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Male use of valproate – regulation before evidence?

PERSPECTIVES

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Regulatory agencies for medicines have tightened restrictions on the use of valproate in men because of concerns regarding neurodevelopmental disorders in their offspring. New analyses raise questions about whether these recommendations were justified.

Valproate is used to treat epilepsy, bipolar disorder and migraine, conditions that often affect people in the process of planning a family. However, this drug is highly teratogenic when used during pregnancy, and its use by women of reproductive age is therefore subject to strict regulation. In 2024, the European Medicines Agency (EMA) issued new safety guidance on valproate, this time for men (1).

The guidance were prompted by Scandinavian registry data suggesting that use of valproate during spermatogenesis may be associated with an approximately 50 % increased risk of autism or other neurodevelopmental disorders in children (2). The Norwegian Medical Products Agency instructed doctors in Norway to inform patients about the potential risk and to consider alternative treatments in men planning to start a family (3). Users of the drug also had to refrain from donating sperm (3).

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The recommendations were more stringent in countries. In England, two specialists were required to independently conclude that valproate was the most appropriate treatment before it could be prescribed (4). The unexpected recommendations were met with immediate criticism from medical communities, which warned of the risks associated with treatment discontinuation and highlighted potential confounding factors, as well as the possibility that the observed risk could reflect underlying genetic factors (4–6). The criticism was compounded by the fact that the data underpinning the recommendations had not been published and that the regulatory agencies' reports were not readily accessible (6–8).

Findings suggesting possible reproductive toxicity associated with medications are published regularly but rarely lead to regulatory action. The notion that paternal medication exposure could adversely affect offspring was both novel and contested (6). Why did the EMA have such a strong response to a single and controversial safety signal? The explanation likely lies in valproate's unique history.

To inform or not to inform

When valproate was introduced to the European market in the 1970s the regulatory authorities were already aware that the drug was teratogenic in animals, and scientific reports soon emerged describing spina bifida and developmental delay in children born to women who had used the drug (Figure 1). Fetal valproate syndrome was first described in 1984 (9). The risk was communicated to prescribing doctors, but not directly to patients via patient information leaflets. There was also no recommendation from the regulatory authorities to change treatment prior to pregnancy. Advisory experts considered that informing patients directly could cause fear and reduce adherence, and that it was preferable for the information to be conveyed by a doctor (9).

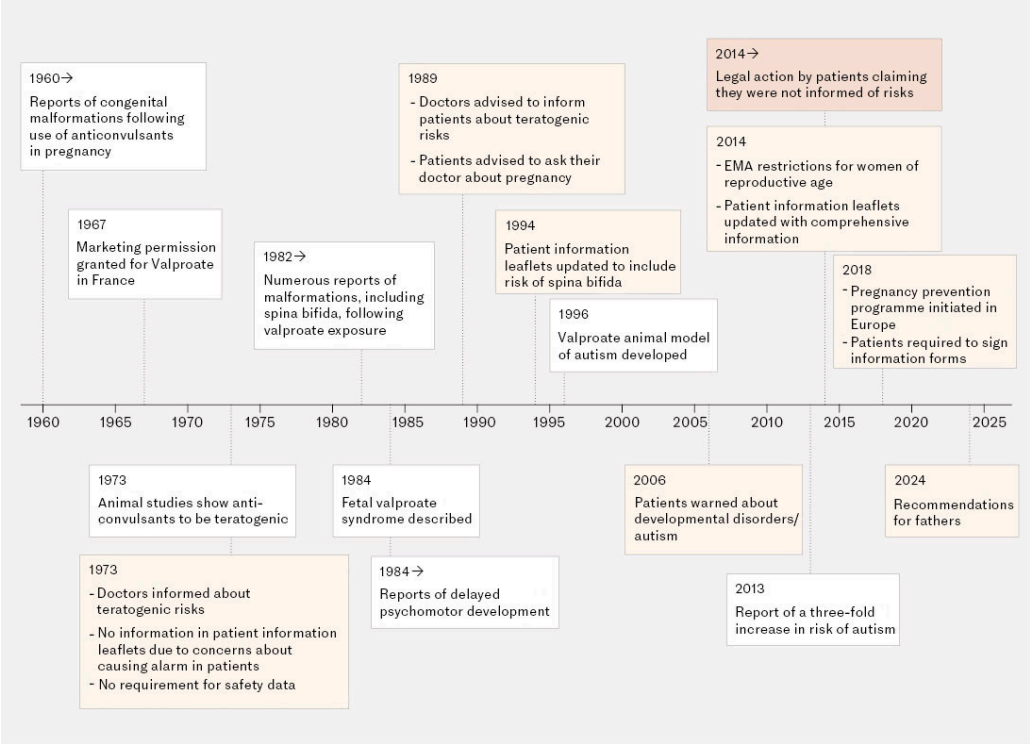

Figure 1 Timeline of scientific knowledge on the reproductive toxicity of valproate and the regulatory authorities' restrictions on prescribing (9). White boxes: evidence of teratogenic effects; yellow boxes: regulatory recommendations.

