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Review Article

Psychiatric Aspects of Epilepsy

Surabhi Sharma[1], Prerak Kumar[2], Saloni Seth[1], Bhavuk Garg[3], Nitin Raut[4], Prerna Kukreti[5]

[1]Junior Resident, [2]Senior Resident, [3]Assistant Professor, [4]Specialist, [5]Associate Professor, Department of Psychiatry and Drug De-Addiction, Lady Hardinge Medical College and SSK Hospital, New Delhi, India.
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I N F O

Corresponding Author:
Surabhi Sharma, Department of Psychiatry and Drug De-Addiction, Lady Hardinge Medical College and SSK Hospital, New Delhi, India.
E-mail Id:
sharma.surabhi016@gmail.com
Orcid Id:
https://orcid.org/0000-0003-1603-5817
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A B S T R A C T

A seizure is defined as transient change in neurological functioning which is characterised by hypersynchronous discharges of neurons in the brain regions whereas epilepsy is defined as a syndrome consisting of various recurrent seizures and it is associated with the psychological and neuropathological effects. Early recognition and management of psychiatric disorders in patients with epilepsy is extremely important, because it improves the quality of life and aids in better seizure control. Newer antiepileptics with less interaction with psychotropics and less behavioural manifestations should be used for management of epilepsy; and psychotropics having low potential for lowering seizure threshold are generally preferred. A holistic approach to assess psychiatric comorbidity and judicious use of medicine can help in comprehensive patient care planning and reduced health burden.

Keywords: Epilepsy, Psychiatric Comorbidities, Seizure Threshold, Newer Anticonvulsants

Introduction

Epilepsy and Various Psychiatric Disorders

Seizure is a transient symptomology including excessive or synchronous neuronal discharge activity in the brain foci whereas Epilepsy is a disorder having clusters of recurrent abnormal seizures and have deleterious effects on psychological, social and neurobehavioral consequences.[1] Psychiatric comorbidity in epilepsy is common. Epilepsy predisposes individuals to develop psychosis, mood disorders, depression and anxiety spectrum disorders in background of genetic susceptibility. Most psychiatric disturbances are mainly found in drug resistant epilepsy and temporal lobe epilepsy. Various risk factors which give rise to psychiatric comorbidities in epilepsy are early age of onset of epilepsy, temporal lobe dysfunction, brain damage, chronicity, necessity for continuing medication, frightening nature of auras and restriction of activity. It is the interplay of genetics, psychosocial and iatrogenic factors that predisposes persons with epilepsy to develop psychiatric disorders.[2] In terms of epidemiology, prevalence of overall psychiatric problems associated with epilepsy according to western studies is 20% to 60% and some Indian studies say it is 20% to 30% (Table 1).[3] Various psychiatric disorders associated with the epilepsy are depression 30%, mania 1% to 1.5%, anxiety 25% to 50%, panic disorder 5%, generalised anxiety disorder 3%, obsessive compulsive disorder 2%, personality disorders 18%, dissociative disorders 30% to 33%, Suicide 3% to 7% and dementia 1.5% to 64%.[4,5] Appropriate psychotropics drugs with less seizure threshold lowering potential should be used. Similarly, anticonvulsants having less behaviour side effects are to be preferred judiciously.6 Early recognition and relation of psychiatric comorbidities with specific ictal phase can help in improving clinical outcomes and plan judicious management.

Table 1.Epilepsy and various psychiatric disorders

Psychiatric disorders	Prevalence in Epilepsy	Salient Features	Management
Depression[7]	30%	Typical + atypical symptoms [brief euphoric mood, irritability, anxiety, paranoid feelings, and somatic symptoms (anergia, atypical pain, and insomnia)]	First line: Selective serotonin reuptake inhibitors- Fluoxetine, Sertraline and Escitalopram Selective norepinephrine reuptake inhibitors- Venlafaxine, Duloxetine Second line: Tricyclic antidepressants Amitriptyline, Imipramine, Clomipramine Cognitive Behaviour Therapy Electroconvulsive therapy.
Bipolar disorder[8]	12.2%	Ictal- Euphoria Over religiosity Grandiosity Gelastic seizure (ictal laughter) Post- ictal- Irritability Overactivity Disinhibited behaviour	Mood stabilizers: Lithium Valproate Carbamazepine Atypical Antipsychotic: Aripiprazole Olanzapine Quetiapine Risperidone
Anxiety[9] Panic disorder- Generalised anxiety disorder Social phobia Specific phobia	5.1% 3.1% 7.2% 6.2%	Worrisome, motor restlessness, breathlessness, fearful to object, fear of closed spaces	Pregabalin: Social phobia, Generalized anxiety disorder, refractory focal epilepsy Lamotrigine: in post- traumatic stress disorder Gabapentin: in social anxiety Psychotherapy- Cognitive behavior therapy Psychodynamic therapy
Personality Disorders[10]	18%	GASTAUT- GESCHWIND SYNDROME: Humourless, Over inclusive, Over religious, Viscosity (repetitive and circumstantial about particular topic), Right temporal region- obsessionality and sadness Left temporal region- paranoia, anger and religiosity	
Suicide[11]	Completed suicide: 3-7%	Sadness of mood, guilt ideations 25 times higher risk in Temporal lobe epilepsy; Contributors: paranoid hallucination, agitated compunction to self- harm and ictal command hallucinations	Antidepressants and electro convulsive therapy
Dementia[12]	1.5- 64%	Cognitive domains most affected are psychomotor speed, higher executive functioning. Memory problems, decision skills deficits	Psychosocial interventions, cognitive enhancers (donepezil)

