Epilepsy and psychosis: a practical approach

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ABSTRACT

The psychoses of epilepsy can be classified according to their temporal relationship with seizures, namely as ictal, postictal and interictal psychosis. Interictal psychosis is the most common and may resemble schizophrenia. They can be challenging to diagnose and to manage, especially given the perception that some antipsychotic drugs may exacerbate seizures, while some antiepileptic medications may worsen psychosis. The current uncertainty around their best management means that some patients may not receive appropriate care. We propose a practical stepwise approach to managing psychosis in patients with epilepsy, summarising the key clinical features. We provide a framework for diagnosis, investigation and management of psychosis in the acute and long term. We also summarise the available evidence on the risk of psychosis with current antiepileptic drugs and the risk of seizures with antipsychotic drugs.

BACKGROUND

The International League Against Epilepsy defines epilepsy as two or more unprovoked seizures more than 24 hours apart or a single unprovoked seizure with a more than 60% risk of recurrence.[1] Its prevalence is around 1% in developed countries, meaning that around 600 000 people in the UK have epilepsy.

Psychosis is a constellation of symptoms ranging from *positive symptoms*—thought disorder, delusions and hallucinations—to *negative symptoms*—lack of volition and social withdrawal with loss of sense of reality (table 1).

Psychosis may occur due to a primary psychiatric disorder, such as schizophrenia, affective disorder and autism, or it may be secondary to neurological disorders, such as epilepsy. The lifetime prevalence of any psychotic disorder in the general population is around 3%. Psychosis develops in 2%–7% of people with epilepsy.[2] One population-based cohort study found that people with epilepsy were twice as likely to develop schizophrenia compared with the general population; gender had no effect, but the risk of co-occurence increased with age.[3] Another study reported a higher prevalence of coexisting epilepsy in patients with a diagnosis of schizophrenia versus the general population.[4] Epidemiological studies thus suggest a bidirectional relationship between psychosis and epilepsy that may be independent of other factors.[5]

Box 1 highlights several reported risk factors for developing a psychosis of epilepsy. Temporal lobe epilepsy appears more closely associated with psychosis than other forms of epilepsy, with a prevalence of between 10% and 15%.[6–8] The risk of psychosis is also higher in people with poorly controlled seizures, a left temporal epileptogenic focus, hippocampal sclerosis, neurodevelopmental disorders, early age at epilepsy onset, a history of status epilepticus and a family history of psychosis or affective disorder.[3 9]

Neurobiology and neuroanatomical studies

The dopamine circuitry has a well-established role in the pathogenesis of schizophrenia and psychosis.[10] Symptoms of schizophrenia in the absence of seizures is linked to a reduction in dopamine activity within dorsolateral and ventrolateral prefrontal cortices and overactivity within mesolimbic structures.[11] The first of these mechanisms may also explain the dysexecutive cognitive deficits in schizophrenia, and the second may explain the positive delusions and hallucinations.[12]

In mesial temporal lobe epilepsy, there is reduced dopamine binding capacity via D2/D3 receptors in the striatum, which may disinhibit thalamocortical connections and enhance cortical hyperexcitability. Conversely, dopamine activity via D2 stimulation in the forebrain appears to behave in an antiepileptic way, whereas selective D1 receptor activation appears

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Table 1 Clinical features of psychotic disorders: Diagnostic and Statistical Manual of Mental Disorders V

Positive symptoms	Negative symptoms
Delusions ► Persecutory ► Referential ► Grandiose ► Religious ► Somatic ► Control	*Affective flattening*: the person's range of emotional expression is clearly diminished; poor eye contact; reduced body language
Hallucinations ► Auditory ► Visual ► Olfactory ► Gustatory	*Alogia*: a poverty of speech, such as brief, empty replies
Disorganised thinking	*Avolition*: inability to initiate and persist in goal-directed activities (such as school or work)

to lower the seizure threshold both clinically and in animal models.[13]

Reduced dopamine activity within prefrontal cortices appears to underpin both epilepsy and schizophrenia; both conditions may in turn lead to dysregulation of mesiotemporal dopamine circuitry and the potential to promote seizures and/or psychosis.

Neuroimaging studies in schizophrenia have shown reduced cortical thickness of the inferior frontal gyrus, which may reflect under activity within this region.[14] In patients with epilepsy and psychosis, structural imaging studies have shown several relevant changes. For example, there may be volume changes within hippocampal and amygdala structures implicating mesolimbic architecture.[15 16] Single-photon emission CT studies have shown increased blood flow within the posterior cingulate gyrus in both epilepsy-related psychosis and schizophrenia.[17] These findings highlight important connections between the limbic and prefrontal circuitry.

