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Review article

Long-term retention rates for antiepileptic drugs: A review of long-term extension studies and comparison with brivaracetam

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ABSTRACT

Antiepileptic drug (AED) retention rates are frequently reported in the literature and used to inform clinical decision-making, but methodological differences in the determination of retention rates make comparisons between trials difficult. Open-label extension (OLE) studies of AEDs in patients with focal epilepsy were identified from the literature. Retention calculation methods were reviewed, and published AED retention rates qualitatively compared with corresponding data for brivaracetam (BRV), a synaptic vesicle protein 2A ligand. The search identified 40 publications (corresponding to 17 studies of nine AEDs: eslicarbazepine, gabapentin, lacosamide, levetiracetam, oxcarbazepine, perampanel, pregabalin, topiramate and zonisamide) meeting eligibility criteria for inclusion in the review. Three methodologies to estimate retention rate were identified, which differed in whether patients randomised to placebo in the preceding randomised controlled trials (RCTs) were included or analysed separately, and whether retention was measured from the start of the OLE or of active treatment exposure. The most robust, conservative approach included all patients and measured retention from start of active treatment exposure, whether during the blinded RCT or at the start of the OLE (placebo RCT patients). Data using this method was available for five AEDs in this review, including BRV. The corresponding BRV 52 week retention rate (modal doses 50–200 mg/day; therapeutic range) was 69.8% (63.3–66.7% for other AEDs at this time point). No statistical indirect comparison was performed, as study populations were clinically heterogeneous. To avoid inconsistencies in methodologies, and allow comparison between AEDs when OLE data are the only long-term data available, retention rate analyses would benefit from the development of consistent reporting standards and guidelines.

1. Introduction

Most patients with epilepsy receive chronic, long-term treatment with one or more antiepileptic drugs (AEDs). Since approximately 30% of patients do not achieve seizure freedom with AED treatment (Kwan and Brodie, 2000), and all AEDs are associated with side effects, the goal for any patient is generally to optimise treatment effectiveness by achieving a balance between seizure frequency reduction and acceptable side effects (Chung et al., 2007; Glauser et al., 2006; Glauser et al., 2013). Long-term retention rates can provide an indication of the expected clinical outcome of AEDs in patients, serving as a proxy measure for efficacy and safety combined over time (Chung et al., 2007).

Brivaracetam (BRV) is an AED in the racetam class and thus exerts its antiepileptic effects via binding to synaptic vesicle protein 2A (SV2A). BRV is indicated as adjunctive treatment in adults with focal seizures, with or without secondary generalisation, and its published 12-month retention rate from long-term, open-label extension (OLE) studies is 79.8% (N = 2051) (Toledo et al., 2016). However, it is difficult to compare retention rates between different AEDs because OLE retention rates published in the literature have been calculated in several different ways, with no standard methodology or time point(s) for reporting.

To attempt to address this, we conducted a literature search to identify OLE studies for AEDs in adult patients with focal epilepsy that reported retention rates, or data allowing calculation of retention rates. This paper will review these published data, identify and evaluate the

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methodologies used and, for each method, qualitatively compare the published retention rates for other AEDs with the corresponding data for BRV.

2. Methods

2.1. Literature review

This literature review and the associated post-hoc analyses did not require approval from an ethics committee. The literature search was conducted in March 2016 to identify reports of OLE studies of AEDs as adjunctive therapy in patients with focal epilepsy. The 14 AEDs of interest (see Table S1) were selected based on their high frequency of use in patients with focal epilepsy and also included the most recently approved AEDs (eslicarbazepine, perampanel, retigabine/ezogabine), which may be expected to become more commonly used over time. To increase comparability with the BRV OLE studies, publications were only included if they reported results from OLE studies that were preceded by a double-blind, randomised, placebo-controlled trial (RCT). The full inclusion criteria are presented in Table S1, and details of the search strategies are shown in Table S2. The process for review, extraction and interpretation of results is also included in the Supplemental Material. Since there are currently no comparable paediatric data available for BRV, only publications reporting data from adults are considered here. Paediatric data were scarce for the other 14 AEDs, with only five of 17 trials providing retention data for children or adolescents (Guerrini et al., 2014; Kumar et al., 2015; Mann et al., 2014; Puri et al., 2011; Wroe et al., 2008). One study included in our analysis had a predominantly adult population, but also included children aged ≥12 years (Wroe et al., 2008).

2.2. Data extraction

For each publication, the reported retention rates were extracted, or the data presented were used to estimate a retention rate. If the available data allowed calculation of retention by multiple methods, or for additional time points, then rates were calculated by every possible method for every possible time point. Where available, reasons for discontinuations were also summarised.

