Seizures and Schizophrenia

by Thomas M. Hyde and Daniel R. Weinberger

Abstract

Patients with epilepsy develop psychosis or schizophrenia at a rate exceeding that expected if the two disorders were independent. Similarly, patients with schizophrenia are more prone to seizures than the general population. This excess vulnerability may be conferred by the neuropathological substrate of schizophrenia itself or by the secondary effects of the illness, including exposure to psychotropic medications that lower the seizure threshold. Neuropathological investigations into the anatomic substrate of seizures in patients with psychosis or schizophrenia are consistent with the notion that there are neurodevelopmental abnormalities involving the mesial temporal lobe. Finally, clinical recommendations for the evaluation and pharmacological management of patients with schizophrenia who have one or more seizures are described.


The interaction between schizophrenia and seizures has been a subject of considerable curiosity in neuropsychiatry for at least 40 years, stimulated by the reports of Gibbs (Gibbs et al. 1948; Gibbs 1951) of an increased frequency of interictal psychoses in patients with complex partial seizure disorders. Recent neuroimaging and neuropathology studies in schizophrenia have identified structural and neurochemical abnormalities in the mesial temporal lobe, including volume loss, cytoarchitectural disorganization, and neurochemical changes (as reviewed by Knable and Weinberger 1995). The mesial temporal lobe also is often the site of origin for epileptiform potentials, which underlie complex partial-seizure disorders. It would not be surprising, therefore, that damage to the mesial temporal lobe might produce both seizures and a chronic psychotic disorder, such as schizophrenia, as alternate manifestations of a single site of pathology. In fact, this perspective was articulated by Gibbs (1951) and Rodin et al. (1957) four decades ago.

For the practitioner, dealing with a single seizure or a seizure disorder in a schizophrenia patient can be a diagnostic and therapeutic challenge. In the sections to follow, the relationship between epilepsy and schizophrenia will be reexamined. The approach to both a single seizure and recurrent seizures in the schizophrenia patient will also be discussed. In addition, the role of neuroleptics and other psychoactive medications will be reviewed. Finally, the role of diagnostic testing in evaluating unusual episodes and seizures in the schizophrenia patient will be discussed. The aim of this review is to provide a useful perspective for addressing the overall issue of seizures in the schizophrenia patient.

Is There an Association Between Schizophrenia and Epilepsy?

A fundamental controversy in the schizophrenia-epilepsy literature is the frequency of the coexistence of these conditions. Many studies purporting to address this issue are limited by both their methodology and their imprecise terminology. First, many studies have failed to discriminate between a single seizure and a seizure disorder. In the course of treatment for a wide variety of medical, neurological, and psychiatric problems, many patients will suffer a single seizure. This is distinctly different from a seizure disorder, in which there is substantial long-term risk for recurrent seizures. In the literature, there is a tendency for the terms seizure disorder and epilepsy to be used interchangeably. Epilepsy refers to a condition characterized by recurrent seizures; seizure disorder does not necessarily imply this. Additionally, when considering

Reprint requests should be sent to Dr. T.M. Hyde, Clinical Brain Disorders Branch, NIMH Neuroscience Ctr., St. Elizabeths Hospital, 2700 Martin Luther King, Jr. Ave., SE, Washington, DC 20032.
patients with seizure disorders and psychoses, postictal confusional states, brief postictal paranoia, and so-called "twilight" states of patients in absence or complex partial status epilepticus must be differentiated from an interictal thought disorder (Flor-Henry 1972; Belafsky et al. 1978; Engel et al. 1978).

When epilepsy and psychosis coexist, the psychosis almost always follows the onset of epilepsy, with an interval ranging from 12 to 27 years (Slater and Beard 1963; Bruens 1971; Kristensen and Sindrup 1978; Perez et al. 1985). However, there are problems in linking schizophrenia to epilepsy in those individuals who develop seizures after the onset of psychotic symptoms. Chronic schizophrenia patients may be more prone to closed-head injury, substance abuse, and other adverse circumstances that might independently predispose the individual toward developing a seizure disorder. In other words, having schizophrenia in and of itself might impose secondary risks that lead to an increased incidence of seizures, but such seizures may not be conferred primarily by the intrinsic neuropathological substrate of psychotic behavior. Seizures arising from these forms of acquired brain injury may contaminate some studies of epilepsy and psychosis, obscuring the link between possible developmental neuropathology implicated in both seizures and psychosis.

