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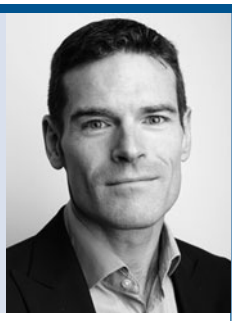
Editorial

Time to re-evaluate the risks and benefits of valproate and a call for action

Oliver D. Howes, Thomas R. E. Barnes, Belinda R. Lennox, Sarah Markham and Sridhar Natesan



Summary

Valproate is widely used in psychiatry and neurology, including off-label use. Here we consider its potential benefits and risks, particularly for women of childbearing potential, and the evidence that clinical guidelines are adhered to. Finally, we consider the implications for clinical practice and research into its efficacy in off-label indications.

Keywords

psychotic disorders; anticonvulsants; drug interactions and side-effects; polypharmacy; education and training.

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Valproate, usually used as its sodium salt, was first developed as an anti-epileptic more than five decades ago. It has proven efficacy for a variety of epileptic disorders, including tonic–clonic, absence and partial seizures.[1] It is also used to treat mania and bipolar depression, and for relapse prevention in bipolar affective disorder.[2,3] Valproate is also commonly used in a number of other neurological and psychiatric disorders where the evidence base is not so robust, including migraine, schizoaffective disorder and schizophrenia.[1,4] It is an effective treatment for many patients and not surprising, then, that it is widely used in psychiatry and neurology. However, mounting evidence of risks indicates that the use of valproate for women needs to be re-evaluated.

The risks of valproate

Preclinical studies have consistently shown that valproate exposure *in utero* results in a range of cognitive and behavioural abnormalities that last into adulthood. There are several theories for the mechanism by which valproate causes teratogenicity, of which folate antagonism and histone deacetylase inhibition are the leading ones. Pharmacoepidemiological studies using real-world patient data have also consistently shown associations between exposure to valproate *in utero* and developmental problems, indicating that effects are seen in humans as well. A number of adverse effects may be apparent *in utero* or at birth, including neural tube defects, growth restriction, decreased brain volume, heart defects, craniofacial dysmorphism and hypospadias. In addition, effects on cognitive and emotional functioning may become apparent later in childhood, and *in utero* valproate exposure is associated with a seven-fold increased risk of autism spectrum disorders relative to no exposure. Many of the individuals affected by *in utero* exposure to valproate require lifelong specialist support and care.[5] It is estimated that up to 4 in 10 babies exposed to valproate *in utero* are at risk of developmental disorders and approximately 1 in 10 are at risk of birth defects. Thus, valproate can have profound consequences for the individuals affected and their families.

Implications for clinical practice

The main clinical problem is managing the high risk of valproate to a fetus in women of childbearing potential. In practice, clinicians often address this risk by warning patients, and valproate labelling in many countries has included a warning about pregnancy risks for many years. Unfortunately, just warning patients that they must not take valproate if they plan to become pregnant is not good enough for the simple reason that a large proportion of pregnancies are unplanned (45% in the general population in England). Moreover, warnings are more likely to be insufficient for people with disorders, such as bipolar affective disorder, where the illness can affect judgement and lead to sexual disinhibition and other behaviours that increase the risk of pregnancy.

What has been done to guide clinicians on when to use valproate?

There is an argument that valproate should not be used in women of childbearing potential at all because of the risk of harm to a developing fetus. However, there are some women for whom valproate is the only effective treatment for their condition, and there would be significant harms to them associated with not using it. Clinicians thus need guidance on when the risk–benefit analysis might warrant prescribing valproate in women of childbearing potential.

To address this, the Psychopharmacology Committee at the Royal College of Psychiatrists issued guidance on the use of valproate as part of the Choosing Wisely UK campaign in 2016. It stated that 'women who are able to conceive should not be prescribed valproate for mental disorders except where there is treatment resistance and/or very high risk clinical situations' (https://www.rcpsych.ac.uk/mental-health/choosing-wisely-a-national-campaign). This makes clear that valproate may be warranted in women who can conceive, but such prescribing should be the exception rather than routine. The Psychopharmacology Committee has subsequently produced further guidance for clinicians on the use of valproate in women, alternatives to it and how to withdraw it

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(see Position Statement PS04/18 at www.rcpsych.ac.uk/docs/default-source/improving-care/better-mh-policy/position-statements/ps04_18.pdf?sfvrsn=799e58b4_2).

What has been done to help clinicians manage risk in women where valproate treatment is warranted?

In the exceptional cases where valproate is still offered as treatment for women, there is the need to substantially reduce the risk of pregnancy. The European Medicines Agency and the medicines regulator in the UK have acted to address the risks of valproate by introducing a pregnancy prevention programme, called 'prevent'. This sets out multiple strategies to reduce the risk of a pregnancy while taking valproate, including the requirement for women to have a pregnancy test before starting valproate and annual tests while taking it, to receive counselling on the risks, to agree to use highly effective forms of contraception and to sign a risk acknowledgment form. The regulators also require the manufacturers to monitor use of valproate. Furthermore, they require that clinicians systematically identify and review all women taking valproate on their case-loads, and ensure that the necessary local training and protocols are in place to meet the regulators' requirements on valproate.

What happens in practice?

