Expert Opinion on Pharmacotherapy

ISSN: 1465-6566 (Print) 1744-7666 (Online) Journal homepage: https://www.tandfonline.com/loi/ieop20

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To cite this article: Benjamin Cretin & Frederic Blanc (2020): How does epilepsy impact the pharmacotherapeutic management of patients with dementia with Lewy bodies?, Expert Opinion on Pharmacotherapy, DOI: 10.1080/14656566.2019.1707185

To link to this article: https://doi.org/10.1080/14656566.2019.1707185

Published online: 03 Jan 2020.

EXPERT OPINION ON PHARMACOTHERAPY
https://doi.org/10.1080/14656566.2019.1707185

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EDITORIAL

How does epilepsy impact the pharmacotherapeutic management of patients with dementia with Lewy bodies?

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ARTICLE HISTORY Received 25 October 2019; Accepted 17 December 2019

KEYWORDS Disease with Lewy bodies; epilepsy; seizures; antiepileptic drugs

1. Introduction

Epilepsy impacts the pharmacotherapeutic management of patients with dementia with Lewy bodies (DLB) in two non-exclusive ways: *first*, epilepsy makes less easy the use of the symptomatic treatments of the disease (Figure 1); *second*, the prescription of antiepileptic drugs (AEDs) in these patients carries a substantial risk of clinical aggravation (Table 1). Such considerations are not theoretical because DLB is a common etiology (the second or third) of cognitive decline and dementia in neuropathological studies: It is now recognized as an important cause of neurocognitive disorder affecting 10–15% of patients [1]. Depending on the clinical stage of the disease, DLB patients are commonly ≥ 70 years old in the prodromal phase (mild cognitive impairment due to DLB) and are logically older in the dementia stage [2]. Thus, DLB concerns older patients with non-neurological (cardiovascular diseases, renal insufficiency, endocrine disorders, etc.) and neurological comorbidities (in particular stroke and traumatic brain injury) [3]. As early as in the prodromal phase, DLB is characterized by aberrant hyperexcitability manifested by common myoclonus and electroencephalographic (EEG) abnormalities [4,5]. The explanation is not completely clear but fundamental data have underpinned the fact that aggregated alpha-synuclein, the major component of Lewy bodies, is epileptogenic by inducing hyperexcitability in affected neurons (whether cortical or subcortical) [4]. Additionally, DLB is commonly accompanied by Alzheimer's disease (AD) co-pathology, which is furthermore epileptogenic [1,6]. Unsurprisingly, in this context, DLB is associated with interictal epileptiform discharges on EEG, seizures, and epilepsy in a substantial proportion of cases (at least 10% according to present knowledge) [4]. Therefore, the treatment of seizures and/or epilepsy in these patients is a frequent issue in clinical practice that requires a minimal conceptual framework to avoid mistreatment and/or cognitive-behavioral aggravation due to inappropriate medications.

2. DLB, relevant clinical–radiological description, and standard therapeutics

Seizures and epilepsy reported in DLB are mainly focal aware, focal with impaired awareness, or secondarily generalized. Primary generalized tonic-clonic seizures (PGTC) are also encountered in DLB [4]. Thus, AEDs effective in focal seizures and/or PGTC may potentially be useful in such cases, with a particular interest for *wide-spectrum molecules* such as levetiracetam (LEV), brivaracetam (BRV), benzodiazepines (BDZ) and other GABAergics, valproate (VPA), topiramate (TPM), zonisamide (ZNS), and perampanel (PER). On the other hand, seizure-specific treatment such as ethosuximide, stiripentol, or rufinamide should not be considered for epileptic DLB patients. Before going further into the use of AEDs in DLB, it is important to bear in mind the core clinical picture of the disease (in the prodromal or the dementia stage) that allows for an appropriate diagnosis when used with related criteria [7]. Most of all, *DLB is a neurocognitive disorder*: It manifests primarily as cognitive decline with particularly common psychiatric comorbidities (depression, psychosis) and spontaneous or provoked delirium [7]. In combination with such psycho-cognitive signs and symptoms, DLB is defined by the occurrence of at least one of the following: parkinsonism, fluctuations of cognition and/or vigilance, sleep disturbances, and visual hallucinations. It must be noted that excessive daytime sleepiness, dysautonomia (i.e., constipation, orthostatic hypotension), and falls are also very common in DLB. Additionally, the disease is characterized by mild cerebral atrophy with a specific pattern in the prodromal phase (affecting the limbic structures predominantly and the insula in particular) [8]. The symptomatic treatment of DLB requires non-pharmacological approaches that are not within the scope of this paper [9]. On the other hand, the following pharmacotherapeutic options are indicated: cholinesterase inhibitors (ChEI; i.e., rivastigmine or donepezil) for cognitive decline and/or hallucinations, L-DOPA for parkinsonism, atypical neuroleptics or pimavanserin for hallucinations and/or psychosis, specific serotonin uptake inhibitors (SSRI) for depression and/or agitation, and melatonin or clonazepam for REM-sleep behavior disorder [10]. If DLB patients have concomi-

