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Risk Management of Valproate and Other Teratogenic Anticonvulsants in the Era of Proliferating Use

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Valproic acid, carbamazepine and topiramate have well-known teratogenic risk and all 3 rank among the top 10 teratogenic medications with the highest prenatal exposure risk. Importantly, pregnancies exposed to valproic acid are not dominated by patients with epilepsy but rather with less serious conditions such as migraine. In the United States, only a weight loss combination product containing topiramate has a mandatory pregnancy prevention program, a so-called Risk Evaluation and Mitigation Strategy (REMS), while prevention of fetal exposure to all three single ingredient products relies on information in the product labeling and a medication guide provided at dispensing.

REMS have been avoided for antinconvulsants because of concerns about reduced medication access for patients with serious conditions such as epilepsy, hence weighting maternal harm due to uncontrolled disease against adverse pregnancy or infant outcomes. However, the broad and growing spectrum of indications for all three medications, paired with increasingly strict abortion laws that may not allow pregnancy termination if accidental fetal exposure occurs, may require re-assessment of the benefit-risk of REMS. Here we argue that formal quantitative approaches are needed that allow assessments of maternal and infant risk, considering maternal disease, adverse pregnancy outcomes and teratogenic effects on infants, and the overall public health impact of REMS for anticonvulsants. For valproic acid, given its broad use, high risk of fetal exposure, and profound impact on child health, we predict the public health impact of a REMS will be favorable.

ABBREVIATIONS FDA, US Food and Drug Administration; REMS, Risk Evaluation and Mitigation Strategies

KEYWORDS anticonvulsants; drug safety; risk management; teratogenicity; valproate

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Introduction

Regulatory agencies use risk management programs—in the United States, so-called Risk Evaluation and Mitigation Strategies (REMS)—to prevent medication-related harm and to ensure that the benefit-risk of a medication is favorable. REMS might include requirements for blood tests to detect early signs of drug toxicity or mandatory provider or patient training to ensure certain safe use behaviors. Among several anticonvulsants with established teratogenic risk, the only marketed product that has currently a REMS to prevent prenatal exposure in the United States is the combination product topiramate-phentermine (Qsymia, Vivus LLC, Campbell, CA), approved for weight loss. This commentary discusses the need for and obstacles to enhanced risk mitigation involving teratogenic anticonvulsants, especially valproate, in an era of expanding use and increasingly strict abortion restrictions.

Teratogenic Risk of Anticonvulsants

Anticonvulsants are one of the most comprehensively evaluated medication classes in pregnancy, with epilepsy-pregnancy registries that have been ongoing for more than 2 decades[1,2] and a broad array of claims-based studies. Well-accepted evidence places valproate among one of the most potent teratogenic medications with links to spina bifida, cardiac septal defects, oral clefts, and adverse neurodevelopmental outcomes.[3] Among other commonly used anticonvulsants, carbamazepine and topiramate have also accumulated substantial evidence supporting teratogenicity. Although associations are less pronounced when compared with valproate, carbamazepine shows consistent links with major malformations,[3] especially with neural tube defects,[4] while topiramate has been closely linked with oral clefts.[5]

Prenatal Exposure to Anticonvulsants

Prenatal exposure to anticonvulsants, whether intended or unintended, is common. Our recent analysis of women in private insurance places valproate, topiramate, and carbamazepine among the top 10 teratogenic medications with exposure during pregnancy.[6] Notably, although initially approved for epilepsy, valproate, topiramate and carbamazepine have several approved and a multitude of off-label indications outside of

epilepsy that account for the vast majority of users and exposures during pregnancy.[7] This is important because the maternal and fetal risk imposed by uncontrolled epilepsy might justify valproate use during pregnancy in rare circumstances, while its more prevalent use for migraine has undoubtedly a negative benefit-risk. Interestingly, we found the highest risk for pregnancy onset among valproate users with migraine or headache (2.7 pregnancies per 100 user-years), which was double the rates observed among patients with epilepsy.[7] Thus, the indications that account for the most valproate use and that have the least favorable benefit-risk during pregnancy account for the largest proportion of pregnancies exposed to valproic acid.

Considering a 10% risk for major malformations[3] or 10% risk for autism,[8] it would seem intuitive that most women with migraine either did not intend to use valproate during pregnancy or did not know about the teratogenic risk. Supporting data are provided by our analysis of the timing of prenatal care initiation: we found that among pregnancies with teratogenic anticonvulsant exposure, most (>80%) of prescription fills occurred during the first trimester when pregnancy may not have been recognized yet.[9] Furthermore, only 10% had prenatal care initiated before the prescription fill, suggesting that discussions about the benefit-risk of use during pregnancy had not commenced.

