Systematic review

Paternal exposure to antiseizure medications and offspring outcomes: a systematic review

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ABSTRACT

Background Concerns have recently been raised about risks to the fetus resulting from paternal exposure to antiseizure medications (ASMs). To address these concerns, we conducted a systematic review of the literature to assess neurodevelopmental and anatomical outcomes in offspring born to fathers taking ASMs at the time of conception.

Methods Electronic searches of MEDLINE, PsycINFO, and Embase were conducted to identify human studies published in English that reported on outcomes, comprising neurodevelopmental disorders, major congenital malformations, small-for-gestational age or low birth weight, in offspring of fathers taking ASMs at conception. Quality analysis of included studies was undertaken using the Newcastle-Ottawa Scale. A narrative synthesis was used to report study findings.

Results Of 923 studies identified by the search and screened by title and abstract, 26 underwent full-text review and 10 met eligibility criteria. There was limited evidence available, but there appeared to be no clear evidence for an adverse impact of paternal ASM use on offspring outcomes. Few isolated adverse findings were not replicated by other investigations. Several methodological limitations prevented meta-analysis, including failure by most studies to report outcomes separately for each individual ASM, heterogeneity in measurement and outcome reporting, and small numbers of monotherapy exposures.

Conclusions Although there were limited data available, this systematic review provides reassuring evidence that paternal exposure to ASMs at conception is unlikely to pose any major risk of adverse outcomes for the offspring. Further research is needed to examine the relationship between preconception ASM use in males and offspring outcomes at birth and postnatally.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ While maternal use of some antiseizure medications carries an elevated risk of adverse outcomes for the developing fetus, it is unclear whether paternal exposure to these drugs also carries risks for the offspring.

WHAT THIS STUDY ADDS

⇒ Our systematic review shows that evidence for any risk to the offspring resulting from paternal exposure to antiseizure medications is scarce and inconsistent, with most studies showing no increased risk compared with unexposed controls. Therefore, the available evidence does not justify major concerns.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The results of our study inform the counselling of males with epilepsy and highlight the need for more research in this area, focusing in particular on risks associated with individual medications.

INTRODUCTION

The teratogenic effects of antiseizure medications (ASMs) taken by mothers are well-documented.[1] In contrast, the outcomes of offspring of fathers taking ASMs have received substantially less attention. In recent years, however, preclinical studies have clearly demonstrated that epigenetic changes in the paternal germline induced by drugs or toxins can lead to anatomical teratogenicity and adverse neurodevelopmental effects in the offspring.[2 3] These findings raised important concerns and highlighted the need to determine their potential applicability to the clinical setting.[4]

Adverse effects of ASMs on male fertility have been frequently documented.[5] Of note, many ASMs, including phenytoin, carbamazepine, benzodiazepines, valproate, gabapentin, topiramate, zonisamide, levetiracetam, pregabalin, and cannabidiol have been reported to cause testicular toxicity or to affect sperm quality in experimental animals.[6–14] Transgenerational effects have also been reported, including anatomical teratogenicity in the offspring of male mice treated with pregabalin,[13] behavioural abnormalities and impaired reproductive function across multiple generations after paternal exposure to cannabidiol in zebrafish,[15] behavioural abnormalities in the offspring of male mice treated with valproate,[16 17] and transgenerational transmission of autism-like phenotypes by the offspring of mice exposed to valproate during pregnancy.[18] Clinically, alterations in sperm count, morphology or motility have been associated with valproate,[19–21] carbamazepine,[20] oxcarbazepine,[20] and levetiracetam,[22] even though for some of these ASMs findings are inconsistent.[23] Because of its common association with anatomical and behavioural teratogenicity after maternal exposure, valproate has undergone particular scrutiny with respect to potential male reproductive toxicity. A 2023 report by the Medicines and Healthcare products Regulatory Agency

(MHRA)[21] in the UK, highlighted that many studies support its testicular toxicity in preclinical models and its effects on human sperm quality, as well as the risk of impaired fertility in men exposed to the drug. A potential transgenerational transmission of anatomical and neurodevelopmental disorders resulting from prenatal exposure to valproate was suggested by a French survey,[24] but the results of this report cannot be meaningfully interpreted due to a high likelihood of reporting and ascertainment bias. Greater concerns, however, were raised by a recent register-based study commissioned by the European Medicines Agency (EMA), yet to be published in full following peer review, which apparently found a 50% increased risk of neurodevelopmental disorders in children born to men taking valproate compared with those born to men on lamotrigine or levetiracetam.[25 26] Notably, the EMA acknowledged that the study was hampered by methodological limitations and could not establish whether the adverse offspring outcomes were actually attributable to paternal valproate exposure.[25]

Motivated by the aforementioned experimental data and the study commissioned by the EMA, we performed a systematic review of the literature in humans to examine the neurodevelopmental and anatomical outcomes in offspring of fathers taking ASMs around the time of conception.

METHODS

Standard protocol approvals, registrations, and patient consents

The protocol for this review was developed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. The review protocol was registered on PROSPERO on 20 November 2023 (registration number CRD42023481600).

Eligibility

This systematic review included articles that reported on the outcomes of children paternally exposed to ASMs, either as monotherapy or polytherapy, with no restrictions placed on the indication of usage. Exposure was defined as paternal use of ASMs at the time of, or in the months before, conception. Eligible study designs included the following: observational cohort studies, population-based datasets, register-based studies, and case-control studies. No restrictions were placed on the time of publication, but eligible studies were required to report original data and be in English language. We excluded animal studies, studies that only reported on child outcomes following maternal ASM exposure, duplicate publications reporting the same data, review articles, commentaries, letters to the Editor, studies where the number of exposed offspring was <10, and studies where the full text was not available.

Literature search and screening

The electronic search terms were developed in consultation with a tertiary librarian (online supplemental file 1). Electronic searches of Medline, PsycINFO, Embase were conducted in November 2023, with additional hand searching of Google Scholar (related articles) and reference lists of included studies to identify articles not captured in primary searches. Electronic searches, utilising the same strategy and screening procedure, were updated in June 2024 to identify any additional eligible studies published since the original searches, resulting in the identification of one new eligible study. Two reviewers (EH and EP) independently screened titles and abstracts for eligibility, reviewed full-text articles for inclusion, extracted data and rated the quality of included studies in Covidence, with discrepancies resolved by a third reviewer (PP).

