Examining the evidence – paternal valproate use, reproductive toxicity and the regulatory response

Royal College of Psychiatrists International Congress

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About UKTIS & Declaration

Funding, remit, staffing & core activities

Commissioned by UK Health Security Agency (UKHSA)

Hosted by the Newcastle upon Tyne Hospitals NHS Foundation Trust

Small team:1 clinician, 6 scientists, 1 admin

Sole dedicated UK provider of teratogen information

National teratogen surveillance/safety monitoring systems

National and international collaborations

uktis
uk teratology information service

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Dr Richardson declares no conflicts of interest for this presentation

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Male reproductive toxicity

Working definition for this session

"Any environmental exposure which can impact a male's ability to reproduce successfully, or which can impact on the offspring's development or their capability to reproduce"

Paternal exposures; teratogenicity or impaired fertility

Mechanisms of interest

Effects on spermatic genome:

a) Chromosome number
b) Chromosome structure
c) Genetic sequence
d) Epigenetic alterations

Transfer of xenobiotic in seminal fluid:

a) Effects on the uterus
b) Direct effects in the embryo/fetus

Sperm impairments:

a) Spermatogensis
b) Viability
c) Motility
d) Morphology

Effects on sexual function:

a) Loss of libido
b) Impotence
c) Loss of ejaculatory function

Paternal exposures; teratogenicity or impaired fertility

Mechanisms of interest

TERATOGENICITY

Effects on spermatic genome:

a) Chromosome number
b) Chromosome structure
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Transfer of xenobiotic in seminal fluid:

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FERTILITY

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a) Spermatogensis
b) Viability
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d) Morphology

Effects on sexual function:

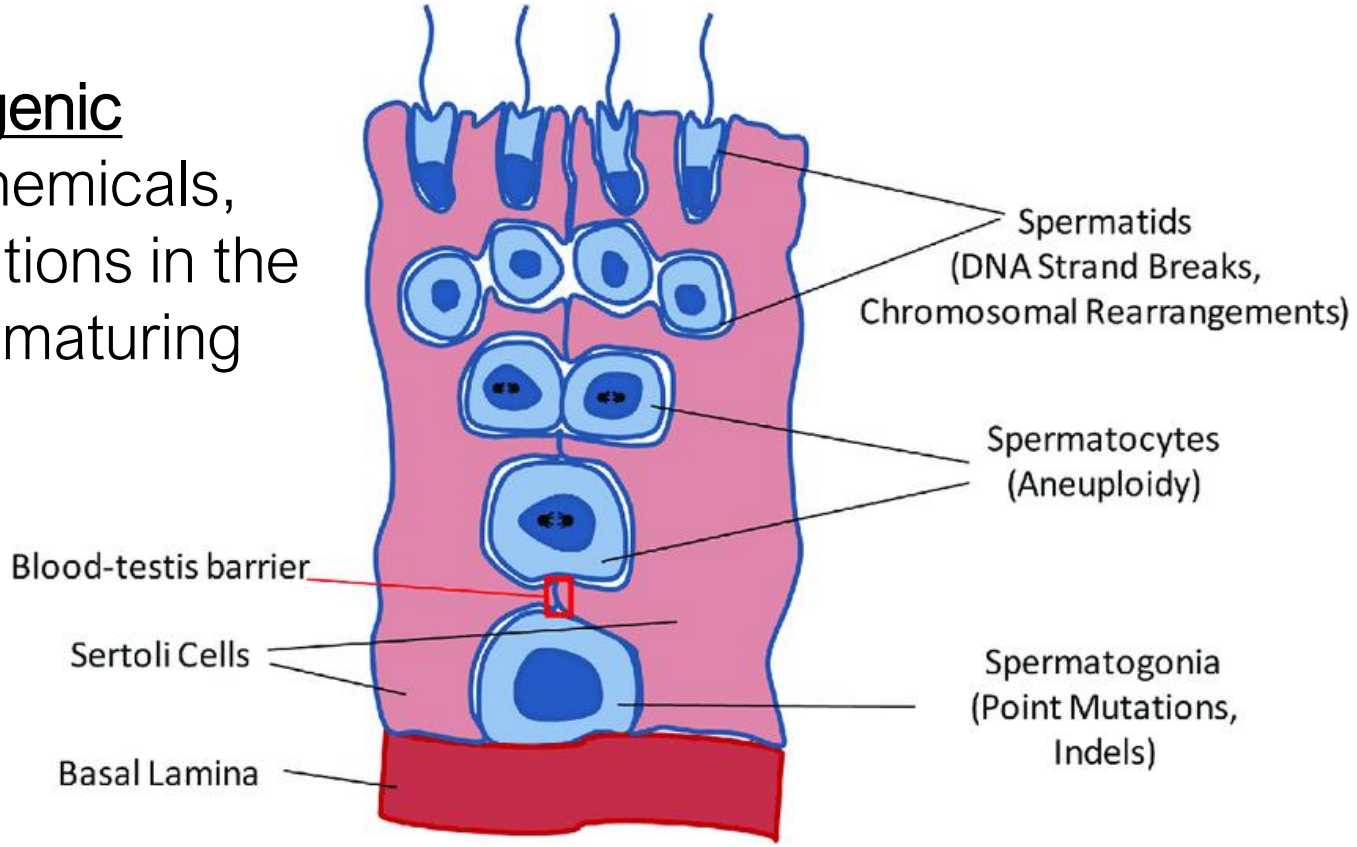
a) Loss of libido
b) Impotence
c) Loss of ejaculatory function

