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Cost-utility analysis of rufinamide versus topiramate and lamotrigine for the treatment of children with Lennox–Gastaut Syndrome in the United Kingdom

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ABSTRACT

Purpose: To estimate the cost-effectiveness of rufinamide relative to topiramate and lamotrigine as adjunctive treatment for children with Lennox–Gastaut Syndrome (LGS).
Methods: A Markov decision analytic model was developed to estimate the incremental cost-effectiveness ratio over a three-year time horizon in patients with LGS uncontrolled by up to three antiepileptic drugs. Utilities were assigned to health states, defined according to a patient's response to treatment (≥75%, ≥50% and <75%, and <50% reduction in tonic–atonic [drop attack] seizure frequency and death). Efficacy and safety estimates were made using indirect/mixed-treatment comparisons of data obtained from published literature. Outcomes included costs and quality-adjusted life-years (QALYs), allowing the incremental cost-effectiveness ratio to be estimated as cost per QALY gained.
Results: Over three years, the total cumulative costs for rufinamide, topiramate, and lamotrigine were £24,992, £23,360, and £21,783, respectively. Rufinamide resulted in an incremental QALY gain of 0.079 relative to topiramate and 0.021 relative to lamotrigine. The incremental costs of rufinamide were £1632 and £3209, relative to topiramate and lamotrigine, resulting in an incremental cost per QALY gained of £20,538 and £154,831, respectively.
Conclusions: Considering the underlying assumptions, this current economic evaluation demonstrates that rufinamide is likely to be a cost-effective alternative to topiramate as adjunctive treatment for children with LGS in the UK. In addition, when compared to lamotrigine, which is an inexpensive treatment, rufinamide should be considered as a cost-effective alternative due to the importance of patient choice and equity of access in such a rare and devastating condition.

1. Introduction

Lennox–Gastaut Syndrome (LGS) is a rare and severe form of childhood epileptic encephalopathy characterized by the presence of multiple seizure types, generalized discharges with slow spike-and-wave complexes in the electroencephalogram, and mental deficiency or learning difficulties.[1–3] The pathophysiology of LGS is varied; in many cases, its aetiology is unknown, although some causes include brain abnormalities and prenatal or neonatal brain injury. LGS accounts for 1–4% of all childhood epilepsies.[4] With a reported prevalence of 0.9 cases per 10,000 population across all age groups,[4,5] LGS has been classified by the European Medicines Agency (EMEA) and US Food and Drug Administration (FDA) as an orphan disease since 2004.[6,7]

LGS is considered to be a catastrophic illness. In addition to the developmental disability experienced by patients with LGS, seizures are intractable and physically damaging, further interfering with the patient's intellectual and social development. Catastrophic epilepsies presenting during the childhood developmental stage halt cognitive and social development, leading to long-term effects.[8] LGS therefore represents a significant burden to both patients and their carers. Furthermore, while LGS-related healthcare costs have not been studied specifically, the direct lifetime costs for a patient in the US with intractable and frequent seizures is estimated to be almost $140,000[9]; therefore, the economic burden per patient with LGS can be reasonably assumed to be significant.

Seizures characteristic in LGS include tonic, atonic, atypical absence, myoclonic, clonic, and partial absence, with unclassified seizures also present.[10] Due to the difficulty in differentiating

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between tonic and atonic seizures, these are often combined in clinical studies of LGS and termed tonic–atonic seizures or 'drop attacks'. These drop attacks are the most physically damaging seizures causing recurrent injuries such as lacerations or head injuries due to falls.[10] As a result, many patients require constant supervision, often need protective headwear, or are confined to wheelchairs. The reduction in drop attack seizure frequency is therefore considered one of the most clinically significant outcomes for patients with LGS.[11]

LGS is a difficult-to-control condition, with considerable uncertainty regarding the optimum therapy[12] and little available guidance to assist specialist physicians in choosing appropriate antiepileptic drugs (AEDs).[13] There is currently no cure for LGS and, since existing treatments seldom offer complete control of seizures, treatment goals are to provide the best control of seizures, using the fewest AEDs, while limiting any adverse events.[14,15] Moreover, the development of novel therapeutic agents for treating LGS is hindered by the absence of an appropriate animal model; as a result, treatment options for this devastating condition are severely limited.[13]

Current first-line treatment involves the use of traditional AEDs (including valproate); none of which has been rigorously studied in controlled clinical trials in a population of patients with LGS. Treatment with these traditional AEDs rarely provides sufficient control of seizures, and newer AEDs are added to achieve a more effective combination therapy.[16] Newer AEDs, such as topiramate (TPM), lamotrigine (LTG), and felbamate, have demonstrated efficacy as adjunctive treatments for patients with LGS in randomized, placebo-controlled clinical trials.[17–19] In the UK, only TPM and LTG are licensed for the adjunctive treatment of patients with LGS. The use of adjunctive felbamate is limited to a 'named patient' basis and its use is restricted to last-line therapy due to the risk of life-threatening adverse events such as aplastic anemia and hepatitis.[20,21]