Data synthesis and reporting

Extracted data pertaining to study information and population characteristics included: study design, country, method of participant recruitment (eg, prospective pregnancy register, national population dataset), demographic and clinical characteristics of the father (age, exposure to other teratogens, education level and health status (if known)), number of exposed offspring and their demographic information (age, sex), and recruitment of comparison group (if applicable). The primary outcome was risk of adverse outcomes, including neurodevelopmental disorders (eg, autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), intellectual disability (ID), developmental delay, or other developmental problems), major congenital malformations (MCMs), small-for-gestational age (SGA), and low birth weight in offspring of fathers treated with ASMs. Extracted outcomes were expressed as odds, hazard, or risk ratios, with associated 95% confidence interval (95% CI).

The quality analysis of included studies was assessed independently by two reviewers (EH and EP) using the Newcastle Ottawa Scale (NOS), a risk of bias tool recommended for evaluating non-randomised studies.[27] Studies received a maximum of 8 points across three domains: selection of study groups (3 points); comparability of study groups (2 points); and ascertainment of exposure and outcomes (3 points).

Due to the small number of eligible studies and heterogeneity of outcomes data, a meta-analysis could not be performed. Extracted data was synthesised into a narrative review reporting the risk of adverse outcomes. Findings were provided separately by ASM type, where applicable, with the strength of evidence commented on within each section.

Data availability statement

Access to the study data will be considered on reasonable request to the corresponding author.

RESULTS

Search results

A total of 1298 titles were identified through electronic and manual searches. After removal of duplicates, 923 articles underwent title and abstract screening (figure 1). Of these, 26 underwent full-text review for assessment of eligibility, yielding 10 studies which were included in the final review. Of the included studies, there were six population-based cohort studies, three prospective cohort studies, and one cross-sectional study. Further details on the studies included in the final review are presented in table 1.

Quality analysis

The quality of the included studies was variable (table 2). One study did not have an unexposed cohort to which outcome data could be compared,[28] which resulted in lower quality assessment ratings. In one study, it was unclear how paternal ASM exposure status was ascertained; the cohort was labelled as 'offspring of men with epilepsy', and it was assumed via the outcome data that all men were ASM-treated but the study methodology lacked sufficient description.[29] Only one study controlled for ASM dose (>750 mg/d vs ≤750 mg/d valproate),[30] and only three studies reported findings separately for each ASM as opposed to a class,[31 32] although some studies controlled for relevant confounding variables in outcome analyses, including paternal or

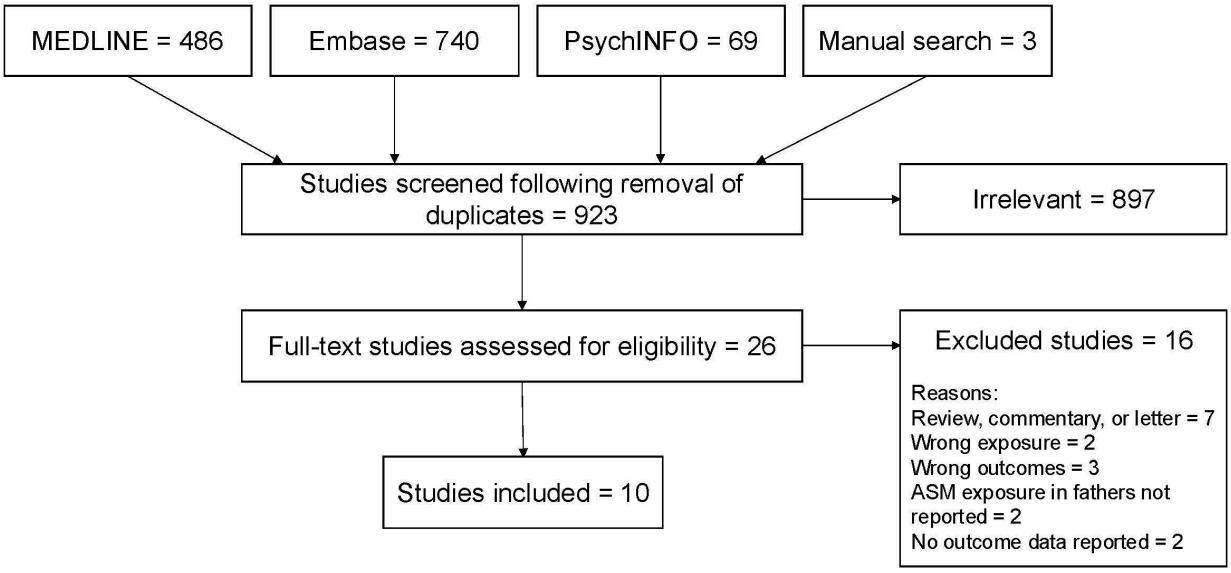

Figure 1 PRISMA flowchart of study selection. ASM, antiseizure medication.

maternal age, past history of psychiatric disorders, and exposure to other teratogens. The quality analysis ratings for the outcome assessment category ratings were the most variable; population-based studies recorded outcomes through secure record linkage to databases which are subject to variable diagnostic accuracy and lack information on important variables, whereas other studies relied on self-reporting, which is subject to recall bias, or did not adequately describe how outcome data were collected.

Neurodevelopmental outcomes

Neurodevelopmental outcomes of offspring paternally exposed to ASMs are summarised in table 3 and online supplemental table 1.

Neurodevelopmental disorders as a composite outcome

A retrospective nationwide population-based study from Denmark found no significant increase in overall risk of neurodevelopmental disorders (composite outcome, comprising ID, ASD, ADHD, and disorders of psychological development) in the offspring of fathers exposed to valproate (n=1336) compared with offspring of valproate-unexposed fathers (n=1,234,017), adjusting for potential confounders.[30] Similar results were obtained when undertaking a series of additional analyses, such as restricting the analysis to offspring of fathers exposed to high-dose valproate (>750 mg/d) or lower doses of valproate, or when excluding disorders of psychological development (table 3).