Another problem with many of the studies of epilepsy and schizophrenialike psychoses is a lack of uniform psychiatric assessment, as most predate the use of standardized diagnostic criteria. A notable exception is the study by Perez and Trimble (1980), which carefully examined the psychotic symptomatology in 24 patients with epilepsy and psychosis using the Present State Examination (Wing et al. 1974). In their cohort, 50 percent of patients had a profile consistent with schizophrenia, while 92 percent had significant first-rank Schneiderian (Schneider 1959) symptomatology. Slater and Beard (1963) had noted that 46 of 69 cases of patients with epilepsy and psychosis had a psychotic disorder typical of chronic paranoid schizophrenia, while 12 of 69 had symptoms compatible with hebephrenic schizophrenia, although no precise clinical criteria were used in making these diagnoses. Just under half of their patients had an insidious course of psychiatric presentation, as well as a predisposition toward chronic illness. Those presenting acutely with psychosis had a better outcome. In this cohort, about half had chronic psychotic symptoms and only five patients from the original cohort made a complete psychiatric recovery. In the Slater and Beard (1963) study, as in many similar studies, the terms psychosis and schizophrenia are loosely defined by today's standards.

Despite the limitations of the earlier studies, their results were fairly consistent. Gibbs and Gibbs (1952) reported that among 678 patients with complex partial seizures, 7.2 percent had unclassified psychoses and 0.2 percent had schizophrenia, while among 1,806 patients with both complex partial and generalized motor seizures, 9.4 percent had unclassified psychoses and 0.8 percent had schizophrenia. In a short report, Hill (1953) mentioned that 25 percent of patients with complex partial seizures suffered some form of psychotic episode. Small and Small (1967) found the prevalence of psychosis among patients with epilepsy to be 4.4 percent. Currie et al. (1971) studied a series of 666 patients with well-defined complex partial seizure disorders and found that while 6 percent (40 of 666) had florid psychiatric disorders, only 1.8 percent (12 of 666) had schizophrenia. However, an additional 17 had "gross hysteria," a term not defined by the authors. Bruens (1971) claimed that 2.4 percent of patients with epilepsy suffer from some form of psychotic episode. Standage and Fenton (1975) found that 8 percent (3 of 37) of patients with epilepsy also had a history of psychosis. Lindsay et al. (1979) followed 87 children with "limbic" seizures for over a decade and found that 9 (10.3%) developed a schizophreniform psychosis. In contrast, in a cohort of 1,073 patients with epilepsy, Bartlett (1957) found only 12 patients (1.1%) with a psychosis of more than 1 year's duration, while Bruens (1971) noted only 1 percent of patients (9 of 900) who had both epilepsy and psychotic symptoms lasting at least several weeks. The random chance of schizophrenia appearing in a large cohort of patients with recurrent seizures should be similar to general population estimates, unless there is a biological link between these two entities. The majority of studies suggest that there are more patients with epilepsy who subsequently develop psychoses than would be expected by pure chance.

One of the best modern studies addressing the association of schizophrenia and epilepsy was conducted by Mendez et al. (1993). Intercital psychoses compatible with DSM-III-R (American Psychiatric Association 1987) criteria for schizophrenia occurred in 9.25 percent of 1,611 epilepsy outpatients, but in only 1.06 percent of 2,167 migraine outpatients of a university medical center. This study overcame the ascertainment bias common at many university medical centers by using a neurological disease cohort as a control group. In addition, this study benefits from the use of standardized psychiatric criteria. It substantiates previous studies that have reported an association between psychosis and epilepsy, most of which suffer from the methodological problems noted above.

Slater and Beard (1963) set forth one of the more complete arguments in favor of a greater association of epilepsy and schizophrenia than one would expect by
chance coincidence. According to their estimates, in the general population the prevalence of schizophrenia is 0.8 percent, while that of epilepsy is 0.5 percent. The chance lifetime association of epilepsy with schizophrenia might therefore be 40 per million. Limiting their study to those individuals who develop psychosis after epilepsy, the lifetime prevalence might be 30 per million. At the time of the study, they estimated that there were 148 individuals with epilepsy and schizophrenia living in their catchment area and that new cases should appear at a rate of 3 to 5 per year. They found 69 new cases of psychosis in patients with history of epilepsy over 11 years in a catchment area of about 10 million, surveying the patients treated at only two hospitals in this catchment area. While there may have been some ascertainment bias, this rate of accrual of new cases greatly exceeded their population estimates if there were purely a chance association between epilepsy and schizophrenia. In fact, they felt that, given the number of neurological and psychiatric facilities in their catchment area, they were probably not seeing all the new cases.

