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Hiding in Plain Sight: A case of post ictal psychosis with suicidal behavior

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ABSTRACT

Postictal psychosis (PIP) is a serious, often unrecognized complication of epilepsy. Early diagnosis and intervention can prevent life-threatening outcomes. We report the case of a 26-year-old woman with childhood-onset frontal lobe epilepsy who attempted suicide, during a postictal psychotic episode, several days after undergoing inpatient video-EEG monitoring. This case presents a real-world scenario with clear guidelines for the on-call neurologist who will need to accurately diagnose and confidently manage PIP with psychotropic medications. Moreover, this case may stimulate discussion about the complex relationship between epilepsy and psychosis.

1. Introduction

It's getting faster, moving faster now, it's getting out of hand,
On the tenth floor, down the back stairs, it's a no man's land,
Lights are flashing, cars are crashing, getting frequent now,
I've got the spirit, lose the feeling, let it out somehow.

– Ian Curtis, lead singer of *Joy Division*; diagnosed with epilepsy and committed suicide at 23.

Postictal psychosis (PIP) is the most common *peri*-ictal psychosis and comprises 25 % of epilepsy-associated psychoses [1]. PIP is a life-threatening complication typically described in the setting of long-term drug-resistant epilepsy [2]. From ancient texts to Jackson's "*Temporary mental disorders after epileptic paroxysms*" [3], epilepsy-related psychoses were classified according to their temporal relationship with seizures [1]. Indeed, cases of postictal psychosis, mania, and aggression were well documented in ancient Babylon and Persia [4,5] and by Jackson himself [3]. Jackson, who was critical of case analysis, developed a practical and scientifically valid bedside approach. In his *Neurological Method* [6], Jackson relied exclusively on sensorimotor signs and symptoms, dismissing mental symptoms as diagnostically unhelpful due to their non-localized nature [6,7]. After Jackson's work, neurology and psychiatry only drifted further apart conceptually, clinically, and institutionally in both clinical practice and scientific inquiry [8]. It was not until 1988 that PIP was first recognized as a distinct clinical entity [9], though it still has not been included in either the general medical (ICD-11) or the psychiatric classification systems (DSM-V) [10,11].

Recent decades have seen a renewal of interest in PIP among neurologists, largely due to the growing recognition of the neurobiological basis of psychotic disorders [12] and their bidirectional relationship with epilepsy [13]. Thus, given its estimated prevalence of 6–7 % during prolonged video- EEG monitoring [14] and its strong association with violence, suicide, and sexual disinhibition [15], neurologists need to become well-acquainted with PIP. When recognized early, PIP is usually short-lived and responsive to treatment [2]. Here, we present a case study from our practice and provide practical tips for prompt diagnosis of PIP, and the safe and effective use of psychotropic medication.

2. Case description

A 26-year-old woman with drug-resistant lesional frontal lobe epilepsy (FLE) and an unremarkable psychiatric history presented to the Emergency Department (ED) following a suicide attempt 48 h after discharge from a video-EEG monitoring unit.

2.1. History of presenting complaint

During the two weeks preceding her suicide attempt, the patient had

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approximately 30 focal impaired awareness seizures (FIAS) with upper limb (right > left) dystonia, facial flushing, unresponsiveness, grunting, and late head deviation to the left, followed by postictal dysphoria. She presented to the ED in a stuporous state. She was on felbamate (1200 mg/day) at the time.

The patient was admitted for 72 h of inpatient video-EEG monitoring; 23 typical seizures were captured, 50 % of which occurred during sleep. Each seizure was associated with bifrontal high-amplitude slow waves, followed by EEG attenuation and subsequent left centroparietal delta-theta activity. Magnetoencephalography revealed epileptiform events localized to the left frontoparietal parasagittal region. Brain MRI showed porencephalic cysts in the left hemisphere, mainly in the parieto-occipital region.

Upon admission, the patient was started on brivaracetam (50 mg/day); complete seizure control was achieved over the subsequent 48 h. At 24 h post-admission, the patient was lucid and deemed to have returned to baseline. At 72 h, she exhibited mood lability, signs of agitation, and early insomnia. At 96 h, the patient remained mildly agitated, but was discharged on brivaracetam (100 mg/day) and felbamate (1200 mg/day).

Two days post-discharge, the patient attempted suicide. Her parents described her running suddenly to the balcony of their 27th-floor apartment and then attempting to climb the balcony railing.

2.1.1. Examination

Neurological examination upon re-admission showed mild right-sided hemiparesis, which was consistent with previous examinations. A psychiatric assessment revealed severe psychomotor agitation but no display of directed or non-directed aggression. She appeared confused but was nevertheless oriented to place, approximate time, and person. Her speech was accelerated and had an "exaggerated childish tone." She reported visual hallucinations of "lights, shadows, and rainbows" as well as a distorted perception of time ("slow motion") and shapes ("walls bending"). Her thoughts were disorganized, at times incoherent, and characterized by tangentiality. Her affect was highly labile ("euphoric" to "miserable") and accompanied by mood-congruent delusions ranging from grandiose ("I can save the planet") to nihilistic ("my brain is rotten") and spiritual ("the rainbow cleanses my soul"). She was amnesic regarding her suicidal behavior. She recalled occasional postictal suicidal thoughts but denied any suicide attempts or deliberate self harm. She denied a history of non-directed aggression and violent behavior. We identified no history of recent head trauma or substance use.