Paternal teratogenicity

Effects on spermatic genome

Paternal exposure to a **mutagenic substances** (e.g. radiation, chemicals, medicines) may induce alterations in the genome of spermatozoa and maturing germ cells

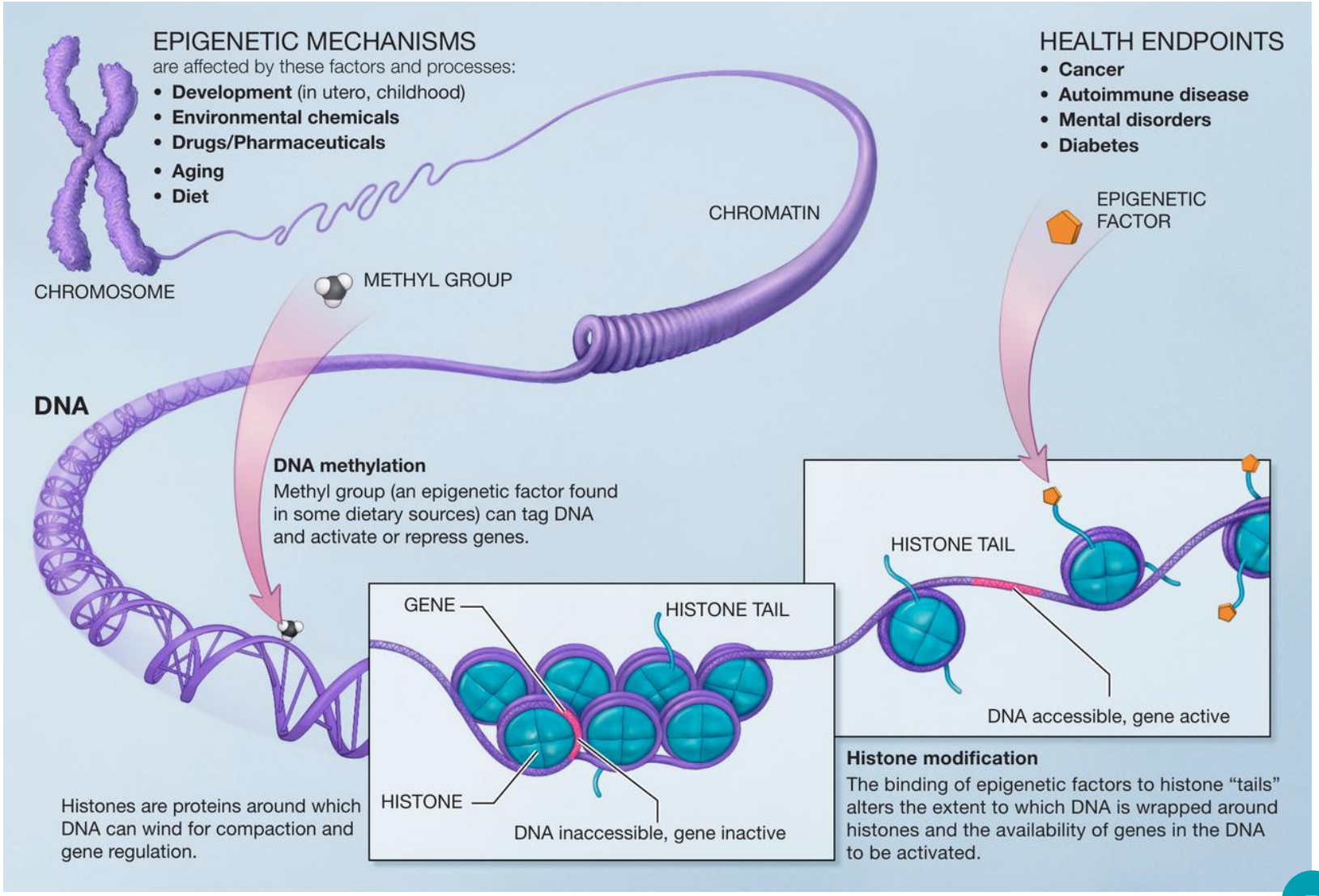
Impacting the karyotype (chromosome number or structure) or genetic sequence



