Listening to the public
Case study - Valproate

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NEWS

Women still not being told about pregnancy risks of valproate

Jacqui Wise

London

Two thirds of women who take the antiepileptic drug sodium valproate said they had not received new safety warnings about the dangers of taking it during pregnancy, a survey carried out by epilepsy charities has found. A similar survey last year found that half of women taking the drug were unaware it could harm their fetus.[1]

The new results are to be presented at a public hearing on the safety of valproate drugs organised by the European Medicines Agency on 26 September in London. This is the first time that the EMA has held a public hearing as part of the safety review of a drug, and it will be broadcast live on the agency's website.[2] The agency's pharmacovigilance risk assessment committee is currently looking at whether the risks of valproate drugs require further restrictions on use

drugs by women and girls. In February 2016 the MHRA launched a valproate toolkit to help health professionals talk to women with epilepsy about the risks during pregnancy, which included leaflets and other materials.[3]

The new survey of 2000 women with epilepsy between the ages of 16 and 50 was commissioned by the Epilepsy Society, Epilepsy Action, and Young Epilepsy in conjunction with the MHRA. Of the 475 women who were taking the drug, 18% did not know that it could harm the development and physical health of their unborn child if they became pregnant. More than a quarter (28%) said that they had not been given any information about the risks for their unborn child, and 68% said that they had not received any of the new toolkit materials.

Bevan University Health Board, Newport NP11 5GH, UK;

of major fetal malformation and also causes

aged 15–45 years with epilepsy. The

Questions doctors had prior to the hearing

- **Similar as patients:**
  - Will it contribute to the decision-making? Or post-hoc explanation of an already made decision?
  - Will it be confrontational, political?
  - A dialogue or series of stakeholders' statements?
- **But also:**
  - Will there be accusations ? Looking for responsible persons ? financial compensation ?
  - Will there be room for evidence based medicine or only for 'emotion based medicine' ?
  - How can PRAC make sure that it gets a balanced view and patients with various situations are heard ? Also those girls and women who desperately need valproate for treatment of their epilepsy ?

Questions doctors had prior to the hearing

- **And also:**
  - How we as the neurology community can take care that the voice that we want to give is heard ?
    - We should actively identify and counsel our female patients who might still be using valproate unnecessarily—eg, women with focal epilepsy for whom treatment alternatives that are at least as effective as valproate are available – we want to stop this unnecessary use of valproate due to increased teratogenicity
    - In some cases, valproate might be the only effective treatment. Therefore, valproate treatment still needs to be allowed for females in the rare instances when other options are ineffective or not tolerated.
    - Other alternative treatments carry also risks, some of which are unknown and some of which (depending on the dose) are nearly the same as with valproate, especially if substituing valproate leads to use of polytherapy

Questions doctors had prior to the hearing

- **And also:**
  - Publicity that generates fear and anxiety without guidance may result in women stopping their treatment without support and increase risk of SUDEP

First EMA Public hearing September 2017

Experiences doctors had in the hearing

- **Similar as patients:**
  - All participants could feel they could talk with equal credibility as others and all opinions were listened to, and different opinions could be confronted
- **But also:**
  - Female patients using valproate, because nothing else helps, were not heard
  - Patients, who told their experiences, did not tell that several of them are still on valproate as it works best
  - Families with daughters needing valproate for severe epileptic encephalopathies were not heard
  - ➢ therefore doctors needed to speak for these patients in order for VPA not be contraindicated in female patients

Experiences doctors had in the hearing

- **And also:**
- Much of the discussion dealt only about warning of pregnancy during valproate, however, many situations are very complex and this complexity and adequate information for fully informed decision between different treatment choices should have been discussed more