Autism spectrum disorder (ASD)

One prospective cohort study found a significantly increased risk of autistic traits among 18-month-old offspring of fathers who took ASMs within 6 months of conception (n=147) compared with unexposed controls (n=60 583).[33] However, there was no significant increase in proportion of offspring meeting the cut-off for ASD on another screening instrument at the same time point, and the increased risk of autistic traits was no longer identified at age 36 months in a smaller cohort (n=110). Three population-based studies found no significantly increased risk of ASD diagnosis compared with unexposed controls among offspring exposed to any ASM (n=2087),[31] benzodiazepines (n=64 570),[34] valproate (any exposure n=1336, >750 mg/d n=715, ≤750 mg/d=721, monotherapy n=1017),[30] valproate monotherapy (n=458),[31] carbamazepine monotherapy (n=582),[31] or other ASM monotherapies (n=605).[31]

Attention deficit/hyperactivity disorder (ADHD)

There was no increased risk of ADHD traits among 36-month-old offspring paternally exposed to ASMs (n=110) compared with unexposed controls (n=43 571) in a prospective cohort study.[33] Population-based studies found no increased risk of ADHD diagnosis compared with unexposed controls following paternal exposures to any ASM (n=2087),[31] benzodiazepines (n=64 570),[34] valproate monotherapy (n=458),[31] carbamazepine monotherapy (n=582),[31] or other ASM monotherapies (n=605).[31]

Intellectual disability (ID)

Intelligence quotient (IQ) at age 4 years was within normal limits among offspring of fathers with epilepsy treated with ASMs at the time of conception (n=396).[29] One population-based study found no increased risk of ID diagnosis compared with unexposed controls for offspring paternally exposed to any ASM (n=2087), valproate monotherapy (n=458), carbamazepine monotherapy (n=582), or other ASM monotherapies (n=605).[31]

Other neurodevelopmental outcomes

In a cohort of ASM-exposed offspring that also had elevated autistic traits, these children (n=147) were significantly more likely to score outside the normal range on a measure of personal-social skills compared with unexposed controls born to fathers without epilepsy (n=60 583).[33] Gross motor skills, fine motor skills, communication skills, aggressive symptoms, and difficult temperament were all within normal limits for ASM-exposed offspring at 18 months (n=177) and at 36 months (n=110) compared with unexposed controls (n=60 583)[33 35] (online supplemental table 1).

Major congenital malformations (MCMs)

A full description of findings on the risk of MCMs following paternal ASM exposure is reported in table 4. Among cross-sectional and prospective cohort studies, there was no elevation in the rate of MCMs among offspring paternally exposed

Table 1 Study characteristics of the included articles

Study	Design	ASM-exposed population	Control/comparison	Sample demographics	Outcomes
Chen *et al* [34]	Retrospective population-based study	n=64 570 offspring aged<14 years whose fathers were treated with a BZD (diazepam, chlordiazepoxide, clonazepam, medazepam, oxazepam, lorazepam, bromazepam, alprazolam, nordazepam, fludiazepam, or clotiazepam) 90 days before and 90 days after conception.	Unexposed population (n=1,440,435) For sibling comparisons, n=50 941 children consisting of 23 961 discordant pairs of differentially exposed siblings, where 24 350 were exposed.	48% of entire cohort (ASM exposed and ASM unexposed) were females. Mean follow-up for entire study cohort was 8.5 years (SD=3.2).	Using a nationwide population database (Taiwan National Health Insurance Research Database), frequency of diagnosis of ADHD or ASD was based on the detection of ICD-9/10 codes of ADHD or ASD in at least one inpatient record or three outpatient records.
Christensen *et al*[30]	Retrospective population-based study	n=1336 offspring of men prescribed VPA within 120 days of conception, of which n=1017 were exposed to VPA monotherapy.	n=1,234,017 VPA-unexposed population.	48.5% of VPA-exposed cohort and 48.7% of VPA-unexposed were female. Mean follow-up for VPA-exposed cohort was 10.1 years (IQR, 5.1–14.8 years), and 10.3 years (IQR, 5.2–15.6 years) for VPA-unexposed children.	Diagnosis of major congenital malformations during the child's first year of life using the Danish National Patient Register from 1 January 1997, to 31 December 2017. Diagnoses of neurodevelopmental disorders (intellectual disability, ASD, ADHD, and disorders of psychological development) identified from the Danish Psychiatric Central Research Register. All diagnoses were based on ICD-10 codes.
Dieterich *et al*[28]	Cross-sectional study	n=22 offspring from 15 fathers (10 with focal epilepsy, 5 with generalised epilepsy) taking the following ASMs: VPA polytherapy (n=1, specific agents in the polytherapy other than VPA not reported), primidone monotherapy (n=1), PHT (n=1), PHT+PB (n=2), PHT+primidone (n=5), PHT+BZD (n=1, BZD type not reported), Unknown (n=11).	n=37 offspring from 22 mothers (seven with focal epilepsy and 15 with generalised epilepsy).	Of the 22 offspring from 15 fathers on ASMs, 11 males (aged 2–17 years) and 11 females (aged 8 months-13 years).	Several methods used to assess MCMs, including physical examination, X-ray, EEG, ECG, echoencephalogram, and chromosome analysis.
Engeland *et al*[36]	Retrospective population-based study	n=87 847 pregnancies where fathers were prescribed at least one drug (including ASMs) in the 3 months before conception. Drug exposures of interest consisted of: VPA (n=347), PHT (n=31), PB (n=21), Diazepam (n=1354)	n=3 36 893 pregnancies included in the Medical Birth Registry of Norway and in the Norwegian Prescription Database (excluding the pregnancies associated with paternal use of the drug or drug class being investigated).	Demographics of study cohort not reported.	Record linkage to examine specific offspring outcome including pre-term birth, perinatal mortality, foetal growth retardation, and birth defects classified according to the ICD-10.
Shapiro *et al*[29]	Prospective cohort study	n=50 282 parent-child pairs enrolled in the Perinatal Collaborative Project (USA), including 396 father-child pairs where the father had epilepsy and was treated with ASMs. Exposure to individual ASMs was not reported.	n=49 590 parent-child pairs where neither parent had epilepsy.	Demographics of study cohort not reported.	Medical records of child's examination at birth, motor and mental developmental assessment at age 8 months, IQ assessment at 4 years.
Tomson *et al*[31]	Retrospective population-based study	n=2087 offspring of ASM-treated fathers with epilepsy who took ASMs within 74 days prior to or at the time of conception. ASMs included: VPA (n=576 total, 458 as monotherapy), CBZ (n=705 total, 582 as monotherapy), LTG (409 total, monotherapy not reported), Other (605 all monotherapy exposures, excluding VPA, LTG and CBZ).	n=2457 fathers with epilepsy not treated with ASMs. n=1 144 795 unexposed population controls.	ASM-exposed children: age range 1–17 years, female n=1,025 (49.1%) Age of fathers with epilepsy on ASM (n=2087): <25 years (4.3%), 25–29 years (18.8%), 30–34 years (33%), >34 years (43.9%).	Diagnosis of MCM during first year of life obtained from the Swedish Medical Birth Register and the National Patient Register. Clinically ascertained diagnoses of ASD, ADHD and intellectual disability were identified from 2006 to 31 December 2017 in the National Patient Register. All diagnoses were classified using ICD-10 criteria.

