Valproate: important new regulatory measures for oversight of prescribing to new patients and existing female patients

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The harmful effects of prenatal exposure to valproate are well documented with congenital malformations and neurodevelopmental disorders which may lead to permanent disability. These effects may be seen in as many as 11% (malformations) and 40% (neurodevelopmental delay) of children exposed to valproate during pregnancy. Furthermore, in addition to valproate's known association with impaired male fertility, medicines regulatory authorities are investigating recent registry data which may suggest an increased risk of neurodevelopmental disorders in children whose fathers took valproate in the three months before conception.

To prevent avoidable harm, the Medicines and Healthcare products Regulatory Agency (MHRA) has in recent years taken increasingly strengthened regulatory action to minimise foetal exposure to valproate including, in 2018, contraindicating the use of valproate in women of childbearing potential unless they meet the conditions of a pregnancy prevention programme. As a result, valproate prescribing has been in decline for many years with the greatest reductions in use seen amongst women and girls of childbearing age.

It is therefore regrettable that, despite these measures, we continue to see cases of valproate being prescribed during pregnancy. Following a comprehensive review of the evidence the Commission on Human Medicines (CHM) has recommended further restrictions to valproate use to reduce avoidable harm which were introduced by the MHRA in January. Those restrictions are that:

- Valproate must not be started in new patients (male or female) younger than 55 years, unless two specialists independently agree and document that there is no other effective and tolerated treatment, except if there are compelling reasons that the reproductive risks do not apply; and
- At their next annual specialist review, female patients of childbearing potential and girls should be reviewed using the latest valproate Annual Risk Acknowledgement Form, which will include the need for a second signatory if the patient is to continue with valproate and subsequent annual reviews with one specialist.

As clinicians we have a critical role to ensure patients in these groups are not started on valproate unless there are exceptional circumstances. Those already taking valproate must be fully informed of its potential risks. We recognise that for some patients with epilepsy and bipolar disorder, valproate may be the only treatment option which offers effective symptom control and changing to an alternative treatment must be an informed and shared decision.

Discussions between clinicians and patients already on valproate must include counselling on alternative treatment options and the benefits and risks associated with any change for patients with epilepsy; this should include a discussion of the risks of sudden unexplained death in epilepsy (SUDEP). New safety and educational materials are now available to support these discussions and hard copies are being disseminated to clinicians to support shared decision making. It is important that these measures are implemented safely and in a way that does not cause alarm. No one should stop taking valproate or other anti-epileptic drugs without advice from their specialist.

Those women and girls of childbearing potential for whom other medicines are ineffective and who choose to continue to take valproate, must be supported to fully adhere to the Valproate Pregnancy Prevention Programme.

We recognise there will be considerable service pressures associated with these important changes but we would urge colleagues that this is undertaken as rapidly as it is possible to do safely. For more information, including details on the new regulatory measures, see the MHRA website.

Llywodraeth Cymru
Welsh Government



Professor Sir Frank Atherton
Chief Medical Officer, Wales

Department of Health
An Roinn Sláinte
Männystrie O Poustie
www.health-ni.gov.uk



Professor Sir Michael McBride
Chief Medical Officer, Northern Ireland

The Scottish Government
Riaghaltas na h-Alba



Professor Sir Gregor Smith
Chief Medical Officer, Scotland

Department of Health & Social Care



Professor Sir Chris Whitty
Chief Medical Officer, England