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Obsessive compulsive disorder[13]	10- 22% in Temporal lobe epilepsy	more symmetry/ exactness obsessions and compulsions	Antidepressants and Psychotherapy
Attention deficit hyperactivity disorder[14]	31.5%	Impulsivity, hyperactivity, inattentiveness. 6.1% of children with attention deficit hyperactivity disorder exhibit an abnormal electroencephalograph (EEG) (Richer et al 2004)	Attention Deficit Hyperactivity Disorder- Psychostimulants
Sleep Disorders[15-17]	hypersomnia: 16.9- 28% Insomnia: 24.6- 34% Restless leg syndrome: 10.2- 28.2%	Lower efficiency of sleep. More N2 nonrapid eye movement sleep. Less rapid eye movement sleep with prolonged latency to Rapid Eye Movement sleep	Gabapentin improves sleep quality Carbamazepine increases the Non Rapid Eye Movement sleep, simultaneously reduces stage 1 and 2 of sleep Phenytoin reduces sleep latency, slightly increases the Non- Rapid Eye Movement sleep. Long time usage reduced sleep latency and had no influence on Rapid Eye Movement sleep.
Migraine[18]	26%	Unilateral pulsatile Headache with auras, photophobia, phonophobia	Anti-migraine, anti-epileptic agents– like sodium valproate and topiramate – may prevent attacks of both migraine and epilepsy. Lamotrigine used in migraine with aura; decrease frequency of aura
Psychosis[19]	12%	Derealization and depersonalization experiences, illusions, hallucination, delusions	Use of antipsychotic having low potential to decrease seizure threshold. Eg Pimozide, Haloperidol. Use of anticonvulsants having low CYP 450 interactions (Gabapentin, Vigabatrin, pregabalin).

Table 2.Relationship of Psychotic symptoms to a particular ictal phase

Ictal phase of occurrence of psychotic symptoms	Proportion of psychotic episode seen in particular ictal phase
Pre-ictal	Unknown (very rare)
Ictal	10%
Post-ictal	60%
Forced normalisation or alternate psychosis	10%
Inter-ictal psychosis	20%

Psychosis in Epilepsy

Psychosis is more commonly associated with partial epilepsies. Mesial temporal lesions, neuronal loss, decreased hippocampus volume and periventricular gliosis are some of the etiological factors. Presentation of psychotic symptoms is also known to vary as per the ictal phase in their prevalence and phenomenology as detailed in Table 2.

Pre-ictal psychosis is characterised by clinical picture of derealization as well as depersonalization, apraxia, Jamais vu, déjà vu, panic attacks, anxious features, feeling of euphoria and perceptual disorders like illusions or hallucinations. It terminates with the episode of seizure without any detectable Electroencephalogram (EEG) findings.

Ictal-psychosis is characterised by alterations in consciousness, automatism, wide range of perceptual, behavioral, cognitive and affective symptoms often in

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connection with typical temporal lobe automatisms and associated EEG changes.

Post-ictal psychosis: Post-ictal psychosis can be diagnosed as per following criteria given by Logsdail and Toone:20

1. Episode of psychosis (often with confusion and delirium), developing within 1 week of a seizure or cluster of seizures
2. Psychosis lasting at least 15 hours and less than 2 months
3. Mental state characterized by delirium or delusions (e.g., paranoid, nonparanoid delusional, misidentifications) or hallucinations (e.g., auditory, visual, somatosensory, olfactory) in clear consciousness;
4. No evidence of:

- A history of treatment with antipsychotic medications or psychosis within the past 3 months,
- Antiepileptic drug toxicity,
- An EEG demonstrating nonconvulsive status,
- A recent history of head trauma or alcohol/drug intoxication or withdrawal

Forced Normalisation

Forced normalization or alternative psychosis refers to phenomenon of emergence of psychoses following the establishment of seizure control in an uncontrolled epilepsy patient. After a seizure episode, phenomenon of clinical improvement in psychotic symptoms was labelled as ''alternative psychosis' given by Tellenbach and normalization of EEG as compared with previous and subsequent electro encephalography findings was labelled as forced or paradoxical normalisation by Landolt.[21] The explanation for such features is still not clear, however, one reason is the disinhibition of the concerned areas of limbic system after seizure is controlled. The cortex has an inhibitory function on the limbic system, but this balance becomes destabilized upon ictal control.[22] Since convulsions generally suppress psychoses, psychotic symptoms can be attenuated by medically induced seizures.[23] Patients and clinicians should function in a mutual way to control seizure and its impact, clinical parameters to be thoroughly studied, EEG recordings changes, and physician to communicate the individuals regarding seizure control method for optimal response and results.[24]

