clearance of valproic acid in newborns and children under 2 months of age than in adults. In children aged 2–10 years, the clearance, on the contrary, is 50% higher than in children over 10 years of age and adults [22]. Also, in this Amendment, the section on the safety profile for children has been expanded. It states that although the safety profile of valproate in children is comparable to that in adults, some adverse reactions are observed only in children, or the degree of their manifestation is more severe compared to the population of adult patients. There is an increased risk of developing severe liver damage in children in the first years of life and young children (especially those under 3 years of age). Young children are also at increased risk of developing pancreatitis. These risks decrease with age. Mental disorders such as aggression, agitation, impaired attention, behavioral disorders, psychomotor hyperactivity, and learning disabilities are mainly observed in children [22]. In addition, in this version of the instructions, information appeared on the need to continue treatment with valproic acid for female children and adolescents, in women in reproductive age, and in pregnant women only under the supervision of a specialist with experience in the treatment of epilepsy and bipolar disorders, with information on the potential of metamizole (Baralgin® (Sanofi, France) Analgin® from different manufacturers, etc.) to reduce the clinical efficacy of valproic acid.

Similar changes were made to Depakine® Chrono Instructions for Medical Use released at different dates: Amendment No. 1 – November 12, 2019, Amendment No. 2 – July 6, 2020, Amendment No. 3 – June 21, 2021, and Amendment No. 4 – July 5, 2021 [23–26]. Interestingly, the same changes were made to the product labels of Depakine® Enteric [17] and Depakine® in the form of a syrup [27], but not in Depakine® in the form of a lyophilisate [28]. This, along with the lack of lyophilisate form availability in pharmacy chains as of September 14, 2021, may indicate that the manufacturer no longer plans to import it into Russia.

These changes in the instructions of the original preparations of valproic acid are absent in the generic drugs that have been in circulation for a long time. Thus, the Instruction of the generic valproic acid Valpravvan® (JSC AVVA-Rus, Russia), registered on July 30, 2021, contains most of the above new informations [29]. In the Instructions for generics of valproic acid of various forms like Convulex® (Bausch Health, USA), on the contrary, new informations on safety and risks are not fully indicated. For example, in the Instructions for the Medical Use of the Convulex® in the form of a solution for intravenous administration, dated September 2, 2021 [30], it is indicated the reversibility of fertility disorders in men after the termination of treatment, which contradicts the Instructions Convulex® in the form of drops dated September 9, 2021 [31], in the form of a syrup dated September 10, 2021 [32], as previously approved versions of the Instructions for Medical Use of their brand-name counterpart (see above). Also in the Instructions of Convulex® in the form of a solution for intravenous administration, dated September 2, 2021 [30], it is stated: "Cases of tinnitus

and hearing loss (reversible and irreversible) were reported, but the connection has not been clarified." This Instruction does not contain information about the possibility of hearing impairment or loss during intrauterine exposure to valproic acid, which does not correspond to the previously approved versions of the Instructions for Medical Use of the original drug (see above). Finally, the Instructions for the Medical Use of Convulex® in the form of prolonged-release film-coated tablets and enteric capsules, which are freely available on the State Register of Medicines website as of September 14, 2021, contain only the changes regarding the registration certificate holders, the manufacturers of the finished dosage form, the descriptions of dosage forms, etc., but nothing in terms of safety, undesirable effects and risks for patients [33, 34]. Considering that at least one of these dosage forms is available to patients in the Apteka.ru [35] and Yandex.Market [36] marketplaces, there is no new information about safety and, in particular, about restrictions on the use of valproic acid in girls and women with reproductive age: this fact in our opinion, can negatively affect patient's safety.

UPDATING BROCHURES ON THE USE OF VALPROIC ACID / ОБНОВЛЕНИЕ БРОШЮР ПО ПРИМЕНЕНИЮ ВАЛЬПРОЕВОЙ КИСЛОТЫ

The information on the risks of using valproic acid preparations prepared in 2019 by the manufacturing company in case of female patients and pregnant women contained three documents:

1) Guide for Healthcare Professionals [37]

2) Patients Brochure "Valproic acid preparation. Contraception and pregnancy: what you need to know" [38].

3) an annually completed informed consent form about risks [39].

Although the cover letter from the originator brand [18] informs about the updated brochures for healthcare professionals and patients, only two documents are available through the download links:

1) Patients Brochure "Valproic acid. Contraception and pregnancy: what you need to know" [40].

2) an annually completed informed consent form about risks [41].

Thus, here we are not considering the changes in the Guide for Healthcare Professionals within the framework of this publication. It may be available for analysis at a later date.

Patient brochures contain stylistic differences, apparently due to the adaptation of foreign materials into Russian. The critical information has increased the emphasis on the role of the doctor: the phrase used in the 2019 brochure "doctor's recommendation" has been replaced by the sentence "doctor's orders". Similarly the recommendation "During the visit to the doctor, you will discuss the informed consent, to ensure that you are well aware of the risks of using valproic acid during pregnancy" [38] is replaced by "At your appointment, your doctor will ask you to discuss the Risk Informed Consent Form to ensure that you are well aware of the risks of using valproic acid during pregnancy and fully comprehend them" [40], i.e., in the 2021 edition, it was demonstrated that the doctor should take the initiative, he /she (and not the patient himself) should make sure that the patient is aware of the risks.

