NHS
North East and North Cumbria

North East and North Cumbria – An ICB Valproate Experience

Rhys Thomas and Helena Gregory

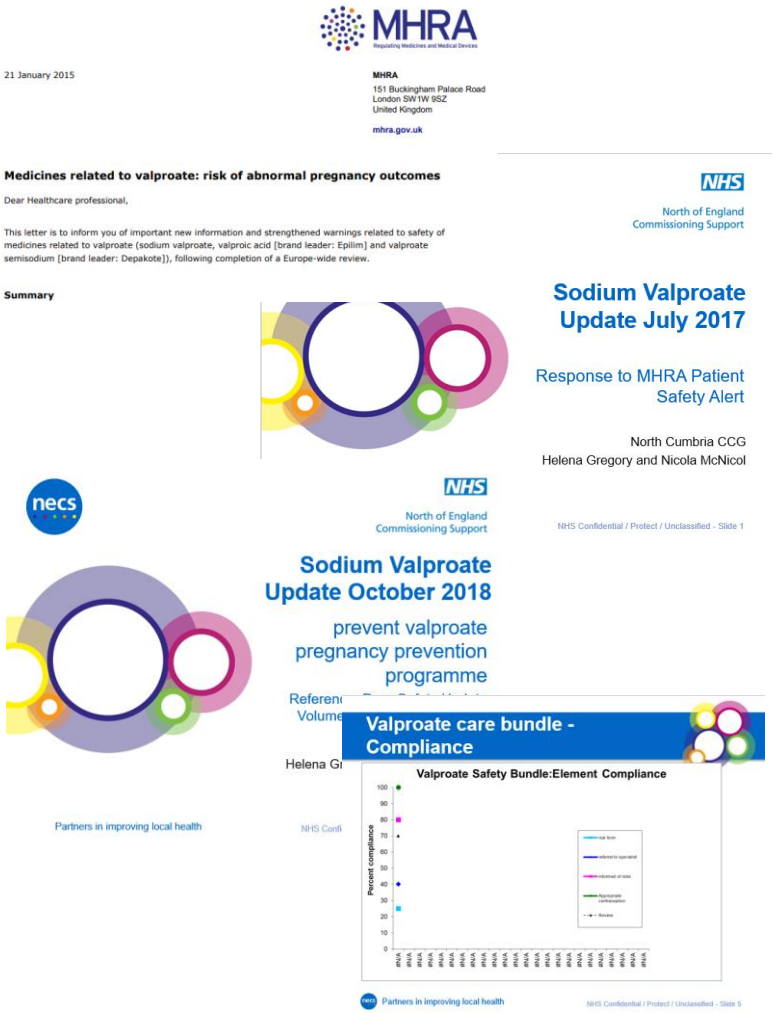
February 2024

Today's presentation

- North East and North Cumbria
- Experience over time with Valproate
- Establishment of our Valproate Working Group
- Learning from workshop:
  - Workforce pressures
  - Calculating the risk
  - Unintended consequences
  - Population health and health literacy
  - Digital and data as enablers
- The contraception question
- What does the future hold?

North East and North Cumbria

Experience over time with valproate


MHRA

21 January 2015

MHRA
151 Buckingham Palace Road
London SW1W 9SZ
United Kingdom
mhra.gov.uk

Medicines related to valproate: risk of abnormal pregnancy outcomes

Dear Healthcare professional,

This letter is to inform you of important new information and strengthened warnings related to safety of medicines related to valproate (sodium valproate, valproic acid [brand leader: Epilim] and valproate semisodium [brand leader: Depakote]), following completion of a Europe-wide review.

