Clinical Perspective

Treatment issues for psychiatric comorbidities of epilepsy

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Practice Points

- Although often encountered, psychiatric disorders in epilepsy are still underdiagnosed and undertreated.
- New psychotropic agents, both antidepressants and antipsychotics, are generally better tolerated with few side effects and a low potential for drug interactions with antiepileptic drugs.
- Individualized titration schedules and careful clinical monitoring improve efficacy and tolerability.
- Selective serotonin reuptake inhibitors or serotonin–norepinephrine reuptake inhibitors can be reasonably considered first choice for the treatment of mood and anxiety disorders in epilepsy.
- Atypical antipsychotics, in particular risperidone, can be reasonably considered first choice for treatment of psychotic symptoms in epilepsy.

SUMMARY Although frequently encountered in epilepsy, psychiatric comorbidities are still underdiagnosed and undertreated. This is related to the lack of standardized treatment approaches and the limited knowledge of neurologists on the treatment of psychiatric disorders. More recently, international panels have published consensus documents in order to favor a homogenous approach to the problem. This article discusses treatment issues of major psychiatric comorbidities of epilepsy, namely mood and anxiety disorders and psychoses. Moreover, specific problems in intellectually disabled patients are presented. In general terms, new psychotropic medications, both antidepressant and antipsychotic drugs, are preferred in terms of safety and efficacy. Careful attention to special needs of the patient, to drug–drug interactions and the adoption of individualized titration schedules represent important variables.

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Psychiatric disorders represent relatively frequent comorbidities in epilepsy, affecting one in every three patients. Prevalence rates for depression are in the region of 30%, while anxiety disorders and psychoses are reported in up to 25 and 2–7%, respectively [1,2]. Although these problems have a deleterious impact on quality of life [3], morbidity and mortality [4] they are, more often than not, ignored, unless they are severe enough to cause major disability. This is due to multiple factors, including the patients' reluctance to spontaneously volunteer information about existing psychiatric symptoms, a paucity of specific training of the treating neurologist to recognize these psychiatric comorbidities and a lack of time in very busy clinics to screen for them [5].

Compared to other medical conditions where psychiatric disorders may occur, the management of epilepsy patients is further complicated by the disorder itself. In fact, it is mandatory to identify the various elements that may contribute to psychiatric symptoms, such as psychosocial issues [4], adverse effects of antiepileptic drugs (AEDs) [6] and neurobiological factors directly related to seizures [7]. Systematic data on treatment strategies for psychiatric disorders in epilepsy remain limited, with clinical practice relying heavily on individual experience. However, during recent years, experts from the USA [8] and an international panel [9] suggested standardized treatment approaches in specific clinical contexts. In general terms, guidelines for treatment of primary psychiatric disorders outside epilepsy are valuable [10,11], taking into account the specificities of the underlying neurological condition.

The present paper discusses treatment approaches in major psychiatric comorbidities of epilepsy, namely mood and anxiety disorders and psychoses. Moreover, specific issues in intellectually disabled patients are presented.

Mood & anxiety disorders

Remission and recovery are the main goals of the acute treatment of depression and avoiding recurrence is the main objective of long-term treatment [12]. In general terms, it is estimated that the percentage of responders to one treatment or a combination of therapeutic interventions is up to 90% for patients with depression and, among these subjects, approximately 50% may recover within 6 months and up to 75% within 2 years [13]. The remaining subjects may require two or more drugs to reach full remission. The probability of recurrence depends on a number of factors such as multiple prior depressive episodes, long-lasting episodes, incomplete recovery from prior episodes and the presence of bipolar or psychotic features. In this regard, it is important to point out that it is still unclear whether patients with seizure disorders respond to antidepressant drugs in the same way as primary psychiatric patients. The general impression is that depression in epilepsy is usually mild-to-moderate in severity [14,15], with good response rates to adequate treatments [16].