2.1.2. Investigations

Extensive blood tests, including calcium, magnesium, thyroid function, vitamin B12, and folic acid, were unremarkable. Urine drug screen and a blood ethanol test were both negative. A routine EEG showed background slowing, with no interictal epileptiform discharges or seizures. Neuroimaging was not repeated.

2.2. Developmental and past medical history

The patient had experienced a left cerebral intraventricular hemorrhage postnatally which resulted in mild right-sided hemiparesis, mild developmental delay, and borderline IQ. At age 8 years, she was diagnosed with epilepsy with FIAS. Despite trials of different anti-seizure medications (ASMs), she continued to experience one seizure per month. She was not considered a candidate for epilepsy surgery.

At age 14 years, she experienced episodes of transient visual loss which were considered non-epileptic because of their complete remission following brief psychotherapy. For almost a decade, the absence of clear EEG findings and the poor response to multiple ASMs fueled the suspicion that her seizures were dissociative in nature.

2.3. Psychiatric history

The patient denied any history of psychotic or affective episodes, substance use, or suicidality. She reported adverse behavioral events secondary to lamotrigine and sulthiame but not levetiracetam. Her father suffered from bipolar disorder.

2.3.1. Management

The patient was diagnosed with postictal psychotic disorder presenting with suicidal behavior. We determined that she could be safely managed on the ward with family supervision. On admission, she refused brivaracetam, which she believed was the cause of her current mental state. She was commenced on lacosamide (100 mg/day) and quetiapine (12.5 mg/day); the latter was changed to aripiprazole (2.5 mg/day) due to over-sedation and lorazepam (1–2 mg/day) to facilitate sleep. Within 48 h, the patient became less agitated and disorganized. After a thorough risk assessment, she was discharged home under the strict care of her parents who were given clear safety instructions.

Following discharge, she reported several breakthrough seizures followed by postictal dysphoria and, on one occasion, fleeting postictal suicidal thoughts. After three days on aripiprazole and lorazepam, her sleep quality, speech, thought form, and perception returned to baseline. Mood swings and nihilistic thoughts persisted, and aripiprazole was increased to 5 mg/day. On day 10, her mood remained dysphoric, but she was no longer psychotic. At her three-week follow-up, she was symptom-free. After two months, she reported feeling better than she had felt for years and asked to continue aripiprazole. One year after her suicide attempt, she was on lacosamide (200 mg/day), felbamate (1200 mg/day), and aripiprazole (5 mg/day). She reported isolated seizures with brief postictal dysphoria, but an otherwise stable mood with no suicidal ideation or psychotic symptoms.

3. Psychiatric diagnosis

PIP is characterized by psychotic episode occurring within 1–7 days following a seizure [9]. PIP typically presents in individuals with long-term drug-resistant epilepsy following a cluster of seizures and has predominantly been associated with temporal lobe epilepsy (TLE) [16,17]. Although FLE accounts for 15–20 % of all focal epilepsies [18], diagnostic overshadowing is not uncommon because frontal lobe pathology is often overlooked [19]. As a result, the frequency of PIP in FLE is likely underestimated [20,21].

In addition to seizure clustering, PIP has been associated with brain injury, intellectual disability, a history of psychosis, a family history of affective disorder [22], a genetic predisposition to schizophrenia, bilateral interictal epileptiform activity, and bilateral independent epileptic foci [2,22–24]. The lucid interval between the end of the postictal state and the onset of PIP symptoms is usually 1–3 days. Oshima et al. [25] suggested that PIP could be further subdivided into *nuclear* and *atypical* types. The familiar *nuclear* PIP is characterized by a definitive lucid interval and complies with the widely accepted Logsdail and Toone's diagnostic criteria for PIP.

However Oshima suggested an *atypical type*, distinguished by the absence of a lucid interval, which would be overlooked by the currently accepted diagnostic criteria. He posited that as the recovery from the ictal state is not always uniform it is feasible that the appearance of post ictal psychotic symptoms may overlap with some residual limbic seizure activity which could obfuscate the lucid interval. The clinical significance of this theoretical construct is unclear and warrants further investigation [25]. In the clinical setting the absence of a lucid interval should *still* be considered the cardinal clinical feature that favors a diagnosis of PIC over that of PIP.

Irritability, insomnia, and hypomania typically precede the onset of pleomorphic psychotic symptoms [14]; a strong affective component accompanies disorientation in clear consciousness. Grandiose and religious delusions and perceptual disturbances are common, as are sexual

disinhibition and amnesia, but none are pathognomonic of PIP [15,26,27].