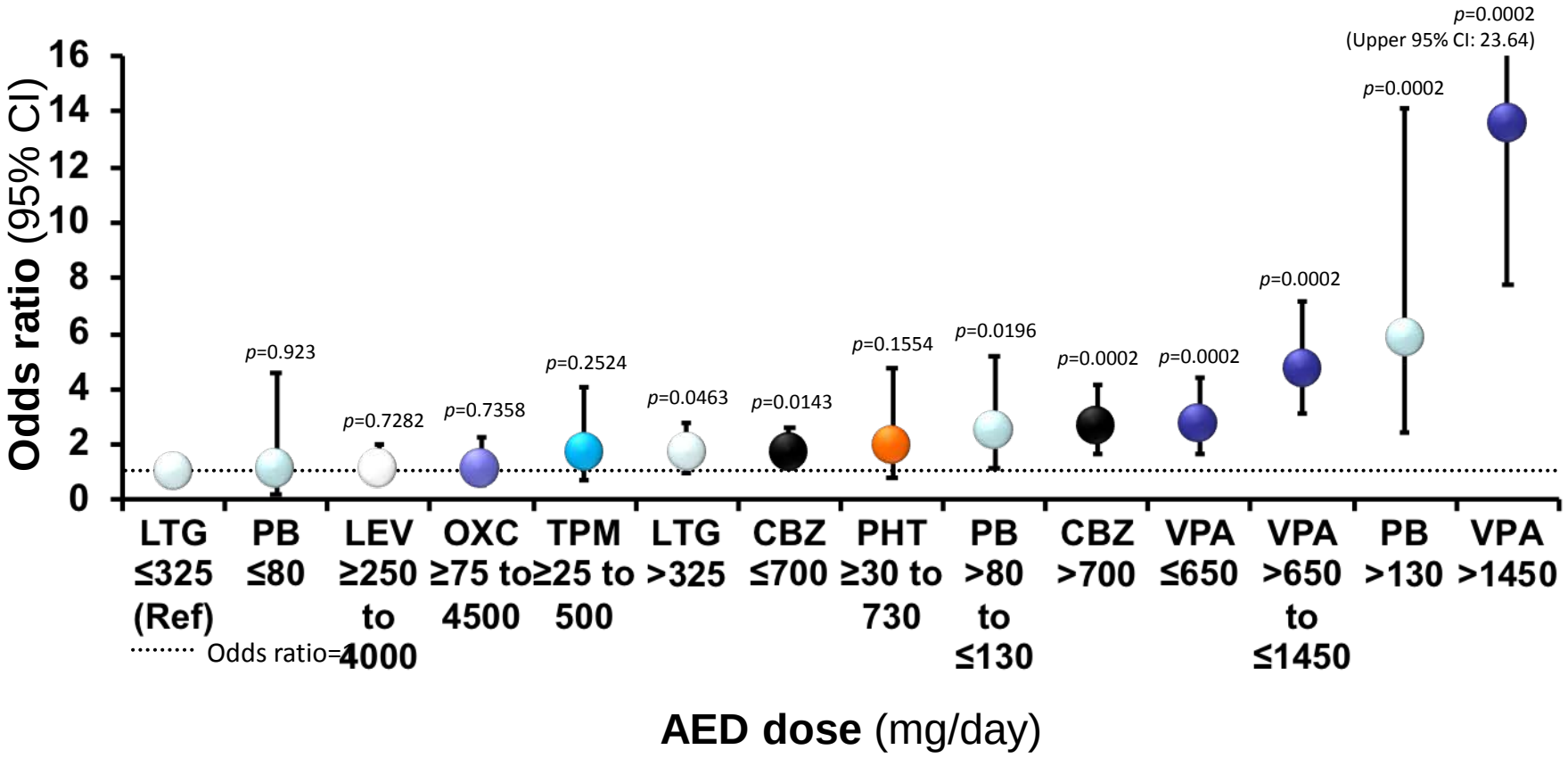
Measures by PRAC February 2018

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

What are the main measures recommended by the PRAC?

