Lamotrigine versus levetiracetam or zonisamide for focal epilepsy and valproate versus levetiracetam for generalised and unclassified epilepsy: two SANAD II non-inferiority RCTs

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Declared competing interests of authors: Anthony G Marson reports grants from the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme during the conduct of the study, and grants from UCB (Brussels, Belgium) outside the submitted work. Graeme Sills reports personal fees from UCB, Eisai Co. Ltd (Tokyo, Japan) and Arvelle Therapeutics GmbH (Zug, Switzerland) outside the submitted work. John Leach reports grants from the University of Liverpool/HTA during the conduct of the study; personal fees from Eisai Co. Ltd; grants and personal fees from UCB; and personal fees from Janssen: Pharmaceutical Companies of Johnson & Johnson (Beerse, Belgium), GlaxoSmithKline plc (Brentford, UK) and GW Pharmaceuticals (Cambridge, UK) outside the submitted work. Philip EM Smith reports being co-editor of *Practical Neurology* (2011–present) and a member of the National Institute

for Health and Care Excellence Guidelines Group for Epilepsy (2019–21). Rajiv Mohanraj reports personal fees from UCB, and grants from UCB and Sanofi SA (Paris, France) outside the submitted work. Catrin Tudur-Smith reports a committee membership (HTA Commissioning Committee) (2015–20). Paula R Williamson was Director of Liverpool Clinical Trials Centre (formerly Medicines for Children Clinical Trials Unit) (April 2005–December 2018), which received funding from NIHR (end date 31 August 2021). She also reports grants from the University of Liverpool and from the NIHR HTA programme during the conduct of the study.

Published December 2021
DOI: 10.3310/hta25750

Scientific summary

Two SANAD II non-inferiority RCTs

Health Technology Assessment 2021; Vol. 25: No. 75
DOI: 10.3310/hta25750

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Levetiracetam (Keppra®, UCB Pharma Ltd, Slough, UK) and zonisamide (Zonegran®, Eisai Co. Ltd, Tokyo, Japan) are licensed for use as monotherapy in focal epilepsy, but there is uncertainty as to whether or not they should be recommended as first-line treatments because of the lack of evidence from randomised trials regarding their longer-term clinical effectiveness and cost-effectiveness.

There is also uncertainty about the clinical effectiveness and cost-effectiveness of levetiracetam for generalised and unclassified epilepsy. This is particularly important for those with newly diagnosed idiopathic generalised epilepsy, for whom valproate (Epilim®, Sanofi SA, Paris, France) is a recommended first-line treatment for men but not women of childbearing potential because it is teratogenic. Despite inadequate evidence, levetiracetam is increasingly prescribed as an alternative to valproate.

The SANAD II trial assessed the longer-term clinical effectiveness and cost-effectiveness of levetiracetam and zonisamide compared with the standard treatment lamotrigine (Lamictal®, GlaxoSmithKline plc, Brentford, UK) for focal epilepsy, and of levetiracetam compared with the standard treatment valproate for generalised and unclassifiable epilepsy.

Methods

The SANAD II trial comprised two randomised unblinded controlled trials running in parallel. One compared the policies of starting treatment with levetiracetam, zonisamide or lamotrigine for focal epilepsy. The second compared the policies of starting treatment with levetiracetam or valproate for generalised or unclassified epilepsy. Adult and paediatric neurology services across the UK recruited participants aged ≥ 5 years who had experienced two or more unprovoked seizures requiring treatment.

The primary outcome was time to 12-month remission. The SANAD II trial was designed to assess the non-inferiority of both levetiracetam and/or zonisamide compared with lamotrigine. The non-inferiority limit was an absolute difference of 10%, which equates to a hazard ratio (HR) of 1.329. The SANAD II trial was also designed to assess the non-inferiority of levetiracetam compared with valproate. The non-inferiority limit was an absolute difference of 10%, which equates to a HR of 1.314.

Secondary outcomes were times to treatment failure overall and for inadequate seizure control (ISC) or unacceptable adverse reactions (UAR) individually, time to first seizure, time to 24-month remission, adverse effects and quality of life. Cost-effectiveness was from the perspective of the NHS and Personal Social Services in the UK, and based on the incremental costs per quality-adjusted life-year (QALY) gained. A HR > 1 indicates that an event is more likely on the standard treatment (lamotrigine or valproate) in each trial.

Results

Focal epilepsy

A total of 990 participants were recruited between April 2013 and June 2017, and were followed up for a further 2 years. The mean age was 39.3 years (range 5.0–91.9 years), 56.7% were male, and the median number of seizures was 6 (interquartile range 3–24). Levetiracetam did not meet the criteria

for non-inferiority (HR 1.329) in the primary intention-to-treat (ITT) analysis of time to 12-month remission [HR vs. lamotrigine 1.18, 97.5% confidence interval (CI) 0.95 to 1.47], but zonisamide did meet the criteria (HR vs. lamotrigine 1.03, 97.5% CI 0.83 to 1.28). The per-protocol (PP) analysis found superiority of lamotrigine over both levetiracetam (HR 1.32, 97.5% CI 1.05 to 1.66) and zonisamide (HR 1.37, 95% CI 1.08 to 1.73). For time to treatment failure (any reason), lamotrigine was superior to levetiracetam (HR 0.60, 95% CI 0.46 to 0.77) and zonisamide (HR 0.46, 95% CI 0.36 to 0.60).