Violence and suicide ideation/attempts are hallmarks of PIP and have been described in 23 % and 7 % of PIP cases, respectively. The occurrence of these symptoms essentially excludes a diagnosis of postictal confusion [15]. In our case, PIP-related suicidality should be differentiated from habitual postictal suicidal ideation. The latter is a lesser-known phenomenon characterized by postictal suicidal ideation following > 50 % of a person's seizures and has been suggested to occur in 15 % of people with FIAS [17]. Our patient's history does not align with habitual postictal suicidal ideation, as she reported occasional postictal dysphoria with only fleeting suicidal thoughts, with suicidal behavior occurring in the context of a postictal psychotic episode.

Suicidality is a complex, multifactorial phenomenon that traverses multiple psychiatric diagnoses [28] and has a bidirectional relationship with epilepsy [29]. As such, personal and family history of psychiatric disorders, history of suicidality, and history of *peri*-ictal suicidal ideation [29,30] should all be considered in the risk assessment of a patient with epilepsy presenting with suicidal behavior.

Most PIP episodes resolve within one month; milder cases may remit spontaneously [31]. Longer PIP episodes are more common in older patients and in those with intellectual disability, a family history of psychosis, and bimodal psychosis (i.e., both interictal and postictal psychosis) [31].

4. Differential diagnosis

The differential diagnosis of PIP in epilepsy is complex **(**Fig. 1**).** Appropriate diagnosis hinges on the identification of risk factors, the temporal relationship of symptoms with seizure activity, a patient's prompt response to a low-dose antipsychotic regimen, and the exclusion of traumatic brain injury or drug toxicity [2].

Preictal psychosis, or psychotic aura, is rare and presents in the hours (or, more rarely, days) preceding a seizure. Patients experiencing preictal psychosis may present with euphoria, anxiety, and perceptual disturbances that are not associated with an EEG correlate [32]. Patients may also present with derealization and depersonalization, which are characterized by the subjective experience of detachment from one's surroundings and oneself, respectively. Our patient's psychotic symptoms emerged after two weeks of increasing seizure activity and were absent beforehand, thereby excluding a diagnosis of preictal psychosis.

Ictal psychosis typically involves non-convulsive status epilepticus, mostly of focal origin. Because automatisms and other typical seizure phenomena can raise the suspicion of ictal psychosis, the final diagnosis of ictal psychosis is based on the EEG [33]. Our patient's psychotic episode was not associated with any ictal EEG changes, thereby excluding this diagnosis.

Postictal behavioral symptoms occur in 80 % of seizures and can cause significant distress, but they remain underreported and poorly understood [34]. Postictal confusion (PIC) presents immediately during the postictal state and can last minutes, hours, or days before a return to baseline. The transition into the postictal state can be brief and overlooked or prolonged (up to ten days), particularly in individuals with intellectual disability; this should be considered before a diagnosis of PIC is excluded prematurely [35]. Furthermore, PIC is associated with non-directed aggression and/or unintended self-harm only, thus differentiating it from intentional violent offenses or deliberate suicidal behavior that are more characteristic of PIP [15]. Our patient's suicidal behavior occurred during a period of clear consciousness following a lucid interval, thus excluding a diagnosis of PIC.

In addition to PIC, postictal anxiety, depression, and mania have been reported in 45 %, 43 %, and 22 % of patients with drug-resistant focal epilepsy, respectively [17]. These symptoms are easily distinguishable from PIP if they are isolated and appear early postictally, even though they mimic the heralding features of PIP. These symptoms may be prolonged in individuals with poor cognitive function, and, if they appear concurrently, can also resemble mild forms of PIP or interictal anxiety or depression. Although our patient reported a history of postictal dysphoria, postictal affective symptoms are unlikely to respond to psychotropics [17] or present as a florid psychotic episode. Postictal mania is particularly difficult to distinguish from PIP because (i) it develops following a lucid interval during the delayed phase of the postictal state and (ii) manic symptoms are common to both conditions. Nishida et al. [35] found that, unlike PIP, postictal mania is not complicated by chronic psychosis, which suggests that they are separate clinical entities. Tarrada et al. [36] suggested the classification of PIP as a secondary affective psychosis. However, as with schizophrenia and bipolar disorder, PIP and postictal mania may represent seizure-related psychotic spectrum disorders; this possibility warrants further investigation.

Interictal psychosis occurs during clear consciousness at least a week after the most recent seizure, presents at an earlier age than PIP, and usually lasts for several months [26]. The lack of previous interictal psychotic episodes, the close temporal relationship between the patient's symptoms and seizures, and the rapid response to very low-dose psychotropics argue against a diagnosis of interictal psychosis. Nonetheless, we note that a thorough history should be elicited in any patient with PIP symptoms because interictal psychosis and PIP (bimodal psychosis) can occur concomitantly [37]. Moreover, interictal psychosis may exacerbate postictal psychiatric symptoms [26].