On the basis of these findings, Slater and Beard (1963) suggested that patients with epilepsy develop schizophrenialike psychosis at a much greater-than-expected frequency. However, a review of general population estimates suggests the 1-year and lifetime prevalence rates for schizophrenia are 1.0 and 1.4 percent, respectively (Karno and Norquist 1995), higher than Slater and Beard’s estimates. If Slater and Beard had underestimated the prevalence rates of these disorders, then their support of a linkage between epilepsy and psychosis might be suspect. In addition, there may be a greater element of ascertainment bias in Slater and Beard’s study population, that they did not acknowledge in their statistical analyses (Stevens 1966). Nevertheless, in addition to Slater and Beard (1963) there are numerous well-designed studies that link schizophrenia with seizure disorders (e.g., Currie et al. 1971; Lindsay et al. 1979; Mendez et al. 1993).

Is There a Preferential Relationship Between Complex Partial Seizures and Schizophrenia?

Complex partial seizure disorders, also known as psychomotor or temporal lobe epilepsy, have been more commonly associated with interictal schizophreniform psychoses than have generalized seizures (Dongier 1959; Beard 1963; Flor-Henry 1969; Bruens 1971; Shukla et al. 1979; Perez and Trimble 1980; Perez et al. 1985). Small et al. (1962) and Stevens (1966) contested this notion. In the former study, while there was an increased frequency of schizophrenia in the temporal lobe epilepsy group (6 of 25 vs. 3 of 25 in the nontemporal lobe epilepsy patients), there was an increased frequency of schizoid personality disorder in the nontemporal lobe epilepsy group (5 of 25 vs. 8 of 25); neither of these rates reached significance. In the latter study, Stevens found a similar rate of residential psychiatric hospitalization among patients with complex partial and generalized motor seizure disorders among 100 consecutive adult patients with seizure disorders at a university clinic. However, that study failed to note that 14 of 17 patients with complex partial seizures and psychiatric hospitalizations received the diagnosis of schizophrenia, versus only 5 of 10 with generalized seizures. Both studies are limited by small sample sizes and by possible ascertainment biases in the patient population base at a university clinic.

In a small sample of postmortem cases, Bruton et al. (1994) did not find an association between complex partial seizures and schizophrenia in comparison to inpatient or outpatient epilepsy cohorts. This study compared patients with epilepsy and a schizophreniform psychosis (n = 10) to patients with epilepsy and an “organic” psychosis (n = 9), an inpatient epilepsy group (n = 21), and an outpatient epilepsy group (n = 15). This study is limited by both the small cohort size and its reliance on a retrospective review of postmortem records, which may or may not have included formal psychiatric evaluations of the nonpsychotic epilepsy groups. It is curious that the schizophrenia group had a very high incidence of petit mal seizures, which has not been reported elsewhere in the literature. Finally, all of these cases were from an autopsy series. The inpatient epilepsy and outpatient epilepsy groups may have been skewed toward those cases with an atypical antemortem history or a suspicious cause of death, including suicide. None of these issues were addressed by the authors. Overall, while conflicting, the literature tends to suggest that patients with complex partial seizures are at higher risk for developing an interictal psychosis than either the general population or patients with other forms of seizure disorders.

Electroencephalographic (EEG) data support the role of the temporal lobe in the psychoses associated with epilepsy. In a study of patients with focal spikes, Gibbs (1951) found that anterior temporal lobe foci were most often associated with psychosis. Hill (1952) found an increased incidence of anterior temporal spike or focal slowing and posterior temporal slowing in schizophrenia patients and “not yet diagnosed” psychotic patients compared to normal controls, although formal statistical analyses were not performed in this study. While Beard (1963) found a relatively equal distribution of dominant, nondominant, and bilateral temporal lobe foci in their
patients with psychosis and epilepsy, Flor-Henry (1969, 1983) found that epilepsy patients with schizophreniform psychoses were more likely to have dominant hemisphere temporal lobe foci. Neither Kristensen and Sindrup (1978) nor Shakla and Katiyar (1980) found any laterality differences in their patients with complex partial seizures and psychosis. However, in a series of 666 patients with well-defined complex partial seizures, Currie et al. (1971) found EEG evidence of a left-sided focus in 52 percent, right-sided in 29 percent, and bilateral in 19 percent. This suggests that left temporal foci are more common in the general population, and any laterality associations with schizophrenia need to be interpreted cautiously. Taken together, these findings support the notion that temporal lobe pathology, the most common etiology of complex partial seizures, may also play an important role in the generation of psychosis.