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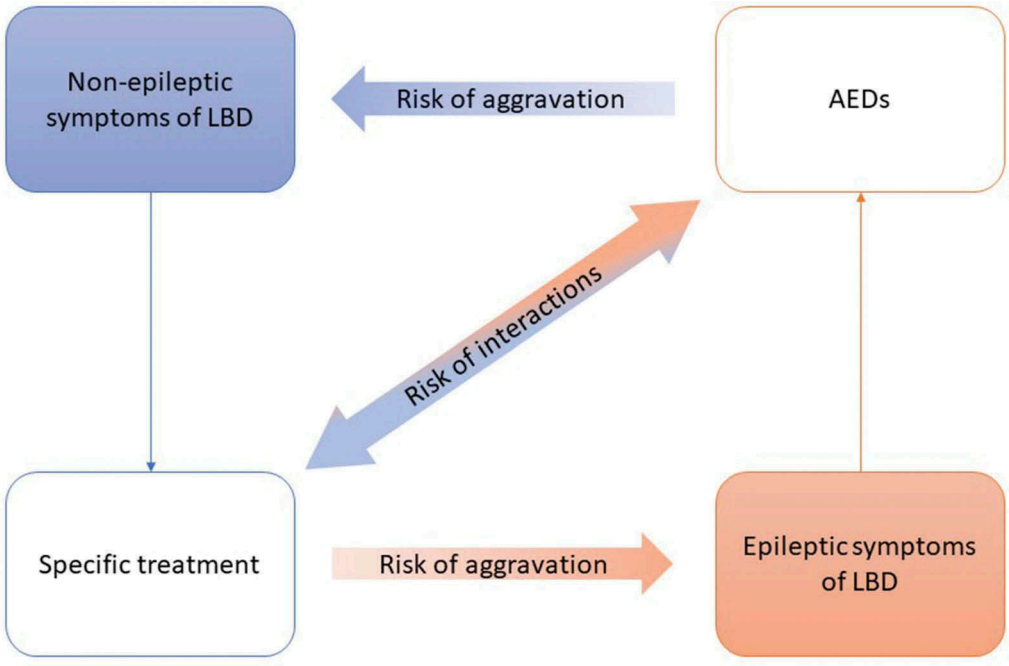

Figure 1. Treatments of ictal and interictal features of DLB and their related risks.

Table 1. Clinical features of DLB and related potentially harmful antiepileptic medications.

Clinical feature of DLB	Potentially aggravating AEDs
Cognitive decline	CBZ, OXC, ESL; GABAergics; TPM, ZNS, VPA
Depression	LEV, BRV, TPM, ZNS, GABAergics
Psychosis	VGB, LEV, BRV, TPM, ZNS, PER
Delirium	BDZ, TGB
Parkinsonism and/or tremor	VPA, LEV
Visual hallucinations	TPM, ZNS, GBP, PGB, PER
Excessive daytime sleepiness	GABAergics, CBZ, OXC, ESL, GBP, PGB
Myoclonus	LTG, CBZ, PHT, OXC, GBP, PGB
Falls	In particular BDZ and PHT (but potentially all AEDs at high doses)
Orthostatic hypotension	TPM, ZNS (du to diuretic effect)
Syncopes	LCS

tant epilepsy, some treatments may interact with such comorbidity: SSRI and neuroleptics are potentially 'epileptogenic', ChEI and memantine are sometimes suspected so (but not on a clear and demonstrated basis) [11–13]. Therefore, when epilepsy is suspected in DLB, their prescription must consider the related risk of seizure aggravation and should follow the initiation of an appropriate AED.