The section "Congenital malformations" added previously missing information about the possibility of hearing impairments up to deafness in offspring when taking valproic acid during pregnancy [40]. It is notably that this information was finally added to the Patients Brochure, albeit very late. After all, the first reports of the development of hearing impairments in children whose mothers used valproic acid during pregnancy appeared in the first decade of the 21st century [42], and the information on these side effects of valproic acid was introduced into the Instruction for Medical Use as early as 2019 [19].

In the section "I am starting treatment with valproic acid" it has been added the information on the need to refer the patient for a consultation with a obstetrician/gynecologist to select the optimal method of contraception [40]. This information was not explicitly available in the 2019 version.

In the section "I am taking valproic acid and planning to have a baby", the previously missing item has been added: "When planning to have a baby, discuss with your doctor the need to take folic acid." Folic acid can reduce the risk of spina bifida and miscarriage early in pregnancy. However, it is unlikely that this can reduce the risk of congenital malformations associated with taking valproic acid" [40]. It should be noted that the Valproic Acid Instruction for Medical Use indicates that, if possible, even before the onset of pregnancy, folic acid should be taken additionally (at a dose of 5 mg/day), since folic acid can reduce the risk of neural tube malformations: however, available data do not confirm its prophylactic action against congenital malformations related to the use of valproic acid [15–17]. However, the 5 mg/day folate dosage appears to be overly high. Clinical guidelines do not consider a folic acid dose of 5 mg/day to be prophylactic for the prevention of neural tube defects. Usually the average recommended dosage is magnitude lower (400 μg/day, or 0.4 mg/day) [43]. Moreover, recent studies have shown that an initially high serum folate concentration (>33.0 ng/ml) is associated with less successful assisted reproductive technologies outcomes, including biochemical and clinical pregnancy and live birth [44–46]. Therefore, we encourage to revise this information in both the patient materials and the valproic acid Prescribing Information.

When prescribing folic acid, women should be monitored for serum folate at the optimal effective level and discontinued as soon as the level reaches the maximum value of the reference range [47].

Key difference in the 2019 and in the 2021 versions of the Informed Consent Form is the cancellation of the obligation to keep it. The 2019 version contains the phrase "A copy of this completed form must be retained/recorded by the specialist" in the part to be filled by the healthcare professional, and in the part to be filled by the patient (or her caregiver) "The specialist must keep/register a copy of this completed form. The prescribing physician is advised to save the electronic version in the patient's file. A copy of the filled and signed form must be retained by the patient" [39], and in the updated version of 2021, the following revision has already been submitted. In the part to be filled in by a healthcare professional: "The informed consent form with risks can be stored by a healthcare professional", and in the part to be filled by the patient (or her caregiver): "The informed consent form with risks can be archived by the healthcare professional. A copy of the form is issued to the patient or her parents/legal representative/caregiver" [41]. Thus, the thesis about the mandatory storage of the signed informed consent forms has been removed, including the recommendation to store them in medical records (card, medical history, file in patient's electronic medical history, etc.) both by healthcare specialist and patient.

From our point of view, this is very reckless, taking into account the recently intensified trend to involve law enforcement agencies in the analysis of existing and imaginary medical errors and the strengthening of the doctor's legal responsibility. Moreover, the sphere of women's health, reproductive medicine, and perinatology are the leading ones in terms of the number of such cases [48, 49]. Therefore, in order to strengthen the legal protection of healthcare professionals, we consider correct to leave in the documents the need of storing completed and signed informed consent forms on the use of valproic acid by females in reproductive age.

CONCLUSION / ЗАКЛЮЧЕНИЕ

Since the increase of contraindications for the use of valproic acid in girls and women in the last 2 years, new data have been accumulated. The key ones are the additions to the Instructions for the Medical Use of drugs containing valproic acid about its capability to cross the placental barrier and the possibility of being associated to hearing impairments both as a result of malformations of the offspring ears and/or nose, and/or as a result of direct toxic effects. There are more data on the likelihood of developing ADHD in children whose mothers used valproic acid. Finally, the product label has been supplemented with information about irreversibility in some cases of fertility disorders in men.

It should be noted that the practice of maintaining regulatory documents leaves room for improvement both for the originator and for manufacturers of generic drugs. Long periods from obtaining evidence in clinical practice to make changes to the Instructions for Medical Use, as well as from the time of making changes to Instructions prior to being included in Patient Brochures can have serious negative consequences.

The proposed changes in the reviewed documents are related to the use of high doses of folic acid to reduce the risk of neural tube malformations, while confirming that there is no real proof of its preventive action against congenital malformations related to valproic acid use, as well as to the abolition of mandatory storage in medical records of the Informed Consent Forms for the use of valproic acid in women of reproductive age can lead to negative consequences and therefore need further consideration and discussion.

The professional community of healthcare professionals should continue to work on further improving the PREVENT program on a multidisciplinary basis, taking into account the accumulated data in the years 2019–2021. Further large-scale real-world studies on the safety of valproic acid in various patient populations are also needed.

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