Neuroimaging studies also support a role for temporal lobe pathology in psychosis and epilepsy. A positron emission tomography (PET) study of cerebral blood flow was conducted on a small cohort of patients with epilepsy and psychosis, one group on neuroleptics and the second off (n = 6 for both groups) (Gallhofer et al. 1985). They were compared with normal and nonpsychotic epileptic controls matched for age and IQ. Epilepsy patients with psychosis had abnormalities localized to the frontotemporal regions. A single-photon emission computerized tomography (SPECT) neuroimaging study revealed medial temporal lobe abnormalities in patients with schizophrenia and seizures (Marshall et al. 1993). In a sample of five patients with schizophrenia and seizures, matched to five epileptic controls by age, age at onset of epilepsy, type of epilepsy, and side of EEG focus, those with schizophrenia showed significant reductions in the left medial temporal cerebral blood flow. However, the control group had higher IQs and more frequent seizures, while the schizophrenia-with-seizures group had evidence of cerebral atrophy on computerized tomography (CT) scan.

Is There a Neuropathological Correlation With Schizophrenia and Epilepsy?

The type of pathology in the mesial temporal lobe appears to influence the propensity toward the development of psychosis in association with epilepsy. Taylor (1975) examined resected tissue from 255 patients who underwent temporal lobectomy to treat intractable complex partial seizures. Comparing 47 patients with "alien tissue"—including small tumors, hamartomas, and focal dysplasia—with 41 patients with mesial temporal sclerosis, 23 percent of the former were psychotic versus 5 percent of the latter group. In addition, females with alien tissue lesions appeared particularly at risk for the development of psychosis along with epilepsy. The association between alien tissue lesions and psychosis might be due to the fetal development of these lesions, as opposed to mesial temporal sclerosis, which is a perinatal lesion. The neurodevelopmental hypothesis of schizophrenia holds that a fixed brain lesion that occurs early in development is functionally quiescent initially (Weinberger 1996). This lesion subsequently interacts with normal cerebral maturation, resulting in the onset of schizophrenia in the second, third, and occasionally fourth decade of life. The type of temporal lobe lesion and the age at which it occurs appear to play a critical role in the propensity of such a lesion to predispose toward the development of psychosis.

The study by Roberts et al. (1990) offered a partial replication of Taylor (1975) and supports a role for medial temporal lobe pathology in schizophrenia in patients with concurrent seizure disorders. Studying specimens from 249 patients who underwent temporal lobectomy for intractable seizures, they identified 16 patients with preoperative schizophrenia. Twelve of these patients had identifiable pathology, and in all cases the lesions were restricted to the medial temporal lobe. However, only two of these cases had alien tissue lesions, while eight had mesial temporal sclerosis, counter to Taylor's (1975) findings. Additionally, Roberts et al. (1990) grouped the different types of pathology by the approximate stage in development at which the lesion occurred. Ten of their 12 cases with preoperative schizophrenia and identifiable pathology had lesions that occurred either embryonically or perinatally. Like Taylor's (1975) work, these findings support the role of neurodevelopmental abnormalities in schizophrenia.

Bruton et al. (1994) performed a retrospective neuropathological study of a small cohort of chronically institutionalized patients with schizophrenia and psychosis and compared them to epilepsy inpatients and outpatients autopsied at community hospitals or coroners' offices. They did not find an increased incidence of focal alien tissue lesions in their epilepsy-with-psychosis groups compared to their pure epilepsy cases. Although this study has serious limitations, as previously noted, the failure to replicate the findings of Taylor (1975) is not easily reconciled.