Tellenbach [38] coined the term *alternative psychosis* to describe acute changes in mental state, notably, psychotic, affective and dissociative symptoms [1], upon attainment of complete seizure control that are not dependent on EEG findings [39]. Alternative psychoses can occur following changes in antiseizure medications as well as after epilepsy surgery or neurostimulation. The persistence of psychotic symptoms following breakthrough seizures in our patient excluded the diagnosis of alternative psychosis.

Diagnosis based on phenomenology alone can be particularly challenging as it presupposes that epilepsy-related psychoses represent distinct clinical categories identical to those defined in the DSM. Cognitive and psychiatric symptoms in individuals with epilepsy may result from subtle cortical and subcortical network dysfunction [40,41]. These symptoms may be biomarkers or neurodevelopmental prognostic indicators [42] rather than comorbidities.

One of the authors (T.F.) suggests the use of a multidimensional *trans*-diagnostic framework (research domain criteria), rather than a categorical approach (DSM criteria), as a way to conceptualize epilepsy-related psychoses by aligning reported behavior and symptom clusters with their neurobiological roots [43–45].

5. Contribution of iatrogenic effects

Iatrogenic psychopathologies can arise following the administration or discontinuation of any anti-seizure therapy. Psychopathology may be ascribed to the negative psychotropic effects of the selected medication, potential drug-drug interactions [46], and/or seizure suppression (alternative psychosis) and EEG normalization ("forced normalization").

Several factors can increase the risk of iatrogenic psychiatric symptoms, including previous iatrogenic psychopathology, intellectual disability, and both a personal and family history of psychiatric disorders [30,47–50].

One in every seven cases of psychosis in individuals with epilepsy is estimated to be iatrogenic in nature [51]. Levetiracetam is the most likely ASM to be associated with psychosis, followed by topiramate, zonisamide, ethosuximide, and vigabatrin [46].

5.1. Treatment with brivaracetam

In a pooled analysis of six placebo-controlled, double-blind, randomized trials of brivaracetam (1,957 patients), 0.2 % of those receiving brivaracetam developed psychotic symptoms compared to only 0.1 % of