The predominance of negative symptoms (compared with the positive symptoms of schizophrenia) may be explained by varying degrees of dysfunction in frontotemporal areas and may be the reason why the psychosis of epilepsy differs from the primary psychotic disorder schizophrenia.

Box 1 Risk factors for developing psychosis of epilepsy

- Family history of psychosis or affective disorder.
- Early age of onset of epilepsy.
- Left temporal epileptogenic focus.
- Hippocampal sclerosis.
- History of status epilepticus.
- History of febrile seizures.
- Structural brain lesions.
- Poorly controlled epilepsy.

MANAGING A PATIENT WITH EPILEPSY AND PSYCHOSIS: A STEPWISE APPROACH

The management of psychosis of epilepsy can present a challenge for clinicians and requires a multidisciplinary approach. We propose a stepwise approach to: making the diagnosis, investigations, acute management and long-term management of psychosis of epilepsy. Figure 1 summarises these steps in a flow diagram. Box 2 gives a clinical case that highlights the key points of our strategy.

Step 1: making the diagnosis

Clinical features of psychosis of epilepsy

The psychoses of epilepsy are currently classified according to their temporal relationship to ictal events: ictal psychosis, postictal psychosis and interictal psychosis. Table 2 highlights the clinical features that distinguish these from schizophrenia. The classification of the psychosis is important since this may influence acute and long-term management.

In the case described, the symptoms began 24 hours after a new-onset cluster of seizures, which is typical for postictal psychosis. However, from experience, many cases of postictal psychosis occur in patients who have had epilepsy, most commonly temporal lobe epilepsy, for many years. In postictal psychosis, as in this case, there is lucid period of between a few hours and a few days, followed by insomnia and agitation, leading to psychosis. The psychotic symptoms are typically positive, with prominent persecutory delusions, and often a strong affective component. Patients may be aggressive with directed violence.[18 19] The symptoms generally last a few (mean 9–10) days, although are sometimes more protracted, lasting weeks to months and requiring psychotropic medication.

Psychotic symptoms sometimes form part of the seizure (ictal psychosis). They are of sudden onset, brief and abort as the seizure aborts. Ictal psychosis may occur in the context of non-convulsive status epilepticus where patients may show bizarre behaviour and thought incoherence, with or without loss of awareness. Delusions and hallucinations are less common than in postictal psychosis; patients may show other seizure features, such as motor or orobuccal automatisms as part of temporal lobe epilepsy.

A more difficult challenge for clinicians is to distinguish interictal psychosis from schizophrenia. Interictal psychosis can manifest as brief or chronic forms. Forced normalisation may cause some cases of brief interictal psychosis, as Landolt initially reported, where control of seizures and normalisation of the electroencephalogram (EEG) disinhibit the limbic system.[20]

The chronic forms of interictal psychosis may closely resemble schizophrenia; however, several features help to distinguish the two. Schizophrenia often begins in young adulthood. The Diagnostic and Statistical Manual of Mental Disorders V criteria for diagnosis are at least two core symptoms lasting for 1 month and a decline in