Treatment failure due to adverse reactions (ARs) was significantly more likely with levetiracetam (HR 0.53, 95% CI 0.35 to 0.79) and zonisamide (HR 0.37, 95% CI 0.25 to 0.55) than with lamotrigine. Although not statistically significant, estimates indicated that treatment failure due to inadequate seizure control was more likely with levetiracetam (HR 0.67, 95% CI 0.45 to 1.01) and zonisamide (HR 0.76, 95% CI 0.50 to 1.15) than with lamotrigine. ARs were reported by 33% of participants starting lamotrigine, 44% starting levetiracetam and 45% starting zonisamide.

In the economic analysis, levetiracetam was associated with a QALY gain of 1.474 years [97.5% central range (CR) 1.393 to 1.523 years], zonisamide with a QALY gain of 1.502 years (97.5% CR 1.418 to 1.566 years), and lamotrigine with a QALY gain of 1.605 years (97.5% CR 1.547 to 1.651 years). The mean total cost was £5104 (97.5% CR £4450 to £6141) for levetiracetam, £5400 (97.5% CR £4659 to £6770) for zonisamide, and £4042 (97.5% CR £3626 to £4983) for lamotrigine. Both levetiracetam and zonisamide were therefore dominated by lamotrigine.

Generalised and unclassifiable epilepsy

A total of 520 participants were recruited between April 2013 and August 2016, and were followed up for a further 2 years. The mean age was 17.0 years (range 5.0–94.4 years), 64.8% were male, 397 participants had generalised epilepsy and 123 had unclassified epilepsy. Levetiracetam did not meet the criteria for non-inferiority in the primary ITT analysis of time to 12-month remission (HR 1.19, 95% CI 0.96 to 1.47; non-inferiority margin 1.314). There was evidence of a non-constant HR over time ($p < 0.01$), and time-to-event probabilities indicate an initial difference that diminished over time. The immediate 12-month remission rate was 26% for those starting levetiracetam and 36% for those starting valproate (difference 9%, 95% CI 1% to 18%). At 3 years, these rates were 74% for those starting levetiracetam and 73% for those starting valproate. The PP analysis of time to 12-month remission found superiority of valproate over levetiracetam (HR 1.68, 95% CI 1.30 to 2.15). Valproate was also superior to levetiracetam for time to 24-month remission (HR 1.43, 95% CI 1.06 to 1.92) and time to first seizure (HR 0.82, 95% CI 0.67 to 1.00).

Valproate was superior to levetiracetam for time to treatment failure (HR 0.65, 95% CI 0.50 to 0.83) and for treatment failure due to ISC (HR 0.43, 95% CI 0.30 to 0.63); treatment failure rates due to UAR were similar (HR 0.93, 95% CI 0.61 to 1.40). AR rates were similar, but profiles differed: there were 220 ARs in 96 (37.4%) participants randomised to receive valproate and 223 ARs in 107 (41.5%) participants randomised to receive levetiracetam. There were psychiatric symptoms in 66 of those randomised to receive levetiracetam and in 36 of those randomised to receive valproate. Eight participants randomised to receive levetiracetam had gained weight, compared with 26 participants who were randomised to receive valproate.

The economic analysis indicated levetiracetam to be associated with a QALY gain of 1.603 years (95% CR 1.500 to 1.631 years) compared with 1.637 years (95% CR 1.565 to 1.673 years) for valproate. The mean total cost was £4350 (95% CR £4136 to £5623) for levetiracetam and £4246 (95% CR £3979 to £5090) for valproate. Levetiracetam was, therefore, dominated by valproate. Levetiracetam is associated with a negative incremental net health benefit (–0.040 95% CR –0.175 to 0.037) at a cost-effectiveness threshold of £20,000 per QALY.

Conclusions

Focal epilepsy

The SANAD II findings do not support the use of levetiracetam or zonisamide as first-line treatments in focal epilepsy. Although zonisamide met the criteria for non-inferiority in the ITT 12-month remission analysis, levetiracetam did not. The PP analysis accounting for treatment failure found both levetiracetam and zonisamide to be inferior to lamotrigine. Levetiracetam and zonisamide were significantly more likely to fail, were associated with more ARs, and did not meet the criteria for cost-effectiveness operating in the NHS.

Generalised and unclassifiable epilepsy

The SANAD II findings do not support the use of levetiracetam as a first-line treatment for newly diagnosed generalised epilepsy. For women of childbearing potential, these results inform discussions about benefit (lower teratogenicity) and harm (worse seizure outcomes and higher treatment failure rate) of levetiracetam compared with valproate.

Trial registration

This trial is registered as ISRCTN30294119 and EudraCT 2012-001884-64.

Funding

This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 25, No. 75. See the NIHR Journals Library website for further project information.

Health Technology Assessment

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.014

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, the Cochrane Library and Clarivate Analytics Science Citation Index.

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This report

The research reported in this issue of the journal was funded by the HTA programme as project number 09/144/09. The contractual start date was in June 2012. The draft report began editorial review in October 2020 and was accepted for publication in August 2021. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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