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Withholding the choice of sodium valproate to young women with generalised epilepsy: are we causing more harm than good?

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Purpose

Although sodium valproate (VPA) remains the most effective antiepileptic for generalised and unclassified epilepsies, clinicians may be failing to discuss this treatment option because of guideline misinterpretation. Current guidelines recommend caution regarding teratogenic risks but do not advocate absolute avoidance.

Methods

We assessed VPA prescribing in young people attending a transition epilepsy clinic. We present six patients with idiopathic generalised epilepsy (IGE) in whom VPA had been initially avoided.

Results

Overall, the results were consistent with VPA's superior antiepileptic efficacy and ability to reduce harmful seizure-related complications. Young people denied of VPA showed prolonged periods of poor seizure control with medical, social and psychological complications. Following contraceptive counselling and VPA introduction, all six patients showed improved seizure control including seizure-freedom during follow-up of up to twenty-four months. There was also evidence of reduced seizure-related morbidity and improved educational and occupational functioning. Prior to referral, documentation revealed no discussion of VPA treatment options.

Conclusion

Failure to prescribe valproate for IGE, particularly when another first-line treatment has failed, may not be in a young woman's best interests particularly when they are most vulnerable to sequelae from uncontrolled seizures. Indiscriminate avoidance of

valproate needs to be recognised as a misinterpretation of current epilepsy guidelines as it may harm young people. Although the use of valproate demands careful consideration, there remains a strong case to always discuss this medication because of its efficacy and potential to reduce seizure-related harm. Patients must be allowed to make their own informed decisions about effective epilepsy treatments.

1. Introduction

Although sodium valproate (VPA) remains the most effective antiepileptic for generalised and unclassified epilepsies,[1-2] current guidelines[3-5] appropriately recommend caution when prescribing the drug for young women of childbearing age. Lamotrigine and levetiracetam are commonly recommended alternatives largely because they are considered to have fewer and less severe adverse side-effects, including fetal teratogenicity. These treatment guidelines are principally informed by observational studies including data from pregnancy registers that show higher rates of major somatic malformations in pregnancies exposed to VPA, for example the EURAP registry[6] showed a rate of 5.6% with <700mg valproate and 24.2% with >1500mg valproate per day, 2.0% with <300mg lamotrigine per day and 4.5% with >300mg per day. Valproate is also associated with impaired cognitive development[7] in the absence of any fetal malformations.

Although lamotrigine may be safer in pregnancy, it is less effective in controlling most seizure types that occur in the idiopathic generalised epilepsies (IGEs) and specifically tonic-clonic seizures; the same is also true of topiramate. There are inadequate comparative efficacy data for levetiracetam. Prescribing a less effective treatment exposes the patient to a greater risk of continuing seizures[8], consequent risk of injury (including rarely, death) and psychological consequences and social disadvantage.[9,10]

Guideline developers must weigh the risk:benefit ratio of treatments when writing their guidance. This is particularly challenging in this scenario as evidence about benefit and harm will come from many different sources. Guidance that is too risk-averse in terms of preventing teratogenicity might expose women to an increased risk of seizures, and particularly tonic-clonic seizures. In addition, the clinical

interpretation and implementation of guidance also requires careful consideration and over-cautious interpretation might have the same effect. Finally, implementation is also limited by a paucity of data that identify the priorities and preferences of young women who are about to start treatment for epilepsy. Such issues highlight the need for examining significant sequalae when operationalizing epilepsy guidelines.

2. Material and Methods

We assessed the impact of treatment approaches for young people attending a transition epilepsy clinic. We report on six young people with an IGE seen in a specialist transition (teenager) epilepsy clinic in the UK accrued over 18 months.[11]. None of the patients had achieved a seizure-free period of more than six months; all had received a range of anti-epileptic medications, either singly or in combination, but never VPA. Following discussion of the different treatment options with the young person and their family, all patients elected for a trial of VPA ; six were converted to valproate monotherapy and one patient continued to receive valproate in combination with another anti-epileptic drug. Details of the six patients are shown in Table 1.

3. Case Series

Five of the six patients had experienced specific adverse consequences from uncontrolled seizures. Prior to commencing VPA, Cases 3 and 5 had a protracted period lasting several years of uncontrolled seizures despite multiple trials of different high-dose monotherapies. Cases 2 and 3 had tried monotherapies and combination therapies and reported adverse effects including renal calculi and sedation. Two patients required acute medical intervention (Cases 1 and 4) for uncontrolled clusters of tonic-clonic seizures and two experienced mental health complications (Cases 3 and 5) that necessitated acute psychological support and psychiatric intervention.

All six patients demonstrated improved seizure control after commencing VPA, , remaining seizure and complication-free throughout the short duration of follow up (three to 24months). Following seizure-cessation, social isolation and clinical depression reduced in Cases 3 and 5, school attendance improved in Case 3 and continuing higher education became a reality for Case 2. Adverse side-effects were experienced by Cases 2, 4 and 5 but these did not necessitate either a reduction in dose or withdrawal of the drug. Although data was unavailable on whether patients were sexually active or using contraception, all women after referral to the transition service routinely received documented nurse-led counselling on contraception and advice about pregnancy.