If the importance of depression in epilepsy has been increasingly recognized, less attention is still being paid to anxiety symptoms [17]. However, anxiety disorders seem to have prevalence rates, among patients with epilepsy, comparable or even higher than those reported for depression. Moreover, anxiety disorders are chronic conditions with a relapsing–remitting time course [18] and a complex psychiatric comorbidity pattern that may develop during the longitudinal phase of the disease [19]. It seems, therefore, evident that treatment of anxiety in epilepsy is of great relevance. In general terms, antidepressant drugs represent first-line agents in the treatment of anxiety disorders outside epilepsy, often in association with psychotherapeutic approaches [20].

Two main issues are relevant when using antidepressant drugs in patients with epilepsy, namely pharmacological interactions (both pharmacodynamics and pharmacokinetics) and the potential impact on seizure threshold [21]. In general terms, new antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) or serotonin–norepinephrine reuptake inhibitors **(Box 1)**, are well tolerated and have a favorable pharmacokinetic profile with a low risk of interactions. Fluoxetine and fluvoxamine represent the only exceptions, being potent enzyme inhibitors [22]. SSRIs have been demonstrated to be reasonably safe in epilepsy, bearing in mind that drug doses need to be adjusted according to clinical response, especially if AEDs with inducing properties are coprescribed [22,23]. In this regard, it is important to consider that SSRIs have significant differences in terms of half-life, with paroxetine and fluvoxamine having a half-life under 24 h, thus explaining the possibility of uncomfortable

symptoms when some doses are missed [24]. On the contrary, fluoxetine possesses a long half-life, limiting the possible impact of missed doses [24]. As far as pharmacokinetics are concerned, fluoxetine, fluvoxamine and nefazodone are the only compounds that are difficult to use. In fact, they are enzyme inhibitors and may potentially increase plasma concentrations of different AEDs, especially carbamazepine and phenytoin [22].

Adverse effects of SSRIs include hyponatremia, sexual dysfunction, bleeding and extrapyramidal symptoms [24]. It is, therefore, important to monitor patients for clinical signs of hyponatremia and test electrolytes when SSRIs are prescribed in combination with oxcarbazepine or carbamazepine. Sexual dysfunction is due to 5-HT_2 receptor stimulation and has been reported in up to 70% of males taking SSRIs [25]. In young men, the use of SSRIs should be carefully considered and other compounds may be considered as an alternative option for the relatively low prevalence of adverse events on sexuality (<30%) [26,27]. Bleeding during treatment with SSRIs has been estimated to occur in one out of 8000 prescriptions [28], but such a risk can be significantly increased when SSRIs are administered in association with salicylates or NSAIDs. Finally, extrapyramidal symptoms may occur in one case out of 1000 treated patients [29]. The mechanism is unclear, but it has been suggested that overactive 5-HT neurons inhibit dopamine synapses in the basal ganglia [30]. It is a rare adverse event that seems to occur quite early during treatment (usually in the first month), especially in elderly subjects when rapid titration schedules are adopted [31]. In this regard, it has to be considered that extrapyramidal symptoms have also been described with valproic acid [32]. Therefore, the prescription of SSRIs with this specific AED may lead to extrapyramidal symptoms in some selected cases.

The issue of seizure worsening with antidepressant drugs represents a special concern for clinicians. However, increasing evidence is supporting a bidirectional relationship between epilepsy and psychiatric disorders, particularly depression [33,34]. Therefore, if depression is a risk factor for epilepsy, the new onset of seizures during treatment with antidepressant medications might have nothing to do with the medication. In this perspective, the fact

Box 1. Classification of major psychotropic medications.

Antidepressant drugs

- Tricyclic antidepressant drugs
  - Amitriptyline
  - Clomipramine
  - Desipramine
  - Imipramine
  - Maprotiline
  - Nortriptyline
  - Protriptyline
  - Trimipramine
- Selective serotonin reuptake inhibitors
  - Citalopram
  - Escitalopram
  - Fluoxetine
  - Fluvoxamine
  - Paroxetine
  - Sertraline
- Selective noradrenergic reuptake inhibitors
  - Reboxetine
- Noradrenaline and dopamine reuptake blockers
  - Bupropion
- Dual serotonin and noradrenaline reuptake inhibitors
  - Duloxetine
  - Venlafaxine
- Noradrenergic and specific serotoninergic antidepressants
  - Mianserine
  - Mirtazapine
- Dual serotonin 2 antagonists/serotonin reuptake inhibitors
  - Nefazodone
  - Trazodone