Continued

Table 1 Continued

Study	Design	ASM-exposed population	Control/comparison	Sample demographics	Outcomes
Veiby *et al*[33]	Prospective cohort study	Offspring of fathers with epilepsy receiving ASM treatment within 6 months of conception prospectively assessed at **birth** (n=241), **18 months** (n=147) and **36 months** (n=110) Exposures to individual ASMs were not reported.	**Birth**: offspring of untreated fathers with epilepsy (n=409) and unexposed population controls (n=106 899). **18 months**: offspring of untreated fathers with epilepsy (n=216) and unexposed population controls (n=60 583). **36 months**: offspring of untreated fathers with epilepsy (n=173) and unexposed population controls (n=43 571).	For fathers with epilepsy on ASMs (n=242), 4.5% were aged >37 years (n=11). For fathers with epilepsy not taking ASMs (n=411), 5.6% were aged >37 years (n=23) Among population controls (n=1 07 597), 4.7% were aged >37 years.	Birth outcomes were obtained from the national Medical Birth Registry of Norway. Adverse outcomes included preterm delivery (<37 weeks), low birth weight (<2500 g), SGA, and low Apgar score (<7 at 5 min). MCMs included those diagnosed during the neonatal period or within the first year of life. For neurodevelopment, the study was based on parent-reported screening tools for ASD, ADHD, communication skills, and behavioural problems.
Veiby *et al*[35]	Prospective cohort study	n=471 offspring of fathers with epilepsy who were participants in the Norwegian Mother and Child Cohort Study. 37.6% (n=177) of the fathers received ASMs within 6 months of conception, the remaining 62.4% (n=294) were untreated. Exposures to individual ASMs were not reported.	n=77 770 offspring of parents without epilepsy.	Demographic information of study cohort not reported.	Results reported at age 6 months. Items measuring motor skills were obtained from the Ages and Stages Questionnaire (ASQ). Rating of social skills was based on the ASQ, supplied by items from the Bayley Scales of Infant Development. Assessment of difficult temperament was obtained from the Infant Characteristics Questionnaire.
Wensink *et al*[37]	Prospective population-based study	Offspring of fathers prescribed either BZD-derived anxiolytics (n=3047) or BZDs as hypnotics or sedatives (n=736) within 90 days of conception, identified through Danish national registries.	n=9 36 706 offspring from unexposed parents in the general population.	Mean age of fathers of unexposed controls was 33.0 (95% CI 29.2 to 36.4) years.	Diagnosis of at least one MCM in the first year of life categorised as per the EUROCAT guidelines.
Yang *et al*[32]	Retrospective population-based study	n=3086 offspring of fathers treated with ASMs within 3 months of conception, identified through Danish national registries. Exposures included VPA, CBZ, OXC, and LTG (actual numbers not reported).	n=7 30 196 offspring born to fathers unexposed to ASMs.	Demographic information of ASM-exposed offspring not reported. Among controls, 48.7% were female.	Congenital anomalies (no differentiation between major and minor) were classified based on public health records using ICD-10 codes.

ADHD, attention deficit/hyperactivity disorder; ASD, autism spectrum disorder; ASM, antiseizure medication; ASQ, ages and stages questionnaire; BZD, benzodiazepine; CBZ, carbamazepine; CI, confidence interval; ECG, electrocardiogram; EEG, electroencephalogram; EUROCAT, European Surveillance of Congenital Anomalies; ICD, International Classification of Diseases; IQ, intelligence quotient; IQR, interquartile range; LTG, lamotrigine; MCM, major congenital malformation; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; SD, standard deviation; SGA, small-for-gestational age; VPA, valproic acid.

Table 2 Quality analysis of studies included in the review

Study	Quality analysis category		
	Selection /3	Comparability /2	Outcomes /3
Chen *et al*[34]	***	*	***
Christensen *et al*[30]	***	**	***
Dieterich *et al*[28]		*	*
Engeland *et al*[36]	***	*	***
Shapiro *et al*[29]	**		**
Tomson *et al*[31]	***	**	***
Veiby *et al*[33]	**	*	*
Veiby *et al*[35]	**	*	**
Wensink *et al*[37]	***	*	***
Yang *et al*[32]	***	**	***

Note: The number of stars (asterisks) in the quality analysis category columns indicate the rating awarded to the study across the three domains, with a greater number of stars indicating a higher quality rating. The domain of 'selection' is rated out of three stars, 'comparability' out of two, and 'outcomes' out of three stars. Studies can receive a zero-star rating within a given category. Highest rating for each domain is indicated by a green box, intermediate rating by an orange box and lowest rating by a red box.