Paternal teratogenicity

Effects on the spermatic epigenome

1. **DNA methylation**
2. **Histone modification**



Paternal teratogenicity

Effects on the spermatic epigenome – valproate?

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Genet Med. 2024 Oct;26(10):101226. doi: 10.1016/j.gim.2024.101226. Epub 2024 Jul 31.

Discovery of DNA methylation signature in the peripheral blood of individuals with history of antenatal exposure to valproic acid

Sadegheh Haghshenas [1], Audrey Putoux [2], Jack Reilly [3], Michael A Levy [1], Raissa Relator [1], Sourav Ghosh [3], Jennifer Kerkhof [1], Haley McConkey [4], Patrick Edery [2], Gaetan Lesca [5], Alicia Besson [6], Christine Coubes [7], Marjolaine Willems [7], Nathalie Ruiz-Pallares [8], Mouna Barat-Houari [8], Eduardo F Tizzano [9], Irene Valenzuela [9], Quentin Sabbagh [7], Jill Clayton-Smith [10], Adam Jackson [10], James O'Sullivan [11], Rebecca Bromley [12], Siddharth Banka [10], David Genevieve [13], Bekim Sadikovic [14]

Affiliations + expand

PMID: 39097820 DOI: 10.1016/j.gim.2024.101226

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Spermatic genome alterations

Theoretical consequences in the conceptus

Genome alterations may result in:

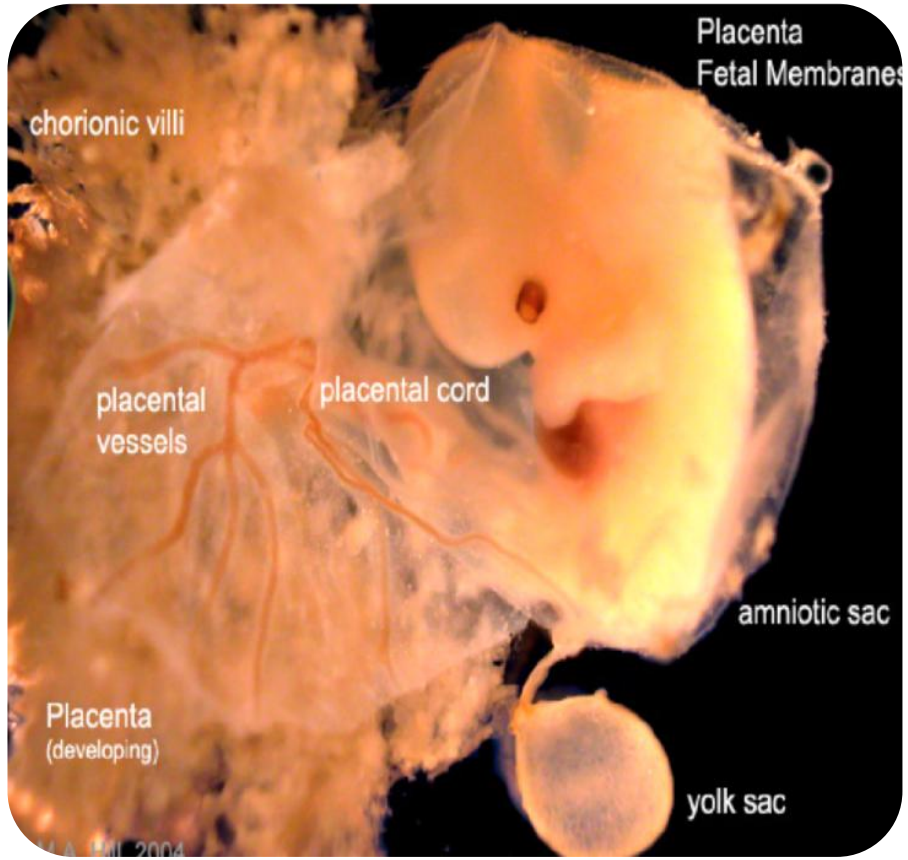
- Embryo-fetal demise*
- Congenital abnormalities or genetic illness
- Neurodevelopmental impairments
- Transgenerational inheritance