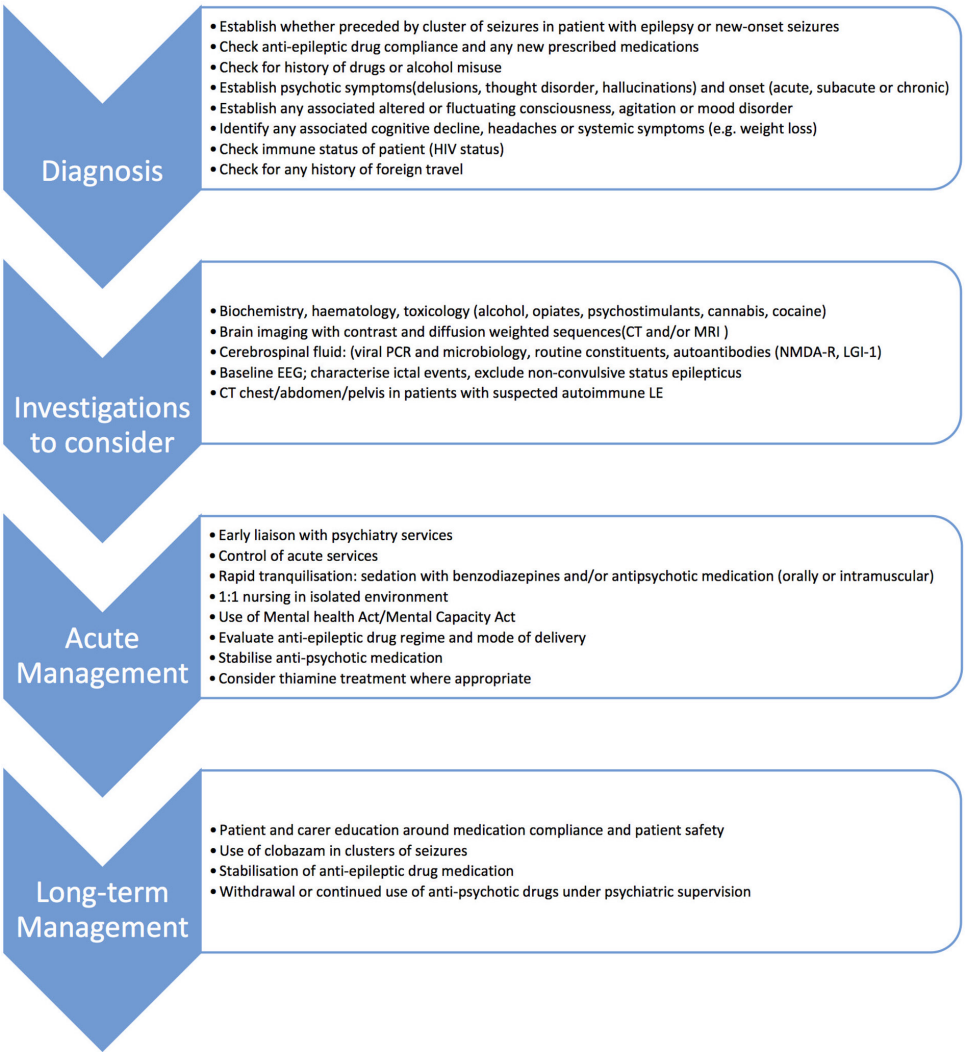

Figure 1 Stepwise management of psychosis of epilepsy. EEG, electroencephalogram; LE, limbic encephalitis; LGI1, leucine-rich, glioma inactivated 1; NMDA-R, N-methyl-D-aspartate receptor.

social, personal and occupational functioning during the period of symptoms. The core features of schizophrenia are positive symptoms (delusions, thought disorder and hallucinations) and negative symptoms (apathy and social withdrawal). Delusions are passive in nature and the hallucinations tend to be third-person auditory. People with schizophrenia often have poor insight into their symptoms and show a decline in their premorbid personality and state.

In contrast, interictal psychosis manifests predominantly with the positive psychotic symptoms of delusions and hallucinations, which are less likely to be third-person auditory, and have better preserved personality traits and no negative symptoms.[21–24] The psychosis can last days to months but may be more protracted. It can be very difficult to distinguish between interictal psychosis and postictal psychosis and in many patients these coexist.

Differential diagnoses

In the initial stages of clinical diagnosis, we need to consider other potential causes of psychosis. Pyschosis can be seen in the context of other medical conditions; for example, limbic encephalitidies (infective or autoimmune), transient psychosis following alcohol or drug misuse, delirium, neurodegenerative dementia syndromes (Alzheimer's disease) and non-convulsive status epilepticus. There are also several psychiatric conditions in addition to schizophrenia where psychosis can manifest; for example, severe depression, borderline personality disorder and mania with psychosis (box 3).

It is important to consider limbic encephalitis in the context of seizures and psychiatric symptoms. Infective causes are usually viral and include herpes simplex virus type 1, varicella zoster virus, enteroviruses and West Nile virus. Knowing the patient's HIV status and travel history is important. The autoimmune encephalitidies are increasingly recognised as a group of disorders manifesting with both seizures and psychiatric symptoms. In the last two decades, around 16 autoantibodies have been reported associated with a broad spectrum

Box 2 Clinical case

Presentation and diagnosis

A 54-year-old right-handed man, previously fit and well, presented with a generalised tonic–clonic seizure on awakening. En route to hospital, he had a further convulsion and two more in the emergency department. On arrival, he was confused, with a mild left hemiparesis, left-sided neglect and dysarthria. He was started on levetiracetam for seizures and started to make a postictal recovery. One day later, his condition changed significantly. He became agitated and disorientated with non-coherent speech, expressing paranoid delusions, grandiose beliefs and somatic delusions (he was fixated on the size of his penis, believing it had been substituted). He absconded from hospital believing that all hospital staff members were corpses. On return to the ward, he was seen by liaison psychiatry team and diagnosed with postictal psychosis.