3. Treating epilepsy in DLB: what is the appropriate AED?

The goal of the treatment is to ensure effectiveness in seizures with a lower impact on frail DLB patients. At present, no relevant trial has evaluated AEDs in DLB. Available data come from very few papers and, in fact, we must admit that no evidence-based AED(s) have been identified for DLB. Nonetheless, given the clinical semiology of seizures, drugs active in focal and tonic-clonic generalized seizures are most probably useful for treating epilepsy in DLB (see § 2). With regard to the old age of DLB patients, some general recommendations can be made, as for AD patients [14]. *First*, the prescribed doses of AEDs should be low at initiation and slowly increased (if necessary) to minimize the risk of side effects, which is, moreover, aggravated by the frequent decreased renal clearance, by the common lower fluid compartment in the body, and/or by low albuminemia in older patients. *Second*, the multifactorial risk of bone fracture (related to osteoporosis, gait and balance impairment, visuospatial deficits, etc.) can be significantly worsened by the following AEDs: phenobarbital (PB), carbamazepine (CBZ), phenytoin (PHT), valproate (VPA), oxcarbazepine (OXC), eslicarbazepine (ESL), and topiramate (TPM). *Third*, dyslipidemia can be favored by CBZ and OXC and have a significant impact on the progression of the disease by increasing the cerebral vascular burden. *Fourth*, DLB subjects often receive antidepressants that may pharmacologically interact with AEDs and alter their effectiveness. *Fifth*, enzyme-inducing (i.e., PB, CBZ, PHT, OXC, ESL, and PER) or -inhibiting (i.e., VPA and PER) AEDs may increase the risk of drug–drug interactions with donepezil, cardiovascular medications, etc. Regarding the key importance of cognitive impairment in DLB, the AEDs used should avoid any psycho-cognitive impact. In this regard, GABAergics (i.e., PB, BDZ, vigabatrin [VGB], tiagabine [TGB], and primidone [PRM]) are not recommended, and neither are anticholinergic AEDs (i.e. CBZ, OXC, and ESL) that have the potential to impede the effect of ChEI. From a cognitive point of view, VPA should be avoided because it may exacerbate cognitive decline and the atrophy rate owing to the frequent underlying AD pathology combined with DLB [1,14]. Moreover, depression can be exacerbated by GABAergics (i.e., VGB, TGB, PB, PRM), TPM, ZNS, LEV, and BRV, and

psychosis by VGB, LEV, BRV, TPM, and ZNS. Furthermore, AEDs can be harmful by aggravating other features of DLB (Table 1).

4. Expert opinion

In view of all the aforementioned considerations (see also Table 1), few molecules are finally appropriate given the risk of their neurological and non-neurological impact. It is reasonable to conceive that the best AEDs available for treating epilepsy in DLB are 'new AEDs' developed after the 1990s that carry a lower risk of drug interactions and enzyme induction/inhibition [14]. Thus, the following appear legitimately suitable for epileptic DLB patients: low to moderate doses of LTG, LCS, LEV or BRV as *first-line treatment*, and low dose of gabapentin (GBP) or pregabalin (PGB) as *second-line treatment*. Even with these, however, close monitoring is required to avoid neuropsychiatric side effects (Table 1) and aggravation of the vicious circle due to iatrogenic impact and pharmacological interactions (Figure 1). But, having posited this, much remains to be done at present. On the basis of appropriate trials, we have to establish which of these five candidate molecules are more relevant for the treatment of epilepsy in DLB. This will not be an easy task. The reason lies in the fact that the diagnosis of epilepsy is particularly challenging in DLB. In fact, the cognitive decline of patients includes an early and peculiar 'insular' impairment that hinders an accurate analysis of interoceptive and exteroceptive perceptions in conjunction with memory deficits [15]. Consequently, patients are not always reliable for remembering and describing subjective ictal semiology and/or for warning when fits or spells occur. Additionally, focal seizures may be confused with cognitive fluctuations and therefore be mistaken as a cardinal sign of the disease instead of suggesting epilepsy work-up. Finally, when such work-up is carried out, EEG abnormalities may not be of epileptic origin but rather from background rhythm alterations related to the disease [16]. For all these reasons, further work is certainly needed to reliably identify epileptic DLB patients and to evaluate their ictal and interictal response to selected AEDs. Inspired by Cumbo et al. [17], a prospective, randomized, two- or three-arm parallel-group, case–control study would improve our knowledge in this field.

Funding

This manuscript has not been funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer Disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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