Paternal teratogenicity

Transfer of xenobiotic in seminal fluid – plausible mechanism for teratogenicity?

Excretion in seminal fluid:

- Likely minimal exposure
- Theoretical risks only



Paternal xenobiotics & teratogenic effects

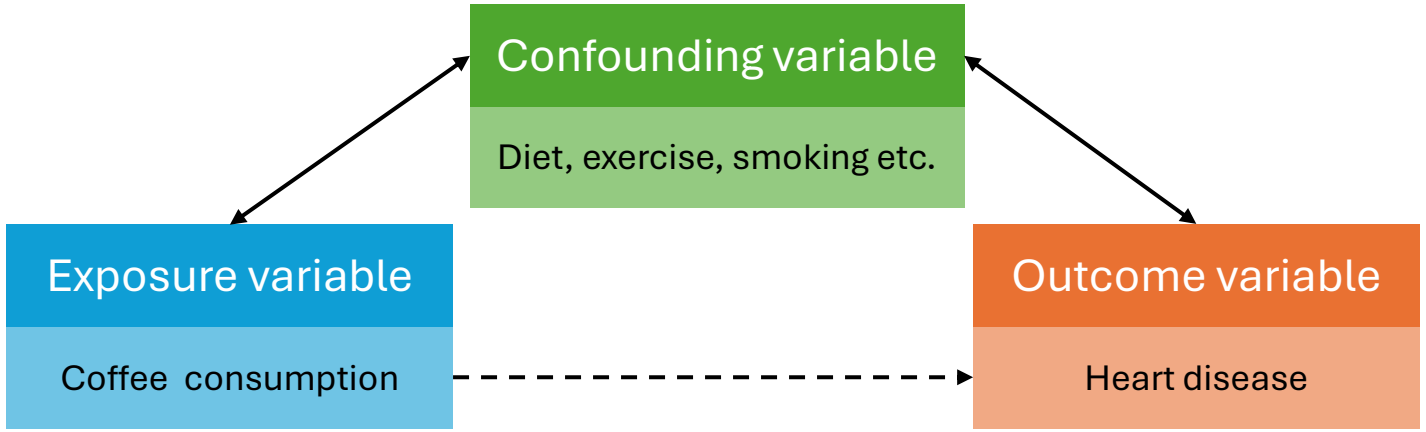
Supporting evidence – Medication examples

No clear supportive evidence of paternal medication acting as human teratogens

Limitations of paternal safety data

Impacting data impretation

- Data quantity and quality are usually highly limited
- **Paternal and maternal exposure** – Similar but not the same
  - Can we look for patterns in the same way?
- **Observational data** – Think data confounding



Paternal valproate

Regulatory recommendations timeline

Jul-20

Medicines & Healthcare products Regulatory Agency

Human data – fertility
Animal data – reprotox, epigenetic, transgenerational effects

"valproate must not be started in new patients (male or female) younger than 55 years, unless two specialists…"

