Newer vs older antiseizure medications – are we any further forward?

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The past 30 years has seen the launch and utilisation of many new antiseizure medications. Many have been licensed on the basis of evidence from add on therapy in resistant epilepsies; there has been little head to head comparative data in newly diagnosed patients[1]. The data from SANAD I, the first standard and new antiepileptic drug trials, provided the first comprehensive data to address this question; lamotrigine was demonstrated to be superior to carbamazepine, gabapentin, oxcarbazepine and topiramate in time to treatment failure[2], and valproate as a clinically and cost effective alternative to lamotrigine or topiramate[3] . However, since these trials, other medications have become licenced for use, and levetiracetam has been increasingly used as a relatively safe alternative in the treatment of both focal and generalised epilepsies despite little head to head comparative data[4], specifically with the increasing concern about the effect of valproate in pregnancy on the unborn child.

In this issue Marson and colleagues report the results of SANAD II; two pragmatic unblinded randomised trials providing useful data in addressing this issue[5,6]. In the study of newly diagnosed focal epilepsy, 990 patients were recruited (43.3% female, mean age 39.9years). Levetiracetam did not meet noninferiority in the intention to treat analysis of time to 12m remission from seizures (calculated as days from randomisation to the first date at which a period of 12 months had elapsed without any seizures) Hazard Ratio (HR) vs lamotrigine 1.19 (97%CI 0.95-1.47), and in per protocol analysis lamotrigine showed superiority and dominant cost utility analysis over levetiracetam and zonisamide. In the second study of newly diagnosed generalised (397 patients) and unclassifiable epilepsy (123 patients) (35.2% female, mean age 17 years) levetiracetam did not meet criteria for noninferiority in the intention to treat analysis of time to 12 month remission HR1.19 (95% CI 0.96-1.47) and in per protocol analysis valproate was superior to levetiracetam for all outcomes.

The trials recruited adults and children from age 5 years; in the focal epilepsy study limited numbers of children (21.2%) were recruited probably related to the fact zonisamide is not licensed in this age group[5]. It also needs to be acknowledged that other seizure medications are now licenced, specifically for focal seizures, that were not included in the studies. This said, the pragmatic design of the studies provides useful data for treatment choice.

In contrast, in the study of generalised and unclassified epilepsies 40.4% were children, and only 35.2% female (26.8% in the 12-50 year age group), perhaps reflecting the concerns about use of valproate in women and girls. Ten pregnancies were recorded, none of whom were on valproate at conception. The trials were unblinded which may have influenced decisions about dose and treatment changes; the trial protocol provided guidance on initial drug titration and maintenance doses based on routine practice, although clinicians were able to tailor this as appropriate[6], emphasising the pragmatic design and wide applicability of results.

The fact that in SANAD II levetiracetam was inferior to valproate in all effectiveness measures set at its tip the dilemma in treating female patients with generalised epilepsy, given valproate's teratogenic potential[7-10]. The advised maintenance dose of valproate to adult participants was 1,000 mg/day in SANAD I and II[3,6]. This is a dose level at which the risk is higher for malformations[9] as well as for poor cognitive outcome[7,8]. It would have been interesting to know how a lower dose of valproate, associated with less teratogenic risks, compares with levetiracetam in efficacy. Sub-analysis in people with unclassified epilepsy found no significant difference between treatments but estimates favoured levetiracetam[6], suggesting a need to address this in further studies

According to the EMA valproate is contraindicated in girls and women able to have children unless the terms of a special pregnancy prevention programme are followed[11]. This means that, unlike men, female patients with generalised epilepsy are denied the most effective treatment. It is an open question if drugs that have been shown inferior in efficacy can be considered suitable alternative treatment or not. The new findings do not change the need to make every effort to avoid unnecessary exposure to valproate in pregnancy. Female patients should be informed of the approximately 10% risk of malformations and considerable risk of adverse neurodevelopmental outcomes in children exposed to valproate in utero[7-10]. But they also have the right to know that treatment alternatives are likely to be less efficacious.

Disclosures

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