CURRENT AND EMERGING DRUG TREATMENTS FOR DEPRESSION IN ADULTS WITH EPILEPSY

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ABSTRACT

Introduction: Depression is the most frequent psychiatric comorbidity among people with epilepsy. It can impact on quality of life and increases the risk of morbidity and premature mortality.

Areas covered: We reviewed available data on current and emerging drug treatments for depression in epilepsy. Sources have been identified through Medline/PubMed searches while ongoing clinical trials have been identified though a search on ClinicalTrials.gov.

Expert opinion: SSRIs are the drug class with the largest amount of data. Though promising, the level of evidence provided by these studies is still low as the majority have relevant methodological limitations. Antiepileptic drugs under development have the unique opportunity to explore multi-use in epilepsy and depression. The serotoninergic system has already been identified as a potential area of interest but new targets are needed in epilepsy and depression. For this reason, basic scientists working on these two conditions should develop collaborative projects and integrate findings.

Key words: epilepsy, depression, SSRIs, antiepileptic drugs, antidepressant drugs

INTRODUCTION

Depression is the most frequent psychiatric comorbidity among people with epilepsy [1]. It is associated with poor quality of life [2], drug-resistance [3,4], increased seizure severity [5], side effects of antiepileptic drugs (AEDs) [6], increased risk of accident and injuries [7], poor outcome after epilepsy surgery [8] and premature mortality [9].

Epidemiological studies show a consistent increased prevalence for depression in epilepsy as compared to the general population, ranging from 4%-9% in people who are seizure free [10], to 17%-22% in the community [11] and up to 55% in people with drug-resistant epilepsy [12]. This partially reflects the severity of the disorder not only in terms of underlying brain dysfunction but also in terms of psychosocial difficulties and side effects from AED treatment. The relationship between epilepsy and depression is, however, more complex than just being comorbid [13]. There are suggestions that either depression represents the premorbid phase of some epileptic syndromes or the occurrence of epileptic seizures is part of the natural course of some depressive disorders [14]. The specific neurobiological underpinnings the bidirectional relationship between epilepsy and depression hasn't been yet established. The standing neurobiological links between epilepsy and depression in terms of anatomical structures involved (i.e. mesial temporal lobe structures) and neurotransmitter changes (i.e. GABA, serotonin and glutamate pathways) have, however, been highlighted [15]. Lastly, the phenomenology of depression in epilepsy is still a matter of debate. It is now established that some individuals may develop depressive symptoms in different clinical contexts such as seizure-related symptoms (i.e. peri-ictal symptoms), adverse effect of the epilepsy treatment (i.e. AEDs or surgery) or in the context of atypical and pleomorphic syndromes such as the controversial interictal

dysphoric disorder [1, 14]. Therefore, it is evident that neurologists need to be cognisant with the pharmacological treatment of depression and emerging drug options in this area.

Over the last decades the pharmacological treatment of depression has dramatically changed, reflecting the increased knowledge of the neurochemistry of the brain and of the pathophysiology of depression. The acute treatment of depression is aimed at remission and recovery, meaning full control of all symptoms (*remission*) for a period of 6 to 12 months (*recovery*). Clinical *response* is usually defined by at least 50% symptom reduction and the Hamilton Depression Rating Scale (HDRS) is usually considered gold standard in clinical trials of depression. The long-term treatment of depression is aimed at preventing *relapse* and *recurrence*. A *relapse* is a clinical deterioration before remission is reached or a new depressive episode before remission has turned into a recovery, while a new depressive episode after complete recovery is called *recurrence*.

Data from the large-scale, National Institute of Mental Health (NIMH)-sponsored Sequenced Treatment Alternatives to Relieve Depression (STAR*D) real-world trial show response rates of 47%, with remission rates (defined by a total HDRS score <7) of 27.5% at 14 weeks of treatment [16]. Overall, outcome data from clinical trials in depression show that around one third of individuals achieve remission within 2-3 months, 50% within 6 months and over 60% remit within 2 years with continued antidepressant drug treatment [17]. Up to a third of people relapse after 4 to 6 months. In fact, even in case of a clinical response, if full remission is not achieved, the presence of residual symptoms represents a risk factor for a relapse and incomplete recovery is the major risk factor for recurrence. For all these reasons, full remission should always be the final goal of the acute treatment of depression.

