

# Treatment of psychoses in patients with epilepsy: an update

Niruj Agrawal and Marco Mula 

*Ther Adv Psychopharmacol*

2019, Vol. 9: 1–10

DOI: 10.1177/  
2045125319862968

© The Author(s), 2019.  
Article reuse guidelines:  
sagepub.com/journals-  
permissions

**Abstract:** Psychotic disorders represent a relatively rare but serious comorbidity in epilepsy. Current epidemiological studies are showing a point prevalence of 5.6% in unselected samples of people with epilepsy going up to 7% in patients with temporal lobe epilepsy, with a pooled odds ratio of 7.8 as compared with the general population. This is a narrative review of the most recent updates in the management of psychotic disorders in epilepsy, taking into account the clinical scenarios where psychotic symptoms occur in epilepsy, interactions with antiepileptic drugs (AEDs) and the risk of seizures with antipsychotics. Psychotic symptoms in epilepsy can arise in a number of different clinical scenarios from peri-ictal symptoms, to chronic interictal psychoses, comorbid schizophrenia and related disorders to the so-called forced normalization phenomenon. Data on the treatment of psychotic disorders in epilepsy are still limited and the management of these problems is still based on individual clinical experience. For this reason, guidelines of treatment outside epilepsy should be adopted taking into account epilepsy-related issues including interactions with AEDs and seizure risk. Second-generation antipsychotics, especially risperidone, can represent a reasonable first-line option because of the low propensity for drug–drug interactions and the low risk of seizures. Quetiapine is burdened by a clinically significant pharmacokinetic interaction with enzyme-inducing drugs leading to undetectable levels of the antipsychotic, even for dosages up to 700 mg per day.

**Keywords:** antiepileptic drugs, antipsychotic drugs, epilepsy, interaction, psychoses, schizophrenia, seizures

Received: 29 March 2019; revised manuscript accepted: 14 June 2019.

## Introduction

Psychotic disorders represent a relatively rare but serious comorbidity in epilepsy. The relationship between these two conditions has been very well known for a long time and it has attracted the interest of not only clinicians and scientists but also artists and novelists. In fact, in *Othello*, William Shakespeare alludes to the possibility of an abnormal mental state after a convulsion and this was also reported by Dostoevsky in many of his novels.

In 1881, Gowers states that ‘...occasionally, after a fit, or, more frequently, after a series of fits, an attack of mental disturbance may come on which lasts for several days. It may be simply a demented state, or there may be hallucinations, with irritability and even violence.’<sup>1</sup> This was already known at

the beginning of the 19th century, as mentioned by Esquirol in his textbook of psychiatry.<sup>2</sup> During the 20th century, the relationship between epilepsy and psychosis has been revitalized by the development of the electroconvulsive therapy by Cerletti<sup>3</sup> and the seminal publications of Hans Landolt on the forced normalization phenomenon.<sup>4</sup>

Modern epidemiological studies are now providing clear estimates about the prevalence of psychotic disorders in epilepsy. A systematic review and meta-analysis of the prevalence of psychosis, schizophrenia and schizophreniform illness in people with epilepsy showed a pooled prevalence of psychosis of 5.6% [95% confidence interval (CI) 4.8–6.4%] in unselected patients, increasing to 7% (95% CI 4.9–9.1%) in people with temporal lobe epilepsy, with a pooled odds ratio

Correspondence to:

**Marco Mula**  
Atkinson Morley Regional  
Neuroscience Centre,  
St George’s University  
Hospitals NHS Foundation  
Trust, Blackshaw Road,  
London SW17 0QT, UK  
[mmula@srgul.ac.uk](mailto:mmula@srgul.ac.uk)

**Niruj Agrawal**  
Atkinson Morley Regional  
Neuroscience Centre,  
St George’s University  
Hospitals NHS Foundation  
Trust, London, UK

Institute of Medical and  
Biomedical Education,  
St George’s University of  
London, UK

Department of  
Neuropsychiatry, South  
West London & St  
George’s Mental Health  
Trust, London, UK

**Marco Mula**  
Institute of Medical and  
Biomedical Education,  
St George’s University of  
London, UK

**Table 1.** Psychotic symptoms in relationship with seizures.

| Relationship with seizures                    | Proportion among all psychotic episodes of epilepsy | Duration   |
|---|---|------------|
| Pre-ictal                                     | Unknown (very rare)                                 | Hours/days |
| Ictal   | 10%   | Hours      |
| Postictal                                     | 60%   | Hours/days |
| Forced normalization or alternative psychoses | 10%   | Days       |
| Interictal psychoses                          | 20%   | Months     |

for risk of psychosis, as compared with the general population, of 7.8 (95% CI 2.8–21.8).<sup>5</sup> These studies also point out that the relationship between epilepsy and psychotic disorders is more complex than expected. In fact, two retrospective cohort studies reported that individuals with schizophrenia have a two- to threefold increased risk of developing epilepsy<sup>6</sup> with an incidence rate of 7 per 1000 person-years.<sup>7</sup> Reasons for this bidirectional relationship are multifaceted and probably related to a number of reasons. Neuroimaging studies in people with schizophrenia have shown abnormalities in brain networks overlapping with those involved in temporal lobe epilepsy, particularly in the amygdala and the hippocampi.<sup>8</sup>