Antipsychotic drugs

- Typical
  - Chlorpromazine
  - Fluphenazine
  - Thyoridazine
  - Mesoridazine
  - Thiothixene
  - Zuclopenthixol
  - Prochlorperazine
  - Droperidol
  - Haloperidol
- Atypical
  - Clozapine
  - Risperidone
  - Olanzapine
  - Quetiapine
  - Iloperidone
  - Ziprasidone
  - Aripiprazole

that the incidence of seizures is less than 0.5% for the majority of antidepressants, might conversely suggest a strong protective factor against seizures [35]. At any rate, this issue is still controversial, and against this point remains the observation that the proconvulsant effect of antidepressants is dose-dependent. SSRIs can be considered reasonably safe while clomipramine, imipramine and maprotiline are the only compounds that may represent a concern [36]. Surprisingly, bupropion seems to be proconvulsant when administered in the immediate-release formulation, while the extended-release formulation is similar to SSRIs [21]. This might be related to a peak concentration effect but further studies are needed. In this regard, it has to be acknowledged that the available information comes from psychiatric samples and it is not known whether such data are applicable to patients with epilepsy [35].

Psychoses

Psychoses and thought disorders are relatively rare in patients with epilepsy but represent serious complications affecting prognosis, morbidity and mortality. Epidemiological evidence points out that the incidence of nonorganic, nonaffective psychoses, including schizophrenia and related disorders, is generally overrepresented (~4–5%) in epilepsy as compared with the general population or other chronic medical conditions [37,38]. Higher prevalence rates have been found in selected samples such as hospital case series [39,40]. Interestingly, a retrospective cohort study using data from two large datasets of linked hospital records in the UK shows a significantly increased risk of epilepsy for patients previously admitted for schizophrenia and *vice versa*. Specifically, the rate ratio for the risk of epilepsy in patients with schizophrenia was in the order of 2.1–3.0:1 and the corresponding rate ratio for the risk of schizophrenia in patients with epilepsy was in the order of 4.5–5.1:1 [41]. All of these data taken together clearly suggest strong neurobiological underpinnings shared by these two conditions.

As for antidepressant drugs, the use of antipsychotics in epilepsy have to be carefully weighed on two main issues: pharmacologic interactions and the potential impact on seizures. Unlike mood disorders, patients with epilepsy and psychoses must always to be treated and followed up in a psychiatric setting. However, neurologists have to be aware of the problem and actively participate with the treating psychiatrist in therapeutic choices. In general terms, the dose of neuroleptics has to always be tailored to the patient's response because, in almost all cases, enzyme inducers reduce the plasma levels of these drugs [21]. In particular, the pharmacokinetics of clozapine are characterized by a high inter- and intra-individual variability and interactions are sometimes difficult to predict [42].

Among the possible adverse effects of antipsychotics, weight gain and sedation may represent a concern [43], and they can be exacerbated by some AEDs such as valproate, carbamazepine or barbiturates [44]. The association of clozapine with AED characterized by bone marrow suppression, especially carbamazepine, needs to be carefully monitored [43].

Regarding the potential deleterious effect on seizures, there is evidence that at least some of the antipsychotic drugs can increase the risk of seizures, particularly at higher doses. However, as for antidepressants, clinical data come from psychiatric samples, thus limiting the applicability of these findings to the epilepsy population. Data are available for chlorpromazine and clozapine at high doses (1000 mg/day for chlorpromazine and >600 mg/day for clozapine) [45]. In particular, clozapine seems to induce epileptiform discharges at the electroencephalogram and seizures even at therapeutic doses. Such an effect is dose- and titration-dependent [46]. Electroencephalogram abnormalities have been reported in 1, 2.7 and 4.4% of patients for clozapine doses <300, 300–600 or 600–900 mg/day, respectively [47]. However, the prevalence of seizures, in subjects without a previous history of epilepsy, seems to be much lower and in the region of 0.9, 0.8 and 1.5% for the same range of doses, respectively [48]. Seizures are mainly myoclonic but generalized convulsions or partial seizures are also reported depending on the individual patient. Atypical antipsychotics (e.g., risperidone, olanzapine or quetiapine) are usually better tolerated than traditional ones (e.g., chlorpromazine and thyoridazine) in terms of extrapyramidal side effects and seem to be reasonably safe as compared with clozapine and chlorpromazine in terms of seizures. In particular, olanzapine and quetiapine demonstrated seizure rates in the region of 0.9% and risperidone had even lower rates (~0.3%) [35].

