Treatment of psychoses in patients with epilepsy: an update

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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

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.'[1] This was already known at the beginning of the 19th century, as mentioned by Esquirol in his textbook of psychiatry.[2] During the 20th century, the relationship between epilepsy and psychosis has been revitalized by the development of the electroconvulsive therapy by Cerletti[3] and the seminal publications of Hans Landolt on the forced normalization phenomenon.[4]

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

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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).[5] 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[6] with an incidence rate of 7 per 1000 person-years.[7] 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.[8]

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[9] (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 nonspecific 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).[10] 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.[11] 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.[12] 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[13,14] 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.[15] The psychopathology of postictal psychoses is polymorphic, but most patients present with an abnormal mood (either depressed or manic) and a paranoid delusion.[13] 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.[16] 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.[15]

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.[17] 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.[4] 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[18] 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.[4] 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.[19]

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.[20]

Interictal psychoses

Psychoses without a clear temporal relationship with epileptic seizures are less frequent than peri-ictal 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.[21] Clinical[22] and neuroimaging findings[23] 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,[24] and gross abnormalities such as enlarged ventricles or periventricular gliosis have also been noted.[25] The association with the dominant hemisphere was initially suggested by early studies on interictal psychoses[10] 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.[26]

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[10,12] while other authors stressed the rarity of negative symptoms and catatonic states.[27] In addition, the long-term prognosis of interictal psychosis seems to be better than that of schizophrenia with less reported long-term institutionalization[28,29] 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%.[30] *De novo* psychoses seem to occur in the context of unsuccessful epilepsy surgery with continued seizures and or surgical complications.[31] However, there are reported cases of *de novo* psychosis after successful epilepsy surgery and, in these cases, the forced normalization phenomenon has been hypothesized.[32] While pre-existing psychiatric conditions, including psychotic disorders, could be a risk factor for psychiatric disorders after epilepsy surgery,[33] 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.[34]

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.[35] However, late-onset disorders have been also described.[36]

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[37,38] 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.[39] 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).[39] 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,[40] 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.[41] Guidelines from the World Federation of Biological Psychiatry (WFSBP)[42] 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.[42]

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[43] 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[44] 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.[41] 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[45] 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.[46] 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.[47]

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).[47] 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) valproate (neutropenia)	Clozapine (agranulocytosis) 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.[48,49] 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.[47]

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).[50] 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.[50] 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.[51] Regarding clozapine, the risk of seizures is clearly dose and titration dependent.[52] 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.[53]

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.[53] 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[54] 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[38] 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.[55] 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.[56,57] However, the use of benzodiazepines, especially clobazam, is quite a popular treatment for postictal psychoses[38,58] among clinicians but this is not based on any evidence.

Lithium
Lithium is occasionally prescribed as an augmentation strategy in drug-refractory schizophrenia[59] but the evidence for that is low.[60] 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.[61] Still, lithium may prevent or mask carbamazepine- or oxcarbazepine-related hyponatraemia.[62] 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.[63] 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).[64] 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.

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