Jan-21

Public Assessment Report of antiepileptic drugs: review of safety of use during pregnancy

Medicines & Healthcare products Regulatory Agency

Research and analysis
Antiepileptic drugs: review of safety of use during pregnancy
Published 7 January 2021

Dec-22

Aug-23

IQVIA

PASS - Paternal exposure to valproate – Updated Abstract Following Reanalysis of Norway Data of Corrigendum to Final Study Report Version 1.1 and Addendum Version 2 Page 1 of 12

Valproate EU consortium

A post-authorisation safety study (PASS) to evaluate the paternal exposure to valproate and the risk of neurodevelopmental disorders including autism spectrum disorder as well as congenital abnormalities in offspring – a population-based retrospective study

Date: 02 October 2023, Updated Abstract Following Reanalysis of Norway Data Corrigendum to Final Study Report Version 1.1 and Addendum Version 2.0

Stand Alone Abstract V2.0

Prepared For:
Valproate marketing authorisation holders being part of study consortium

Jan-24

Medicines & Healthcare products Regulatory Agency

"increased risk of neurodevelopmental disorders in children fathered by men on valproate"

Jun-24

Paternal valproate and offspring neurodevelopment

What data were available prior to the MHRA review?

One study published prior to Jan-21 MHRA review:

J Neurol Neurosurg Psychiatry. 2020 Sep;91(9):907-913. doi: 10.1136/jnnp-2020-323028. Epub 2020 Jul 10.

Paternal exposure to antiepileptic drugs and offspring outcomes: a nationwide population-based cohort study in Sweden

Torbjörn Tomson [1], Giulia Muraca [2 3], Neda Razaz [3]

Affiliations + expand

PMID: 32651245 DOI: 10.1136/jnnp-2020-323028

- 576 paternal valproate vs. 2,457 ASM untreated (with epilepsy)
- After adjustment, no statistically significant increased risk of:
  - Autism spectrum disorder (1.7% vs. 1.3%)
  - Attention deficit hyperactivity disorder (2.2% vs. 2.1%)
  - Intellectual disability (0.9% vs. 0.6%)