Evaluation of the Schizophrenia Patient Who Suffers a Seizure

In many respects, the evaluation of a schizophrenia patient with a seizure is the same as the evaluation of anyone who suffers a seizure. As always, the first and imme-
Seizures and Schizophrenia

Immediate intervention is to check the stability of a patient's vital signs. If stable, the next step is to evaluate the clinical characteristics of the episode to establish that the patient did in fact suffer a true seizure. Many events can simulate a seizure, including acute dystonic reactions and other paroxysmal movement disorders, acute hypotensive episodes, syncope of both cardiac and noncardiac origin, transient ischemic attacks, transient global amnesia, benign paroxysmal vertigo, migraine, panic attacks, intermittent explosive disorder, sleep disorders (especially narcolepsy), pseudoseizures, and acute intoxication (Morrell 1993). A complete history, including interviews with witnesses of the event, can be the single most helpful strategy in establishing the correct diagnosis. After a generalized tonic-clonic convulsion or complex partial seizure, the overwhelming majority of patients will have elevated serum prolactin levels, which can be useful in differentiating seizures from pseudoseizures and other nonepileptic events (Trimble 1978; Yerby et al. 1987). The rise peaks within about 20 minutes after the event, returning to baseline after about 60 minutes. An elevation of two to three times baseline is usually considered indicative of a true seizure (Yerby et al. 1987). Measuring serum prolactin levels can be less valuable in the schizophrenia patient after a possible seizure because neuroleptics can markedly elevate baseline serum prolactin levels.

Several factors peculiar to schizophrenia patients must be weighed in the event of a seizure (table 1). Metabolic factors are the first level of consideration. Hyponatremia is common among a subset of schizophrenia patients, secondary to psychogenic polydipsia (Jose and Perez-Cruet 1979; Vieweg et al. 1985); therefore, serum sodium levels must be checked as soon as possible following a seizure in all schizophrenia patients. Serum glucose should be obtained if the patient is diabetic, since hypoglycemia can cause seizures and schizophrenia patients may not regulate their insulin or diet correctly. Rarely, either hyperthyroidism or hypothyroidism can cause seizures. Insofar as schizophrenia patients are poorly compliant with their medications and may not seek attention for medical problems, thyroid function tests should be considered in all schizophrenia patients after a first-time seizure. Finally, toxin ingestion, including illicit drugs, can cause seizures and must be considered, especially as the patient may not provide a reliable history. Schizophrenia patients are at a much higher risk for suicide than the general population, and they may ingest unusual substances in an attempt to overdose. Appropriate blood and urine screening studies are essential for diagnostic purposes.

In addition to toxic and metabolic factors, prolonged sleep deprivation can also lower the seizure threshold. While prolonged sleep deprivation is much more common in the manic phase of bipolar disorder, schizophrenia patients may have periods in which their sleep cycle is markedly altered. During these periods, they are vulnerable to seizures, especially when they are on neuroleptics or other psychoactive medications that further lower the seizure threshold.

### Table 1. Differential diagnosis of seizure-like episodes in schizophrenia

<table>
<thead>
<tr>
<th>Category</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syncope</td>
<td>Orthostatic hypotension</td>
</tr>
<tr>
<td></td>
<td>Cardiac arrhythmias</td>
</tr>
<tr>
<td></td>
<td>Valvular heart disease</td>
</tr>
<tr>
<td></td>
<td>Coronary artery disease (angina)</td>
</tr>
<tr>
<td></td>
<td>Micturition syncope</td>
</tr>
<tr>
<td></td>
<td>Vasovagal episodes</td>
</tr>
<tr>
<td>Cerebrovascular events</td>
<td>Transient ischemic attacks</td>
</tr>
<tr>
<td></td>
<td>Transient global amnesia</td>
</tr>
<tr>
<td></td>
<td>Complex migraine headaches</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Pseudoepileptic seizures</td>
</tr>
<tr>
<td></td>
<td>Dissociative disorders</td>
</tr>
<tr>
<td></td>
<td>Rage attacks</td>
</tr>
<tr>
<td></td>
<td>Panic attacks</td>
</tr>
<tr>
<td></td>
<td>Hallucinations</td>
</tr>
<tr>
<td>Medication side effects</td>
<td>Acute dystonic reactions</td>
</tr>
<tr>
<td></td>
<td>Intermittent tremor</td>
</tr>
<tr>
<td></td>
<td>Toxic encephalopathies</td>
</tr>
<tr>
<td>Toxic/metabolic disorders</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td></td>
<td>Hypocalcemia</td>
</tr>
<tr>
<td>Other neurological events</td>
<td>Paroxysmal choreoathetosis or dystonia</td>
</tr>
<tr>
<td></td>
<td>Hyperexplexia (enhanced startle reaction)</td>
</tr>
<tr>
<td></td>
<td>Tics</td>
</tr>
<tr>
<td></td>
<td>Stereotypes</td>
</tr>
<tr>
<td></td>
<td>Myoclonus</td>
</tr>
<tr>
<td></td>
<td>Titubation</td>
</tr>
<tr>
<td>Sleep disorders</td>
<td>Narcolepsy/cataplexy</td>
</tr>
<tr>
<td></td>
<td>Sleepwalking</td>
</tr>
<tr>
<td></td>
<td>Night terrors</td>
</tr>
<tr>
<td></td>
<td>Sleep automatisms</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>Restless-leg syndrome</td>
</tr>
</tbody>
</table>