Summary

NHS
North of England Commissioning Support

Sodium Valproate Update July 2017

Response to MHRA Patient Safety Alert

North Cumbria CCG
Helena Gregory and Nicola McNicol

NHS
North of England Commissioning Support

NHS Confidential / Protect / Unclassified - Slide 1

necs

Sodium Valproate Update October 2018

prevent valproate pregnancy prevention programme

Partners in improving local health

Valproate care bundle - Compliance

Valproate Safety Bundle:Element Compliance

Percent compliance

Partners in improving local health

NHS Confidential / Protect / Unclassified - Slide 5


Clinical Medicine 2018 Vol 18, No 2: s1–s8 LINACRE LECTURE

Valproate: life-saving, life-changing

Author: Rhys H Thomas[A]

Antiepileptic medications, and val

The drug that's harmed more children than Thalidomide

SUE REID on how an epilepsy drug that's STILL being given in pregnancy has left 20,000 British children with a host of physical or mental problems

The Daily Telegraph

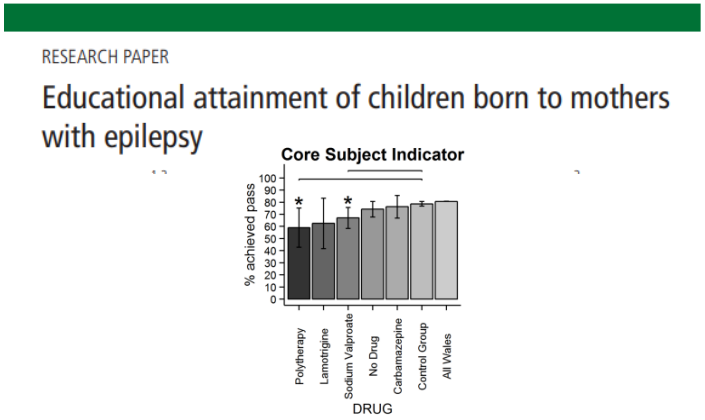
'Worst child poisoning case since thalidomide'

MY EPILEPSY DRUGS LEFT MY children disabled

I want a public inquiry into epilepsy drug that harmed my five babies

Why are doctors still not warning about the 'new Thalidomide'?

Rhys spoke at the Royal College of Physicians as the Linacre Lecturer 2017 about valproate and scholastic impact in exposed children


RESEARCH PAPER

Educational attainment of children born to mothers with epilepsy

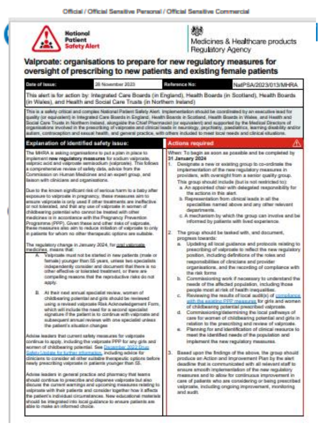
Core Subject Indicator

% achieved pass

Polytherapy
Lamotrigine
Sodium Valproate
No Drug
Carbamazepine
Control Group
All Wales

DRUG

Establishment of our Valproate Working Group



Official / Official Sensitive Personal / Official Sensitive Commercial

National Patient Safety Alert

Medicines & Healthcare products Regulatory Agency

Valproate: organisations to prepare for new regulatory measures for oversight of prescribing to new patients and existing female patients

Date of issue:	28 November 2023	Reference No:	NatPSA/2023/013/MHRA

This alert is for action by: Integrated Care Boards (in England), Health Boards (in Scotland), Health Boards (in Wales), and Health and Social Care Trusts (in Northern Ireland)

This is a safety critical and complex National Patient Safety Alert. Implementation should be coordinated by an executive lead for quality (or equivalent) in Integrated Care Boards in England, Health Boards in Scotland, Health Boards in Wales, and Health and Social Care Trusts in Northern Ireland, alongside the Chief Pharmacist (or equivalent) and supported by the Medical Directors of organisations involved in the prescribing of valproate and clinical leads in neurology, psychiatry, paediatrics, learning disability and/or autism, contraception and sexual health, and general practice, with others included to meet local needs and clinical situations.

Explanation of identified safety issue:

The MHRA is asking organisations to put a plan in place to implement **new regulatory measures** for sodium valproate, valproic acid and valproate semisodium (valproate). This follows a comprehensive review of safety data, advice from the Commission on Human Medicines and an expert group, and liaison with clinicians and organisations.