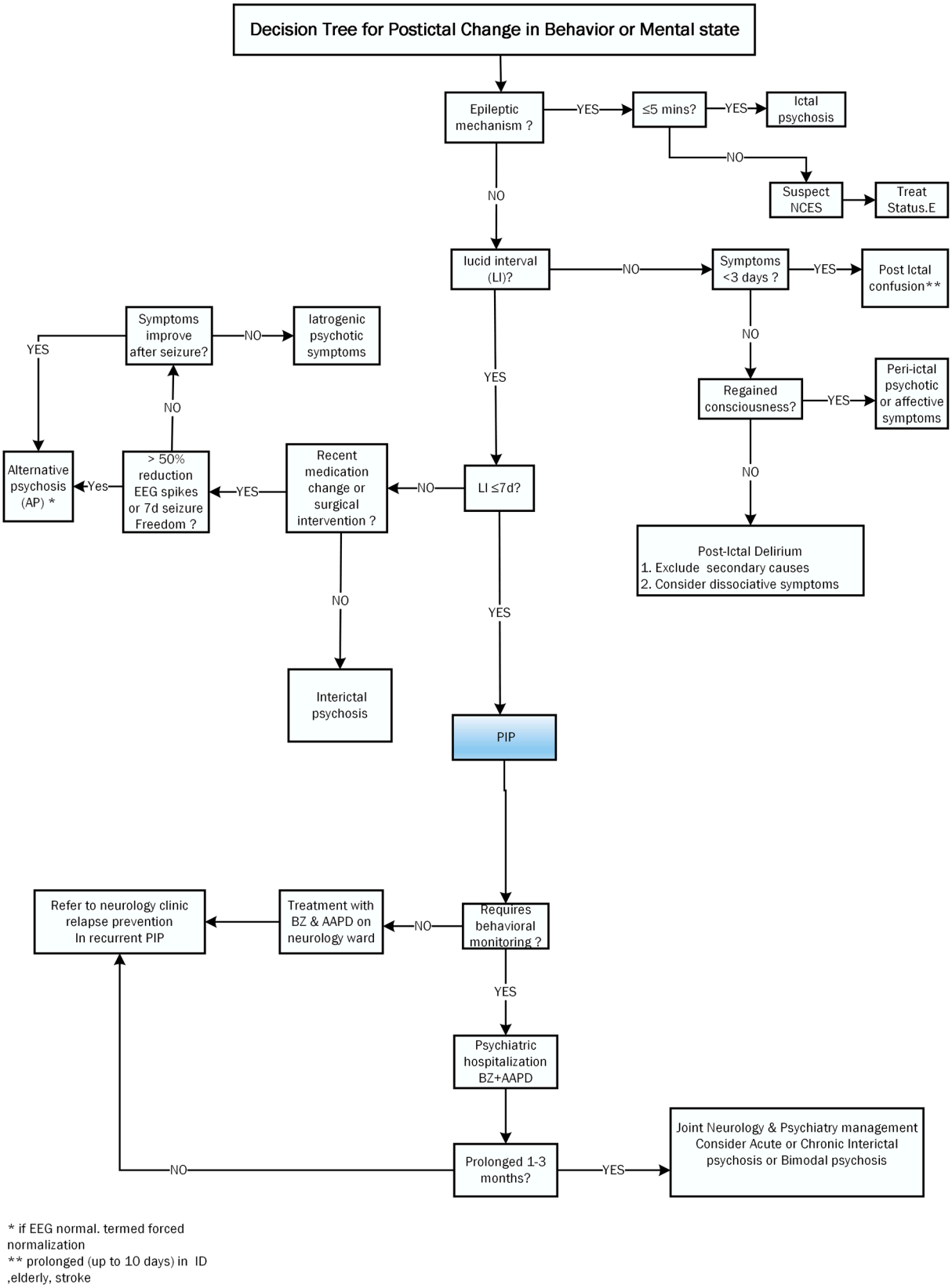

Fig. 1. Algorithm to assist with clinical decision-making in the setting of postictal change in behavior or mental state. **KEY: AAPD** atypical antipsychotic drug; **BZ** benzodiazepines; **EEG** electroencephalography; **FN** forced normalization; **ID** intellectual disability; **LI** lucid interval; **N** normal; **NCSE** non-convulsive status epilepticus; **PIP** postictal psychosis

those receiving placebo [52]. Our patient's psychotic symptoms worsened following the discontinuation of brivaracetam, making a causal, iatrogenic relationship unlikely [51].

Behavioral adverse events and depressed mood occur more frequently in patients receiving brivaracetam than was initially predicted from the aforementioned pooled analysis [52–54]. Our patient's history of medication-associated behavioral symptoms and her family history of bipolar disorder point to an increased risk of developing iatrogenic psychopathology. However, as her suicide attempt (a hallmark of PIP) presented in the context of an acute psychotic episode following multiple seizures, it is unlikely that brivaracetam was the direct cause of her suicidal behavior.

5.2. Treatment with felbamate

A case series described irritability following adjunctive felbamate treatment and one case of psychosis following felbamate monotherapy [55]. At presentation, our patient was taking felbamate (1200 mg/day) and denied any recent change in dose or prior felbamate-related behavioral symptoms.

6. Screening instruments

Patients at risk of PIP should be routinely monitored for the appearance of heralding symptoms following cluster seizures [1]. However, psychotic symptoms in individuals with epilepsy are frequently overlooked [56]. There is no reliable screening instrument that can be used to identify a psychotic episode in clinical practice [57].

Patients at risk of PIP should also be routinely screened for anxiety and depression, as exacerbations of interictal psychotic or affective disorders are associated with more severe *peri*-ictal psychotic and postictal depressive symptoms [50].

7. Pharmacological treatment of PIP

Evidence-based guidelines for the treatment of epilepsy-associated psychosis are lacking [58,59]. As such, basic principles for the treatment of primary psychiatric disorders have been adapted for use in epilepsy [59].

Atypical antipsychotic drugs (AAPDs) are currently the first-line treatment for psychosis primarily because of their positive effects on mood stability, cognitive function, and behavioral regulation, as well as their reduced toxicity and lower risk of chronic and irreversible movement disorders compared to first-generation antipsychotic drugs (APDs) [60,61]. Compared to the general population and patients with primary disorders, AAPD dose range is lower and up-titration speed is slower in people with epilepsy including in those with PIP [59,62]. In the absence of evidence-based guidelines, an AAPD is chosen based on its side effect profile and pharmacokinetic properties, the patient's symptom profile, multimorbidities, prescriber and patient preference, as well as drug cost and availability.

Benzodiazepines are recommended for patients who develop heralding symptoms of PIP (e.g., lorazepam 1–2 mg up to twice per day). If insomnia persists or a paradoxical reaction develops (e.g., children or individuals with intellectual disability), low-dose quetiapine is recommended. Antipsychotics should be considered at the first appearance of uncharacteristic or threatening behavior, odd or disorganized thinking, suspiciousness, or affective lability.

Quetiapine is a second-generation APD that serves as a dopamine D2 and serotonin 2A (5HT2A) receptor antagonist, thereby acting on the mesolimbic pathway and frontal cortex, respectively [63]. It can be administered orally at a starting dose of 12.5 mg/day and can be repeated if the first dose is not overly sedating or sufficiently anxiolytic. This dose should be slowly up-titrated with increments of 12.5–25 mg/day based on its efficacy and level of sedation. If a patient remains aggressive or disorganized on 50–75 mg/day, inpatient treatment should be seriously considered and the dose rarely exceeds 100 mg/day. Pharmacokinetic drug-drug interactions, poor adherence, or misdiagnosis should be considered in poor responders.