### Diagnostic Tests

The most important diagnostic test in evaluating a patient after a seizure, other than the serological studies reviewed previously, is the electroencephalogram (EEG). A sleep-
Neuroimaging studies play an important role in assessing the etiology and risk of recurrent seizures after a single seizure; they also dictate some forms of treatment. Magnetic resonance imaging (MRI) is the most sensitive test for lesion detection (Sperling 1993). While CT is less sensitive, it is still valuable in patients who cannot have an MRI (Ramirez-Lassepas et al. 1984). A CT scan is also valuable if an intracranial hemorrhage is suspected. It should be noted that there is a high degree of agreement between focal findings on neurological examination and lesions on neuroimaging studies. If a patient has a nonfocal neurological examination 48 hours after a seizure (by which time any postictal transient neurological abnormality, “Todd’s paresis,” should have remitted), a neuroimaging study is probably going to be much less valuable (Russo and Goldstein 1983). Sperling (1993) recommends that all patients have an MRI scan of the brain at initial evaluation. Certainly, those patients with focal findings on neurological examination or abnormalities on EEG should have a neuroimaging study to screen for structural lesions.

Role of Neuroleptics and Other Psychotropic Medications in Seizure Induction

Neuroleptics and other psychotropic medications may play a role in the induction of a seizure. In fact, psychotropic agents are the class of medications most commonly associated with a drug-induced generalized convolution (Messing et al. 1984). Most of the literature regarding psychotropics and seizures are case reports. Seizures attributable to a medication usually occur within several weeks of the initiation of therapy or after a change in medication dosage. Many of the case reports involve very high doses of medication; for example, Messing et al. (1984) reported a case of a seizure after 2,000 mg of amitriptyline. Toone and Fenton (1977) reported that polypharmacy, changes in medication dosage, and postnatal brain damage predisposed individuals to drug-induced seizures.

Not all neuroleptics are equally epileptogenic. Both animal and human studies have been used to assess the relative risk of seizure induction from neuroleptics. One animal study suggested that haloperidol is most potent in the induction of spike activity. Chlorpromazine, thioridazine, and pimozide had inverted U-shaped dose-risk curves. Molindone, pimozide, and fluphenazine produced
the least amount of spike activity in a study of in vitro tissue slices (Oliver et al. 1982). Chen and colleagues (1968) found that chlorpromazine and haloperidol lowered the seizure threshold at low doses and actually raised it at higher doses. However, the clinical experience with neuroleptics often does not mirror in vitro and animal studies. In humans, clozapine and chlorpromazine are thought to have the highest propensity toward seizure induction. About 9 percent of patients on doses of chlorpromazine over 1 gram per day may experience seizures (Logothetis 1967). Perphenazine, thiothixene, loxapine, and haloperidol are intermediate. Thioridazine, fluphenazine, and molindone are considered the safest (Logothetis 1967; Itil and Soldatos 1980; Peterson 1981). Logothetis (1967), in a study of 859 patients treated with a variety of phenothiazines over a 4½-year period, found that 1.2 percent suffered seizures. While additional evidence is necessary, initial clinical experience with risperidone, olanzapine, and sertindole suggests that they carry a low risk of seizure induction (Casey 1996). Itil and Soldatos (1980) proposed that highly sedating neuroleptics with a low incidence of extrapyramidal side effects are more likely to induce seizures. As newer neuroleptics with low extrapyramidal side-effect profiles become available, this hypothesis may need revision.