Interestingly, there are no outcome data for depression in epilepsy and it is still unknown whether people with epilepsy and depression have similar remission and recovery rates than those with depression alone.

We review available data on current and emerging drug treatments for depression in adults with epilepsy. References have been identified through Medline/PubMed searches until February 2018 using the terms “epilepsy” AND “depression” limiting to “clinical trials”. Ongoing clinical trials have been identified though a search on *ClinicalTrials.gov* till February 2018 using the terms “epilepsy” and “depression”. Additional publications (e.g. books or book chapters) were hand searched if relevant for the discussion. Data on psychological or behavioural treatments as well as trials comparing drug treatment with psychological/behavioural interventions have been excluded as the primary aim is drug treatments and not the treatment of depression in general.

1. CURRENT DRUG TREATMENT OPTIONS

1.1 Antidepressant drugs in epilepsy

Data on treatment of depression in epilepsy is still limited and relies heavily on individual clinical experience [18]. A Cochrane Review on this subject highlights the limited evidence on the efficacy and safety of antidepressants in epilepsy and the low quality of available studies [19].

There are only two published randomised controlled trials for depression in epilepsy. One published over three decades ago and compares nomifensine, amitriptyline and placebo in 45 individuals with epilepsy and depression over a period of 12 weeks [20]. Response rates in the region of 43% for amitriptyline and 79% for nomifensine were

reported but remission rates are not presented. The other study assesses the antidepressant effect of a traditional Chinese medicine remedy, Xylaria Nigripes, as compared to placebo in a 12-week, randomised, double-blind, controlled study in 104 people [21]. Treatment with Xylaria Nigripes seems associated with a significant reduction in mean HDRS scores but neither response rates nor remission rates are provided. The Cochrane Review [19] has also identified two additional randomised, controlled studies in Chinese journals. One compares paroxetine with doxepin in 67 individuals with epilepsy and depression [22] while the other is a controlled trial of venlafaxine versus no treatment in 64 individuals [23]. A response rates of 82% for paroxetine and of 71% for doxepin at 8 weeks is reported [22] while the other study reports a response rates of 69% for venlafaxine at 8 weeks [23] but neither present data on remission rates.

Apart from these few controlled trials, there are several uncontrolled trials in small unselected samples of people with different epileptic diagnosis. Most are of Selective Serotonin Reuptake Inhibitors (SSRIs) such as sertraline [24,25], citalopram [26–28] and fluoxetine [25] or other antidepressants like reboxetine [28] and mirtazapine [28]. One study is of interest as it reports on children and adolescents with epilepsy and depression [25]. In general terms, all these studies seem to suggest that antidepressant drugs are well tolerated by people with epilepsy with no significant seizure aggravation. Response rates are, however, very heterogeneous ranging from 24% [27] to 97% [25]. This high variability is likely due to the heterogeneity of participants (from newly diagnosed epilepsy to drug-resistant epilepsy) and a possible role of pharmacokinetic interactions, especially the effect of inducers on the antidepressant treatment [18].

1.2 Antiepileptic drugs for the treatment of depression in epilepsy

A few studies investigate the potential antidepressant effect of AEDs in people with epilepsy. The main theoretical background for this relates to the possibility of tailoring AED treatment in people with epilepsy and depression, selecting the most appropriate compound. Three studies investigate the effect of Lamotrigine (LTG) while one focuses on Oxcarbazepine (OXC).

The antidepressant effect of LTG as adjunctive treatment in a randomised, double-blind, placebo-controlled study, involving 70 individuals with epilepsy and depression was reported [29]. This is, however, a secondary analysis of an efficacy study of LTG in people with generalised epilepsies [30]. It shows that LTG is associated with a significant reduction in depressive symptoms, as measured by the Beck Depression Inventory (BDI), when compared to placebo. Remission rates are not provided and neither whether the reduction in BDI scores reported is clinically relevant.