Management Strategies for Epilepsy with Psychosis

- Establish a clear diagnosis by ascertaining relationship with ictal phase if possible, considering possibility of ictal/ peri-ictal/ postictal psychotic phenomena; evaluate the severity of their symptoms and level of their disturbances.
- Assess the patient's capacity to give a consent to treatment and/ or to participate in the decision-making process; seek views from family members and/ or carer when necessary.
- Make a treatment strategy, for example, psychosocial interventions or watchful wait in outpatient clinics, pharmacologic treatment (with or without other treatment options) as an outpatient or inpatient.
- Optimize AED regimens where possible by reducing polypharmacy and adjusting the dose to aim for therapeutic serum levels. Choice of AED to be considered carefully considering behavioral side effects of AED.
- Antipsychotic Drug (APD) Timing: early intervention is preferable .
- Choice of Psychotropic: Consider the psychotropic with fewer or lesser adverse effects, taking into account availability, and affordability. Extent of seizure lowering threshold of psychotropic drugs25 to be considered while choosing any drug (Table 3).
- Provide basic psychosocial approaches, for example, psychoeducation, self-help, and reframing, and support for family and carers.[26]

Table 3.Seizure threshold lowering potential of antipsychotic drugs

High	Moderate	Low
Chlorpromazine	Most Piperazines	Fluphenazine
Clozapine	Thiothixene	Haloperidol
Thioridazine	Ziprasidone	Loxapine
Perphenazine		Molindone
Olanzapine		Pimozide
Quetiapine		Risperidone
		Paliperidone
		Aripiprazole

Antiepileptic Drugs and Behavioural Effects

Some antiepileptic drugs can cause behaviour manifestations or encephalopathic changes which may occur at toxic levels of antiepileptics (Table 4). In treating psychiatrically disturbed epileptic patient consideration to be given on these behavioural effects. Anxiety, depression and insomnia are the most common associated behavioural manifestations but psychosis may also occur.[27]

Newer Antiepileptic Drugs

After the introduction of sodium valproate in 1967, there are approximately ten new antiepileptic drugs launched during the last two decades known as "decades of Brains." These newer drugs expanded the armamentarium of therapeutics for intractable epilepsies and used as adjunct to conventional antiepileptics. Some of the newly discovered antiepileptics are depicted in Table 5.

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Table 4. Behavioural effects of Antiepileptic drugs

Antiepileptics	Effects
Barbiturates	Depression, irritability, aggression, impaired cognition and attention, hyperactivity
Carbamazepine	Irritability, impaired attention
Felbamate	Depression, anxiety, irritability
Gabapentin	Behavioral problems in children
Phenytoin	Encephalopathy, depression, impaired attention
Lamotrigine	Insomnia, agitation, emotional lability
Levetiracetam	Irritability, emotional lability
Topiramate	Depression, psychomotor slowing, psychosis, impaired cognition (word finding and memory)
Valproate	Encephalopathy, depression

Table 5. Behavioural effects of New Antiepileptic drugs

Drug	Mechanism	indication	side effect
Stiripentol[28]	Increase GABA	Dravet Syndrome	Ataxia, tremor, psychotic aggression
Retigabine[29]	Open Voltage gated KCNQ 2/3 and KCNQ3/5 K channel	Benign familial neonatal convulsions	Confusion, tremor, Psychotic disorder (<1%)
Brivaracetam	Affinity for SV2A	Adults with photosensitive epilepsy, refractory partial-onset epilepsy	Sedation, skin rash, dizziness
Ganaxolone[30]	Allosteric modulator of the GABA-A receptor	Refractory infantile spasms, catamenial epilepsy	Somnolence, fatigue, nausea
Eslicarbazepine	Block Na channel Increase K conduction	Partial seizures	Diplopia, vomiting, depression, hyponatremia
Perampanel[31]	Non-competitive antagonist of AMPA glutamate receptor	Refractory partial-onset seizures	Vertigo, psychotic aggression (>10%), headache

Conclusion

Psychiatric co-morbidities in patients with epilepsy are relatively frequent which may be due to shared pathophysiological mechanisms, mostly associated are depression, anxiety; less common being psychosis. Early recognition and management of psychiatric disorders in patients with epilepsy is extremely important, because it improves the quality of life and aids in better management. Newer antiepileptics with less interaction with psychotropics and less behavioural manifestations should be used for management of epilepsy; and psychotropics having low potential for lowering seizure threshold to be judiciously used. Several new genes and biomarkers have been identified in patients with epilepsy and give insight regarding neuropathological foci of epilepsy which updates our management.

Conflict of Interest: None

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