Clozapine merits special comment. According to premarketing studies by the manufacturer, 3.5 percent of patients treated with clozapine had a seizure, although rates up to 10 percent have subsequently been reported (Povlsen et al. 1985; Wilson and Claussen 1994; McEvoy 1996a). The risk appears to be dose-related (Honigfeld and Patin 1990). Patients with a previous history of seizures are at higher risk for a clozapine-induced seizure (Wilson and Claussen 1994). If a patient suffers a seizure while on clozapine, the dose should be lowered, and a broad-spectrum anticonvulsant, such as valproate or phenytoin, should be added (Haller and Binder 1990). Once a therapeutic trough serum level of the anticonvulsant has been reached, the dose of clozapine may be slowly increased. Doses above 600 mg per day are generally to be avoided following a clozapine-induced seizure. A final caveat: Other causes of seizures in schizophrenia patients must be considered and ruled out, even when a seizure occurs in a patient who is receiving clozapine.

Among nonneuroleptics, tricyclic antidepressants—especially imipramine, amitriptyline, and protriptyline (Betts et al. 1968; Dallos and Heathfield 1969; Itil and Soldatos 1980)—are fairly epileptogenic. About 1 percent of patients on tricyclic therapy for more than 1 week will have a medication-related seizure (Lowry and Dunner 1980). In an in vitro study of seizure induction in tissue slices with tricyclic antidepressants, imipramine was the most potent at therapeutic serum levels, while amitriptyline, nortriptyline, maprotiline, and desipramine were less effective (listed in descending order of epileptogenic potency). Doxepin and nomifensine increased spike activity at low doses but reduced it at higher levels. Protriptyline and trimipramine actually suppressed spike activity with increasing doses (Luchins et al. 1984). However, the validity of extrapolating epileptogenic potential from slices of tissue in a laboratory to humans is not well established for psychoactive drugs (Trimble 1980). From clinical experience, bupropion and lithium are also fairly epileptogenic, particularly at higher clinical doses and more frequently, following overdose (Ghadirian and Lehmamn 1980; Itil and Soldatos 1980; Davidson 1989; Johnston et al. 1991; Spiller et al. 1994). The risk of seizure on bupropion is greatest at daily doses of 450 mg or more (Davidson 1989). However, lithium has also been demonstrated to have anticonvulsant properties at therapeutic serum levels in patients with preexisting seizure disorders (Erwin et al. 1973). Selective serotonin-uptake inhibitors and monoamine oxidase inhibitors are comparatively safe with respect to seizures. Benzodiazepines and barbiturates are anticonvulsants, but rapid withdrawal or abrupt cessation of therapy with these medications can result in withdrawal seizures or even status epilepticus.

The possibility that certain individuals may be more vulnerable to medication-induced seizures should be considered. Patients with a history of serious closed-head injury—especially if associated with amnesia, coma, or intracranial hemorrhage—may, for the rest of their lives, be more vulnerable to seizures from a wide variety of provocations, including medications. Focal findings on a neurological examination may indicate a focal central nervous system lesion, which may, in turn, predispose toward seizures. Finally, a childhood history of febrile convulsions might suggest a developmental predisposition toward seizures. In such individuals, careful consideration should be given to the type of neuroleptic therapy. If clozapine is to be used, concurrent therapy with a broad spectrum anticonvulsant might be advisable.

**Risk Factors for Recurrent Seizures**

Several historical factors place an individual at increased risk for recurrent seizures following a single event. A history of febrile convulsions in childhood places children (and probably adults) at increased risk of recurrent seizures after a non-febrile-associated event (Hirtz et al. 1984; Shinnar et al. 1990). Age at onset of seizures is also important. Adolescent onset has a worse prognosis than childhood onset, whereas adult onset has a nominally...
higher risk of relapse than childhood onset (Shinnar and Berg 1995). A partial seizure is a positive predictor of recurrence in studies of children (Hirtz et al. 1984; Camfield et al. 1985; Shinnar et al. 1990) and in one study of adults (Annegers et al. 1986). In these studies, any form of partial seizure is a positive predictor, not just complex partial seizures. However, Callaghan et al. (1988) found that patients with a history of complex partial seizures with secondary generalization are more likely to relapse following discontinuation of anticonvulsant therapy after a 2-year seizure-free period than patients with generalized seizures and complex or simple partial seizures without secondary generalization. Children with Jacksonian seizures, complex partial seizures, or multiple seizure types are more likely to relapse when off of anticonvulsants than children with generalized motor or absence seizures (Thurston et al. 1982).

