Prenatal valproate exposure and autism in children

A population-based cohort study suggests that the risk of autism may be tripled in children born to mothers who took valproate during pregnancy.

Overview: Around 27,000 people in the UK are newly diagnosed with epilepsy each year (about 1 in every 2000 people). The incidence of epilepsy is highest in children and in older people. The clinical features of epilepsy are specific to the type of seizure, which can occur as transient disturbance of consciousness, behaviour, emotion, motor function, or sensation, due to abnormal electrical activity in the brain.

The term ‘autism’ describes qualitative differences and impairments in reciprocal social interaction and social communication, combined with restricted interests and rigid and repetitive behaviours. A recent study has estimated that the prevalence of autism in 8 year olds in the UK is 3.8 per 1000 boys and 0.8 per 1000 girls (Taylor et al. 2013). Annual incidence rates were estimated as 1.2 per 1000 boys and 0.2 per 1000 girls.

See the NICE Evidence Services topic page on epilepsies for a general overview of this condition.

Current advice: NICE’s clinical guideline on epilepsy recommends sodium valproate as first-line treatment for newly-diagnosed generalised tonic-clonic, myoclonic, tonic or atonic seizures and as an option for first-line treatment of absence seizures. It additionally warns to be aware of teratogenic risks of sodium valproate, and suggests alternative prescribing options in girls and women of childbearing age.

The Medicines and Healthcare Products Regulatory Agency has issued a special reminder on the risk of neurodevelopmental delay in children following maternal use of sodium valproate. The regulator recommends that sodium valproate should not be used during pregnancy and in women of childbearing potential unless clearly necessary.

The NICE clinical guideline on diagnosis of autism in children and young people lists maternal use of sodium valproate in pregnancy as a risk factor associated with an increased prevalence of autism.

The NICE Pathways on autism and epilepsy bring together all related NICE guidance and associated products on the conditions in a set of interactive topic-based diagrams.

New evidence: Christensen et al. (2013) reported a cohort study investigating the effects of prenatal valproate exposure and the risk of children having a diagnosis of autism. The Danish Civil Registration System was used to identify children (n=655,615) who had an estimated date of conception from 1 February 1996 and were born alive up to 31 December 2006. Children whose gestational age could not be accurately calculated were excluded.

The Danish Prescription Register was used to identify filled prescriptions of antiepileptic drugs in the same period. The exposure window was defined as from 30 days before conception to birth. The Danish Psychiatric Central Register was used to identify children diagnosed with autism (n=5437) and
parents diagnosed with psychiatric disorders before the birth of their child. Hazard ratios were adjusted for risk factors for autism (such as parental parity, age at conception, and psychiatric history, and the child’s sex, gestational age, birth weight, and congenital malformations).

Overall, 2644 children were exposed to antiepileptic drugs during pregnancy, with 508 children exposed to valproate. The overall risk of autism spectrum disorder was 1.53% (95% confidence interval [CI] 1.47% to 1.58%), which increased with valproate use in pregnancy to 4.42% (95% CI 2.59% to 7.46%; adjusted HR=2.9, 95% CI 1.7 to 4.9). The overall risk of childhood autism was 0.48% (95% CI 0.46% to 0.51%), which increased with valproate use in pregnancy to 2.50% (95% CI 1.30% to 4.81%; adjusted HR=5.2, 95% CI 2.7 to 10.0). The risks of autism spectrum disorders and autism in children exposed to valproate during pregnancy were increased to a similar extent when the comparator was children whose mothers previously used valproate but stopped at least 30 days before conception. Carbamazepine, clonazepam, lamotrigine and oxcarbazepine were not associated with increased risk of autism spectrum disorder or autism.

The authors noted the possibility that children exposed to valproate in pregnancy may be examined more closely for autism spectrum disorders because of previously identified links between prenatal valproate and autism. This possible bias could result in overestimation of the effect of valproate. The study also relied on the assumption that women who filled a prescription for anti-epileptic drugs used at least some of the prescription.

**Commentary:** “The potential for in utero valproate exposure to cause structural malformation and developmental delay is well recognised. However, longer term neurobehavioural effects of prenatal exposure have yet to be defined.

“This database linkage study provides evidence that maternal valproate use in pregnancy is associated with a 4–4.5% risk of autism spectrum disorder, compared to 1–1.5% in unexposed children. This higher risk was not observed with the other antiepileptic drugs studied. Fetal brain development continues to term, so it is therefore not surprising that the association with autism was not limited to exposure during the first trimester. This new evidence raises questions around the practice of re-introducing valproate after 12 weeks gestation. The observation of an increased risk of autism following antenatal exposure to doses below those previously associated with fetal valproate syndrome is also a concern. However, the data on which these findings are based are limited and further studies are necessary before firm conclusions can be drawn.

“Wherever possible valproate use in girls or women of childbearing potential should be avoided. If valproate is considered necessary, it is imperative that dose and need for treatment are regularly reviewed. New evidence relating to the teratogenic potential of valproate should be considered and discussed with the patient.” – Dr Laura Yates, Consultant in Clinical Genetics, Newcastle upon Tyne Hospitals NHS Foundation Trust, and Head of the UK Teratology Information Service (UKTIS)

**Study sponsorship:** European Research Council and Danish Medical Research Council.

**About this article:** This article appeared in the February 2014 issue of the Eyes on Evidence e-bulletin. This free monthly e-bulletin from NICE Evidence outlines interesting new evidence and what it means for current practice. They do not constitute formal NICE guidance. The opinions of contributors do not necessarily reflect the views of NICE.

To receive the Eyes on Evidence e-bulletin, please complete the [online registration form](#).

---

**Visit Evidence Search**

Copyright © 2014 National Institute for Health and Care Excellence. All Rights Reserved.