Aripiprazole is a third-generation APD that acts as a 5HT2A antagonist and partial D2 agonist to regulate dopaminergic activity along the mesolimbic and mesocortical pathways [63]. Unlike other second-generation antipsychotics, aripiprazole is a partial 5HT1A agonist and may therefore increase dopamine activity in the prefrontal cortex, thus explaining its positive effect on cognition in people with schizophrenia [64]. In 2009, aripiprazole was approved for the off-label treatment for challenging behavior in individuals with neurodevelopmental disorders [65,66]. However, its use in individuals with epilepsy has not been rigorously evaluated [67,68]. We recommend an oral starting dose of 2.5 mg/day. In the absence of agitation and akathisia, the dose can be increased to 5 mg/day within several days [67,68], although doses exceeding 15 mg/day are uncommon. Notably, delusional thinking and mood usually take longer to respond to AAPDs than disorganized behavior and thought disorders [69].

Although PIP symptoms typically resolve within a week of AAPD treatment [58], extended symptoms are more common among older patients and those with developmental delay and/or a family history of psychosis [31]. If symptoms respond poorly to treatment, drug-drug interactions, iatrogenic response, or seizure activity should be ruled out before switching treatment. Once remission has been achieved, we recommend gradual down-titration over 5–7 days until termination. However, if the psychotic or affective symptoms persist for more than one month, treatment should be extended for an additional three months. Kerr et al. [58] recommend gradual dose reduction over two months once the patient has been asymptomatic for at least two months.

7.1. Recurrent PIP episodes

Recurrent postictal psychotic episodes (often occurring 2–3 times/year), chronic interictal, and bimodal (i.e., PIP and interictal psychosis) psychoses have been estimated to occur in 50 %, 10–15 %, and 8 % of patients who have experienced a first episode of PIP, respectively [37].

For recurrent PIP, maintenance treatment with low-dose AAPDs and benzodiazepines should be considered, with up-titration of AAPD doses after seizure clusters [59]. It is unclear whether low-dose AAPDs or benzodiazepines can successfully prevent or abort future episodes of PIP. Patients with recurrent PIP who have developed chronic psychotic symptoms might be switched to a therapeutic agent with a lower cardiometabolic risk, for example, aripiprazole [70].

7.2. Adverse events associated with AAPDs

AAPDs are frequently associated with severe cardiometabolic complications, poor bone health, sedation, sexual dysfunction, and to a lesser extent extrapyramidal symptoms. Most AAPDs have comparable efficacy, thus treatment decisions are largely guided by patient characteristics rather than drug potency (Tables 1–2) [71].

7.3. Safety for use in epilepsy

Patients with epilepsy-related psychosis often remain undertreated due to the common misconception that *all* psychotropic agents are highly proconvulsant. However, the recognition of a bidirectional relationship between various psychiatric disorders and epilepsy suggests instead an inherent susceptibility to seizures due to a shared underlying pathology [1,72].

Studies of the proconvulsant risk of individual AAPDs are frequently contradictory and of low quality [67]. While AAPD-induced changes in EEG patterns are well-documented [73], these changes are rarely clinically significant [67,74,75]. Clozapine carries the highest proconvulsant risk, while olanzapine and quetiapine are associated with a mild-to-moderate increased risk of seizures [75]. Aripiprazole and

Table 1
Adverse effects of atypical antipsychotic drugs.

OSTEOPOROSIS [97]	**EXTRAPYRAMIDAL** [98]	**CARDIAC-QT PROLONGATION** [99,100]	**METABOLIC** [101,102]
Mechanism: D2 antagonism increases prolactin, which increases osteoclast activity	*Mechanism of Parkinsonism:* D2 antagonism on the nigrostriatal pathway *Mechanism of akathisia:* Partial agonist activity at the 5ht1a receptor increases noradrenergic activity	*Mechanism:* Delayed repolarization at the potassium rectifier channel resulting in QTc prolongation	*Mechanism of weight gain:* • Histamine 1 antagonist increases appetite • Muscarinic 3 antagonist activity causes insulin resistance. • Increase in leptin 5HT2C antagonist increases appetite
Patient-related risk factors: • Intellectual disability • Adolescents and post-menopausal women • Low BMI • Alcohol consumption • Family history of OP • Reduced outdoor physical activity	*Patient-related risk factors:* Parkinsonism – cognitive impairment Akathisia – bipolar disorder, intellectual disability	*Patient-related risk factors:* • Long QT syndrome • Low serum potassium, calcium, and magnesium • Uncontrolled epilepsy is associated with ventricular arrhythmias, including post-ictal arrhythmia	*Patient-related risk factors:* • Polycystic ovaries • Intellectual disability • Family history of obesity or diabetes
Prolactin raising AAPDs: Risperidone +++ Olanzapine ++/+ **Quetiapine** +/- **Aripiprazole** – minimal effect	*AAPDs causing parkinsonism:* Risperidone ++ **Olanzapine** + **Quetiapine** + **Aripiprazole** +/- *AAPDs causing akathisia:* Aripiprazole +++ Risperidone ++ **Olanzapine** +/- **Quetiapine** +/-	*AAPDs causing QT prolongation:* Ziprasidone +++ Quetiapine ++ (at very high doses) Risperidone ++/+ **Olanzapine** + **Aripiprazole – no effect**	*AAPDs causing weight gain (dose-related)*Olanzapine +++ Quetiapine ++ Risperidone +/++ Aripiprazole + (more in children)
Signs and symptoms: * • Reduced libido and sexual function • Amenorrhea, fertility problems • Reduced bone density, bone pain	*Signs and symptoms:* Parkinsonism: resting tremor, bradykinesia, cogwheel rigidity Akathisia: subjective feeling of inner restlessness	Signs and symptoms: ** • Dizziness • Syncope • Ventricular arrhythmias	*Signs of metabolic syndrome:* • Impaired fasting glucose/ glucose tolerance • Hypertension • Dyslipidemia • Increase in waist circumference • High BMI