Newer AEDs are considered to offer an improved side effect profile relative to older agents; however, those commonly used for adjunctive use in LGS are not free from adverse events. Life-threatening skin reactions such as Stevens–Johnson Syndrome have been associated with LTG[20], while TPM is associated with impaired cognition[22] and weight loss.[23]

The effects of TPM on cognition include impaired concentration, confusion, memory loss, psychomotor slowing, and speech disorder.[24] Since the impact of LGS on cognition is also well documented,[8] with patients often experiencing reduced alertness after seizures and being less responsive between seizures, medications that potentially compound the inherent cognitive disability seen in LGS would be undesirable to both caregivers and patients. Similarly, patients with LGS are often underweight and more prone to illness, as frequent seizures and constant physical activity utilize energy, resulting in both difficulties in eating and fatigue. Consequently, LGS treatments that induce a loss of appetite and weight loss, such as felbamate[21] and TPM,[23] can exacerbate the problems associated with being underweight, having a profound impact on patient well-being. Weight loss associated with TPM is particularly marked, to the extent that it has been extensively studied as a treatment for obesity.[25]

Despite these undesirable adverse events, many patients with LGS often persist with their treatment due to the lack of alternative options. This situation highlights the need to develop new AEDs that are both effective in treating the multiple seizure types associated with LGS, and which also have an improved tolerability profile.

Rufinamide (RUF) is a structurally distinct AED licensed as adjunctive therapy for patients with LGS aged four years and over. RUF principally acts by prolonging the inactive state of sodium channels, inhibiting the firing of sodium-dependent action potentials.[26] A Phase III, double-blind, placebo-controlled clinical trial has shown RUF to be effective in reducing seizure frequency in patients with LGS.[15] RUF was significantly more effective than placebo in reducing total seizure frequency (32.7% reduction versus 11.7%, respectively, $p = 0.0015$) and drop attacks (42.5% reduction versus 1.4% increase, respectively, $p = 0.0041$). Furthermore, a significantly higher proportion of patients receiving RUF achieved greater than 50% reduction in total seizure frequency, compared with placebo (31.1% of patients versus 10.9%, respectively, $p = 0.0045$). This study also demonstrated that RUF was well tolerated, with the most commonly reported adverse events (including somnolence, vomiting, pyrexia, and diarrhea) being mild in intensity.[15] Importantly, a separate study also showed that RUF does not adversely affect cognition, even at high therapeutic doses.[27]

As newer drugs are often more costly than existing therapies, and may offer only marginal benefits, it is important that decision-makers are able to effectively assess the value of new treatments relative to existing therapies. Health technology assessment bodies in the UK (e.g., the National Institute for Health and Clinical Excellence [NICE] and the Scottish Medicines Consortium [SMC]) prefer to measure cost-effectiveness in terms of cost per quality-adjusted life-year (QALY).[28] This allows comparisons of cost-effectiveness across therapeutic areas and provides a measure of the opportunity costs of new health technologies. In the UK, NICE does not use an absolute willingness to pay (WTP) threshold in its cost-effectiveness analyses of new technologies, but generally considers a WTP threshold range of £20,000 to £30,000 per QALY as an acceptable incremental cost-effectiveness ratio (ICER). In cases where new therapeutic interventions possess an ICER in excess of £20,000 per QALY, threshold factors such as uncertainty around the point estimate of the ICER, adequately captured evidence on improvements in health-related quality of life, and the innovative nature of the new technology are taken in account. In situations where an ICER exceeds £30,000 per QALY, a stronger case, in regard to the factors listed, is necessary in order for NICE to deem the intervention an effective use of NHS resources.[38]

This method of appraisal often poses challenges for orphan drugs, for which the price and cost-effectiveness estimates are generally high,[29,30] and for which any economic analysis often relies heavily upon assumptions and evidence synthesis due to the paucity of appropriate clinical data. In addition, there may also be no validated disease-specific tools to assess health-related quality of life or, due to the rarity of orphan diseases, small clinical study samples make it difficult to make meaningful assessments of improvements in health-related quality of life with new interventions.

The objective of this study was to evaluate the cost-effectiveness of RUF relative to TPM and LTG as adjunctive treatment for children with LGS in the UK.

2. Methods

2.1. Model structure

A Markov decision analytic model was developed to estimate the cost-utility of RUF versus TPM (or LTG) as adjunctive treatment for a hypothetical cohort of patients with LGS uncontrolled by up to three AEDs (Fig. 1). In economic decision analytic models, mathematical relationships are used to define a series of possible consequences that would stem from the set of alternative options being evaluated.[31]

Markov models are commonly used in health economic decision analyses, and are particularly well suited to modeling the progression of chronic diseases. For such analyses, the disease