Investigations

A CT scan and subsequent MR scan of brain showed a right anteromedial frontal lobe infarct. Serum biochemistry, haematology, autoimmune screen and alcohol and toxicology screening on admission were normal or negative. Subsequent cerebrospinal fluid analysis was normal. The first electroencephalogram (EEG) showed normal background dominant posterior rhythm with frequent bursts of bifrontal high amplitude and slow waves. Repeat EEG during the psychotic episode showed no evidence of non-convulsive status epilepticus. Serum antibody screening for voltage-gated potassium channel complex, *N*-methyl-D-aspartate-receptor, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor and gamma-aminobutyric acid-B receptor autoantibodies were all negative.

Acute management

He received diazepam and quetiapine, with limited effect. After changing the quetiapine to olanzapine, his symptoms began to settle over the next 3 weeks. He had no further clinical seizures during the admission and successfully switched from levetiracetam to sodium valproate due to concerns about psychiatric side effects with levetiracetam.

Long-term management

We advised him and his partner about the potential for symptom recurrence after clusters of seizures. He was followed up in outpatient neuropsychiatry and gradually came off antipsychotics over several weeks without any recurrence of psychosis.

of clinical presentations. These autoantibodies recognise either intracellular antigens (eg, anti-Hu) and are strongly linked to malignancy or extracellular epitopes of ion channels or receptors (eg, *N*-methyl-D-aspartate (NMDA) receptor) and have variable association with underlying malignancy, for example, teratoma.

Pertinent to psychosis and seizures are antibodies to NMDA receptors, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, gamma-aminobutyric acid (GABA)-A and GABA-B receptors and the voltage-gated potassium channel complex 'leucine-rich, glioma inactivated 1' (LGI1). The clinical presentation is an antibody-mediated limbic encephalitis. Patients present with a subacute fluctuating reduction in consciousness with altered memory and cognition. Psychiatric symptoms can manifest early in the clinical state, and patients may show psychosis, anxiety, aggression, compulsive behaviours and elevated mood. Some autoantibodies are more commonly linked to psychosis (NMDA receptors, AMPA receptors and GABA-B receptors), status epilepticus (NMDA receptors, GABA-B receptors and GABA-A receptor) and faciobrachial dystonic seizures (LGI1). Antibodies to glutamate decarboxylase (GAD65) may also present with difficult to control seizures and cognitive deficits. Other autoimmune-related conditions that predispose to seizures and psychosis include systemic lupus erythematosus and acute disseminated encephalomyelitis.[25]

Psychosis and seizures may also form part of the constellation of symptoms associated with thiamine deficiency in Wernicke-Korsakoff syndrome. The definition of this syndrome states that a history of alcohol abuse is required, although it may result from malnutrition, as occurs with gastric cancer, gastrectomy or anorexia nervosa. Clinical features include acute onset of ophthalmoplegia, confusion and gait ataxia with possible seizures, followed by a more protracted history of anterograde amnesia and other associated cognitive deficits (dysexecutive syndrome), confabulation and hallucinations.

A wide variety of illicit drugs induce seizures and psychotic symptoms, including phencyclidine, inhalants, cocaine and psychostimulants. A disturbing trend is the increased use of the inhaled synthetic cannabinoid '*Spice*'. These compounds, previously termed 'legal highs', are agonists for the CB1 receptor, a target for endogenous cannabinoid-like substances, which may lead to reduced GABA synaptic transmission and a propensity to cause psychosis, agitation and seizures.