4. Discussion

All six patients experienced prolonged periods of poor seizure control and consequently suffered physical, psychological and social complications during treatment regimes that had excluded VPA. Following the introduction of VPA, seizure control improved in all six; all had achieved seizure freedom during the four to 24 month follow-up. None of the patients subsequently experienced any medical

complications (including injuries) whilst on valproate and a number demonstrated improved psychosocial functioning. This would suggest that, had VPA been introduced earlier in their management, they would have experienced fewer, if any, medical and psychological consequences associated with poor seizure control. Clearly, this hypothesis cannot be proven. However, the superiority of VPA compared to other anti-epileptic medications in enabling seizure-freedom has been demonstrated in randomised trials. For example, alternatives to valproate such as lamotrigine and topiramate for generalised epilepsies are likely to bring an increased risk of treatment failure and seizures (hazard ratio 1.25 and 1.89 respectively for time to treatment failure).[1]

4.1 Uncontrolled seizures: Significant medical, psychological and social complications

Medical complications associated with poor seizure control are well-recognised and include accidental injuries, death (including from sudden unexpected death in epilepsy [SUDEP] or suicide) and mental health disorders. Anti-epileptic regimes that optimise seizure control are considered likely to minimise the medical complications and maximise quality of life.[10]

Generalised tonic-clonic seizures during pregnancy can lead to fetal loss through severe hypoxia, direct trauma and intracranial haemorrhage. Convulsive (tonic-clonic) status may be associated with fetal death in 50% of cases.[12] It is also possible that poorly controlled seizures could adversely affect psychomotor development of the child. Finally, poorly controlled seizures may also have financial consequences for the woman as well as the NHS and other healthcare institutions.

Three of our cases experienced significant psychological complications, two serious and requiring psychiatric intervention, predominantly because of poor seizure control. Clearly, there may have been confounding factors, including their pre-morbid mental health status and the adverse effects of medication, and specifically, topiramate. Seizures may affect relationships, self-esteem, continuing education, career opportunities and driving which in turn may limit social functioning, stigma and quality of life.[10] Such factors must be carefully considered in the discussion of all available treatment options with young people and their families.

4.2 Towards individualised Care

Treatment options should always be tailored to a patient's circumstances and priorities. There should be an open and realistic discussion about treatment alternatives that should include a balanced discussion of relative risks and benefits. Such discussions may need to occur at the time of diagnosis and particularly in girls of childbearing age. Whilst this might be considered a statement of the obvious, this approach is not always followed in clinical practice as demonstrated in all six of our cases where there was no documented discussion on treatment choices. It may also be difficult to provide a balanced discussion without prejudicial bias by the clinician. An over-liberal use of valproate might result in increased fetal exposure to valproate with consequent malformations and cognitive delay. Conversely, overly-restricted use of valproate might result in unnecessary seizures and associated consequences.

Decisions made by patients are heavily dependent upon the information provided by clinicians. If the clinicians' interpretation of current evidence is that preventing teratogenicity is the priority, the risk of teratogenicity might be emphasised in any discussion and valproate might not even be offered as a treatment option.

Decisions made in clinic consultations might be helped by better evidence about the priorities and preferences of young people with epilepsy although there is a currently a dearth of such evidence.

In conclusion, VPA is clearly an effective anti-epileptic drug but it may equally be associated with significant adverse side-effects including fetal teratogenicity and cognitive and language dysfunction in children exposed to the drug, particularly in the first few months of pregnancy. Valproate will always be a treatment option for the treatment of the generalised epilepsies and this must be openly and honestly discussed with the young person or teenager and where appropriate their family. This must include the discussion of the implications of poor seizure control and its consequences as well as the implications of an unplanned pregnancy on the fetus. Other factors that are relevant to VPA prescribing to women include the risk of weight gain and endocrinological side effects. Whilst there has not been a sufficiently powered study linking VPA to PCOS the body of evidence as it stands, strongly suggests that VPA has the potential to cause this disorder - which may be relevant to young women. This does not mean that VPA can't be used, but it does mean that weight and (if appropriate) the regularity of periods should be checked regularly as a bare minimum. The teenager's decision will be based upon their practical priorities at the time of this discussion; clearly, their priorities may subsequently change depending on the young person's situation, as this is a critical and dynamic time of their life. In a woman who is at risk of becoming pregnant, if the decision in her best interests is to prescribe valproate, then it should be at the lowest effective dose and in conjunction with folic acid and advice on contraception and pregnancy. Ultimately the woman needs to be given reliable, information with which to make an informed choice, and she may choose to continue taking VPA when planning a pregnancy, particularly if her epilepsy has been resistant to other treatments. It is important that information given

provides patients with a balanced and un-prejudiced view about different treatment options that should include valproate. It must be emphasised that current epilepsy guidelines encourage this individual, tailored approach rather than attempting absolute risk-avoidance or physician-centred decision-making. Current guidelines do not state that valproate should be universally avoided and patients must be allowed to make their own informed decisions about their epilepsy treatment.