Due to the known significant risk of serious harm to a baby after exposure to valproate in pregnancy, these measures aim to ensure valproate is only used if other treatments are ineffective or not tolerated, and that any use of valproate in women of childbearing potential who cannot be treated with other medicines is in accordance with the Pregnancy Prevention Programme (PPP). Given these and other risks of valproate, these measures also aim to reduce initiation of valproate to only in patients for whom no other therapeutic options are suitable.

The regulatory change in January 2024, for oral valproate medicines, means that:

A. 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 that the reproductive risks do not apply.

B. At their next annual specialist review, women of childbearing potential and girls should be reviewed using a revised valproate Risk Acknowledgement Form, which will include the need for a second specialist signature if the patient is to continue with valproate and subsequent annual reviews with one specialist unless the patient's situation changes.

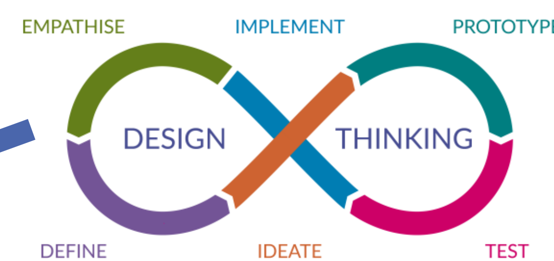
Advise leaders that current safety measures for valproate continue to apply, including the valproate PPP for any girls and women of childbearing potential. See December 2022 Drug Safety Update for further information, including advice for clinicians to consider all other suitable therapeutic options before newly prescribing valproate in patients younger than 55.

Advise leaders in general practice and pharmacy that teams should continue to prescribe and dispense valproate but also discuss the current warnings and upcoming measures relating to valproate with their patients and consider together how it affects the patient's individual circumstances. New educational materials should be integrated into local guidance to ensure patients are able to make an informed choice.

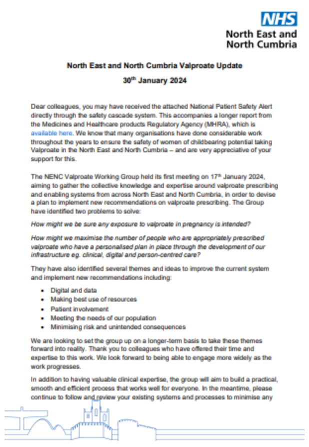
Actions required

When: To begin as soon as possible and be completed by **31 January 2024**

1. Designate a new or existing group to co-ordinate the implementation of the new regulatory measures in providers, with oversight from a senior quality group.
   This group should include (but is not restricted to):
   a. An appointed chair with delegated responsibility for the actions in this alert.
   b. Representation from clinical leads in all the specialities named above and any other relevant departments.
   c. A mechanism by which the group can involve and be informed by patients with lived experience.
2. The group should be tasked with, and document, progress towards:
   a. Updating all local guidance and protocols relating to prescribing of valproate to reflect the new regulatory position, including definitions of the roles and responsibilities of clinicians and provider organisations, and the recording of compliance with the risk forms.
   b. Commissioning work if necessary to understand the needs of the affected population, including those people most at risk of health inequalities.
   c. Reviewing the results of local audit(s) of compliance with the existing PPP measures for girls and women of childbearing potential prescribed valproate.
   d. Commissioning/determining the local pathways of care for women of childbearing potential and girls in relation to the prescribing and review of valproate.
   e. Planning for and identification of clinical resource to meet the identified needs of the population and implement the new regulatory measures.
3. Based upon the findings of the above, the group should produce an Action and Improvement Plan by the alert deadline that is communicated with all relevant staff to ensure smooth implementation of the new regulatory measures and to allow for continuous improvement in care of patients who are considering or being prescribed valproate, including ongoing improvement, monitoring and audit.



Now	January 2024	Not happening
• Improving reliability of Pregnancy Prevention Programme • Optimising shared decision making in medication review	• Two independent specialists agree to initiation for all under 55's • Switching to alternatives unless patient and two independent specialists agree to continuation	• Valproate products withdrawn • Valproate blacklisted • Patients forced to stop or switch



NHS
North East and North Cumbria

North East and North Cumbria Valproate Update

30th January 2024

Dear colleagues, you may have received the attached National Patient Safety Alert directly through the safety cascade system. This accompanies a longer report from the Medicines and Healthcare products Regulatory Agency (MHRA), which is available here. We know that many organisations have done considerable work throughout the years to ensure the safety of women of childbearing potential taking Valproate in the North East and North Cumbria – and are very appreciative of your support for this.