A US multicentre open label study assessed the antidepressant effect of LTG in an unselected population of 158 people with epilepsy (50% with generalised epilepsies) [31]. Clinical response rates (as measured with the BDI) ranging between 51% and 71% was reported but no remission rates are provided. A sub-analysis of people older than 50 years, show similar results [32].

A single open label study in 40 individuals with focal epilepsy and depression investigates the antidepressant effect of OXC as adjunctive treatment [33]. People were assessed with the BDI, HDRS and the Cornell Dysthymia Rating Scale (CDRS) and a significant reduction in all depressive scores. A remission rate of 13% as measured with the CDRS is provided but remission rates with usually used outcome scales, such the HDRS or the BDI, are not provided.

2. EMERGING DRUG TREATMENT OPTIONS

2.1 Current antidepressant drug studies in epilepsy

In terms of ongoing or recently finished studies of antidepressant drugs in epilepsy, two Phase IV studies investigate the antidepressant effect of Escitalopram. One is a randomised, double-blind, placebo-controlled trial in people with temporal lobe epilepsy and depression (NCT00595699). The study has been completed but results are still unavailable. The second is a 12-week, open label study (NCT01244724) in people with epilepsy and depression which was terminated due to failure to recruit the target numbers. Results of 15 participants are available on the *ClinicalTrial.gov* database and suggest a mean change in HDRS score from 25.5 at baseline to 13.3 after 12 weeks of treatment but no response or remission rates are available.

2.2 Emerging drugs for epilepsy and depression

Among different compounds with novel mechanisms of action currently under investigation for the treatment of epilepsy, some modulate neurobiological targets which may be relevant in depression.

At least three compounds target the serotoninergic system, Fenfluramine, Naluzotan and Buspirone.

Fenfluramine is a substituted amphetamine, acting primarily as a serotonin releasing agent with less effect on the release of noradrenaline and dopamine, which are primarily mediated by its metabolite Norfenfluramine. It was first approved in the US in the 1970s and later marketed for obesity [34]. It was withdrawn in 1997 after reports

of cardiac effects (valve disease and fibrosis) and pulmonary hypertension [35]. The use of Fenfluramine in epilepsy was first reported in the 1980s. More recently, Fenfluramine has been investigated in Dravet syndrome showing a significant reduction in focal motor seizures [36]. Fenfluramine is currently under Phase III development by Zogenix (ZX008). Three double-blind, randomised, placebo-controlled studies for the adjunctive treatment in Dravet syndrome are being conducted and a long-term, open-label extension is planned [37]. The mechanism of action suggests an antidepressant effect but evidence is not available. The safety profile suggests potential limitations in terms of long term tolerability but this is under review.

Buspirone and Naluzotan (PRX-00023) are 5HT1A receptor agonists and are under investigation for the treatment of epilepsy [35] but are also well known anti-anxiety and antidepressant agents.

Buspirone is already available in several countries for the treatment of anxiety and depression. It has shown to be effective for the treatment of depression either as monotherapy [38] or as augmentation therapy in people who do respond to SSRIs or in males who develop sexual dysfunction as a side effect of SSRIs [39]. The US National Institute of Neurological Disorders and Stroke (NINDS) has sponsored a randomised, double-blind, placebo-controlled, cross-over Phase II study of Buspirone for the adjunctive treatment of seizures in people with focal epilepsy (NCT01496612). Results are not currently available.

Naluzotan is another 5HT1A receptor agonist and is similar to Buspirone but clinical data are limited. Results of Phase II and III studies in generalised anxiety disorders are available and show that it is effective not only for anxiety but also for depressive symptoms [40–42]. NINDS has sponsored a randomised, double-blind, placebo-

controlled, cross-over Phase II study of Naluzotan (PRX-00023) for the adjunctive treatment of seizures in people with focal epilepsy (NCT01281956). Results are not currently available.

