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Valproate: UK regulator looks into possible transgenerational effects

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The UK's medicines regulator is examining animal data that show that the epilepsy drug sodium valproate could trigger genetic changes that are passed on to future generations.

The Medicines and Healthcare Products Regulatory Agency (MHRA) said that as part of its ongoing review of the safety of sodium valproate it has sought independent advice from the Commission on Human Medicines about animal data that show changes to the testes in juvenile male animals and transgenerational effects in mice.

In April new figures showed that valproate was still being prescribed to women of childbearing age.[1 2]

Valproate is highly teratogenic, and evidence supports a rate of congenital malformations of 10% in infants whose mothers took valproate during pregnancy and neurodevelopmental disorders in 30-40% of children in this group.

Data from NHS Digital show that 206 women aged under 54 were started on sodium valproate for the first time in September 2021, up 6% on the same month a year earlier. And 25 women had the drug prescribed during pregnancy from April 2021 to September 2021.

After the figures were published Jeremy Hunt, chair of the Commons Health and Social Care Committee, called for a ban on prescribing sodium valproate to pregnant women with epilepsy.

Patient information

In 2018 the MHRA said that valproate should not be prescribed to women or girls of childbearing age unless other treatments were ineffective or not tolerated, as judged by an experienced specialist. If the drug is prescribed a pregnancy prevention programme must be in place, and patients must be given safety information every time they attend their appointments or receive their medicines.

But in April this year the *Sunday Times* reported that some patients were being given the drug without safety information leaflets or clear warnings on the packaging.[3]

The MHRA has launched a review into safety issues around prescribing sodium valproate and is seeking views from patients and healthcare professionals. A spokesperson said, "As part of our ongoing review of the safety of sodium valproate, we have been carefully assessing all available data on its benefits and risks and have sought independent advice from the government's expert scientific body, the Commission on Human Medicines, on the effectiveness of the current measures to support safe use of valproate."

"We will communicate further on the outcome of these discussions as soon as the advice is finalised. No one should stop taking sodium valproate without advice from a healthcare professional."

The MHRA added that the product information already included a warning about behavioural abnormalities reported in the first generation offspring of mice and rats after exposure to sodium valproate during pregnancy. In some mice exposed to teratogenic levels of sodium valproate during pregnancy some of these behavioural changes have been observed in their second generation offspring and, although less pronounced, in the third.

A patient report of 90 affected families who had been exposed to valproate in utero and were parents themselves also pointed to a possible transgenerational effect.[4] Among their 187 children, 23% reported malformations and 44% reported neurodevelopmental disorders. However, the malformations and medical diagnoses were not confirmed with medical records or professional diagnoses.

Further study

Commenting on the animal data, Peter Turnpenny, consultant clinical geneticist at the Royal Devon University Healthcare NHS Foundation Trust, told *The BMJ*, "It's concerning enough that we should undoubtedly look at this in the human population. What we need is a proper study. We need to find children with a confirmed diagnosis of fetal valproate spectrum disorder who have had children themselves. Those children should then be rigorously assessed both physically and in terms of their neurodevelopmental progress."

However, he added that "it seems counterintuitive" that a second generation would be affected. He said that you would not ordinarily expect a drug that has crossed the placenta and had an effect on the development of the unborn baby to directly influence its genetic makeup. "But you have to be open minded and investigate thoroughly," he said.

In 2020 the Cumberlege report looked at the negative outcomes of three medical interventions used in the NHS—Primodos, sodium valproate, and pelvic mesh. It found many occasions where regulatory bodies could have acted sooner and where poor communication with and between doctors had prevented patients from knowing about the risks of these interventions.[5]

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3 Lintern S. A scandal worse than thalidomide. *Sunday Times* 2022 Apr 16. https://www.thetimes.co.uk/article/the-new-thalidomide-d5lmlwvdc

4 Martin M, Hill C, Bewley S, etal. Transgenerational adverse effects of valproate? A patient report from 90 affected families. *Birth Defects Res* 2022;114:13-16. doi: 10.1002/bdr2.1967. pmid: 34866359

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