

### INTRODUCTION

On 8 July 2020, following a 2-year independent inquiry, Baroness Julia Cumberlege published her report *First Do No Harm*,<sup>1</sup> looking into sodium valproate, pelvic mesh, and Primodos oral pregnancy tests, and the resulting harm to women and their children:

*'We have found that the healthcare system ... is disjointed, siloed, unresponsive and defensive. It does not adequately recognise that patients are its raison d'être. It has failed to listen to their concerns and when, belatedly, it has decided to act it has too often moved glacially.'*<sup>1</sup>

The report is highly relevant to medicines safety in relation to women's health and pregnancy. This editorial concentrates on valproate, a medicine prescribed by GPs, with relevance for other commonly prescribed teratogenic medicines. Primodos is no longer used but there will be women cared for in general practice, including those affected by pelvic mesh use, for whom this report is also highly relevant.

The 268-page report documents the protracted history of harms of valproate with similarities to thalidomide, which affected 10 000 surviving children worldwide.<sup>2</sup> Thalidomide is now part of an historic lesson online at the Science Museum, and similarities with valproate are striking.<sup>2</sup> Valproate, licensed in 1972 despite early concerns of teratogenicity, had clear evidence of physical malformations by 1984, with over 20 000 exposed pregnancies to date in the UK alone.<sup>1</sup> Forty per cent of these were likely to have been associated with significant neurodevelopmental or physical harm to the children.<sup>1</sup> The report highlights themes common to both tragedies including early signals of concern, multiple and systematic organisational failures, including pharma industries and their regulators, and the determined groups of affected women and their advocates, who persisted over many years to have their voices and concerns adequately addressed.

### RISK REVIEWS FOR OTHER MEDICINES IN PREGNANCY

Women's experiences of living with epilepsy or bipolar disorder are often complex, with care typically split between multiple agencies.<sup>3</sup> The report reminds GPs that their

role as an advocate for the patient is critical; conveying risks and pregnancy protection, navigating patients in fragmented systems, or supporting patients once the worst has occurred.

Shared decision making requires support for proactive engagement of patients in their own management as early as possible in the therapeutic journey and at all ages. The report recommends improved care pathways and completion of an 'Annual Acknowledgement of Risk' form for all medication considered to have teratogenic potential prescribed to women or girls with childbearing potential. Commonly used potential teratogens include ACE inhibitors,<sup>4,5</sup> carbamazepine, carbimazole, lithium, and oral isotretinoin.<sup>6</sup> It is estimated that annually 1 in 500 pregnant women are exposed to oral isotretinoin.<sup>7</sup> Although the UK Teratology Information Service maintains a list of teratogenic medicines,<sup>8</sup> an agreed list of common teratogens with similar interventions to reduce pregnancy exposure in general practice remains an outstanding task for regulatory and professional bodies. The Royal College of Psychiatrists guidance now states that valproate should no longer be prescribed for psychiatric reasons to women and girls of childbearing potential.<sup>9</sup>

### TRAINING AND LINKED RECORDS

Safer systems involve training of GPs, nurses, and pharmacists, as well as staff administering the underpinning systems, to ensure that complete annual reviews are recorded and maintained. Access to and visibility of both GP and hospital records is crucial as care is so often split between several clinicians. Better digitally integrated real-time record systems with improved communication for direct care can ensure that both clinicians and their patients are fully informed. As well as signed risk acknowledgement, the report recommends audio or video recording of conversations on consent should be added to the patient record and shared with them.<sup>1</sup>

### COMMUNICATION, RECORDING, AND REVIEW OF RISK REDUCTION

Although the Medicines and Healthcare products Regulatory Agency (MHRA) provides clear guidance for GPs on contraception for teratogenic medicines,<sup>10</sup> there is evidence this is poorly recorded,<sup>11</sup>

and the Cumberlege report found a continuing lack of clarity about the roles, responsibilities, and organisation of routine care for women on valproate, including a clear process for risk counselling and contraceptive advice.<sup>1</sup>

Actionable care requires built-in, fail-safe procedures to avoid gaps in the system. Though valproate prescribing has substantially reduced since the 2017 MHRA warning, the extent to which potentially exposed women are reviewed is unknown.<sup>12</sup> Our research,<sup>5</sup> and that of others,<sup>11,13</sup> suggests that systems for monitoring and review are seriously inadequate, with fewer than half of those taking potentially teratogenic medicine having any recorded information on risk or contraceptive advice. There is currently no national scheme to electronically monitor the completeness of such risk reviews or ensure the results are routinely available to GPs and patients. The report recommends inclusion of safety for all medicines with major teratogenic risk as part of the Quality and Outcomes Framework, or national enhanced service specifications to act as a record of performance and a focus for action.<sup>1</sup> This requires major changes in current practice.

### LONG-TERM MONITORING

The lack of long-term monitoring is a predominant thread throughout the report.<sup>1</sup> While the yellow card system should be used to report possible pregnancy exposure, registers and long term built-in surveillance of children born to women taking such medicines would be more effective. This requires improved data collection and better use of existing data, including linkage to hospital and school records, and for longer term follow-up of women and their children. These actions need to align with European Medicines Agency recommendations,<sup>14</sup> with alignment of data collection with European registries to facilitate large-scale studies.<sup>7,15</sup>

### BUILDING A TRUSTED SYSTEM

Responding to the profound loss of trust, the report recommended the appointment of a patient safety commissioner to provide a focus for patient voices on safety, and a new independent redress agency to look at systemic failings, rather than blaming individuals. Improvements in MHRA safety, improved transparency of conflicts of interest, and specialist centres

to support affected individuals were also recommended.<sup>1</sup>

For the parents of affected children, this report provides some recognition of their experience:

*... we were given the wrong information ... despite the facts being known and repeated requests for information ... the result is devastating on us as a family.*<sup>1</sup>

However, trust will be contingent on the extent to which this report is implemented. For GPs this is a critical account of system failures in which their own advice and prescriptions are an integral part. While teratogenic medicines should be avoided wherever possible, where prescription is unavoidable there is a duty to ensure patients are fully informed and protected by appropriate contraception. It has taken 40 years to develop the current MHRA advice on valproate.<sup>10</sup>

The report recommends similar diligence for a wider range of potential teratogens. GPs may wish to review their current procedures for improved communication and safer care so that the next time they prescribe valproate or other potentially teratogenic medicine, including ACE inhibitors, carbamazepine, carbimazole, lithium, or oral isotretinoin to a girl or woman, the patient and their clinical team can be assured this will occur in the context of a system they can trust.<sup>1</sup>

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