KEY: **O/P** Osteoporosis **AAPD** Atypical antipsychotic +/- minimal risk + mild risk ++ moderate risk +++ high-risk **QTc** QT prolongation **h/o** history of **BMI** body mass index.
* Epilepsy is associated with a 2–6-fold increase in fractures.
** Epilepsy, intellectual disability, and schizophrenia are associated with an increased risk of sudden cardiac death.

risperidone have a relatively lower risk of inducing seizures [75]. Except for clozapine, AAPDs are not contraindicated in patients with epilepsy. However, lower doses and slower dose titrations are advised, and the use of additional agents that may reduce the seizure threshold should be avoided [75].

If a patient with epilepsy experiences a seizure after commencing AAPDs, potential confounders should be excluded, including drug-drug interactions, lack of adherence to antiseizure medications, and/or recognized seizure triggers.

7.4. Pharmacokinetic drug-drug interactions

Most AAPD-ASM interactions depend on the induction or inhibition of cytochrome P450 (CYP) metabolizing enzymes. CYP-inducing ASMs, including carbamazepine, phenytoin, and phenobarbital can reduce the serum concentrations of several AAPDs [76]. While carbamazepine may reduce the serum concentrations of most AAPDs, its effect on quetiapine is clinically significant because quetiapine is metabolized almost exclusively by the cytochrome isoenzyme 3A4 [76]. Accordingly, carbamazepine discontinuation results in increased AAPD serum concentrations and an increased risk of associated adverse events (e.g., risperidone-induced Parkinsonism, quetiapine-induced sedation). Conversely, quetiapine administration increased the ratio of carbamazepine epoxide to carbamazepine, which may result in toxicity [76]. The CYP2D6 inhibitors fluoxetine, paroxetine, escitalopram, and to a lesser extent, clobazam can increase the serum concentrations of aripiprazole. Fluoxetine is also an inhibitor of CYP3A4 and can increase the serum concentrations of aripiprazole and quetiapine [77,78].

In our case, although felbamate may induce or inhibit CYP enzymes, no relevant interactions with AAPDs have been documented [76]. Lacosamide neither induces nor inhibits CYP enzymes or any known drug transporter systems and has no clinically relevant interactions with commonly prescribed medications, including AAPDs [76].

7.5. Pharmacodynamic drug-drug interactions

Pharmacodynamic interactions between AAPDs and ASMs can be either favorable or harmful. For example, combining valproate, lamotrigine, carbamazepine, or clobazam with most AAPDs may be beneficial in the treatment of mixed affective, depressive, aggressive, and anxiety symptoms, respectively; however, doing so can risk additive oversedation or akathisia. Combining levetiracetam and aripiprazole may increase the risk of akathisia, which is an independent risk factor for suicidality [79]. Co-prescription of valproic acid and olanzapine can increase the risk of adverse metabolic effects and neutropenia [80]. Sedation secondary to olanzapine administration may worsen topiramate-associated cognitive slowing [77].

8. The role of epilepsy therapies in treating PIP

Seizure control, including the prevention of seizure clusters, is a treatment priority in patients with PIP. Although the mood-stabilizing

Table 2
Cardiometabolic monitoring and psychotropic medication.

POSITIVE CARDIOMETABOLIC HEALTH FRAMEWORK
If psychotropic medication (excluding stimulants) is commenced, please use the following schedule:
Note: More frequent monitoring should occur if clinically indicated. Some medications, such as clozapine, have additional monitoring requirements. Consider EKG/cardiology review if there are concerns regarding QT prolongation or if cardiovascular risk factors are present.