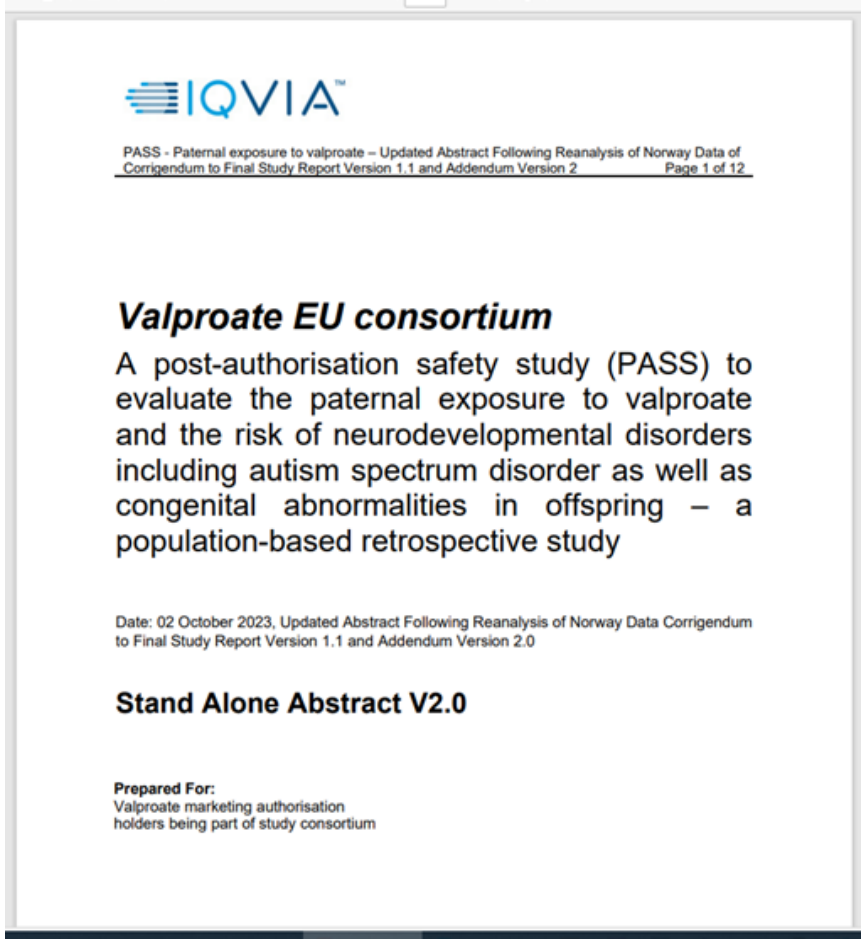
IQVIA Study

Data source and findings

Study Sample: Offspring of males using valproate from 3m pre-conception compared with those using lamotrigine/levetiracetam; n=2,213 vs. n=3,740

Pooled 10-year adjusted HR for any NDD 1.50, 95%CI; 1.09-2.07

Small increase in absolute risk (~3 additional cases for every 200 exposed)



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IQVIA Study

International critique from teratology experts

Birth Defects Res. 2024 Aug;116(8):e2392. doi: 10.1002/bdr2.2392.

Paternal Valproate Treatment and Risk of Childhood Neurodevelopmental Disorders: Precautionary Regulatory Measures Are Insufficiently Substantiated

Joan D Garey [1], Per Damkier [2 3], Anthony R Scialli [1], Shari Lusskin [4], Stephen R Braddock [5], Laurent Chouchana [6], Brian Cleary [7 8], Elizabeth A Conover [9], Orna Diav-Citrin [10 11], Rachel S Dragovich [12], Facundo Garcia-Bournissen [13], Ken Hodson [14], Debra Kennedy [15], Steven H Lamm [16], Sharon A Lavigne [17], Sarah G Običan [18], Alice Panchaud [19 20], Kirstie Perrotta [21], Alfred N Romeo [22], Svetlana Shechtman [10], Corinna Weber-Schoendorfer [23]

Affiliations + expand

PMID: 39189597 DOI: 10.1002/bdr2.2392

- Paternal indications varied (66% vs. 44% epilepsy)
- Sensitivity analyses produced conflicting findings which were difficult to explain
- Genetic basis of NDD not assessed
- Small increased risks demonstrated likely heavily influenced by confounding
- Regulatory guidance insufficiently substantiated

Christensen Study

Data source and primary findings

JAMA Netw Open. 2024 Jun 3;7(6):e2414709. doi: 10.1001/jamanetworkopen.2024.14709.

Valproate Use During Spermatogenesis and Risk to Offspring

Jakob Christensen [1 2], Betina B Trabjerg [3 4], Julie Werenberg Dreier [3 4]

Affiliations + expand

PMID: 38833248 PMCID: PMC11151155 DOI: 10.1001/jamanetworkopen.2024.14709

- 1,336 children of male valproate users vs. 1.2m unexposed
- No increased risk of NDD (6.34% vs. 4.17%) – aHR 1.10 (95%CI; 0.88 to 1.37)
- No increased risk of ASD (2.5% vs. 1.9%) – aHR 0.92 (95%CI; 0.65 to 1.30)

Christensen Study

Sensitivity analyses – No dose response relationship

	Valproate-exposed children[a]	Reference children[a]	Neurodevelopmental disorders		HR (95% CI)	
			Valproate-exposed children	Reference children	Unadjusted	Adjusted[b]
High dose (≥750 mg/d)	715	1 234 017	44	51 437	1.48 (1.10-1.98)	1.10 (0.81-1.49)
Low dose	621		41		1.70 (1.25-2.31)	1.10 (0.80-1.50)

Christensen Study

Sensitivity analyses – No increase vs. VPA unexposed disease-matched controls (epilepsy)

Valproate-exposed children[a]	Reference children[a]	Neurodevelopmental disorders		HR (95% CI)	
		Valproate-exposed children	Reference children	Unadjusted	Adjusted[b]
1052	11 308	70	622	1.00 (0.78-1.28)	1.09 (0.85-1.39)

Christensen Study

Sensitivity analyses – No increase vs. active comparators (lamotrigine exposed)