Abnormalities on EEG may be important in predicting the risk of recurrent seizures after a single event, as well as after a long seizure-free interval when under anticonvulsant treatment. EEG abnormalities present before the initiation of anticonvulsant therapy and that persist despite treatment are associated with a higher risk of seizure recurrence when off anticonvulsants (Callaghan et al. 1988; Shinnar and Berg 1995). Another study reported that the presence of spikes on the EEG increases the risk of seizure recurrence (Tennison et al. 1994). In contrast, Thurston et al. (1972, 1982) found no predictive value for the risk of seizure relapse in the type of EEG abnormality.

The clinical characteristics of a brain injury have predictive value in assessing the risk of recurrent seizures. A history of mental retardation or motor dysfunction is positively correlated with an increased risk of seizure relapse in children and adolescents (Thurston et al. 1972, 1982; Tennison et al. 1994). Following head trauma, seizures within the first week of injury and those that occur months later are associated with posttrumatic epilepsy. Patients with persistent focal neurological deficits following closed-head injury have an increased risk of recurrent seizures. Penetrating head trauma produces an even higher risk of recurrent seizures (Caveness 1976), and head injuries with an intracerebral hematoma are particularly associated with the subsequent development of a seizure disorder (Jennett 1975; Feeney and Walker 1979). Although a single seizure does not necessarily require chronic anticonvulsant therapy, evaluation after an initial seizure may identify specific unremediable factors that make recurrent seizures likely. In such a setting, chronic anticonvulsant therapy may be prudent.

Anticonvulsant Choice in a Patient With Schizophrenia

If a patient is felt to be at risk for recurrent seizures, then anticonvulsant therapy should be initiated. The choice of anticonvulsant depends in part on the type of seizure. Valproate is the drug of choice for generalized seizures, including motor, absence, and myoclonic forms; phenytoin and phenobarbital are secondary choices. Carbamazepine is the drug of choice for complex partial seizures; gabapentin, lamotrigine, and even valproate can also be used. The addition of an anticonvulsant can alter the metabolism and distribution of antipsychotic medication, lowering serum concentrations and diminishing efficacy, so adjustments in the antipsychotic dosage may be necessary. Furthermore, antipsychotic medications can increase the serum levels of anticonvulsants, precipitating toxic effects (Mendez et al. 1984, 1986). Anticonvulsant levels must be monitored carefully in a patient receiving antipsychotic medications, especially if there is a change in clinical state. Since both clozapine and carbamazepine can depress white blood cell counts and even produce agranulocytosis, combination therapy with these two medications should be avoided if possible. Clonazepam and valproate should not be combined as they can precipitate absence status in some individuals (McEvoy 1996b). Finally, epilepsy surgery, with resection of the epileptic focus, is an option in refractory patients, that is, those with persistent seizures despite multiple trials of single and combination anticonvulsants at therapeutic doses or those who suffer from intolerable medication side effects (Devinsky and Pacia 1993). Unfortunately, temporal lobectomy has little or no effect on preexisting psychoses (Roberts et al. 1990).

Conclusions

Schizophrenia patients probably are more prone to seizures than the general population. This vulnerability may be conferred by the neuropathological substrate of schizophrenia itself, as well as by the secondary effects of the illness and by exposure to medications that lower the seizure threshold. For the schizophrenia researcher, the increased incidence of seizures in patients with schizophrenia may offer important insights into the neurobiology of schizophrenia. Complex partial seizures are the most common type of seizure in schizophrenia. In addition, focal temporal lobe abnormalities are commonly seen in patients with schizophrenia and seizure disorders.
These findings support the contention that a lesion in the mesial temporal lobe may underlie both schizophrenia and a seizure disorder. For the clinician, seizures in schizophrenia require careful evaluation and selection of medications, both anticonvulsants and antipsychotics. Patients with schizophrenia and seizure disorders offer useful insights into the biology of schizophrenia and pose special challenges for the clinicians who care for them.

References


Wirtz, W.v.R.; David, J.J.; Rowe, R.T.; Wampler, G.J.; Burns, W.J.; and Spradlin, W.W. Death from self-induced water intoxication among patients with schizophrenic dis-

Weinberger, D.R. On the plausibility of “the neurodevelopmental hypothesis” of schizophrenia. *Neuropsychopharmacology*, 14(Suppl.):1–11, 1996.


**The Authors**

Thomas M. Hyde, M.D., Ph.D., is Special Expert, and Daniel R. Weinberger, M.D., is Branch Chief, Clinical Brain Disorders Branch, Intramural Research Program, National Institute of Mental Health Neuroscience Center, St. Elizabeths Hospital, Washington, DC.

**Recent Books**