Around 30% of patients presenting with delirium have psychotic symptoms in the form of visual illusions or hallucinations. Delirium is confirmed using the confusion assessment method, requiring an acute onset and fluctuating course and inattention either with disorganised thinking (eg, illogical flow of ideas) or altered level of consciousness (eg, lethargy and drowsiness). It can be associated with altered

Table 2 Clinical features distinguishing psychosis of epilepsy from schizophrenia

	Ictal	Postictal	Interictal	Schizophrenia
Prevalence in epilepsy	Unknown	6%	2%–10%	1%
Onset	Unknown History of epilepsy	10–20 years postepilepsy diagnosis	10–15 years postepilepsy diagnosis	Insidious usually in late teens early 20s
Symptoms	▲ Fear or anxiety aura. ▲▲▲ Mood disturbance (15%). ▲ Depersonalisation and derealisation. ▲ Fluctuating consciousness. ▲▲ Delusions and hallucinations uncommon.	▲▲ Lucid interval (8–72 hours). ▲▲ Delusions: commonly ones are grandiose, religious and somatic. ▲▲ Visual or auditory hallucinations. ▲▲▲ Preserved insight. ▲▲▲ Strong affective component. ▲▲▲ Clouding of consciousness may occur. ▲▲ Amnesia for events in some cases.	▲ Delusions: (referential, perceptual, persecutory common). ▲▲ Mystical experiences. ▲▲▲ Visual or auditory hallucinations. ▲▲▲ Command hallucinations uncommon. ▲▲▲ Better preservation of affect. ▲▲▲ Preserved premorbid personality. ▲▲▲ Negative symptoms less common. ▲▲ Clear consciousness.	▲▲ Delusions: (passivity, persecutory). ▲▲ Auditory hallucinations (third-person or command hallucinations). ▲ Negative symptoms. ▲▲ Social withdrawal. ▲▲ Avolition. ▲▲ Blunted affect. ▲▲▲ Prodromal phase with gradual onset. ▲▲▲ Younger age. ▲▲▲ Lack of insight. ▲▲▲ No association with seizures.
Duration	Minutes	Days to weeks	Months to years	Months to years

Box 3 Differential diagnosis of psychosis of epilepsy

- Psychosis of epilepsy.
- Delirium.
- Non-convulsive status epilepticus.
- Schizophrenia.
- Acute transient psychosis (may relate to alcohol or drug use).
- Unipolar or bipolar depression.
- Mania with psychosis.
- Limbic encephalitidies (infective or autoimmune).
- Alzheimer's disease.

cognition, agitation and altered sleep–wake cycle. Risk factors include: age 65 years or older, current hip fracture, cognitive impairment or dementia and severe illness (a condition deteriorating or at risk of deterioration). Precipitating factors are often multifactorial but include drugs, electrolyte imbalance, pain, infection, respiratory failure, constipation, urinary retention and metabolic disorder.

Psychotic symptoms and seizures are also recognised clinical features of Alzheimer's disease. Seizures are not reported in dementia with Lewy bodies, despite its association with recurrent complex visual, auditory and somatic hallucinations and delusions.

History taking and clinical examination

The clinician should undertake a detailed assessment, starting with an accurate history including any collateral history from relatives, friends and employers. Key questions include the following:

1. Does the patient have an established diagnosis of epilepsy or a history of new-onset seizures?
2. Was there a deterioration in seizure control or a cluster of seizures before the onset of psychotic symptoms?
3. Has there been poor adherence to prescribed regular antiepileptic medication?
4. Has any new medication been prescribed for seizures or other indication?
5. Is there a history of drugs or alcohol misuse?
6. What are the psychotic symptoms (delusions, thought disorder, visual or auditory hallucinations) and onset (acute, subacute or chronic)?
7. Are the psychotic symptoms associated with an altered or fluctuating consciousness?
8. Are there associated symptoms of aggression or agitation?
9. Are there any symptoms of an underlying mood disorder?
10. Has there been any cognitive decline?
11. Have there been any systemic symptoms (eg, weight loss, altered appetite and fever)?
12. Is the patient immunocompromised (HIV status)?
13. Is there a history of foreign travel?

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General physical examination should look for signs of alcohol or drug misuse, metabolic disease or malignancy. A neurological examination should include assessment for evidence of continuing seizure activity, space-occupying lesion or neurodegenerative disorder. Mental-state examination should include assessment of level of alertness, orientation and memory recall, and where possible a cognitive assessment, such as the revised Addenbrookes Cognitive Examination. The patient's appearance (kempt or unkempt), rapport, eye contact, speech (pressure of speech and poverty of speech), stream of thoughts (thought disorder), content of thoughts (delusions), perceptual abnormality (auditory/visual hallucinations) and insight into symptoms are all important facets of the examination.

Step 2: investigations

Investigation requires a systematic approach and is guided by the clinical presentation. In the acute setting, all patients should undergo routine biochemical and haematological screening blood tests and urine toxicology that may include: alcohol, amphetamines, cannabis, benzodiazepines, opiates and psychoactive substance or 'legal highs'.

