

# COMMENTARY: REVISED RECOMMENDATION FROM CMDH ON USE OF VALPROATE IN WOMEN IS ETHICALLY INCOMPLETE AND NEGLECTS THE INTERESTS OF WOMEN



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of birth defects and cognitive deficits in potential babies exposed to valproate in utero. Although the goal of the CMDh recommendation to avoid birth defects in potential babies is ethically laudable, the strict recommendation as currently written fails to account for another, equally important ethical component of the decision process—the woman’s interests in preserving her health, and her potential strong preference to begin valproate immediately to avoid potentially fatal seizures by using the most effective drug for generalized idiopathic epilepsy. In this commentary, I argue that the current recommendation of the CMDh, as interpreted in the preceding text, is inappropriate for a complete ethical analysis of the complex and difficult decisions necessitated by the comparative risks in this situation because it focuses solely on the goal of protecting potential fetuses without considering the health interests, personal values, and goals of women with particular types of epilepsy. Instead, I will support a more nuanced, casuistry-based ethical argument that flexibly permits assessment, in consultation with her physicians and after a thorough informed consent process, of all the particular circumstances of each individual woman’s case and encourages weighing the interests, burdens and benefits, and personal values of both woman and potential child.

## HARD QUESTIONS

As noted in the accompanying article by Tomson, et al.,<sup>1</sup> the Coordination Group for Mutual Recognition and Decentralised Procedures-Human (CMDh) of the European Medicines Agency (EMA) has recently strengthened warnings on the use of valproate in women and girls.<sup>2</sup> The CMDh recommendations to healthcare professionals (HCPs) now include the following admonition: “For treatment of epilepsy and bipolar disorder in female patients who can have children, *only* prescribe valproate medicines for epilepsy and bipolar disorder *if* other treatments are ineffective or are not tolerated.” [emphasis added]<sup>3</sup> One possible interpretation of this recommendation is that the intent of CMDh is to urge HCPs to prescribe all other possible drugs before prescribing valproate, without regard to complex clinical and psychosocial circumstances such as the type of epilepsy, patients’ goals for childbearing, and varying tolerance of individual patients to their comparative risks of mortality or severe morbidity from tonic-clonic seizures versus elevated risks

The current restrictive CMDh recommendation raises numerous questions that are unanswerable in the absence of individual clinical and value-based knowledge about the particular woman being treated. For women with idiopathic generalized epilepsies, if trials of inferior drugs are required before using valproate, how many drugs must be tried? For what duration? What level of severity of side effects is needed to properly deem them “not tolerated”? What degree of health risk should be imposed on, or permitted to, a willing woman to prevent the possibility of an impaired fetus that does not yet, and may never, exist? If the woman receives an alternative drug (or drugs) and then dies or becomes severely disabled as a result, what are the legal consequences for HCPs? If such legal consequences emerge, how will they influence physicians’ practice patterns and the way they view their professional duty to patients? Will the integrity of the physician–patient relationship be compromised as a result? To what extent is a potential mother required to risk her life in order to achieve a healthy and eagerly anticipated baby? How can a fair and impartial informed consent process be ensured—one that

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does not discourage a woman from attending to her own health interests in lieu of the potential fetus? To what extent should contraception alternatives be an integral part of the informed consent process, and the medication prescribing decision process, for women who oppose it on religious or moral grounds? What range of options should be available for a woman already taking valproate and seizure-free, who has an unplanned pregnancy? To what extent should alternative means of family composition (i.e., adoption or assisted reproductive technologies, including in vitro fertilization combined with a surrogate carrier) be advocated in these decisions? In such cases, who pays for the often-elevated expenses of the alternative means? These questions drive home the likelihood and importance of unintended consequences from a recommendation that oversimplifies such a complex decision process.

### THE SOURCE OF THE PROBLEM

Many of the preceding questions can be traced to a common source: the use of the apparently strict conditional phrasing in the recommendation “only . . . if . . .” When construed literally, the recommendation could have a chilling effect by making physicians reluctant to prescribe valproate to patients who could potentially benefit from it, without exhaustive trials of alternative drugs, as well as adding unnecessary uncertainty to the medication management process and possible fears of legal complications. Such a strict conditional statement seems likely to make the antiepileptic medication decision process more difficult for both physicians and patients, as well as neglecting to consider the woman’s interests. A more suitable approach would be a policy that does the following: first, encourages extensive discussions between patient and physician about comparative possible medical risks and benefits for women and potential fetuses; second, emphasizes that different types of epilepsy may require different recommendations; and third, encourages dialogue to explore ways that the values of each individual patient affect her personal benefit-burden calculation.