This is a narrative review of the most recent updates in the management of psychotic disorders in epilepsy taking into account the clinical scenarios where psychotic symptoms can occur in epilepsy. Treatment issues are discussed, taking into account specific needs of people with epilepsy, namely interactions with AEDs and the risk of seizures with antipsychotics. References have been identified through Medline searches from February 2009 until February 2019 using the terms ‘epilepsy’, ‘psychosis’, ‘antipsychotic drugs’. Additional articles were identified from the authors’ own files and from chosen bibliographies. Abstracts from congresses were excluded.

### Psychotic symptoms in epilepsy: phenomenology and clinical presentations

#### *Peri-ictal psychoses*

Psychotic symptoms in epilepsy have been historically classified according to their temporal relationship with seizures<sup>9</sup> (Table 1).

Among peri-ictal psychoses, pre-ictal ones are perhaps the least common and least understood. Pre-ictal psychosis presents with a variety of non-specific symptoms during the hours (rarely up to 3 days) leading up to a seizure. These symptoms include derealization and depersonalization experiences, forced thinking, ideomotor aura, déjà vu, jamais vu, anxiety, euphoria and perceptual experiences including hallucinations or illusions. These symptoms usually end with the seizure but are not associated with detectable electroencephalogram (EEG) changes. Optimized management of the seizures helps the control of pre-ictal psychosis and psychotropic medications are not generally indicated.

Ictal psychoses are episodes of nonconvulsive status epilepticus mostly of temporal lobe origin, very rarely extratemporal (i.e. the frontal lobe).<sup>10</sup> They generally present with a wide range of perceptual, behavioural, cognitive and affective symptoms often in connection with typical temporal lobe automatisms. There may also be alterations in consciousness during the episode and patients may have no recollection of what happened during the event. The presence of automatisms and other typical epileptic phenomena can help the clinician in distinguishing a nonconvulsive status with psychic symptoms from a brief psychotic episode and the final diagnosis is based on the EEG.<sup>11</sup> Ictal psychoses resolve with effective management of the epilepsy, with no need to treat the psychosis directly. Antipsychotic medications are not indicated.

Postictal psychoses represent the most commonly encountered peri-ictal psychoses, accounting for approximately 25% of all psychoses of epilepsy. (Table 1) They are usually precipitated by a cluster of focal to bilateral tonic-clonic seizures and

are characterized by quite peculiar clinical features.<sup>12</sup> Postictal psychoses seem to occur in patients with a late age of onset of the epilepsy and with temporal-lobe epilepsy with temporal- and extratemporal-structural lesions<sup>13,14</sup> Postictal psychoses are very rarely reported in subjects with a generalized epilepsy type. The lucid interval (i.e. a period of normal mental state preceding the onset of the psychotic episode) is another typical feature described in almost all patients, lasting from 1 to 6 days.<sup>15</sup> The psychopathology of postictal psychoses is polymorphic, but most patients present with an abnormal mood (either depressed or manic) and a paranoid delusion.<sup>13</sup> Some patients are confused throughout the episode but others present with fluctuating consciousness and disorientation. Delusions of grandiosity, mystical experiences with religious content, often associated with an elevated mood, are also reported, as well as aggressive behaviour or suicidal attempts.<sup>16</sup> Psychotic symptoms usually remit spontaneously within days or weeks, with no need for long-term antipsychotic treatment, which is mainly prescribed to reduce mortality and morbidity. However, in one out of four cases, the postictal psychosis may progress into a chronic psychosis.<sup>15</sup>

#### *Para-ictal psychoses (the forced normalization phenomenon)*

Drug-related psychotic symptoms in epilepsy can occur in different clinical contexts from toxic encephalopathies or, more rarely, for the so-called forced normalization phenomenon.<sup>17</sup> This concept refers to the publications of Heinrich Landolt, who reported a group of patients having florid psychotic episodes with ‘normalization’ of the EEG. Subsequently, Tellenbach introduced the term ‘alternative psychosis’ for the clinical phenomenon of the reciprocal relationship between abnormal mental states and seizures, which did not, as Landolt’s term did, rely on EEG findings.<sup>4</sup> Since the early observations of Landolt, a number of patients with alternative psychoses have been described to put the existence of this phenomenon beyond doubt. Forced normalization has been described with all AEDs, suggesting that this is not a drug-specific phenomenon but instead linked to the neurobiological mechanisms underlying seizure control. In fact, cases of an alternative psychosis have been described with vagus nerve stimulation<sup>18</sup> and it is possible that this phenomenon is involved in *de novo* psychoses after epilepsy surgery. However,

the exact neurobiological mechanisms underlying this phenomenon are still unknown.