Table 3 Neurodevelopmental outcomes of offspring paternally exposed to ASMs at time of conception

Study	Autism	ADHD	Intellectual (dis)ability	Other neurodevelopmental disorders
Chen *et al*[34]	Diagnosis of ASD in offspring of fathers of taking BZD during the first trimester (n=64 570) vs unexposed population controls (n=1,440,435): aHR=0.94 (95% CI 0.87 to 1.02).	Diagnosis of ADHD in offspring of fathers of taking BZD during the first trimester (n=64 570) vs unexposed population controls (n=1,440,435): aHR=1.03 (95% CI 1.00 to 1.08).	n/r	n/r
Christensen *et al*[30]	n=34 offspring born to fathers taking VPA (n=1336) were diagnosed with ASD compared with n=24 479 of VPA-unexposed offspring (n=1,234,017): aHR=0.92 (95% CI 0.65 to 1.30). Among n=715 children paternally exposed to high-dose valproate (>750 mg/d), n=13 were diagnosed with ASD (aHR=0.66 (95% CI 0.38–1.15)). Among n=621 offspring exposed to low-dose valproate (≤750 mg/d), n=21 had a diagnosis of ASD (aHR=1.20 (95% CI 0.78–1.86)).			n=85 offspring born to fathers taking VPA (n=1336) were diagnosed with a neurodevelopmental disorder compared with n=51 437 of VPA-unexposed offspring (n=1,234,017): aHR=1.10 (95% CI 0.88 to 1.37). Among n=715 offspring paternally exposed to high-dose valproate (>750 mg/d), n=44 were diagnosed with a neurodevelopmental disorder (aHR=1.10(95% CI 0.81–1.49)), and in n=621 offspring paternally exposed to low dose valproate (≤750 mg/d), n=41 were diagnosed with a neurodevelopmental disorder (aHR=1.10(95% CI 0.80–1.50)). n=76 offspring born to fathers taking VPA (n=1336) were diagnosed with a neurodevelopmental disorder (excluding disorders of psychological development) compared with n=47 671 of VPA-unexposed offspring (n=1,234,017): aHR=1.06 (95% CI 0.84 to 1.34).
Shapiro *et al*[29]	n/r	n/r	Compared with children of parents without epilepsy (n=49 590), mental and motor scores at age 8 months and IQ at 4 years were lower in children of mothers with epilepsy (n=305), but not in children of fathers with epilepsy (n=396).	n/r
Tomson *et al*[31]	1.2% (n=25) of offspring paternally exposed to ASMs (n=2087) diagnosed with ASD compared with 1.3% (n=32) of offspring born to fathers with epilepsy not taking ASMs (n=2457): aHR=0.9 (95% CI 0.5 to 1.7) **VPA monotherapy:** 1.7% (n=8) of offspring paternally exposed to VPA (n=458) diagnosed with ASD compared with 1.3% (n=32) of offspring born to fathers with epilepsy not taking ASMs (n=2457): aHR=1.4 (95% CI 0.6 to 3.1). **CBZ monotherapy:** 1.4% (n=8) of offspring paternally exposed to CBZ (n=582) diagnosed with ASD compared with 1.3% (n=32) of offspring born to fathers with epilepsy not taking ASMs (n=2457): aHR=1.0 (0.4–2.1). **Other monotherapies:** 0.3% (n=2) of offspring paternally exposed to other ASM monotherapies (n=605) diagnosed with ASD compared with 1.3% (n=32) of offspring born to fathers with epilepsy not taking ASMs (n=2457): aHR=0.3, (95% CI 0.1 to 1.3).	1.6% (n=34) of offspring paternally exposed to ASMs (n=2087) diagnosed with ADHD compared with 2.1% (n=51) of offspring born to fathers with epilepsy not taking ASMs (n=2457): aHR=1.1 (95% CI 0.7 to 1.9) **VPA monotherapy:** 2.2% (n=10) offspring paternally exposed to VPA (n=458) diagnosed with ADHD compared with 2.1% (n=51) of offspring born to fathers with epilepsy not taking ASMs (n=2457): aHR=1.4 (95% CI 0.7 to 2.8) **CBZ monotherapy:** 1.5% (n=9) of offspring paternally exposed to CBZ (n=582) diagnosed with ADHD compared with 2.1% (n=51) of offspring born to fathers with epilepsy not taking ASMs (n=2457): aHR=0.9 (0.4–1.9) **Other monotherapies:** 0.7% (n=4) of offspring paternally exposed to other ASM monotherapies (n=605) diagnosed with ADHD compared with 2.1% (n=51) of offspring born to fathers with epilepsy not taking ASMs (n=2457): aHR=0.5, (95% CI 0.2 to 1.5).	0.7% (n=14) of offspring paternally exposed to ASMs (n=2087) diagnosed with ID compared with 0.6% (n=14) of offspring born to fathers with epilepsy not taking ASMs (n=2457): aHR=1.3 (95% CI 0.6 to 2.8) **VPA monotherapy:** 0.9% (n=4) of offspring paternally exposed to VPA (n=458) diagnosed with ID compared with 0.6% (n=14) of offspring born to fathers to epilepsy not taking ASMs (n=2457): aHR=1.6 (95% CI 0.5 to 5.1) **CBZ monotherapy:** 0.3% (n=2) of offspring paternally exposed to CBZ (n=582) diagnosed with ID compared with 0.6% (n=14) of offspring born to fathers to epilepsy not taking ASMs (n=2457): aHR=0.6 (0.1–2.9) **Other monotherapies:** 0.7% (n=4) of offspring paternally exposed to other ASM monotherapies (n=605) diagnosed with ID compared with 0.6% (n=14) of offspring born to fathers to epilepsy not taking ASMs (n=2457): aHR=1.4 (95% CI 0.5 to 4.3)	n/r

