Valproate and childbearing potential: new regulations

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Each encounter between a patient and clinician is likely to include an explicit or implicit evaluation of benefit versus risk and should always be an exercise in person-centred medicine. New stipulations from the Coordination Group for Mutual Recognition and Decentralised Procedures-Human (CMDh), a regulatory body representing European Union member states, about the use of valproate in women of childbearing potential\(^1\) bring these age-old considerations into sharp relief. There will be a change in the marketing authorisation: valproate will be contraindicated in pregnancy and women of childbearing potential not using effective contraception. This requires all clinicians who see people with epilepsy to think carefully again, even before changes to UK use of valproate are enforced by changes in the licence from the UK Medicines and Healthcare products Regulatory Agency (MHRA). The many challenges are brought out in two accompanying articles in this issue.\(^2\)\(^,\)\(^3\) Importantly, no one should stop valproate use abruptly because of this announcement, without consulting their doctor as doing so could result in harm to themselves or to an unborn child.

The background is well established and largely derived from prospective registries.\(^4\) Babies born to mothers who take valproate medicines during pregnancy have up to a 10% risk of birth defects, compared with 2%–3% background risk,\(^5\) and a variable, sometimes unknown, risk on polytherapy with other antiepileptic drugs.\(^6\) Some of these malformations may necessitate early corrective surgery; some are inoperable. There is an average reduction in IQ estimated at 6–11 points\(^7\)\(^,\)\(^8\) and 30%–40% risk of developmental disability.\(^9\)\(^–\)\(^11\) Compared with the general population, the risk of autism spectrum disorders is threefold and that of attention-deficit hyperactivity disorder is fivefold.\(^12\)\(^–\)\(^14\) These consequences may come with a lifetime burden of medical and social care for the family and the state. While some structural abnormalities may be detectable on prenatal screening, the intellectual and behavioural outcomes cannot be predicted. Animal models suggest that some risks may be passed to unexposed generations epigenetically\(^15\): this work needs replication and there are no studies in humans. Whatever additional risks emerge, there are already significant known risks associated with the use of valproate in pregnancy. We should not assume any disease specificity: any use of valproate for any condition brings these age-old considerations into sharp relief.

In response to the accumulated evidence on risks, the MHRA issued advice to prescribers in 2015 and again in 2016 (https://www.gov.uk/drug-safety-update/medicines-related-to-valproate-risk-of-abnormal-pregnancy-outcomes). Materials to communicate the risks included a booklet for professionals, a consultation checklist and a guide and card for patients. However, patient surveys suggested that the message had not got through: about one in five women of childbearing potential remained unaware of the risks (https://www.epilepsysociety.org.uk/news/Women-not-aware-epilepsy-medicine-risk-pregnancy-27-09-2017). Following a further review and public hearing in London by the European Pharmacovigilance Risk Assessment Committee (PRAC), further guidance was issued by the PRAC and subsequently now by CMDh. These measures will strengthen restrictions on valproate use and introduce new measures to require appropriate counselling and information for affected women. A mandatory pregnancy prevention programme will be introduced, supported by a revised
Valproate should never be started unless alternative treatments are not suitable.

In pregnancy, valproate must not be used. However, it is recognised that for some women with epilepsy, it may not be possible to stop valproate and they may have to continue treatment (with appropriate specialist care) in pregnancy.

In female patients able to have children, valproate must not be used unless the conditions of the new pregnancy prevention programme are met.

There will be changes to the product information reflecting the new conditions.

Outer packaging of all valproate medicines must include a visual warning about the risks in pregnancy. In addition to boxed text, this may include a symbol/pictogram, with the details to be adapted at national level.

A patient reminder card will also be attached to the outer package for pharmacists to discuss with the patient each time the medicine is dispensed.

Companies that market valproate should also provide updated educational materials in the form of guides for healthcare professionals and patients.

The main points of the new valproate pregnancy prevention programme are:

- Assessing patients for the potential of becoming pregnant
- Pregnancy tests before starting and during treatment as needed
- Counselling patients about the risks of valproate treatment
- Explaining the need for effective contraception throughout treatment
- Carrying out reviews of treatment by a specialist at least annually
- Introduction of a new risk acknowledgement form that patients and prescribers will go through at each such review to confirm that appropriate advice has been given and understood.
- It is important that no woman should stop taking sodium valproate without first consulting her doctor. Sodium valproate is available in the UK under brand names such as Epilim, Epival, Episenta, Convulex and Orlept.
support groups may help, and alternative childbearing options may be relevant. It would not be appropriate to admonish either prescribers who accommodate this option or the women themselves, but this decision must be well documented and should be periodically revisited.

There will never be a trial of valproate and pregnancy outcomes in women of childbearing potential; so it is more important than ever that historical observational data are collected systematically and published. Fundamental research into the mechanisms of action and toxicity of valproate and possible genetic or other biomarkers of toxicity is essential, because as far as we can tell from the current data, some exposed children are not affected. But unless and until rational and effective selection of valproate as a credibly safe therapy for some individual women becomes a reality, we should follow the new regulations. These regulations aim to increase safety, and where their application may be complex, epilepsy specialists should be involved. We need to manage and minimise risk.


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Patient Consent Not required.

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REFERENCES