A CT scan of head with contrast in the emergency setting or ideally MR scan of brain with contrast and diffusion-weighted imaging should be arranged to exclude a space-occupying lesion or cerebrovascular event, as in the illustrated case. MR brain imaging in patients with infective or autoimmune limbic encephalitis may be normal or may show increased T2 signal abnormality within the mesial temporal structures.

Cerebrospinal fluid (CSF) analysis, where safe to do so, is required if infective limbic encephalitis is a possibility; fluid should be sent for viral PCR, Gram stain, culture and routine constituents. Immunoglobulin G to the NMDA receptor and other cell surface antibody tests are most sensitive and specific within CSF. While NMDA-receptor IgM and IgA responses may occur in patients with schizophrenia and other psychiatric disease, and up to 10% of normal controls, patients with schizophrenia do not show IgG responses associated with anti-NMDA-receptor encephalitis. CSF testing for GAD65 and LGI1 antibodies may support a diagnosis of autoimmune limbic encephalitis, although it requires careful interpretation, particularly within the context of other autoimmune disorders (eg, type 1 diabetes mellitus) in the case of GAD65 or low-level titres in the case of LGI1.

Baseline electroencephalography can help to characterise ictal events to exclude non-convulsive status epilepticus or to demonstrate specific patterns relating to limbic encephalitidies. For example, patients with anti-NMDA-receptor encephalitis may show the extreme delta brush pattern, a marker of a poor prognosis. EEG monitoring may be required in patients whose clinical course does not improve, or where seizure control is problematic requiring anaesthesia.

Step 3: acute management strategy for psychosis of epilepsy

The acute management of psychosis of epilepsy requires a multidisciplinary approach with early involvement of liaison psychiatry or neuropsychiatry. The key aims include protective measures (sedation and antipsychotics) and preventative measures (treating the underlying cause of symptoms, eg, seizures).

It is important to use the correct legal framework in managing psychotic symptoms, in countries where it is applicable. In England and Wales, this may involve using the Mental Capacity Act, deprivation of liberty safeguards or the Mental Health Act.[26] The general rule is that if the patient lacks capacity but does not object to treatment, the Mental Capacity Act may be considered over the Mental Health Act. We would advise discussions around the legal framework with psychiatry.

An acutely psychotic patient should ideally be nursed in an isolated environment with low stimulation and one-to-one observation. Patients with agitation and/or aggression may require seclusion or restraint. Communication to patients and their relatives is important at all stages to provide reassurance that symptoms will improve but that they may take days to weeks to resolve fully.

Rapid tranquilisation

An initial phase in managing a patient with postictal psychosis or interictal psychosis is the instigation of rapid tranquilisation. Some patients may not require this if de-escalation and other strategies have already calmed them. Rapid tranquilisation may be needed to achieve a state of calm and to reduce the risk to both the patient and others. It is not without risk itself and requires close monitoring to minimise effects of oversedation and respiratory depression. The choice of medication and its mode of delivery largely depend on the patient's state. From our clinical experience, agitated patients often improve with optimisation of antiepileptic medication and/or use of benzodiazepines. However, in patients with florid psychotic symptoms, it is advisable to use a short-term antipsychotic, either alone or combined with a benzodiazepine. For example, in a cooperative patient with florid psychotic symptoms, an oral antipsychotic medication may suffice. In an uncooperative patient, we would advise a benzodiazepine as a first choice, although there is no evidence as to which benzodiazepine has most effect. Our experience suggests that lorazepam 0.5–4 mg or diazepam 5–10 mg are both useful in this setting and can be combined with antipsychotic medication, for example, haloperidol.

In postictal psychosis, antipsychotic medication can be used with or without benzodiazepines for a short duration, at most 3 months. Because many cases remit within 2–3 weeks, antipsychotic medication may not be needed, since they have a delayed onset of action over several