Continued

Table 3 Continued

Study	Autism	ADHD	Intellectual (dis)ability	Other neurodevelopmental disorders
Veiby *et al*[33]	*Autism checklist (age 18 months):* 11.0% (n=16) of offspring paternally exposed to ASMs (n=147) met cut-off for autistic traits compared with 7.8% of unexposed offspring (n=60 583): OR=1.6 (95% CI 1.0 to 2.7). *Autistic traits (age 18 months*): 2.8% (n=4) of offspring paternally exposed to ASMs (n=147) met cut-off for autistic traits compared with 0.9% of unexposed offspring (n=60 583): OR=3.7 (95% CI 1.4 to 10.1), p<0.05. *Autistic traits (age 36 months*): 0.9% (n=1) of ASM-exposed offspring (n=11) met cut-off for autistic traits compared with 1.5% of unexposed offspring (n=43 571): OR=0.6 (95% CI 0.1 to 4.2).	*ADHD symptoms (age 36 months):* 2.8% (n=3) of offspring paternally exposed to ASMs (n=110) met cut-off for ADHD symptoms compared with 4.0% of unexposed offspring (n=43 571): OR=0.7 (95% CI 0.2 to 2.1).	n/r	

ADHD, attention deficit/hyperactivity disorder; aHR, adjusted hazard ratio; aOR, adjusted odds ratio; ASD, autism spectrum disorder; ASM, antiseizure medication; BZD, benzodiazepine; CBZ, carbamazepine; CI, confidence interval; ID, intellectual disability; IQ, intelligence quotient; n/r, not reported; OR, odds ratio; VPA, sodium valproate.

to ASMs (n=396) compared with maternal ASM exposures (n=305), or unexposed offspring (n=49 590)[29]; no MCMs reported among 22 ASM-exposed offspring[28]; and no significant increase in MCMs among 241 ASM-exposed offspring compared with unexposed controls (n=106 899).[33] In population-based studies, no increased risk of MCMs was found among offspring of fathers exposed to diazepam (n=1354),[36] benzodiazepine-derived anxiolytics (n=3047) or benzodiazepines as hypnotics/sedatives (n=736),[37] any ASM (n=2087,[31] valproate (monotherapy n=458[31] any exposure n=805[32], any exposure n=1,336[30], >750 mg/d n=715[30], ≤750 mg/d n=621[30]), carbamazepine (monotherapy n=582[31], any exposure n=687[32]), or other ASM monotherapies (n=605)[31] compared with unexposed offspring.

One study found a mildly increased risk of congenital anomalies in offspring exposed to any ASM, as well as lamotrigine (n=612) and oxcarbazepine (n=587).[32] However, the study did not distinguish between minor and major anomalies, and did not report the type of ASM treatment (monotherapy or polytherapy) or doses used. Moreover, based on additional comparisons, the authors concluded the difference may be attributable to the underlying indication rather than ASM exposure.

Small-for-gestational age (SGA)/birth weight

Data on SGA or birth weight in relationship to paternal ASM exposure are provided in table 4. There was no significant increase in the number of infants born SGA in one prospective cohort study of ASM-exposed offspring (n=241) when compared with unexposed offspring (n=106 899).[33] One population-based study of diazepam-exposed infants (n=1354) found an increase in the rates of SGA compared with unexposed offspring (n=3 36 893); however, the authors noted that the finding may be confounded by maternal age and smoking status.[36]

One cross-sectional study reported normal birth weight for infants paternally exposed to ASMs (n=22),[28] and a prospective cohort study found no increase in the number of ASM-exposed infants (n=241) with low birth weight compared with unexposed controls (n=106 899).[33]

Other outcomes

One prospective cohort study found no increase in the rates of low APGAR scores or pre-term births among infants exposed to ASMs (n=241) compared with unexposed offspring (n=1 06 899)[33] (online supplemental table 1). A population-based study of offspring paternally exposed to diazepam (n=1354) found more than a two-fold increased risk of perinatal mortality compared with unexposed offspring (n=3 36 893); however, the study failed to control for maternal age and smoking status, and maternal diazepam exposure.[36] The same study found no increased risk of spontaneous abortion, pre-term birth, Down's syndrome, or other chromosomal abnormalities for offspring paternally exposed to diazepam, compared with unexposed offspring.[36] In a small cohort study, infants paternally exposed to ASMs (n=22) were reported to have normal birth length.[28]

DISCUSSION

This systematic review is timely in view of the 2024 public release by the EMA[25] and the MHRA[38] of the main results of a meta-analysis of data from a retrospective observational study on birth outcomes in children born to men taking valproate, lamotrigine or levetiracetam at about the time of conception. The study, based on data from multiple registry databases in Denmark, Sweden, and Norway, is yet to be published after peer review and therefore could not be included in our analysis. However, an extended abstract has been made available recently on the EMA website.[26] The findings of the study indicated that paternal exposure to valproate in the 3 months before conception was associated in the offspring with a pooled adjusted HR of 1.50 (95% CI: 1.09 to 2.07) for neurodevelopmental disorders (a composite outcome comprising intellectual disabilities, ASD and ADHD) compared with exposure to lamotrigine or levetiracetam. The adjusted cumulative risk of neurodevelopmental disorders was estimated to be 'around 5%' in the valproate-exposed cohort compared with 'around 3%' in the lamotrigine- and levetiracetam-exposed cohorts.[25] No difference between exposure groups was found for congenital malformations in a pooled analysis across Denmark and Norway (crude pooled OR=0.81, 95% CI: 0.48 to 1.36).[26] Overall, the study

Table 4 Anatomical outcomes in offspring paternally exposed to ASMs at time of conception