### CASUISTRY AS A RESPONSE

Difficult questions like these demonstrate the weakness of recommendations that neglect essential ethical constituents of complex issues with potentially severe consequences. The recognition that, in disciplines like medicine that are part art and part science, consideration of specific circumstances—a process known as casuistry—is necessary for ethical analysis, can be traced to Aristotle. In the *Nicomachean Ethics*, he noted that “so much depends on particular circumstances that only general rules can be given” and “agents are compelled at every step to think out for themselves what the circumstances demand, just as happens in the arts of medicine [and navigation].”<sup>4</sup> This practice is con-

sidered both a moral and intellectual virtue. After centuries of being ignored, casuistry was revived in the 1970s and 1980s by modern scholars, including Stephen Toulmin and Albert Jonsen, who employed it successfully in analyzing complex cases in clinical bioethics that emerged from the multitude of technological advances in biomedical science during the mid-20th century. These scholars have described how relying on probabilism rather than certitude is, for many, the preferred way to accommodate intricate cases such as those faced by women with idiopathic generalized epilepsies contemplating how their own health needs should be balanced against those of potential fetuses. Jonsen and Toulmin note: “The work of the casuists was precisely the analysis of complex cases in the light of ‘a thousand difficulties.’ Because that analysis moves further and further from the cases on which ‘all agree,’ its results inevitably will be marked by greater or lesser plausibility rather than certainty.”<sup>5</sup> These “thousand difficulties” mirror the hard questions discussed earlier. Hence, casuistry allows those parties most directly affected to acknowledge that such decisions require accepting uncertainty as an inevitable component. Uncertainty plays a vital role in these epilepsy treatment decisions because women’s values and preferences about potential childbearing may change over time due to varying intensity of desire for children, as well as experiences of the side effects of inferior epilepsy medications or seizures resulting from foregoing optimal treatment. In such cases, all particular circumstances must be considered as part of the ethical analysis, including the interests of *both* women and possible fetuses; these cumulative circumstances should then be assessed to compare, contrast, and balance the health interests, and potential burdens and benefits of treatment, of all affected parties. This challenging task should properly fall to individual women and their physicians acting jointly, rather than being constrained by incomplete ethical recommendations. Furthermore, to promote an ethical informed consent process it is crucial that, when participating in such discussions, physicians make vigorous efforts to present clinical information in an objective manner. Such efforts may assist in ensuring the integrity of the informed consent process and avoid undue influence during the disclosure process.

### CONCLUDING REMARKS

After reviewing its report, I support the recommendations of the Joint Task Force of the International League Against Epilepsy—Commission on European Affairs, and European Academy of Neurology (Task Force) for the reasons that follow. First, the Task Force has followed a detailed casuistic ethical analysis that has produced rules that differ according to circumstances, as well as considering the interests and values of women. This approach properly includes many particular clinical and psychosocial factors, recognizing that there are numerous types of epilepsy that respond to

different medicines, and that complete and meticulous informed consent is necessary in order to facilitate women, along with their physicians, to make careful, individualized decisions about these exceedingly difficult choices. Second, the Task Force has specifically proposed recommendations that distinguish choices of medicines between first-line and second-line therapies according to diagnostic criteria. Third, the Task Force recommends that valproate should be avoided where possible, especially for focal epilepsy, but also should be permitted as first-line therapy for the types of epilepsy for which valproate is reasonably known to be the preferred treatment on the basis of available evidence and after thorough discussion with the patient about relative burdens and benefits. Fourth, the Task Force recognizes that regular follow-up in all women is essential for ongoing assessment of the most appropriate treatment. Of course, the scope of the Task Force's excellent analysis and recommendations exceeds the features I have highlighted. It is a work of considerable substance that brings proportionate attention to the ethical interests of all parties involved—women, physicians, and potential babies. Because of its comprehensive and nuanced treatment of particular circumstances including both medical and social elements, I argue that the Task Force's approach is ethically superior to the current CMDh recommendations. Decisions to discern the proper course of action in this type of case have profound implications and meanings that differ between persons according to their values; each situation is unique.

In my view, a policy allowing these meanings to be expressed while considering implications for all parties involved is ethically preferable to a more rigid and incomplete structure that, by definition, elevates the ethical interests of some parties above others.

## DISCLOSURES

The author reports no conflicts of interest. I confirm that I have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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