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There was also no requirement for additional safety data. Even after animal studies in the 1990s demonstrated autism-like behaviour following in utero exposure to valproate, regulators failed to call for systematic studies of risk in pregnancy (9). The finding that pregnant mice exposed to valproate produced offspring with autistic-like traits gave rise to the 'valproate animal model of autism', which was quickly adopted in behavioural research. However, this new insight did not lead to a greater focus on reproductive safety in humans.

Doctors were expected to explain the risks associated with valproate to patients, but in practice many women were not informed and used the drug at high doses during pregnancy (9). Before 2004, there was no mention in patient information leaflets that valproate was not recommended during pregnancy (9). The risks and the requirement to inform women were only clearly communicated by regulatory authorities in the period 2012–15. This followed studies showing that children exposed in utero had an approximately 9–25 % risk of congenital malformations, a two- to five-fold increased risk of autism spectrum disorders, and an IQ ten points lower on average than that of unexposed children (10). These risk communication measures had limited impact on patient awareness (11), and three years later the EMA introduced a comprehensive pregnancy prevention programme for valproate users.

Valproate should not be used in girls and women of reproductive age unless other treatments are ineffective or not tolerated. Users must be monitored by a specialist, use effective contraception, undergo pregnancy testing and complete an annual risk assessment in which healthcare personnel review specified information points with the patient.

In the years that followed, legal action was taken against manufacturers, authorities and individual doctors. In France, 1660 patients have received nearly €80 million in compensation. Pharmaceutical companies have been ordered to pay damages but argue that the teratogenic risks have been communicated to *doctors* since the 1980s, and that it is the regulatory authorities who determine what is included in patient information leaflets (12). In the United Kingdom, significant government compensation is being considered for up to 20,000 individuals harmed by valproate (13).

Attention turns to paternal exposure

During the EMA's safety assessment in 2018, concerns were also raised regarding neurodevelopmental disorders and malformations in children whose fathers had used valproate. Could the medicine affect a child's development via sperm? EMA experts considered this possible. They referred to animal studies in which epigenetic changes in sperm from male mice treated with valproate were transmitted to the fetus (14).

The EMA instructed manufacturers to investigate the risk and approved the study design to be used. Norway was selected as one of the participating countries because its high-quality registries make it possible to link paternal medication use to child developmental outcomes. The report on findings described neurodevelopmental disorders in 5 % of children whose fathers had received valproate from a pharmacy during spermatogenesis, compared with 3 % among those whose fathers had received lamotrigine or levetiracetam (hazard ratio (HR) 1.5 (95 % confidence interval (CI) 1.1 to 2.1) (8)). Following closed consultations with affected parties, the EMA published new regulatory recommendations (1).

> ***«Regulation of valproate use in women was delayed and characterised by regulatory inertia. Meanwhile, recommendations regarding paternal exposure seem disproportionate in relation to the limited evidence base»***

But were the Scandinavian findings in the 2023 report commissioned by the EMA correct? Independent analyses from Norway (15, 16), Sweden (15), Denmark (17) and Taiwan (16) have not been able to replicate the increased risk. The pooled hazard ratio in a meta-analysis was 1.1 (95 % CI 0.9 to 1.3) (18). In an analysis of French health registries commissioned by the national medicines regulator, a slight increase in risk was observed (HR 1.2; 95 % CI 1.1 to 1.4), with considerable variation between subgroups, some of which showed substantially higher risks (19). The reason for the discrepancies between studies is unclear, as the underlying data sources are broadly similar. The EMA has initiated further studies to investigate methodological factors.

The valproate case raises fundamental questions about what evidence is needed to make regulatory recommendations, and how patient information can be effectively communicated. Regulation of valproate use in women was delayed and characterised by regulatory inertia. Meanwhile, recommendations regarding paternal exposure seem disproportionate in relation to the limited evidence base. The response is also paradoxical given the lack of systematic safety data for a range of other medicines used during pregnancy, despite individual studies suggesting possible reproductive toxicity.

To ensure safe treatment for future parents, it is essential that regulatory authorities for medicines now establish broad, systematic and predictable pharmacovigilance frameworks, transparent regulatory processes (7) and effective communication with prescribers.

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