For many years, there has been a strong debate on whether forced normalization tends to occur in patients with a specific epileptic syndrome. Initially, drug-refractory temporal lobe epilepsy was claimed to be the prototype but subsequent literature on alternative psychoses favoured generalized epilepsies.<sup>4</sup> There is now general agreement that the forced normalization phenomenon occurs with both generalized and focal epilepsies but it is rare in patients with mainly generalized tonic-clonic seizures (e.g. idiopathic generalized epilepsy of awakening) and in extratemporal lobe epilepsy.<sup>19</sup>

The clinical presentation is nonspecific and there are no agreed diagnostic criteria for para-ictal psychosis associated with forced normalization. It generally presents with behavioural disturbances of acute or subacute onset associated with a thought disorder, delusions, hallucinations, significant mood change (hypomania or depression) and anxiety with depersonalization and derealization symptoms. It is associated with reduction in the total number of spikes or clinical report of complete cessation of seizures for at least 1 week.<sup>20</sup>

#### *Interictal psychoses*

Psychoses without a clear temporal relationship with epileptic seizures are less frequent than perictal psychoses. However, they are clinically relevant in terms of severity and duration than peri-ictal ones, because they tend to have a chronically unremitting course. Interictal psychoses seem to start after many years of active temporal lobe epilepsy.<sup>21</sup> Clinical<sup>22</sup> and neuroimaging findings<sup>23</sup> support a link between mesial-temporal structures and psychosis. Historically, neuropathology studies of resected temporal lobes from patients with interictal psychoses have suggested a link with hamartomas and gangliogliomas rather than mesial-temporal sclerosis,<sup>24</sup> and gross abnormalities such as enlarged ventricles or periventricular gliosis have also been noted.<sup>25</sup> The association with the dominant hemisphere was initially suggested by early studies on interictal psychoses<sup>10</sup> but subsequent authors showed a complex network reflecting the interplay of psychosis-related genetic factors and the cumulative effects of seizure activity on the brain rather than a simple laterality effect.<sup>26</sup>

Clinical studies have pointed out that the phenomenology of interictal psychoses of epilepsy differ from that of schizophrenia. Some authors described the typical presence of religious mystical experiences and the preservation of affect<sup>10,12</sup> while other authors stressed the rarity of negative symptoms and catatonic states.<sup>27</sup> In addition, the long-term prognosis of interictal psychosis seems to be better than that of schizophrenia with less reported long-term institutionalization<sup>28,29</sup> and this is probably due to the tendency of psychotic symptoms to attenuate over time and the rarity of personality deterioration.

#### *Postsurgical psychoses*

Temporal lobectomy is an established treatment for patients with intractable epilepsy. Ever since the early series, the possibility that surgery may be associated with the development of psychiatric disorders, in particular, psychoses, has been discussed. Most centres have stopped operating floridly psychotic patients, based on the observation that psychoses generally do not improve with the operation. Only a few centres, however, regularly include psychiatric screening as part of their preoperative assessment and even less centres consider postoperative psychiatric follow up, in contrast to the often scrupulous recording of neuropsychological deficits.

A number of psychiatric complications have been reported after epilepsy surgery, including exacerbation of pre-existing conditions, *de novo* depressive or anxiety symptoms, or psychotic disorders, as well of psychogenic nonepileptic seizures. In a well-designed prospective study, the prevalence of *de novo* psychoses after epilepsy surgery was 1.1%.<sup>30</sup> *De novo* psychoses seem to occur in the context of unsuccessful epilepsy surgery with continued seizures and or surgical complications.<sup>31</sup> However, there are reported cases of *de novo* psychosis after successful epilepsy surgery and, in these cases, the forced normalization phenomenon has been hypothesized.<sup>32</sup> While pre-existing psychiatric conditions, including psychotic disorders, could be a risk factor for psychiatric disorders after epilepsy surgery,<sup>33</sup> they should not represent a contraindication for epilepsy surgery *per se*. In fact, epilepsy surgery can result in improvement in other epilepsy-related symptoms such as peri-ictal psychoses and sometimes interictal psychoses.<sup>34</sup>

The majority of postsurgical complications start within 1 year from epilepsy surgery and it is

important to inform patients and relatives that up to one third of subjects may experience mood or anxiety symptoms requiring treatment during the first trimester after surgery.<sup>35</sup> However, late-onset disorders have been also described.<sup>36</sup>

#### **Pharmacological management of psychotic symptoms in epilepsy**

Studies on the treatment of psychotic disorders in epilepsy are scant. During the last 10 years, a couple of consensus papers from internal experts in the field have been published<sup>37,38</sup> providing some guidance to clinicians. However, at the moment, it seems reasonable to follow internationally adopted guidelines for treatment outside epilepsy, adapting them to the individual needs of patients with epilepsy and to the specific clinical scenario.<sup>39</sup> Obviously, it is still unknown whether patients with epilepsy present with the same response and remission rates of people with schizophrenia. For all these reasons, patients with epilepsy and psychotic disorders need to be carefully monitored.