Specific issues in patients with intellectual disability

Community studies show that epilepsy is present in people with intellectual disability, with prevalence rates ranging between 26 and 40% [49], and it is widely accepted that even higher rates of epilepsy are found in individuals with more severe intellectual disability [50]. In patients with epilepsy and autism, disruptive behavior and self-injurious behavior may represent a concern [51,52]. Still, patients with autism and severe intellectual disabilities, particularly those with difficulties in verbal expression, often also manifest with epilepsy [52]. Mood disorders in patients with intellectual disabilities are often atypical, with rapid-cycling features and a chronic course. Moreover, diagnosis is often problematic, making treatment even more difficult. Patients with intellectual disabilities often manifest depressive symptoms in the form of somatization (e.g., fatigue or regression), dysphoria or sudden sadness, rather than by explicitly saying that they feel depressed.

Data about treatment of behavioral disorders in patients with epilepsy and intellectual disabilities are more than insufficient. In the case of antidepressants, SSRIs seem to be safe and effective in this group of patients, even in the presence of autism, but some authors have noted the development of transient treatment-emergent adverse effects such as irritability aggressiveness or excitation, which, in fluoxetine studies, occurred in 25% of patients [53]. Benzodiazepines can be considered for short-term treatment of anxiety, although patients with intellectual disabilities may present a paradoxical deterioration in behavior [54]. This phenomenon has been observed also in children [55].

As with antidepressants, data on antipsychotics in patients with epilepsy and intellectual disabilities are still limited, being based on anecdotal reports or open trials in small samples. Conversely, controlled studies are available outside epilepsy [56]. In general terms, atypical antipsychotics are preferred, not least for their potential efficacy on negative symptoms (e.g., flattened affect, social indifference or other autism spectrum symptoms) and because of the reduced risk for long-term development of extrapyramidal motor symptoms. The use of clozapine needs to be carefully weighed up, taking into account the potential difficulties in managing dangerous side effects in this group of patients. Among atypical antipsychotics, the majority of published data focus on risperidone, with good results in aggressive behavior, self-injury, isolation, suspiciousness and social withdrawal [57–59]. If weight gain can be a problem with antipsychotic drugs, it represents a specific concern in intellectually disabled patients. Therefore, in patients with epilepsy and intellectual disabilities, the use of specific AEDs, such as topiramate, may also be preferred for this reason [60,61].

Conclusion

Psychiatric disorders can often be encountered in epilepsy patients. However, such comorbidities are still underdiagnosed and undertreated; this is partly related to the lack of standardized guidelines of treatment. In fact, available data are still based on anecdotal reports or open studies. More recently, international panels are publishing consensus documents in order to favor a standardized and homogenous approach to the problem. Careful attention to the special needs of the patient, to drug–drug interactions and the adoption of individualized doses and titration schedules represent important considerations for a successful approach.

Future perspective

Controlled trials for treatment of psychiatric disorders in epilepsy are needed in order to clarify responder rates and specific treatment approaches in this special population of patients. Data on the needs of patients with specific epilepsy syndromes are warranted. Currently, international panels of experts are publishing guidance of treatment of psychiatric comorbidities of epilepsy. Data on the efficacy and effectiveness of such approaches are needed. Increased attention is required for behavioral problems in intellectually disabled patients with epilepsy. Controlled data in this subgroup of patients are required.

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