Despite the initiatives discussed above, valproate continues to be regularly prescribed to women of childbearing potential and implementation of the 'prevent' pregnancy prevention programme is inconsistent. For example, clinical audit data submitted by 64 UK mental health trusts in 2020 found that the 'prevent' programme was fully implemented with only a quarter of women under 55 years of age for whom pregnancy was biologically possible and who were prescribed valproate (Prescribing Observatory for Mental Health, 2021, Topic 20a: CCQI 359 – Improving the quality of valproate prescribing in adult mental health services, and CCQI 362 – Supplementary report on meeting the requirements of 'prevent'; data available from POMH-UK@rcpsych.ac.uk). In just over 70% of cases where 'prevent' was not fully implemented, no reason was given in the clinical records. Even where the reasons for patients not being in the pregnancy prevention programme were documented, not all of these referred to permanent protection against pregnancy (e.g. the patient was currently using contraception, or on a single-sex ward or in a same-sex relationship). Further analysis of the data found that more than half of the women with no documented reason for not implementing 'prevent' were 46 years of age or older and may have been, or were assumed to be, post-menopausal or the intention was to discontinue valproate treatment. Notwithstanding these possibilities, the audit indicates that there continues to be a large number of women of childbearing potential taking valproate for whom the 'prevent' programme has not been fully implemented.

What do these findings mean for prescribers?

These findings highlight the need for clinicians to tighten their implementation and documentation of 'prevent'. All clinicians are recommended to audit their case-loads and ensure that the regulatory requirements for valproate are implemented and not wait until the patient's next routine medication review. We should also review our prescribing habits to stop prescribing valproate to women of childbearing potential except in exceptional clinical circumstances or as part of an approved research study.

What about the off-label use of valproate?

Another important issue is that valproate is widely used for psychiatric conditions such as schizophrenia or schizoaffective disorder, where the evidence-base remains limited. This is not to say that valproate is ineffective for these conditions, but that there have been too few high-quality studies to know conclusively one way or the other.[4] Given this clinical equipoise, there is an urgent need to obtain high-quality data to determine whether valproate is effective in these disorders. One initiative to address this is the Anticonvulsant Augmentation Trial in Schizophrenia (ATLANTIS) study (www.kcl.ac.uk/research/atlantis-anticonvulsant-augmentation-trial-in-schizophrenia). This placebo-controlled study funded by the UK's National Institute for Health and Care Research aims to evaluate the efficacy and cost-effectiveness of valproate for schizophrenia or schizoaffective disorder in men and women (UK clinicians who wish to refer male or female patients to the study can do so by e-mailing: atlantis@kcl.ac.uk). The women are all helped to adhere to the pregnancy prevention programme. However, this and other studies will take time to accrue evidence. In the meantime, given the risks and lack of high-quality data, clinicians should not be using valproate for women with these conditions except in very rare circumstances.

Conclusions

It is important that as a profession we show patients and regulators that the use of valproate in women of childbearing potential is being addressed. To that end, clinicians are encouraged to review their case-loads, participate in quality improvement programmes addressing the use of valproate, and take part in research to determine its effectiveness in off-label indications. The time to act on valproate prescribing in women is now.

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Psychiatry in Pictures

The persecuted

Stephen Wilson

Albert Londres was a pioneer of investigative journalism. Travelling across France in 1925, he managed to gain access to a variety of institutions housing people who were mentally ill, sometimes using subterfuge and often met with official resistance. His findings, illustrated by Rouquayrol were reported in *Le Petit Parisien*, and later published in book form by Albin Michel (1925) under the title *Chez Les Fous*.[1] His descriptions are compassionate and ring true.

Fig. 1 By artist George Rouquayrol, image in public domain.

What's poignant, is the persecuted madman. His madness gives him no respite. It grips him, pursues him, tortures him. In the night *it* lies in wait for him, *it* spies on him, *it* insults him. 'It' or 'they' are his enemies! They are in the ceiling, in the wall, in the floorboards.

— In the coal hole you see *it* there all black, sending me waves?

It never stops watching over him, *it* hits him, *it* pinches him, *it* martyrises him with electricity, iron rods, fire, sheets of water, gas.

He blocks his eyes, his ears, his nose, in vain! He always sees his persecutors. He hears himself being threatened, he smells burning.

He lives in trances, he sleeps in a nightmare.

— What? What's happening? Behind! There they are! They're here!

To begin with, he doesn't accuse a specific person. Then the phantom takes a form. It's an individual unknown to him, or it's a sect, a secret society, an association, a consortium; they're the Jesuits, the free-masons, the Salvation Army, an insurance company. They're the physicists. It's Edison, it's Marconi, it's Branly.

It used to be the devil. The devil's dethroned. He only works for backward peasants. Modern inventions have returned him to his hell, today's persecutor is the cinematograph, the phonograph, the wireless, the plane, the x-ray machine, the loudspeaker…

Remorse racks them. They accuse themselves of crimes. It's they who have caused catastrophes.

A man hits his chest with forceful blows of his fist. He doesn't spare himself. His thorax serves as an echo chamber.

— It's me! It's me! It's me! he repeats. It's he who was responsible for the evacuation of the Ruhr!

Their pain isn't always expressed in the form of excitation, their madness is circular, so there's a period of depression. At such times their suffering is mute. It's as if they were inundated. Overwhelmed on a bench, eyes exhausted and lost in the distance, their *fault* gnaws at them.

— Come on, Madame Garin, walk a little, go for a stroll, chase away your nasty thoughts.

— How can I, sir, when it's I who declared war! I've caused the death of millions of men. There isn't a more hideous criminal than me, I shouldn't be here, no, not here.

— And where should you be, Madame Garin?

— Doing hard labour.

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