- Where licensed for ***migraine*** or ***bipolar disorder***:
  - In *pregnancy* - valproate must not be used.
  - In *female patients from the time they become able to have children* – valproate must not be used unless the conditions of a new ***pregnancy prevention programme*** (see below) are met.
- For ***epilepsy:***
  - In *pregnancy* - valproate must not be used. However it is recognised that for some women with epilepsy it may not be possible to stop valproate and they may have to continue treatment (with appropriate specialist care) in pregnancy.
  - In *female patients from the time they become able to have children* – valproate must not be used unless the conditions of the new ***pregnancy prevention programme*** are met.
- The PRAC has also recommended that the outer packaging of all valproate medicines must include a ***visual warning*** about the risks in pregnancy. In addition to boxed text, this may include a symbol/pictogram, with the details to be adapted at national level.
- A ***patient reminder card*** will also be attached to the outer package for pharmacists to discuss with the patient each time the medicine is dispensed.
- Companies that market valproate should also provide ***updated educational materials*** in the form of guides for healthcare professionals and patients.

Risk of major congenital malformations with different AED monotherapies compared with lamotrigine ≤325 mg/day



AED, antiepileptic drug; CBZ, carbamazepine; CI, confidence interval; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; Ref, reference; TPM, topiramate; VPA, valproate.

Tomson T, *et al. Lancet Neurol* 2018;17:530–8.

Dose-dependent teratogenicity of valproate in mono- and polytherapy: An observational study.

Tomson, Torbjorn; Battino, Dina; Bonizzoni, Erminio; Craig, John; Lindhout, Dick; Perucca, Emilio; Sabers, Anne; Thomas, Sanjeev; Vajda, Frank

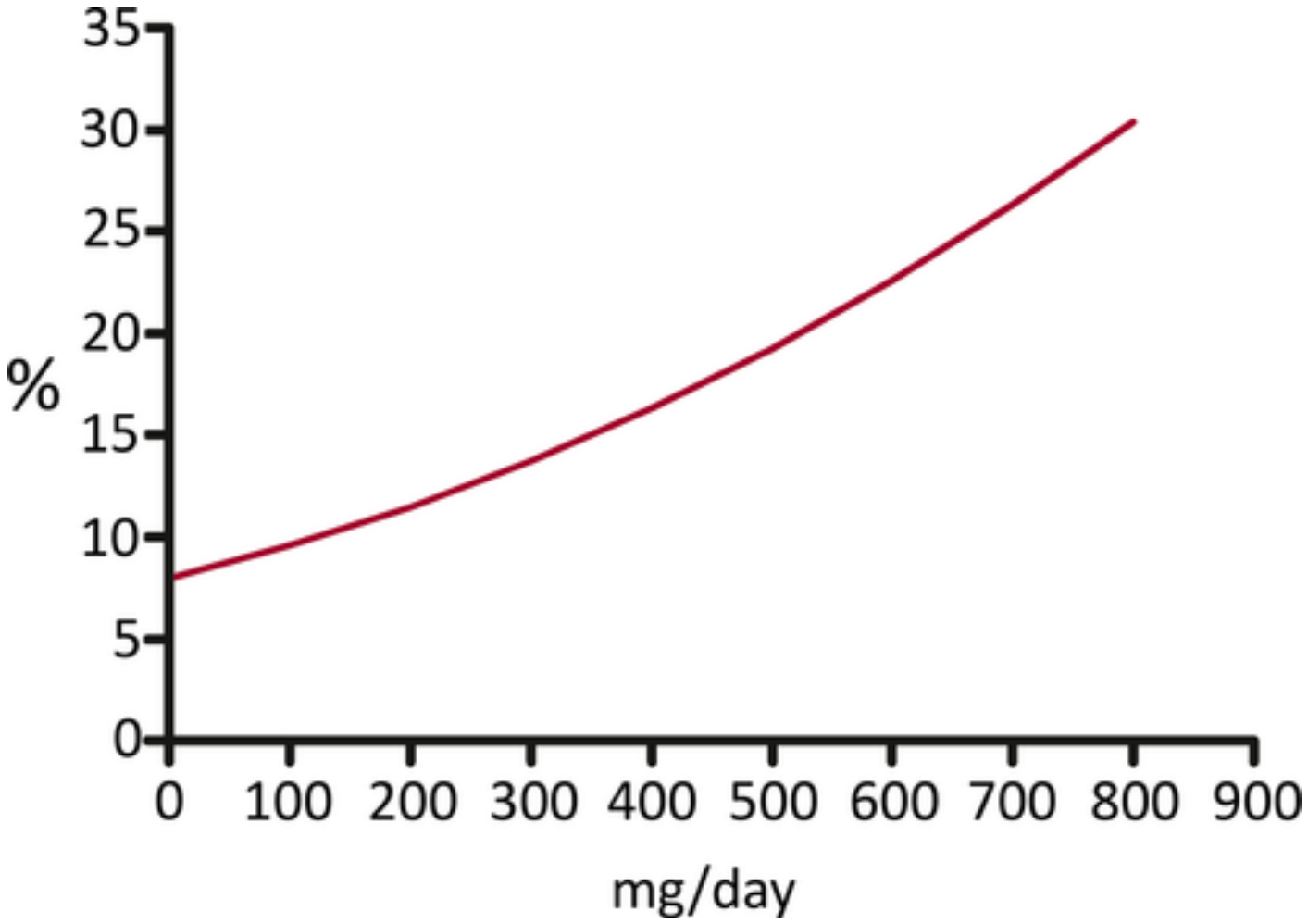
Neurology. 85(10):866-872, September 8, 2015.