The NENC Valproate Working Group held its first meeting on 17th January 2024, aiming to gather the collective knowledge and expertise around valproate prescribing and enabling systems from across North East and North Cumbria, in order to devise a plan to implement new recommendations on valproate prescribing. The Group have identified two problems to solve:

How might we be sure any exposure to valproate in pregnancy is intended?

How might we maximise the number of people who are appropriately prescribed valproate who have a personalised plan in place through the development of our infrastructure eg. clinical, digital and person-centred care?

They have also identified several themes and ideas to improve the current system and implement new recommendations including:

- Digital and data
- Making best use of resources
- Patient involvement
- Meeting the needs of our population
- Minimising risk and unintended consequences

We are looking to set the group up on a longer-term basis to take these themes forward into reality. Thank you to colleagues who have offered their time and expertise to this work. We look forward to being able to engage more widely as the work progresses.

In addition to having valuable clinical expertise, the group will aim to build a practical, smooth and efficient process that works well for everyone. In the meantime, please continue to follow and review your existing systems and processes to minimise any

Learning from workshop

Huge passion and experience from the group – great collective ‘hive mind’.

Will implementing double signature fix underlying issues?

What is the quality of consultations?

Is there risk of unintended consequences from focusing resource on this issue?

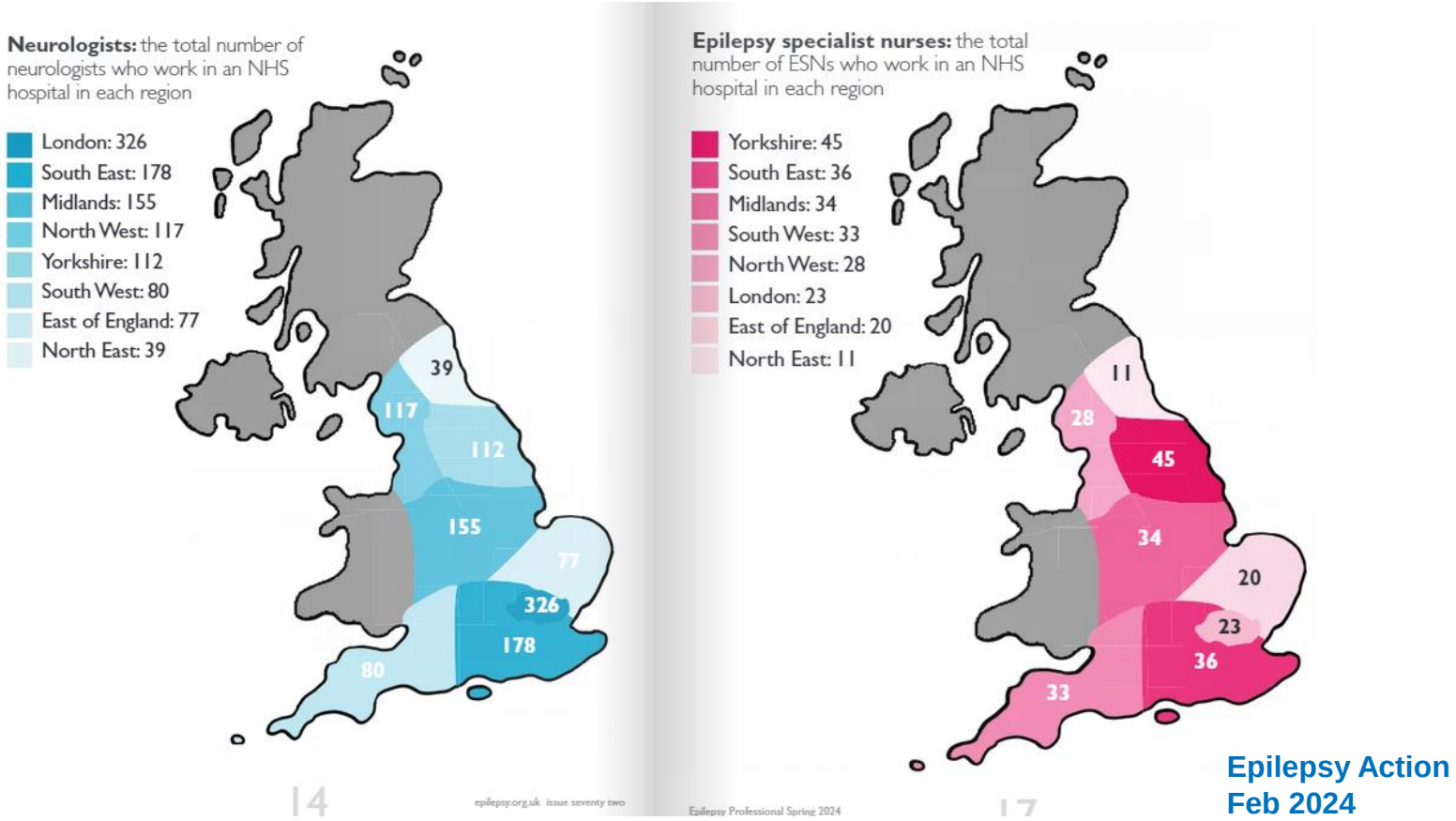
Who is holding the risk from this issue?