#### *Antipsychotics*

Antipsychotic drugs can be divided into first-generation (FGAP) and second-generation (SGAP).<sup>39</sup> SGAPs have progressively replaced old compounds in many high-income countries due to the lower propensity for long-term side effects such as extrapyramidal symptoms and tardive dyskinesia, as compared with FGAPs but there is no clear evidence that one generation is more effective than the other. Still, antipsychotic drugs are usually more effective on positive symptoms (e.g. delusions, hallucinations, formal thought disorders and bizarre behaviour) rather than on negative symptoms like blunted affect and apathy.

As already alluded to, the evidence for the use of antipsychotics in epilepsy is more than limited. According to a Cochrane Review on this subject,<sup>40</sup> there is a single, randomized, controlled study comparing olanzapine (10 mg/day) with haloperidol (12 mg/day) in 16 people with schizophrenia-like psychosis of epilepsy, favouring olanzapine. This, however, was published more than 15 years ago, as a conference abstract and the study were never published in a peer-reviewed journal. For this reason, as previously stated, standard guidance for treatment should be followed in people with epilepsy.

According to the National Institute for Health and Care Excellence (NICE; Clinical Guidance 178), the choice of the antipsychotic medication for a first-episode psychosis should take into account the likely benefits and possible side effects of each drug, including metabolic (i.e. weight gain and diabetes), extrapyramidal (i.e. akathisia, dyskinesia and dystonia), cardiovascular (i.e. long QT) and hormonal (i.e. increased prolactin levels) side effects.<sup>41</sup> Guidelines from the World Federation of Biological Psychiatry (WFSBP)<sup>42</sup> recommend either olanzapine, quetiapine or risperidone as first-line treatment for first-episode schizophrenia and this is based on full evidence from controlled studies on a balance of safety and efficacy data. In fact, clozapine and haloperidol have the same level of evidence in terms of efficacy but they are both burdened by a lower tolerability.<sup>42</sup>

In the case of an acute relapse, the WFSBP guidelines state that both FGAPs and SGAPs have been shown as equally effective and the antipsychotic selection should be undertaken individually, taking into account the patient's experience with certain drug classes and the individual side-effect profile. Before switching to another antipsychotic drug, a treatment trial at the optimal dose should last for at least 2 weeks but no longer than 8 weeks, unless unacceptable side effects occur.

The duration of the antipsychotic-drug treatment is controversial even in the psychiatric literature. Guidelines from the WFSBP<sup>43</sup> state that continuous antipsychotic treatment for at least 1 year is recommended in patients with first-episode psychosis, while in patients with previous history of multiple episodes, treatment should be maintained for 2–5 years, but both recommendations have a level C of evidence. Indefinite continuation is recommended for patients with a history of suicide attempts or violent and aggressive behaviour or very frequent relapses.

Clinicians need to bear in mind that poor or partial adherence to oral antipsychotics occurs in more than 40% of patients<sup>44</sup> and for this reason, depot/long-acting injectable antipsychotics should be considered. According to NICE, depot should be offered to patients who would prefer such a treatment or where avoiding covert nonadherence is a clinical priority.<sup>41</sup> However, long-acting formulations also have disadvantages, including the low flexibility of administration and

dose adjustment and the delayed disappearance of distressing side effects.

#### *Special considerations in patients with epilepsy*

As previously stated, internationally adopted guidelines of treatment of psychotic disorders should be adapted to the epilepsy population, taking into account phenomenological peculiarities of psychotic disorders in epilepsy, interactions with AEDs and increased risk of side effects.

In terms of choice of the antipsychotic agent, clinicians should bear in mind the risk of pharmacokinetic and pharmacodynamic interactions and seizure risk.

Regarding pharmacokinetic interactions, AEDs with inducing properties (i.e. phenytoin, carbamazepine, barbiturates) reduce the blood levels of all antipsychotics<sup>45</sup> and this interaction is particularly evident for quetiapine, which is mainly metabolized by the CYP 3A4, leading to undetectable blood levels of quetiapine even at dosages of 700 mg per day in combination with carbamazepine.<sup>46</sup> Oxcarbazepine is a keto-analogue of carbamazepine but seems to be a modest CYP 3A4 inducer and for this reason, pharmacokinetic interactions with antipsychotics are usually not clinically relevant. As far as all other AEDs are concerned, they do not seem to have a major impact on SGAP metabolism but individual differences in treatment response have to be carefully considered, especially for drugs like olanzapine and clozapine which have a complex metabolism with multiple enzymatic pathways involved.<sup>47</sup>

Although valproate is usually considered an inhibitor, there are no reports of increased antipsychotic-drug blood levels when prescribed in combination. Conversely, it seems to mildly induce, in some selected cases, the metabolism of some SGAP (i.e. olanzapine, aripiprazole, clozapine, quetiapine).<sup>47</sup> These interactions are rarely clinically relevant and should be considered on an individual basis.

All antipsychotics do not seem to have major influence on enzymatic pathways of AEDs and for this reason, they do not seem to affect their blood levels.