Mitigation of Prenatal Exposure Risk to Teratogenic Anticonvulsants

These findings then lead to the question of how prenatal exposure to valproate, but also carbamazepine and topiramate, can be prevented. In the United States, valproate carries a black box warning about its teratogenic risk, while the labelling for carbamazepine and topiramate addresses teratogenicity only in the warning and precaution section. All 3 medications have a requirement for a medication guide with varying messaging regarding use during pregnancy, which must be dispensed by pharmacies. Knowledge assessments following exposure to medication guides have shown limited value and whether and how such knowledge might translate into enhanced safe use behaviors is largely unknown.[10]

For reference, REMS programs for other teratogenic medications include a combination of mandatory provider and/or patient training, pharmacy registration, pregnancy tests, restricted medication quantities or restricted distribution, or written patient consent regarding use of contraception. Although the effectiveness of each individual component is unclear, several implemented REMS programs have demonstrated a reduction in prenatal exposure risk.[11–13]

Considering the magnitude (risk, severity, and certainty) of teratogenicity and the benefit of REMS programs, we must wonder why no REMS programs for pregnancy prevention have been considered for these agents. Some insight is provided by experience with the topiramate-phentermine weight loss product, which was approved with a REMS that required patient education through specialty pharmacies. In its advisory committee briefing document, the US Food and Drug Administration (FDA) noted that although it might be preferable to institute a more restrictive REMS that requires pregnancy testing, this would cause undue burden on patients receiving topiramate for seizure disorders or migraine prophylaxis.[14] In other words, the burden of a REMS, which potentially reduces access to a lifesaving medication that in certain circumstances may even retain a favorable benefit-risk during pregnancy, must be weighed against its benefit in preventing fetal harm. Limiting such a restrictive REMS to the weight loss product only, the FDA noted, may in turn result in use of the single generic ingredients without a REMS, hence circumventing the burden but also the benefit of risk mitigation. Indeed, topiramate initiation rates more than doubled within 1 year of the combination product approval, likely not because of REMS burden but because of lower costs.[15] Importantly, the REMS attached to the combination product has indeed demonstrated benefit in reducing exposure during pregnancy, while topiramate shows similar pregnancy rates as other non-teratogenic weight loss products.[13]

Rethinking the REMS Benefit-Risk Equation

Where does this leave us in promoting healthier pregnancies? As demonstrated for topiramate, it appears that the public health impact of a REMS is indication specific. For severe indications, a REMS may reduce access to a lifesaving medication while potentially having only a minor impact on preventing fetal harm because of patients' and providers' commitment to pregnancy planning (given disease severity). For less severe indications, a REMS may have a significant benefit in reducing unintended and unnecessary exposure during pregnancy with limited concern about (reduced) access.

Importantly, this relationship defining the positive or negative public health impact of a REMS hinges on the assumption that REMS programs reduce access to a medication, which has yet to be quantified. Recent data suggest that providers might actually get reassurance from additional oversight provided by REMS, which might therefore increase rather than reduce prescribing and patient access to a medication.[16] This is particularly important in light of increasing restrictions to abortion, which might persuade physicians to omit teratogenic medications when treating persons of child-bearing potential.[17] This would imply that a REMS could actually become an enabling component in health care delivery, for example, by ensuring that effective contraception is in place before teratogenic medications are initiated. More research that quantifies

the effect of REMS on reduced medication access is needed to facilitate a comprehensive assessment of their public health benefit.

Moving Ahead

Assuming that indications do play a role in whether the public health impact of a REMS is overall positive or negative, there are 2 ways forward. Designing indication-specific REMS programs is complicated because in the United States, indications are currently not captured in the prescribing process. Cost containment strategies implemented by payers (e.g., for diagnostic procedures) have solved this problem by requiring that specific diagnoses accompany procedural charges, which raises the question of whether similar requirements could not be embedded into electronic prescriptions. If such a solution remains elusive, decisions about REMS should consider their overall public health impact, as aggregate of the net benefit for each indication, considering the probability and severity of uncontrolled maternal disease(s) on one hand, and of infant morbidity on the other. Quantification of these probabilities, while complex, is feasible with pharmacoepidemiologic methods, and tradeoffs between consequences for the mother versus child and the types of adverse outcomes can be captured with decision-science approaches. Such an evidence-based approach in regulatory decision-making would ensure that the public health benefit of REMS is optimized. For anticonvulsants, the myopic focus on epilepsy in evaluating REMS benefit needs to be broadened to consider the evolving spectrum of users. For valproate, given its broad uses and prenatal exposure risk, I predict the overall public health benefit is dominated by its profound impact on child health, arguing strongly in favor of a REMS.

Article Information

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