What are the constraints on our resource (workforce, financial)?

How are our population different from other areas – geography, demography, health literacy?

How do we get this right for our teams for 2024 and beyond?

Workforce pressures



Epilepsy Action
Feb 2024

Four fold discrepancy There is one neurologist for every 755 people with epilepsy in the North East compared with one for every 191 in London

Calculating the risk

We could identify women on VPA rates for ICB and could estimate which centre was their lead

Neurology ~67% (but no team 8%)

Approximately 50% of women taking VPA carry little long-term pregnancy risk due to 'behavioural or biological' reasons - the attempt to look at ARAF exclusions missed severe LD, same sex relationship

The 'PPP declined' rate was negligible (less than 1%) but primary care coding poor

My centre – 350 annual reviews

With a second signature the cost of this changes from one new clinic a year to two

Unintended Consequences

Our ICB

Estimated 1.4 exposed pregnancies a year

- we cannot find a single woman delivering on valproate at our neuroscience centre since 2018

Estimated 1 epilepsy related death a week

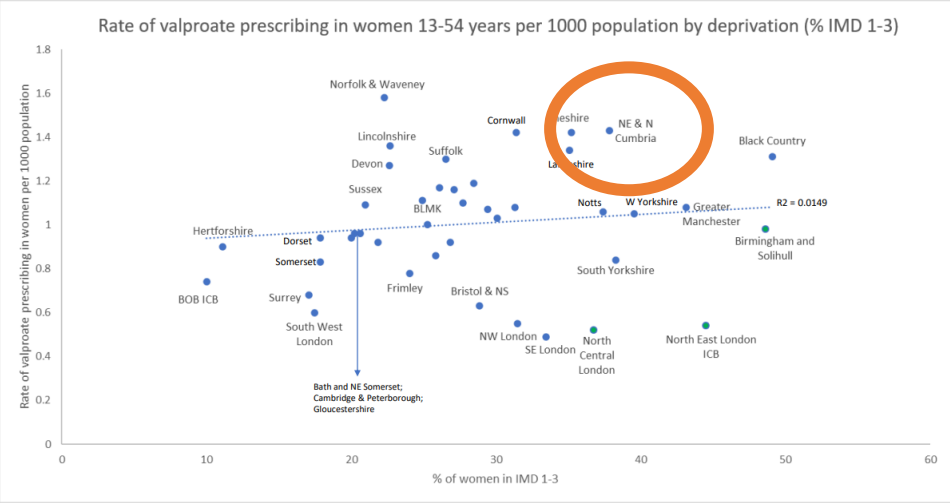
- of which up to 80% may be preventable, including SUDEP