Data on pharmacodynamic interactions are generally limited but it is important to consider



**Table 2.** Similar side effects reported for both antipsychotics and antiepileptic drugs leading to potentially negative pharmacodynamic interactions.

| Side effect                    | Antiepileptic drugs  | Antipsychotics   |
|--------------------------------|--|--|
| Dizziness and falls            | Almost all AEDs but less described with levetiracetam                                    | Orthostatic hypotension with phenothiazines, clozapine, iloperidone, quetiapine, risperidone   |
| Extrapyramidal symptoms        | Valproate  | All (less evident with aripiprazole and risperidone)   |
| Liver dysfunction              | Carbamazepine, phenytoin, felbamate, valproate   | Steatosis with clozapine or olanzapine   |
| Long QT                        | Felbamate  | Amisulpride, haloperidol, iloperidone and ziprasidone  |
| Osteopenia                     | Carbamazepine, oxcarbazepine, phenytoin, primidone, phenobarbital, valproate, topiramate | Amisulpride, paliperidone and risperidone through hyperprolactinaemia  |
| Sedation                       | All, but less frequent with lacosamide, lamotrigine, felbamate                           | All, but less evident with haloperidol and risperidone   |
| Sexual dysfunction             | Carbamazepine, phenytoin, barbiturates, pregabalin, topiramate                           | All, but especially olanzapine, risperidone, clozapine, haloperidol and thioridazine   |
| Weight gain                    | Valproate, carbamazepine, clobazam, pregabalin, gabapentin, perampanel                   | All, but less evident with haloperidol, aripiprazole, ziprasidone (clozapine, olanzapine and quetiapine may cause hyperlipidaemia directly, without weight gain) |
| White cell blood count changes | Carbamazepine (agranulocytosis)<br>valproate (neutropenia)                               | Clozapine (agranulocytosis)<br>Quetiapine (neutropenia)  |

AED, antiepileptic drug.

implications of combining antipsychotics and AEDs with a similar spectrum of side effects (Table 2). Additive sedation with antipsychotics seems to be relevant for many AEDs, while weight gain is particularly evident for olanzapine in combination with valproate, pregabalin, gabapentin and carbamazepine.<sup>48,49</sup> The combined treatment with carbamazepine and clozapine is not recommended due to the increased risk of agranulocytosis but it is recommended to be clinically vigilant for possible leukopenia, also when valproate is prescribed with clozapine or olanzapine.<sup>47</sup>

Regarding risk of seizures with antipsychotics, clozapine is the antipsychotic drug associated with the highest risk of seizures compared with placebo with a standardized incident ratio of 9.5 (95% CI 7.2–12.2).<sup>50</sup> Olanzapine and quetiapine also seem to carry some risk, though to a lesser extent than clozapine, while all other antipsychotics, including risperidone, show no difference as compared with placebo.<sup>50</sup> A large community-based study comparing first- and second-generation antipsychotics showed that first-generation

compounds such as chlorprothixene, thioridazine and haloperidol have a slightly higher risk than second-generation agents such as risperidone and aripiprazole.<sup>51</sup> Regarding clozapine, the risk of seizures is clearly dose and titration dependent.<sup>52</sup> A US case series documented a mean prevalence of seizures during clozapine treatment of 2.9% with prevalence rates of 1%, 2.7% and 4.4% for dosages of <300 mg, 300–600 mg and >600 mg, respectively.<sup>53</sup>

All these data come from people with primary psychiatric disorders; whether these findings can be applied to people with epilepsy is still unknown. In the case of clozapine, there are some data suggesting that the prevalence of seizures is higher in patients with a previous history of seizures as compared with those without.<sup>53</sup> However, it is unknown whether seizure-free patients on a stable regime with AEDs present a higher risk as compared with the general population.

Clozapine has been also associated with the occurrence of epileptiform abnormalities on the

EEG, even in people without epilepsy, in up to 5% of cases<sup>54</sup> but whether this is a predictive factor for clozapine-induced seizures is still unknown.

Regarding the duration of treatment, interictal psychotic episodes in epilepsy are more likely to be recurrent than in primary schizophrenia<sup>38</sup> and, for this reason, many patients with epilepsy and psychotic disorders tend to be on a long-term treatment. However, there are no studies specifically investigating this point and data from retrospective studies suggest that approximately 15% of interictal psychotic episodes may be self-limiting, with no need for antipsychotic treatment.<sup>55</sup> For this reason, duration of treatment after a first psychotic episode should follow international guidelines outside epilepsy.

There are no studies specifically investigating depot or long-acting injectable antipsychotics in people with epilepsy and whether they are associated with an increased risk of seizure deterioration as compared with oral formulations.

#### *Benzodiazepine*

Outside epilepsy, benzodiazepines alone do not represent usual pharmacological options in patients with psychotic disorders. In fact, benzodiazepines alone may be associated with paradoxical excitement and are not as effective as antipsychotics in rapid tranquillization of violent and agitated patients.<sup>56,57</sup> However, the use of benzodiazepines, especially clobazam, is quite a popular treatment for postictal psychoses<sup>38,58</sup> among clinicians but this is not based on any evidence.