Lastly, the potential role of neurosteroids for the treatment of epilepsy and depression needs mentioning. The term “neurosteroid”, originating in the 1980’s, refers to a class of endogenous steroids synthesized from cholesterol in the CNS which are potent and effective modulators of the GABA-ergic and Glutamatergic systems [43]. Studies suggest that the effects of neurosteroids go beyond the simple interaction with GABA-A and NMDA receptors, preventing plastic changes in the limbic system induced by stress [44]. Among different compounds, Ganaxolone is the one with more data on epilepsy and depression, though still preliminary [37]. Even if data on efficacy are promising, the low aqueous solubility and poor oral bioavailability represent a significant limitation for almost all neurosteroids [45]. Other potential complicating issues with this class of drugs include possible endocrine effects via actions on intracellular (hormonal) steroid receptors which need clarification [44].

3. CONCLUSION

Available data on efficacy and safety of antidepressants in epilepsy are still limited. Most of available studies on current and also emerging treatments focus of the serotoninergic system. This probably reflects a few decades of “serotonin domination” in the treatment of depression. Given the high prevalence of depression in epilepsy, it is important that neurologists are familiar with the mechanism of action of antidepressants, side effect profile and the potential interactions with AEDs [18]. New AEDs targeting both conditions would be ideal in this setting but results are still preliminary.

4. EXPERT OPINION

High level evidence on this subject is almost non-existent. The few available studies have relevant limitations in terms of methodology as simple outcome measures like remission and recovery rates are usually not provided. It is still challenging to ascertain whether people with epilepsy have similar remission and recovery rates of those with depression without epilepsy and this represents a serious gap of current literature.

SSRIs are the drug class with the largest amount of data but the level of evidence provided is still low. Given the total lack of high level evidence in epilepsy, it seems, therefore, reasonable to follow internationally accepted guidelines for the treatment of depression outside epilepsy, taking into account individual characteristics of people with epilepsy, such as comorbidities, interactions with AEDs and potential effects on seizure threshold [46]. This approach has also been endorsed by the International League Against Epilepsy [47][48]. Proper treatment outcome studies of depression in epilepsy are, however, still urgently required.

Regarding the potential effect of antidepressants on seizure threshold, the lack of controlled studies in epilepsy does not allow any definite conclusion. Results from open studies are promising but as they have been conducted in heterogeneous epilepsy populations, it is not possible to clarify whether people with specific epileptic syndromes are more at risk. Given the lack of high quality safety data in epilepsy, it seems still reasonable to take into consideration findings on seizure prevalence arising from antidepressant drug trial in depression. These findings may, however, be

potentially biased by a possible bidirectional relationship between depression and epilepsy. It is not possible, for instance, to exclude that seizures, in some cases, was the result of the natural history of their depressive disorder rather than resulting from antidepressant treatment. In fact, it has been suggested that when the increased risk of seizures in depression is taken into account, reports of epileptic seizures in antidepressant drug trials are even less than expected [18].

The ultimate goal of future research on this subject should be: i) To provide Class I evidence that antidepressant drugs are effective and safe in people with epilepsy; ii) To provide good treatment outcome data including not only response rates but also remission and recovery rates; iii) To clarify whether different epilepsy syndromes present with different risks in seizure relapse during antidepressant treatment.

Future controlled studies will need to take into account potential interactions with AEDs as it is known that some of them may reduce the effect of antidepressants. For this reason, a fixed-dose and a flexible-dose design approach should be adopted. The HRSD has been validated in epilepsy [49] and should be adopted in clinical trials of depression in epilepsy in order to have comparable treatment outcome measures.

Studies on AED under development have the unique opportunity to explore double indication for epilepsy and depression. New compounds may be selected in that sense from Phase I development in order to address both problems at the same time. The serotoninergic system has been already identified as a potential target but new targets are needed in epilepsy and depression. Basic scientists working on these conditions should develop collaborative projects and integrate findings at an early stage [50].

5. ARTICLE HIGHLIGHTS

- High evidence outcome data about efficacy and safety of antidepressant drugs in epilepsy are still limited
- It is still unknown whether people with depression and epilepsy have similar remission and recovery rates than those with depression but without epilepsy
- Given the lack of any strong evidence in epilepsy, it seems reasonable to follow internationally accepted guidelines for the treatment of depression outside epilepsy
- It is still unknown whether different epilepsy syndromes are associated with different seizure relapse during treatment with antidepressants
- New potential targets for drug development in both epilepsy and depression are needed

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