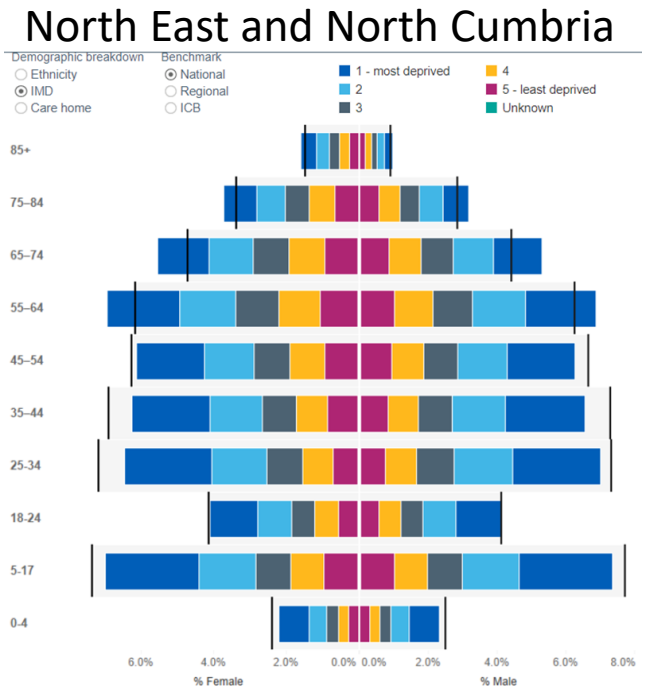
So is the majority of the risk carried by people with epilepsy? Or by people who do not attend clinics?

Population health and health literacy

Health literacy team – new patient guide has a reading age of 17y, whereas we need 9-11y for our population

North East and Cumbria learning disability network





Digital and data as enablers

Useful to understand national work e.g. pilots, national register, digital ARAF, systems – what can we adapt/ adopt?

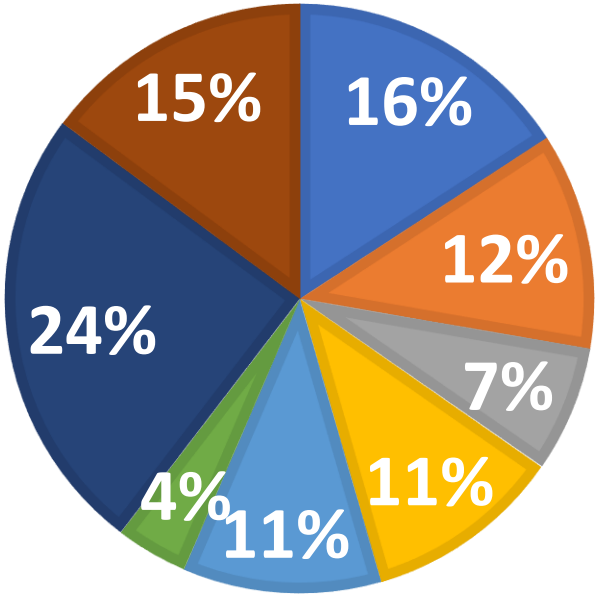
Interesting to explore local options e.g. Great North Care Record – what can we develop/ create?

Are we considering human factors around use of digital resources – how do people use digital tools so we can make them work for them?

Very helpful data process already undertaken to inform group

Associate Chief Clinical Information Officer key team member – also on ICB Medicines Safety Group

The contraception question



- On highly effective contraception
- On effective contraception
- No evidence at all
- No evidence but discussed
- No evidence but unlikely to occur
- No evidence but effective+barrier
- Record includes permanent coding
- Other

Pregnancy testing and contraception for pregnancy prevention during treatment with medicines of teratogenic potential

- **Risk of pregnancy should be assessed prior to each teratogen prescription**
  - Risk of pregnancy may be high at start of a method or when switching between methods due to risk of pregnancy from unprotected sex prior to starting the method, unreliable use of the previous contraceptive method, and/or time needed to establish contraceptive efficacy at the start of the new method.
  - Pregnancy tests at start of contraceptive method may not detect an early pregnancy following unprotected sex in the last three weeks;
- **Any starter on new method contraception should have a repeat pregnancy test at 3 weeks if there is any risk of pregnancy at start of contraceptive method**
- The duration of teratogen prescriptions may need to be shortened for patients who use contraceptive methods that require frequent pregnancy testing