#### *Lithium*

Lithium is occasionally prescribed as an augmentation strategy in drug-refractory schizophrenia<sup>59</sup> but the evidence for that is low.<sup>60</sup> The use of lithium in epilepsy is very rarely considered, as many AEDs are also first-line treatment in bipolar disorder. However, in case lithium is clinically indicated, clinicians need to bear in mind that lithium is associated with an increased risk of thyroid toxicity when in combination with carbamazepine.<sup>61</sup> Still, lithium may prevent or mask carbamazepine- or oxcarbazepine-related hyponatraemia.<sup>62</sup> The combination lithium–valproate is associated with an increased risk of tremor, sedation and weight gain, while the prescription with topiramate can reduce lithium clearance, potentially

leading to toxic levels.<sup>63</sup> For the remaining AEDs, there are no major problems.

In terms of proconvulsant effect, seizures seem to occur in the context of toxic levels (higher than 3 nmol/l).<sup>64</sup> The majority of centres consider a therapeutic level between 0.4 mmol/l and 0.8 mmol/l for the prophylactic treatment of mood episodes and between 0.6 mmol/l and 1.0 mmol/l for the acute treatment of mania. Symptoms of toxicity start for levels above 1.5 mmol/l but it is advisable to always maintain concentrations below 1.0 mmol/l.

### **Conclusions**

Psychotic disorders represent a relatively rare but serious comorbidity in epilepsy. The first step in managing psychotic symptom in epilepsy is to clarify the clinical context where these symptoms occur, especially if they have a clear relationship with seizure activity or with the antiepileptic treatment. Given the lack of evidence-based options for interictal psychoses, internationally adopted guidelines of treatment should be followed. In particular, risperidone can be considered first-line treatment, given the low propensity for drug–drug interactions and the low seizure risk. Pharmacokinetic interactions involve mainly quetiapine, as its clearance is highly dependent on the CYP 3A4. Combining drugs with a similar toxicity spectrum may lead to intolerable side effects; for this reason, both neurologists and psychiatrists need to be aware of the common side effects of both antiepileptic and antipsychotic drugs. Clozapine should be used in selected cases, when clinically indicated, but a slow titration regime and close clinical monitoring is recommended. In postictal psychoses, benzodiazepines, especially clobazam, in combination with antipsychotics, still represent a very popular treatment option despite evidence being almost nonexistent. Lithium is rarely used but can be safely prescribed in the majority of patients.

### **Funding**

The author(s) received no financial support for the research, authorship, and/or publication of this article.

### **Conflict of interest statement**

The authors declare that there is no conflict of interest with the present paper. Outside the submitted work, Dr Mula has received consultancy fees from UCB Pharma, Eisai Europe Limited,

Bial and Elsevier. Dr Mula also has intellectual property rights with Elsevier and Springer.