Table 3 Frequency of MCMs at different dose categories of VPA, in association with VPA in monotherapy or 2 different types of AEDs polytherapy

	VPA dose			
Type of treatment	<700 mg/d	≥700 to <1,500 mg/d	≥1,500 mg/d	p
VPA monotherapy	5.9; 4.2-8.3 (31/522)	11.0; 8.8-13.8 (66/598)	24.0; 16.8-33.1 (25/104)	<0.0001
VPA + LTG	7.0; 3.0-15.4 (5/71)	6.8; 2.7-16.2 (4/59)	31.0; 17.3-49.2 (9/29)	<0.01
VPA + other AEDs	5.4; 1.9-14.9 (3/55)	11.2; 6.4-19.0 (11/98)	19.2; 10.8-31.9 (10/52)	0.084
Total	6.0; 4.4-8.1 (39/648)	10.7; 8.7-13.1 (81/755)	23.8; 18.2-30.4 (44/185)	<0.0001

Abbreviations: AED = antiepileptic drug; LTG = lamotrigine; MCM = major congenital malformation; VPA = valproic acid.
Data represent frequency of MCMs; 95% confidence interval (n) of MCMs at indicated dose categories of VPA.

Predicted malformation risk of topiramate drug dose for the 484 AED polytherapy exposed pregnancies NOT INVOLVING VALPROATE



Antiepileptic drug combinations not involving valproate and the risk of fetal malformations, Vajda FJ, O'Brien TJ, Lander CM, Graham J, Eadie MJ. Epilepsia. 2016 Jul;57(7):1048-52.

Conclusions

- The decision making surrounding valproate will remain complex
- Women with epilepsy have to be treated very individually, especially if poorly controlled and wanting to become pregnant
- Adequate information for fully informed decision
- Information and decision making process needs to be documented
- Polytherapy with and without VPA carry high-risks for the fetus (higher than VPA monotherapy !)
- Uncontrolled seizures carry high-risk for the mother

Conclusions

- Parents of children with fetal valproate syndrome express grief and anger at delays in recognition of the problem, delays in diagnosis, and inadequate support for those with lifelong disabilities.
  - the support, however, does not differ from other disabilities and should of course have been given and should be given regardless of the etiology or the causality
- My personal impression is that more women now decide not to have children than before and we see this influence in the pregnancy registry data, where women tend to have similar seizure-control with less VPA-use – risk for increasing stigma related to epilepsy