2.3. Retention rate calculations for BRV

Our retention analyses were based on the pooled BRV population published by Toledo et al. (2016) (Toledo et al., 2016). This population comprised all patients who had received BRV in any of six core Phase IIb and III RCTs (N01114/NCT00175929 (Van Paesschen et al., 2013), N01193/NCT00175825 (French et al., 2010), N01252/NCT00490035 (Ryvlin et al., 2014), N01253/NCT00464269 (Biton et al., 2014), N01254/NCT00504881 (Kwan et al., 2014), N01358/NCT01261325 (Klein et al., 2015)), and/or their four subsequent OLE studies (N01125/NCT00175916, N01199/NCT00150800, N01379/NCT01339559, N01372/NCT01728077) (Toledo et al., 2016). Patients were included in this retention population if they received a modal BRV dosage within the therapeutic range (50–200 mg/day). Patients receiving subtherapeutic BRV dosages (< 50 mg/day) were excluded because their retention was expected to differ from those receiving effective dosages, leading to a biased estimation of the retention rate. The overall BRV retention population totalled 2051 patients, of whom 1884 entered one of the OLE studies. As reported by Toledo et al. (2016) (Toledo et al., 2016), patients ongoing at the cut-off date of January 2014 were censored.

BRV retention was calculated by three different methods, as illustrated in Fig. 1a and b. Method 1 assessed retention at 52 weeks from the start of the OLE (N = 1884, due to exclusion of patients who did not enter the OLE studies) using a Kaplan–Meier analysis and censoring ongoing patients. Any prior exposure to BRV during the preceding RCT was disregarded and patients who discontinued during the RCT were not included in the analysis. In Method 2, retention was again measured at 52 weeks, but taken from the start of BRV exposure rather than the start of the OLE (N = 2051), still using a Kaplan–Meier analysis and censoring ongoing patients. Method 3, published by Toledo et al. (2016) (Toledo et al., 2016), also assessed retention at 52 weeks from the start of BRV exposure (N = 2051). However, patients who completed the studies, and those discontinuing the study with a main reason other than adverse event (AE) or lack/loss of efficacy (LOE), were censored at the date of the discontinuation/completion visit (e.g. lost to follow-up) for the Kaplan–Meier analysis.

3. Results

3.1. Literature review

The literature search identified 1247 journal articles and 85 congress presentations. Of these, 40 publications (covering 17 studies) met the eligibility criteria for inclusion in the analysis (Fig. 2). Relevant publications were found for nine AEDs: eslicarbazepine (ESL, 2 publications), gabapentin (GBP, 1), lacosamide (LCM, 3), levetiracetam (LEV, 1), oxcarbazepine (OXC, 1), perampanel (PER, 17), pregabalin (PGB, 1), topiramate (TPM, 10) and zonisamide (ZNS, 4). No eligible publications were found for carbamazepine, lamotrigine, phenytoin, retigabine/ezogabine or valproate. Details of the publications, including study numbers and numbers of patients, are shown in Table S3.

3.2. Overview of published retention rate methodologies

Three different retention rate methodologies were identified in the publications (Fig. 1b). The first two measure retention from the start of the OLE, whereas the third measures retention from the start of exposure to the active treatment.

Method A, equivalent to BRV Method 1, measures retention in all patients from the start of the OLE, regardless of whether they received active treatment or placebo in the preceding RCT. To facilitate comparisons for each AED using this method, if data were available from multiple studies reporting on the same AED then these retention rates were pooled as weighted averages.

Method B excludes patients who received placebo in the RCT (see Table S3 for patient numbers). Retention is still measured from the start of the OLE, but the analysis population only includes patients who were randomised to active treatment in the RCT. No comparable data were calculated for BRV, due to the risk of bias associated with measuring retention from the start of the OLE study and exclusion of the patients who originally received placebo.

In Method C, the retention starting point differs depending on the treatment received during the RCT. For patients receiving active treatment in the RCT, retention is measured from the start of the RCT. For patients randomised to placebo in the RCT, retention is measured from the start of the OLE (i.e. when they start active treatment [see Table S3 for numbers of patients randomised to active treatment and placebo]). Retention calculated by this method may be reported as a composite value, as for the published BRV data (Toledo et al., 2016), or separately for the two groups (prior active treatment and prior placebo).

3.3. Published retention rates and comparison with BRV

Method A was most commonly used in the literature, with data available for nine of the 14 AEDs of interest. Data were available at multiple time points in publications LCM2 (Rosenow et al., 2015) and PER4 (Krauss et al., 2014); however, the most commonly reported time point was 52 weeks. Retention rates at 52 weeks were available for six AEDs, ranging from 45.2% (ZNS2 (Brodie, 2004)) to 83.6% (OXC1