Table 3 First-generation and second-generation antipsychotic drugs

Antipsychotic drug	Dose range	Side effects
Amisulpride	50–800 mg	Hyperprolactinaemia
Aripiprazole	5–30 mg	Insomnia Agitation
Clozapine	12.5–900 mg	Hypotension Myocarditis Agranulocytosis Hypersalivation
Haloperidol	0.5–20 mg	Extrapyramidal QT interval prolongation
Olanzapine	2.5–20 mg	Weight gain Hyperglycaemia
Quetiapine	25–750 mg	Hypotension Hyperglycaemia
Risperidone	0.5–16 mg	Extrapyramidal Hyperprolactinaemia

weeks. However, some studies suggest that most of the benefit from antipsychotic treatement occurs within the first 2 weeks. We would therefore argue that there is a role for early antipsychotic medication but that the decision should be guided by the patient's clinical state. The priority is the resolution of symptoms and minimisation of unnecessary patients and carer distress.[27] Most patients with postictal psychosis respond well to these short term measures; however, if symptoms have not entered into a remission by this stage, then they may need a more long-term strategy as in the case of interictal psychosis (see step 4).

Antipsychotic medication

Antipsychotics are broadly classified as first generation and second generation. First-generation antipsychotic drugs, for example, chlorpromazine, fluphenazine, trifluoperazine and haloperidol, primarily block D2 receptors in the brain. They are not selective for the four main dopamine pathways in the brain and so can cause a range of side effects, particularly extrapyramidal symptoms and elevated serum prolactin concentration. Second-generation antipsychotics (often referred to as atypical) act on a range of receptors and have more distinct clinical profiles compared with first-generation drugs, particularly with regard to side effects. Examples include olanzapine, risperidone, quetiapine, amisulpride, lurasidone, aripiprazole and clozapine (table 3).[28]

Early use of psychotropic medication, particularly in agitated and aggressive patients, may reduce the duration of a psychotic episode. In a cooperative patient, antipsychotic treatment could be given orally, for example, olanzapine 2.5–20 mg/day or risperidone 0.5–6 mg/day. In uncooperative patients, treatment may need to be given intramuscularly, for example, haloperidol 2–5 mg with lorazepam 1–2 mg. Olanzapine and lorazepam should not be given together via the intramuscular route due to their potential for causing orthostatic hypotension.

There is very limited evidence regarding the efficacy and safety for antipsychotics in patients with psychosis of epilepsy. There has been one published Cochrane review that included one randomised controlled trial that compared olanzapine (10 mg/day) with haloperidol (12 mg/day) in 16 people suffering from schizophrenia-like psychosis of epilepsy. Thirteen participants completed the study. Significant improvement was associated with use of olanzapine. No seizure outcomes were reported.

Two large non-commercial clinical trials—the US Clinical Antipsychotic Trials of Intervention Effectiveness and the UK Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study—compared first-generation and second-generation antipsychotic drugs for people with chronic schizophrenia. Neither trial showed any clinical advantage in terms of efficacy or adverse effects of second-generation compared with first-generation antipsychotics. In particular there were no significant differences in rates of extrapyramidal side effects. Individual drugs differed in specific side effects: for example, olanzapine caused most weight gain and dyslipidaemia, quetiapine caused most anticholinergic effects and risperidone caused the most hyperprolactinaemia and sexual side effects.[29] Table 2 highlights some of the more commonly associated adverse effects with certain antipsychotic drugs.

Uncontrolled studies in patients without epilepsy have suggested a dose-dependent risk of seizures with antipsychotics of between 0.1% and 1.5%. Clozapine appears to be associated with the most risk of seizures.[30–32]

Prolongation of the QTc interval may occur with antipsychotic medication, especially with first-generation antipsychotic drugs. The ECG should form part of the initial workup of patients with epilepsy and psychosis, and the QTc interval should be assessed before and during treatment.[33]

Antiepileptic medications

In suspected ictal psychosis and postictal psychosis, we recommend using benzodiazepines for clusters of seizures either as a course of oral clobazam 10 mg twice daily over several days or via an intravenous or intramuscular route (ie, lorazepam) in agitated patients.

Agitated patients require a review of their antiepileptic medication regimen and, where applicable, changes to their drug, dose and mode of delivery. Some patients may need to stop the medication, as in the illustrated case. In agitated patients or those refusing oral treatment, clinicians should consider converting oral antiepileptic drugs to intravenous, intramuscular or subcutaneous forms.