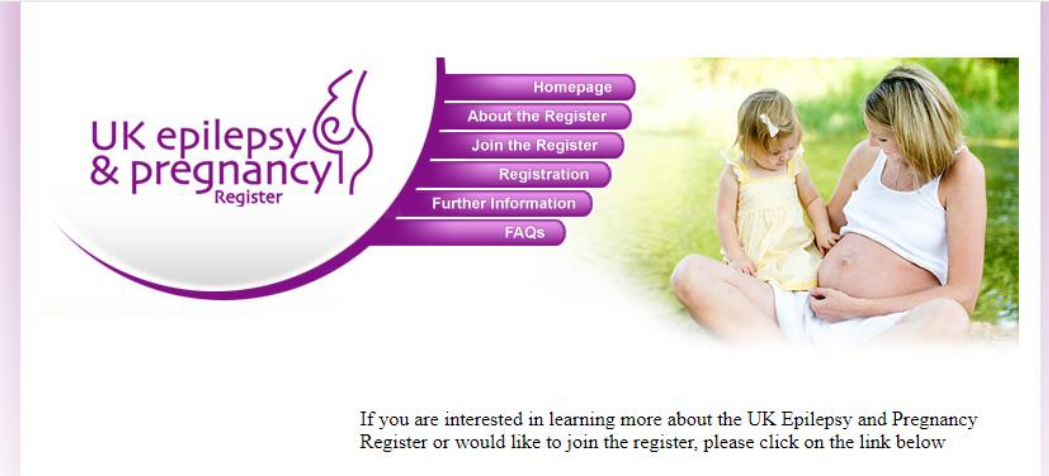
Effectiveness of contraceptive in typical use[1]	Contraceptive method	Duration contraceptive method used / other situations	Pregnancy test needed before next teratogen prescription?
Highly effective methods **(Typical use failure rates less than 1%)**	Copper intrauterine device (copper IUD)	Established user more than 3wks to 5-10 yrs (depending on IUD[2])	No
	Levonorgestrel-releasing intrauterine system (LNG-IUS)	Established user more than 3wks to 3-5 yrs (depending on IUS[2])	No
	Progestogen Implant	Established user more than 3wks to 3yrs	No
		Established user (more than 3wks), but concurrent use of interacting medicines which may affect efficacy[3]	Yes + review / refer for contraceptive advice
Effective methods **(Typical use failure rates greater than 1%)** **Additional barrier methods are advised during teratogen use**	Depot medroxyprogesterone acetate (DMPA) subcutaneous (SC) or intramuscular (IM) injections[4]	Established user (more than 3wks + repeat injections on schedule) and less than 13 wks since last injection + documented as administered by healthcare professionals	No
		Established user (more than 3wks + repeat injections on schedule and less than 13 wks since last injection) but self-administered or undocumented administration	Yes, test if any suspected risk of pregnancy
		More than 13 wks since last injection (ie beyond recommended duration of use of last injection)	Yes + review / refer for contraceptive advice
	Combined hormonal contraceptives (pills, patches or vaginal ring) or progestogen-only pills	Established user (more than 3wks), reliable and consistent use	Yes, test if any suspected risk of pregnancy
		Established user (more than 3wks) but with unreliable or inconsistent use of method, eg: • missed pills, late patch • Diarrhoea or vomiting; • use of other interacting medicines that may affect efficacy[3]	Yes + review / refer for contraceptive advice
	Other methods or no contraception	Any duration of use of other methods	Yes + review / refer for contraceptive advice;
		No contraception	Assess need for contraception + test if any suspected risk of pregnancy + review / refer for contraceptive advice;

What does the future hold?

Our prevalent male VPA population is 9 males to every 1 woman (national average 4:1)

Other medicines e.g. topiramate, pregabalin?

Funding of our national surveillance system?



Thanks a lot

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