	Baseline	Weekly	3/12	6/12	9/12	Annually
Family history Diabetes, obesity, cardiovascular disease in first-degree relatives, kidney disease	X					X
Blood pressure, Heart rate and BMI	X		X			X
Personal and medication history Cause of intellectual disability, polycystic ovary syndrome, past psychotropic medication use (dose, efficacy, and adverse effects), current medications	X					X
Lifestyle review Smoking, alcohol, physical activity, diet	X		X	X	X	X
Weight/waist circumference	X	X	X	X	X	X
Fasting lipids and glucose	X		X	X		X
HbA1c * In people with well-controlled diabetes, HbA1c testing may be performed every 3–6 months	X					X

Cardiometabolic monitoring health framework extracted with permission from: Julian Trollor, Carmela Salomon, Jackie Curtis, Andrew Watkins, Simon Rosenbaum, Katherine Samaras & Philip B. Ward, 2016, Positive cardiometabolic health for adults with an intellectual disability: an early intervention framework. UNSW Australia Adapted with permission from Curtis J, Newall H, Samaras K. ©HETI 2011.

effects of certain ASMs (e.g., valproate and lamotrigine) are well-recognized, the therapeutic effects of ASMs on psychotic symptoms remain poorly understood. In a study of 40 patients with epilepsy and concurrent psychiatric disorders [81], over half reported that their *peri*-ictal psychotic symptoms had diminished following treatment with lacosamide, an improvement attributed primarily but not exclusively to an improvement in seizure control.

Future studies of the potential role of these drugs in mitigating the severity of both peri- and postictal psychiatric symptoms are warranted. The potential role of benzodiazepines in preventing the development of PIP should also be investigated.

Vagus nerve stimulation may improve postictal psychotic symptoms in patients with drug-resistant epilepsy independently of any anti-seizure effect [82]. Surgical resection may also mitigate *peri*-ictal psychotic symptoms and psychotic aura [83,84]. However, neither approach is suitable for the acute management of PIP. The role of other treatments, including the ketogenic diet [85], deep brain stimulation, and responsive neurostimulation, in patients with recurrent PIP or bimodal psychosis remains unclear [1].

9. Psychotherapy

A strong therapeutic alliance between the physician and the patient is in itself psychotherapeutic and strongly correlates with patient adherence [86], fewer psychotic and disorganized symptoms, improved psychosocial and family functioning, and a better quality of life [87]. Empathy and open communication are essential to encourage patient self-disclosure which is essential for the accurate diagnosis of psychosis and suicidality. Early psychosis prevention and intervention is an evidence-based approach for first-episode psychosis [87] which could be adapted for use in patients with recurrent PIP.

This model emphasizes psychoeducation (an evidence-based therapeutic intervention that provides information and supports a patient's ability to cope and self-manage illness) as well as recognition of heralding symptoms, relapse prevention, resilience, acceptance of the diagnosis, self-management, and cardiometabolic health [88].

10. When to refer to a psychiatrist?

Psychiatry referrals depend on service availability, the neurologist's perceived efficacy and attitude toward psychiatry, and patient preferences that frequently favor prescribing by neurologists over referral to psychiatry [89]. However, a referral to psychiatry is highly advised in patients presenting.

With:

1. Suicidality, aggression or acutely psychotic symptoms;
2. Persistent postictal symptoms;
3. Recurrent PIP or chronic psychosis;
4. Concurrent psychiatric or neurodevelopmental disorders;

Suspected malingering following a violent offense should be referred to a forensic psychiatrist.

11. Concluding remarks

Most neurologists report limited clinical exposure to the neuropsychiatric manifestations of epilepsy [90]. We discussed the diagnosis and management of PIP [91] and provided practical clinical tips. However clinical decision-making is also influenced by dualistic thinking [92], stigma [93], cognitive biases [94], fear of psychotic patients [95], and negative attitudes toward psychiatry [96]. These factors can lead to diagnostic overshadowing [19,21] and the misdiagnosis of both FLE and PIP.

The following are critical take-home messages for the clinical neurologist:

i) Maintain a high index of suspicion in individuals with long-standing epilepsy who have been admitted to video-EEG monitoring units or who have presented to ED following seizure clusters.
ii) Assess cognition, mood, thoughts, and behavior according to their temporal relationship to seizure activity and postictal stage. This relationship is more helpful than the type of perceptual disturbance, delusional belief, or mood disturbance (Fig. 1).
iii) Remember that all AAPDs except for clozapine, are safe for use in individuals with epilepsy. Treatment should be initiated at a lower dose and increased at a slower rate in individuals with epilepsy.
iv) Consider a patient's vulnerability to iatrogenic psychopathology when choosing ASMs. Inquire about past iatrogenic behavioral responses as well as the patient's past and family history of psychiatric disorders.
v) Monitor all individuals treated with AAPDs (Table 2) for the development of cardiometabolic complications and other multimorbidities (Table 1).

vi) Ensure a positive doctor-patient encounter to improve patient disclosure, adherence, and health outcomes.

Ethical statement

The case report was partly based on a real patient; no identifying features have been published that could expose the patient's identity and many of the details have been changed for educational purposes.

Credit authorship contribution statement

Tamara Fischl: Writing – original draft, Conceptualization. **Piero Perucca:** Writing – review & editing, Supervision.

Declaration of competing interest

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