#### ORCID iD

Marco Mula  <https://orcid.org/0000-0002-9415-3395>

#### References

- Gowers WR. *Epilepsy and other chronic convulsive diseases: their causes, symptoms, & treatment*. London: Churchill, 1881.
- Esquirol E. *Des maladies mentales considérées sous les rapports médical, hygiénique et médico-legal*. J-B Baillière, 1838.
- Cerletti U. Electroshock therapy. *J Clin Exp Psychopathol* 1954; 15: 191–217.
- Trimble MR and Schmitz B. *Forced normalization and alternative psychoses of epilepsy*. Wrightson Biomedical Pub., 1998.
- Clancy MJ, Clarke MC, Connor DJ, *et al*. The prevalence of psychosis in epilepsy; a systematic review and meta-analysis. *BMC Psychiatry* 2014; 14: 75.
- Wotton CJ and Goldacre MJ. Coexistence of schizophrenia and epilepsy: record-linkage studies. *Epilepsia* 2012; 53: e71–e74.
- Chang Y-T, Chen P-C, Tsai I-J, *et al*. Bidirectional relation between schizophrenia and epilepsy: a population-based retrospective cohort study. *Epilepsia* 2011; 52: 2036–2042.
- Dean DJ, Orr JM, Bernard JA, *et al*. Hippocampal shape abnormalities predict symptom progression in neuroleptic-free youth at ultrahigh risk for psychosis. *Schizophr Bull* 2016; 42: 161–169.
- Kanner AM and Rivas-Grajales AM. Psychosis of epilepsy: a multifaceted neuropsychiatric disorder. *CNS Spectr* 2016; 21: 247–257.
- Trimble MR. *The psychoses of epilepsy*. Raven Press, 1991.
- Mula M. Epilepsy-induced behavioral changes during the ictal phase. *Epilepsy Behav EB* 2014; 30: 14–16.
- Hilger E, Zimprich F, Pataraja E, *et al*. Psychoses in epilepsy: a comparison of postictal and interictal psychoses. *Epilepsy Behav EB* 2016; 60: 58–62.
- Oshima T, Tadokoro Y and Kanemoto K. A prospective study of postictal psychoses with emphasis on the periictal type. *Epilepsia* 2006; 47: 2131–2134.
- Cleary RA, Thompson PJ, Fox Z, *et al*. Predictors of psychiatric and seizure outcome following temporal lobe epilepsy surgery. *Epilepsia* 2012; 53: 1705–1712.
- Adachi N, Ito M, Kanemoto K, *et al*. Duration of postictal psychotic episodes. *Epilepsia* 2007; 48: 1531–1537.
- Kanemoto K, Tadokoro Y and Oshima T. Violence and postictal psychosis: a comparison of postictal psychosis, interictal psychosis, and postictal confusion. *Epilepsy Behav EB* 2010; 19: 162–166.
- Chen Z, Lusicic A, O'Brien TJ, *et al*. Psychotic disorders induced by antiepileptic drugs in people with epilepsy. *Brain J Neurol* 2016; 139: 2668–2678.
- Gatzonis SD, Stamboulis E, Siafakas A, *et al*. Acute psychosis and EEG normalisation after vagus nerve stimulation. *J Neurol Neurosurg Psychiatry* 2000; 69: 278–279.
- Mula M. The Landolt's phenomenon: an update. *Epileptologia* 2010; 18: 39–44.
- Krishnamoorthy ES and Trimble MR. Forced normalization: clinical and therapeutic relevance. *Epilepsia* 1999; 40(Suppl. 10): S57–S64.
- Adachi N, Matsuura M, Okubo Y, *et al*. Predictive variables of interictal psychosis in epilepsy. *Neurology* 2000; 55: 1310–1314.
- Mula M, Cavanna A, Collimedaglia L, *et al*. Clinical correlates of schizotypy in patients with epilepsy. *J Neuropsychiatry Clin Neurosci* 2008; 20: 441–446.
- Tebartz Van Elst L, Baeumer D, Lemieux L, *et al*. Amygdala pathology in psychosis of epilepsy: a magnetic resonance imaging study in patients with temporal lobe epilepsy. *Brain J Neurol* 2002; 125: 140–149.
- Taylor DC. Ontogenesis of chronic epileptic psychoses: a reanalysis. *Psychol Med* 1971; 1: 247–253.
- Bruton CJ, Stevens JR and Frith CD. Epilepsy, psychosis, and schizophrenia: clinical and neuropathologic correlations. *Neurology* 1994; 44: 34–42.
- Gutierrez-Galve L, Flugel D, Thompson PJ, *et al*. Cortical abnormalities and their cognitive correlates in patients with temporal lobe epilepsy and interictal psychosis. *Epilepsia* 2012; 53: 1077–1087.
- Getz K, Hermann B, Seidenberg M, *et al*. Negative symptoms and psychosocial status in temporal lobe epilepsy. *Epilepsy Res* 2003; 53: 240–244.