Study	Congenital anomalies	SGA / birth weight
Christensen *et al*[30]	n=48 VPA-exposed offspring (n=1336) had an MCM compared with n=43 855 of VPA-unexposed children (n=1,234,017): aRR=0.89 (95% CI 0.67 to 1.18). In n=715 children paternally exposed to high-dose valproate (>750 mg/d), n=26 had an MCM (aRR=0.91(95% CI 0.62–1.33)) and of n=621 offspring exposed to low-dose valproate (≤750 mg/d), n=22 had an MCM (aRR=0.87(95% CI 0.57–1.32)).	n/r
Dieterich *et al*[28]	No MCMs were reported among n=22 offspring of ASM-treated fathers with epilepsy.	Normal birth weight reported for n=22 offspring of ASM-treated fathers with epilepsy
Engeland *et al*[36]	Among n=1354 offspring paternally exposed to diazepam, 2.2% (n=30) had a serious birth defect compared with unexposed offspring (N and % n/r): OR=1.0 (0.72–1.5).	13% (n=178) of n=1354 offspring of fathers taking diazepam at time of conception were born SGA compared with unexposed offspring (N and % n/r): OR=1.4 (95% CI 1.2 to 1.6)
Shapiro *et al*[29]	4.5% (n=18) offspring of ASM-treated fathers with epilepsy (n=396) had an MCM, compared with 6.6% (n=20) offspring of mothers with epilepsy on ASMs (n=305), and 2.7% (n=1355) offspring where neither parent had epilepsy (n=49 590).	n/r
Tomson *et al*[31]	4.8% (n=100) of n=2087 paternally ASM-exposed offspring born to fathers with epilepsy had MCMs compared with 4.9% (n=121) of n=2457 unexposed offspring born to fathers with epilepsy: aOR=0.9 (95% CI 0.7 to 1.2). ASM monotherapy-exposed offspring vs offspring born to fathers with epilepsy not taking ASMs (N and % n/r), aOR=0.85 (95% CI 0.62 to 1.16). **VPA monotherapy:** 4.8% (n=22) offspring of n=458 VPA-treated fathers with epilepsy had MCMs compared with 4.9% (n=121) of n=2457 offspring born to fathers with epilepsy not taking ASMs: aOR=0.9 (95% CI 0.6 to 1.5). **CBZ monotherapy:** 5.5% (n=32) offspring of n=582 CBZ-treated fathers with epilepsy had MCMs compared with 4.9% (n=121) of n=2457 offspring born to fathers with epilepsy not taking ASMs: aOR=1.0 (95% CI 0.6 to 1.5). **Other monotherapies**: 3.8% (n=23) offspring of n=605 fathers with epilepsy on other ASM monotherapies had MCMs compared with 4.9% (n=121) of n=2457 offspring born to fathers with epilepsy not taking ASMs: aOR=0.7 (95% CI 0.4 to 1.1)	n/r
Veiby *et al*[33]	2.1% (n=8) of n=241 ASM-exposed offspring of fathers with epilepsy had MCMs compared with 2.9% (n=3100) of n=106 899 unexposed controls: OR=0.6 (95% CI 0.2 to 1.5). 2.9% (n=12) of n=409 offspring born to fathers with epilepsy not taking ASMs had MCMs compared with unexposed controls: OR=1.0 (95% CI 0.6 to 1.8).	10% (n=24) of n=241 ASM-exposed offspring of fathers with epilepsy born SGA, compared with 7.5% (n=8017) of n=106 899 unexposed controls: OR=1.4 (95% CI 0.9 to 2.2). 7.4% (n=30) of n=409 offspring born to fathers with epilepsy not taking ASMs were born SGA compared with unexposed controls: OR=1.0 (95% CI 0.7 to 1.5). 3.3% (n=8) of n=241 ASM-exposed offspring of fathers with epilepsy had low birth weight, compared with 4.7% (n=5024) of n=106 899 unexposed controls: OR=0.7 (95% CI 0.4 to 1.5). 4.9% (n=20) of n=409 offspring born to fathers with epilepsy not taking ASMs had low birth weight compared with unexposed controls: OR=1.1 (95% CI 0.7 to 1.7).
Wensink *et al*[37]	**BZD-derived anxiolytics:** 3.2% (n=97) had at least one MCM compared with unexposed controls (N and % n/r): aOR=1.02 (95% CI 0.83 to 1.25). **BZDs as hypnotics and sedatives:** 2.9% (n=21) had at least one MCM compared with unexposed controls (N and % n/r): aOR=0.93 (95% CI 0.60 to 1.43).	n/r
Yang *et al*[32]	12.05% (n=372) offspring of n=3086 ASM-treated fathers with epilepsy had congenital anomalies (no differentiation between major and minor) compared with 10% (n=73 073) of offspring of fathers with epilepsy not taking ASMs (n=730 196): aOR=1.23 (95% CI 1.10 to 1.37), aOR with further adjustment for paternal age=1.19 (95% CI 1.05 to 1.34) **VPA:** 11.19% (n=90) offspring of n=805 VPA-treated fathers with epilepsy had congenital anomalies compared with 10% (n=73,073) of offspring of fathers with epilepsy not taking ASMs (n=730 196): aOR=1.12 (95% CI 0.90 to 1.40), aOR with further adjustment for paternal age=1.05 (95% CI 0.84 to 1.32). **CBZ:** 10.06% (n=69) offspring of n=686 CBZ-treated fathers with epilepsy had congenital anomalies compared with 10% (n=73,073) of offspring of fathers with epilepsy not taking ASMs (n=730 196): aOR=1.00 (95% CI 0.78 to 1.28), aOR with further adjustment for paternal age=0.95 (95% CI 0.73 to 1.22). **LTG:** 13.24% (n=81) offspring of n=612 LTG-treated fathers with epilepsy had congenital anomalies compared with 10% (n=73,073) of offspring of fathers with epilepsy not taking ASMs (n=730 196): aOR=1.36 (95% CI 1.08 to 1.72), aOR with further adjustment for paternal age=1.28 (95% CI 1.01 to 1.63). **OXC:** 13.78% (n=81) offspring of n=588 OXC-treated fathers with epilepsy had congenital anomalies compared 10% (n=73,073) of offspring of fathers with epilepsy not taking ASMs (n=730 196): aOR 1.41 (9%% CI 1.11 to 1.78), aOR with further adjustment for paternal age=1.32 (95% CI 1.04 to 1.69).	