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- Highlights
- Sodium valproate for idiopathic generalised epilepsies has unsurpassed efficacy
- Guidelines recommend caution offering valproate and not absolute avoidance
- We show six young patients in whom physicians had persistently avoided valproate
- Uncontrolled seizures and severe distressing sequalae followed
- Patients must be involved and allowed to decide on their own epilepsy treatment

Table 1 Clinical characteristics and seizure-related outcomes before and after sodium valproate

Patient no: sex, age	ILAE diagnosis, (investigations)	Failed treatment regimens prior to commencing valproate	Type and frequency of seizures	Complications before valproate monotherapy	Outcomes after commencing valproate
Uncontrolled seizures with complications					
1: F, 17	JME diagnosed aged 12. tonic-clonic seizures	(i) LEV 3g daily (maximum dose)*	Continuing generalised tonic-clonic seizures every other month typically around menstruation	Uncontrolled seizures. Seizure whilst using hair straighteners resulting in deep lower limb burns requiring extensive plastic surgery	Remained seizure-free throughout 14-month follow-up. Referred to nurse-led pre-conceptual counselling clinic
2: F, 20	IGE (EEG markedly abnormal. Frequent generalised onset. Rhythmic spike and slow waved activity and poly spike activity)	(i) LEV 4g daily (ii) TOP 400mg daily (iii) LTG*	Regular tonic clonic seizures every 6 weeks. Daily absence seizures	Uncontrolled seizures. Lamotrigine side effects: Admitted with renal calculus whilst on lamotrigine (listed as common side effect in British National Formulary)	Remained seizure-free throughout 4-month follow-up. Absences reduced to few times per week having previously been daily. Tiredness the only reported side effect.
3: F, 17	IGE diagnosed aged 12 (tonic-clonic and absence seizures. MR Brain unremarkable)	(i) LTG (maximum dose) (ii) LEV (iii) TOP 150mg daily and clobazam (iv) LEV 1.5g daily and lamotrigine 600mg daily*	Multiple absence seizures daily	Uncontrolled seizures. Levetiracetam side effects: severe sedation ("sleeping for 16 hours/day"). Depression: "tearfulness, problems at school…lost interest in not just her school work but also her friends and leisure pursuits" - considered related to ongoing intrusive seizures	Remained seizure-free throughout 20-month follow-up. Mood improved – may have benefited from both antiepileptic and antidepressant effects of VPA
4: F, 19	IGE (CT head unremarkable)	(i) LEV 4g daily*	Tonic-clonic seizures every 2 months, typically within an hour of waking, had never achieved seizure freedom for more than 4 months	Uncontrolled seizures. Worse with Alcohol. Fall during seizure resulting in subluxed upper central incisors. Laceration to upper lip and mucosa requiring suturing and splinting	Remained seizure-free throughout 43-month follow-up. Advised to avoid switching generic brands of valproate. Enrolled in university education. Occasional vomiting with generic formula, appetite increase, hair loss. Explanation given on contraception and availability of different choices given that P450 enzyme inducers would not be used. Commenced on folic acid
5: F, 24	IGE diagnosed at 11 months (EEG showed generalised polyspike and wave abnormality induced by hyperventilation and associated with blinking)	(i) ETX (ii) CBZ (iii) LTG 600mg daily and LEV 1g daily (iv) LTG 600mg daily, LEV 1g daily and clobazam 10mg daily with PRN clobazam (v) CBZ and LEV 2.5g daily*	Treated initially with VPA as a young child but was discontinued as she grew older and was switched to ETX. Subsequent worsening control of seizures during stressful periods revising for GCSE school examinations	Uncontrolled seizures. Suffered multiple seizures whilst attempting to go on holiday. Required referral to clinical neuropsychology for stress counselling and CBT on her return. Substantial seizure psychosocial complications identified: "She now feels her epilepsy has affected her social life…[she is] unable to do very straight forward things such as get on a bus on her own…she finds it difficult at this time in her life, where she has stressful factors such as college exams and other teenage worries…"	Remained seizure-free throughout 24-month follow-up on VPA 1g daily and LTG 150mg daily. Hair loss and fine tremor noted. Orlistat commenced for weight gain and driving licence successfully applied for.

Uncontrolled seizures without complications					
6: M, 15	JME diagnosed aged 14 (Myoclonic, tonic-clonic and absence seizures, EEG showed generalised spike and wave discharges at 4hz)	(i) LEV 2g daily for 4 months (ii) LTG 400mg daily added for 5 months before referral for second opinion*	Daily myoclonic seizures and weekly tonic-clonic seizures	Uncontrolled seizures. "Withdrawn, refused to attend school and talked about self-harm because of daily myoclonic seizures"	Remained seizure-free throughout 5-month follow-up. Increased appetite but no significant weight gain. School attendance improved and participating in all previous activities and interests on 1.2g VPA daily

* No documented discussion or offering of valproate to patient before referral to our clinic
CBZ=carbamazepine; CLB=clobazam; ETX=ethosuximide; LEV=levetiracetam; LTG=lamotrigine; VPA=valproate