Valproate-exposed children[a]	Reference children[a]	Neurodevelopmental disorders		HR (95% CI)	
		Valproate-exposed children	Reference children	Unadjusted	Adjusted[b]
1336	1663	85	66	0.95 (0.68-1.31)	0.97 (0.68-1.38)

Christensen Study

Sensitivity analyses – vs. active comparators (lamotrigine exposed) matched for year of birth (equal follow-up time in the study)

Valproate-exposed children[a]	Reference children[a]	Neurodevelopmental disorders		HR (95% CI)	
		Valproate-exposed children	Reference children	Unadjusted	Adjusted[b]
1043	1043	56	49	1.15 (0.79-1.69)	1.03 (0.68-1.57)

Christensen Study

Sensitivity analyses – vs. NaVal exposed >2y prior to conception

Valproate-exposed children[a]	Reference children[a]	Neurodevelopmental disorders		HR (95% CI)	
		Valproate-exposed children	Reference children	Unadjusted	Adjusted[b]
1336	690	85	46	0.87 (0.61-1.25)	0.96 (0.64-1.44)

Christensen Study

Research letter 2025

JAMA Netw Open. 2025 May 1;8(5):e2512139. doi: 10.1001/jamanetworkopen.2025.12139.

Risk of Neurodevelopmental Disorders and Paternal Use of Valproate During Spermatogenesis

Jakob Christensen [1 2], Betina B Trabjerg [3 4], Julie Werenberg Dreier [3 4]

Affiliations + expand

PMID: 40402499 PMCID: PMC12100447 DOI: 10.1001/jamanetworkopen.2025.12139

- Alignment with IQVIA study exposed group definitions
- No replication of IQVIA findings

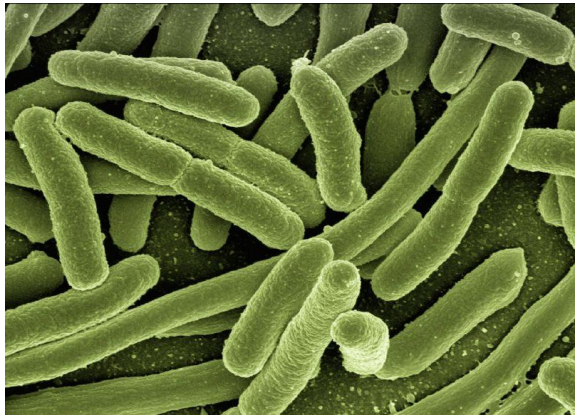
Thoughts on these data

How to interpret?

- *Conflicting results* – largest study suggests increased risk
- *Data quality differences* – one smaller study applied valuable sensitivity analyses showing near unity in risk
- *Study limitations* – impact of unmeasured confounding
- *Mechanism* – Questionable biological plausibility

Biological mechanism

Genotoxicity data



- Manufacturer (GLP-compliant) *in vitro* & *in vivo* tests - negative
- Non-GLP-compliant *in vivo* studies (mice) – conflicting results
- Epigenetics – inconclusive
- MHRA – *"In considering the totality of the available evidence and limitations that exist, the weight of evidence suggests that valproate is unlikely to be genotoxic"*

Paternal valproate data

Timeline – what comes next?

Data modelling criticisms:

- Variable selection
- EMA PRAC request
- Updated analyses to be conducted under a new protocol
- Awaiting the results

Medicines & Healthcare products Regulatory Agency

Paternal exposure to valproate and risk of neurodevelopmental disorders and congenital malformations in offspring

Review of results from a Scandinavian post-authorisation safety study (PASS)

Public Assessment Report

September 2024

Thank you

Get in touch:

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Clinical enquiries – 0344 892 0909 (Mon-Fri, 9am-5pm)

Socials:

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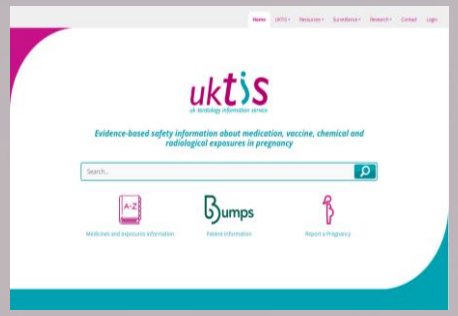

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