AHR, adjusted hazard ratio; aOR, adjusted odds ratio; aRR, adjusted risk ratio; ASM, antiseizure medication; BZD, benzodiazepine; CBZ, carbamazepine; CI, confidence interval; LTG, lamotrigine; MCM, major congenital malformation; n/r, not reported; OR, odds ratio; OXC, oxcarbazepine; SGA, small-for-gestational age; VPA, sodium valproate.

had several major methodological limitations, largely related to inability to account for potential major confounders. In particular, the analysis could not control for the paternal condition for which the treatments were prescribed, even though epilepsy was more common in the valproate cohort (57–70%, depending on country) than in the combined levetiracetam/lamotrigine cohort (41–59%). Likewise, the study did not control for the type of epilepsy, which probably differed across exposure groups and may have influenced neurodevelopmental risks. There was also considerable heterogeneity in datasets and outcomes across countries, and across treatment groups. Importantly, duration of follow-up of exposed offspring differed across ASM groups, being longer for valproate. In Sweden and Denmark, the proportion of offspring followed up for >8 years was almost twice as large in the valproate group compared with the lamotrigine/levetiracetam group (Sweden: 41.8% vs 23.3%; Denmark: 74.3% vs 40.2%). Since the probability of identifying a neurodevelopmental disorder, including ASD, is age-dependent and is likely

to be highest when children start school, this may have biased the risk estimate against the valproate-exposed group. The EMA's public release and the study abstract do acknowledge the study limitations, including the inability to identify the type(s) of neurodevelopmental disorders at putatively increased risk, and emphasise that because of potential confounders a cause-effect relationship with paternal valproate exposure could not be established.

Our systematic review did not find clear evidence of an increased risk of adverse outcomes among offspring paternally exposed to ASMs. While there were some isolated unfavourable findings, these were not confirmed by other studies. Specifically, an increased prevalence of autistic traits reported at age 18 months in ASM-exposed offspring was not confirmed using a more robust assessment tool at the same age, or replicated by another ASD screening tool in the same cohort at age 36 months,[33] or confirmed by other population-based studies.[30 31 34] Other signals included a report of abnormal personal-social skills at age 18 months in the same cohort of ASM-exposed offspring with autistic traits,[33] an increased risk of SGA following paternal exposure to diazepam that was likely confounded by maternal factors,[36] and an increased risk of birth defects reported in a study that was hampered by combining minor and major malformations[32] and was not replicated by other investigations.[28–33 36 37] While nothing especially alarming emerges from this review, only a few studies were included and some of these had a relatively small sample size and therefore low power to detect treatment effects. Moreover, many studies combined ASM exposures together, precluding detailed analysis of outcomes associated with individual ASMs. Of note, risks associated with paternal valproate exposure were investigated by only three studies with respect to risk of congenital malformations,[30 31 32] and by only two studies with respect to risk of neurodevelopmental disorders.[30 31] Of note, the latest population-based study from Denmark, published after the release of the MHRA restrictions, focused specifically on neurodevelopmental disorders after paternal valproate exposure compared with unexposed controls, and found no significant increase in risk, with the upper limit of the 95% CI of the adjusted HR being below the risk estimate of the EMA-commissioned study.[30]

There were several methodological weaknesses identified by our review. In addition to failure by most studies to provide data on risks associated with specific ASMs, only one study[30] assessed the influence of paternal ASM dose, which is known to affect the risk of MCMs and adverse neurodevelopmental outcomes in offspring of ASM-treated mothers.[39 40] Moreover, many studies neglected to control for confounders, such as age, educational attainment, exposure to other teratogens, relevant medical and psychiatric history, and other factors. There was heterogeneity in the length of follow-up for some studies, particularly those aimed at investigating neurodevelopmental outcomes, with some conducted during infancy[35] or early childhood[29 33] and others extending follow-up into adolescence.[31 34] Furthermore, there was heterogeneity in how neurodevelopmental disorders were measured and defined, with some studies investigating the presence of specific traits,[33 35] and others quantifying the risk of diagnosis of neurodevelopmental disorders at a population level.[30 31 34] For studies aimed at investigating the risk of MCMs, there was variability in how congenital anomalies were measured, with some applying stringent classification systems (eg, the European Surveillance of Congenital Anomalies (EUROCAT), and the International Classification of Diseases (ICD)-10) for the definition of MCMs,[30–32 41] whereas another measured the presence of any defect with no distinction made between major or minor anomalies.[32] This variability in the definition and measurement of both MCMs and neurodevelopmental outcomes hindered data synthesis and prevented meta-analysis for this review.

Evaluating second generation adverse effects of medications is methodologically challenging because these effects can only be investigated in observational studies. These studies are subject to bias from unmeasured potential confounding variables, and therefore an understanding of risks requires a clear signal across multiple investigations, which is precisely what is lacking based on the evidence reviewed. To date, the only signal of concern was raised by the EMA-commissioned study which, as discussed above, could be affected by major confounders. The European regulator acknowledged that available data are inconclusive in establishing cause-effect relationships, but recommended that doctors should inform males taking valproate about the potential risks, discuss the possibility of effective contraception, and review regularly the need for valproate therapy particularly for individuals planning fatherhood.[25] The MHRA took a more restrictive approach, apparently influenced by preclinical data on valproate reproductive toxicity and potential association with reduced fertility, and determined that, as from 31 January 2024 'valproate must not be started in new patients (male or female) younger than 55 years unless two specialists independently consider and document that there is no other effective or tolerated treatment, or there are compelling reasons why the reproductive risks do not apply'.[38] The wisdom of the UK regulatory changes has been questioned[42] because restricting the use of valproate could result in prescription of a less effective medication, particularly in individuals with generalised epilepsies where valproate is the most effective ASM.[43] Avoidance of valproate or its delayed introduction in individuals that require this medication for seizure control is likely to lead to an increased risk of morbidity and mortality, including an increased risk of sudden unexpected death in epilepsy (SUDEP). A significant increase in maternal SUDEP has already been shown in the UK during a period in which the stricter guidelines for prescribing valproate in females were introduced.[44] There is also a risk of generating anxiety among valproate-treated men with epilepsy, ultimately leading to poor medication adherence and breakthrough seizures. In view of the findings of this systematic review, particularly the reassuring results from the recent large population-based study from Denmark,[30] the MHRA restrictions regarding the use of valproate in men should be reappraised and potentially revised.

While the findings summarised in our systematic review are overall reassuring for males taking ASMs including valproate, it is clear that the potential reproductive implications of ASM exposure in males remain an under-investigated area of research that should be prioritised over the next decade. Future research should aim at replicating the methodology of maternal ASM studies and employ detailed clinical evaluations of offspring paternally exposed to different ASM monotherapies through implementation of large prospective investigations. Some of these studies could use the infrastructure already established for prospective pregnancy registries of women taking ASMs and begin to enrol males on ASMs to assemble a well-characterised cohort of offspring outcome data.

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