Several antiepileptic drugs have been associated with a small risk of psychotic symptoms, with reported prevalences of 1%–2% (topiramate (0.8%), vigabatrin (2.5%), zonisamide (1.9%–2.3%), levetiracetam (0.3%–0.7%) and gabapentin (0.5%)).[34–36] A more recent study from Melbourne, Australia, examined

the records of 2630 patients and identified 98 with psychotic disorders, 14 of which were diagnosed with drug-induced psychosis. Levetiracetam was used more in the affected group ($P<0.01$), whereas carbamazepine use was higher in the group without any history of psychotic disorders ($P<0.05$). The symptoms were shorter lasting and had a better outcome compared with other causes of psychotic symptoms.[37] Clinicians should consider using levetiracetam carefully in patients with a history of psychiatric problems, family history of psychiatric problems or of learning difficulties, and avoid rapid titration.[31]

Pharmacokinetic drug interactions (with potential effects on the drug metabolism) need to be considered in patients taking enzyme-inducing antiepileptic drugs (carbamazepine) or non-enzyme-inducing antiepileptic drugs (valproate) in conjunction with antipsychotic treatment.

Epilepsy surgery in carefully selected patients with hippocampal sclerosis can achieve seizure freedom in 70% of cases.[38] There is also evidence from prospective surgical cohorts of a positive effect on reducing psychotic episodes and symptoms. Patients with pre-existing psychotic illness, however, require careful evaluation by mental health services before undergoing temporal lobe surgery.

Step 4: long-term management of psychosis of epilepsy

Around 95% of patients with postictal psychosis have full resolution of symptoms within 1 month, with symptoms lasting a mean of 9–10 days. Most patients therefore require at most up to 3 months of treatment. Symptoms lasting beyond a few months or interictal psychosis may require long-term continuation of antipsychotics with careful surveillance under neuropsychiatry or liaison psychiatry. As with acute management of psychosis of epilepsy, there are no specific studies in this group of patients to influence treatment policy on the choice of antipsychotic or the duration of treatment required. People with recurrent postictal psychosis may require long-term treatment, although there is only limited evidence around its use and prevention of psychosis.

We strongly recommend using clobazam for seizure clusters and educating patients and relatives around the importance of adherence to antiepileptic medication and managing other seizure risk factors.

Conclusions

Psychosis of epilepsy may affect up to 7% of people with epilepsy. The risk factors include left-sided temporal lobe epilepsy, drug-resistant seizures, structural brain lesions and a family history of psychosis. Making the diagnosis of psychosis of epilepsy can be a challenge since many features overlap with other medical and psychiatric conditions. The autoimmune limbic encephalitidies is an expanding range of conditions where a knowledge of antibody-associated clinical phenotypes and treatment options are important. There are low quality retrospective data suggesting a higher risk of antiepileptic drug-induced psychosis with levetiracetam, zonisamide and vigabatrin. Clinicians should therefore be cautious when prescribing these medications in patients with a psychiatric history.

The acute management of psychosis of epilepsy involves a multidisciplinary approach with early involvement of specialist psychiatry. Patients may need rapid tranquilisation with benzodiazepines and antipsychotic drugs, optimisation of seizure control and further investigation into underlying causes and other treatments. There is currently no evidence on which to base a choice of antipsychotic drug in psychosis of epilepsy and any choice may be driven by mode of delivery and patient comorbidities. Most patients with postictal psychosis require up to 3 months of treatment with antipsychotic medication, with most achieving remission in symptoms allowing a slow withdrawal. For patients with more protracted symptoms, as in relapsing postictal psychosis or interictal psychosis, medication may be required for months to years under psychiatric supervision.

Contributors JS is the coauthor along with MM, who is the first author. MM was responsible for drafting the review and

Key points for clinicians

- Establishing the correct diagnosis requires thorough systematic history taking and clinical evaluation.
- Controlling seizures is paramount, first using medications that are less likely to cause psychosis (eg, carbamazepine).
- Timely involvement of mental health services is crucial in assessing and managing psychotic symptoms.
- There is no evidence on which to base a choice among antipsychotic drugs in psychosis of epilepsy, and duration of treatment is gauged by symptom remission.
- Consider clobazam or, where appropriate, buccal midazolam to abort seizure clusters.
- Patient and carer education is an important part of successful long-term management.

Key points for carers

- Psychosis can occur in patients with frequent epileptic seizures or clusters of seizures.
- Good adherence to antiepileptic medication is paramount in preventing psychosis.
- Psychosis of epilepsy has a better prognosis than schizophrenia.
- Treatment with antipsychotic medication may be required as a short-term course.
- Psychosis of epilepsy can recur, and carers need to be vigilant to any changes in behaviour, thought patterns, hallucinations and agitation.

final approval of the published version. JS contributed to the writing and content of the final review. AGM provided critical appraisal of the review and overall guidance.

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