28. Ashidate N. [Clinical study on epilepsy and psychosis.] *Seishin Shinkeigaku Zasshi* 2006; 108: 260–265.
29. Fiseković S and Burnazović L. Epileptic psychoses - evaluation of clinical aspects. *Bosn J Basic Med Sci* 2007; 7: 140–143.
30. Devinsky O, Barr WB, Vickrey BG, *et al.* Changes in depression and anxiety after resective surgery for epilepsy. *Neurology* 2005; 65: 1744–1749.
31. Macrodimitris S, Sherman EMS, Forde S, *et al.* Psychiatric outcomes of epilepsy surgery: a systematic review. *Epilepsia* 2011; 52: 880–890.
32. Nadkarni S, Arnedo V and Devinsky O. Psychosis in epilepsy patients. *Epilepsia* 2007; 48(Suppl. 9): 17–19.
33. Iranzo-Tatay C, Rubio-Granero T, Gutierrez A, *et al.* Psychiatric symptoms after temporal epilepsy surgery. A one-year follow-up study. *Epilepsy Behav EB* 2017; 70: 154–160.
34. Buranee K, Teeradej S, Chusak L, *et al.* Epilepsy-related psychoses and psychotic symptoms are significantly reduced by resective epilepsy surgery and are not associated with surgery outcome or epilepsy characteristics: a cohort study. *Psychiatry Res* 2016; 245: 333–339.
35. Koch-Stoecker S, Schmitz B and Kanner AM. Treatment of postsurgical psychiatric complications. *Epilepsia* 2013; 54(Suppl. 1): 46–52.
36. Vivekananda U, Cock H and Mula M. A case of de novo psychosis ten years following successful epilepsy surgery. *Seizure* 2016; 41: 4–5.
37. Kerr MP, Mensah S, Besag F, *et al.* International consensus clinical practice statements for the treatment of neuropsychiatric conditions associated with epilepsy. *Epilepsia* 2011; 52: 2133–2138.
38. De Toffol B, Trimble M, Hesdorffer DC, *et al.* Pharmacotherapy in patients with epilepsy and psychosis. *Epilepsy Behav EB* 2018; 88: 54–60.
39. Taylor DM, Barnes TRE and Young AH. *The Maudsley prescribing guidelines in psychiatry*. John Wiley & Sons, 2018.
40. Farooq S and Sherin A. Interventions for psychotic symptoms concomitant with epilepsy. *Cochrane Database Syst Rev* 2015; (4): CD006118.
41. National Institute for Health and Care Excellence. Psychosis and schizophrenia in adults: prevention and management. Guidance and guidelines, <https://www.nice.org.uk/guidance/cg178> (accessed 18 February 2019).
42. Hasan A, Falkai P, Wobrock T, *et al.* World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia, part 1: update 2012 on the acute treatment of schizophrenia and the management of treatment resistance. *World J Biol Psychiatry Off J World Fed Soc Biol Psychiatry* 2012; 13: 318–378.
43. Hasan A, Falkai P, Wobrock T, *et al.* World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia, part 2: update 2012 on the long-term treatment of schizophrenia and management of antipsychotic-induced side effects. *World J Biol Psychiatry Off J World Fed Soc Biol Psychiatry* 2013; 14: 2–44.
44. Cramer JA and Rosenheck R. Compliance with medication regimens for mental and physical disorders. *Psychiatr Serv Wash DC* 1998; 49: 196–201.
45. Mula M. The pharmacological management of psychiatric comorbidities in patients with epilepsy. *Pharmacol Res* 2016; 107: 147–153.
46. Nickl-Jockschat T, Paulzen M, Schneider F, *et al.* Drug interaction can lead to undetectable serum concentrations of quetiapine in the presence of carbamazepine. *Clin Neuropharmacol* 2009; 32: 55.
47. De Leon J, Santoro V, D'Arrigo C, *et al.* Interactions between antiepileptics and second-generation antipsychotics. *Expert Opin Drug Metab Toxicol* 2012; 8: 311–334.
48. Meltzer HY, Bonaccorso S, Bobo WV, *et al.* A 12-month randomized, open-label study of the metabolic effects of olanzapine and risperidone in psychotic patients: influence of valproic acid augmentation. *J Clin Psychiatry* 2011; 72: 1602–1610.
49. Biton V. Weight change and antiepileptic drugs: health issues and criteria for appropriate selection of an antiepileptic agent. *Neurologist* 2006; 12: 163–167.
50. Alper K, Schwartz KA, Kolts RL, *et al.* Seizure incidence in psychopharmacological clinical trials: an analysis of Food and Drug Administration (FDA) summary basis of approval reports. *Biol Psychiatry* 2007; 62: 345–354.
51. Wu C-S, Wang S-C, Yeh I-J, *et al.* Comparative risk of seizure with use of first- and second-generation antipsychotics in patients with schizophrenia and mood disorders. *J Clin Psychiatry* 2016; 77: e573–e579.
52. Williams AM and Park SH. Seizure associated with clozapine: incidence, etiology, and management. *CNS Drugs* 2015; 29: 101–111.

53. Pacia SV and Devinsky O. Clozapine-related seizures: experience with 5,629 patients. *Neurology* 1994; 44: 2247–2249.
54. Varma S, Bishara D, Besag FMC, *et al.* Clozapine-related EEG changes and seizures: dose and plasma-level relationships. *Ther Adv Psychopharmacol* 2011; 1: 47–66.
55. Adachi N, Kanemoto K, De Toffol B, *et al.* Basic treatment principles for psychotic disorders in patients with epilepsy. *Epilepsia* 2013; 54(Suppl. 1): 19–33.
56. Alexander J, Tharyan P, Adams C, *et al.* Rapid tranquillisation of violent or agitated patients in a psychiatric emergency setting. Pragmatic randomised trial of intramuscular lorazepam v. haloperidol plus promethazine. *Br J Psychiatry J Ment Sci* 2004; 185: 63–69.
57. Allen MH, Currier GW, Carpenter D, *et al.* The expert consensus guideline series. Treatment of behavioral emergencies 2005. *J Psychiatr Pract* 2005; 11(Suppl 1): 5–108; quiz 110–112.
58. Devinsky O. Postictal psychosis: common, dangerous, and treatable. *Epilepsy Curr* 2008; 8: 31–34.
59. Siskind DJ, Lee M, Ravindran A, *et al.* Augmentation strategies for clozapine refractory schizophrenia: a systematic review and meta-analysis. *Aust N Z J Psychiatry* 2018; 52: 751–767.
60. Leucht S, Helfer B, Dold M, *et al.* Lithium for schizophrenia. *Cochrane Database Syst Rev* 2015; (10): CD003834.
61. Kramlinger KG and Post RM. Addition of lithium carbonate to carbamazepine: hematological and thyroid effects. *Am J Psychiatry* 1990; 147: 615–620.
62. Vieweg V, Glick JL, Herring S, *et al.* Absence of carbamazepine-induced hyponatremia among patients also given lithium. *Am J Psychiatry* 1987; 144: 943–947.
63. Abraham G and Owen J. Topiramate can cause lithium toxicity. *J Clin Psychopharmacol* 2004; 24: 565–567.
64. Erwin CW, Gerber CJ, Morrison SD, *et al.* Lithium carbonate and convulsive disorders. *Arch Gen Psychiatry* 1973; 28: 646–648.