Medical comorbidities in the treatment of epilepsy

Alexis Boro and Sheryl Haut*

Department of Neurology, Comprehensive Epilepsy Management Center, Montefiore Medical Center and the Albert Einstein College of Medicine, 111 East 210th Street, Bronx, NY 10467-2490, USA

Received 28 July 2003; accepted 28 July 2003

Abstract

The treatment of epilepsy extends far beyond seizure control. Many comorbidities have a significant impact on the medical management and quality of life of patients with epilepsy. In this review, we examine interactions between epilepsy and some common medical conditions. Psychiatric disorders with a high prevalence in epilepsy include mood disorders, anxiety disorders, and psychosis. Depression is common, psychosis occurs both in direct relation to seizures and interictally, and suicide rates are increased. Changes in sexual function and reduced fertility and marriage rates are described, including a discussion of polycystic ovary syndrome, which is increased in women with epilepsy. The effects of other chronic medical comorbid conditions are reviewed, including the effects of antiepileptic medications on bone health and the impact of renal insufficiency on pharmacological therapy of epilepsy.

© 2003 Elsevier Inc. All rights reserved.

Keywords: Epilepsy; Medical; Comorbidity; Psychiatric; Reproduction; Cardiovascular

1. Introduction

“Seizures well controlled, renew current medications.” In today’s medical environment, the encounter between doctor and patient has become increasingly problem oriented and focused, and in the seizure clinic, this focus is all too often on “seizure control” alone. All patients with epilepsy, whether their seizures are well controlled or intractable, have to contend with the threat of seizures and their physical and psychosocial consequences, but many additional problems may be associated with this disease. Fortunately, caregivers involved in the treatment of epilepsy are becoming increasingly aware of the impact that a multitude of other factors may have on the quality of life of our patients. While no single review can span this multitude, what follows is an exploration of some prominent comorbidities of epilepsy.

2. Psychiatric disorders

It will come as no surprise to experienced caregivers that of all comorbidities encountered in the treatment of epilepsy, psychiatric issues are the most common. Although incidence and prevalence rates vary widely among studies (Table 1), there is little question that psychiatric disorders are more common in patients with epilepsy as compared with both the general population and patients with other chronic medical disorders [1]. Psychopathology may coexist with epilepsy, may be directly related to seizure activity, or may be associated with the postictal state. The spectrum of psychiatric disorders in epilepsy appears fairly constant across culture [2], across gender, and across age [1]. Mood disorders, predominantly major depression, and anxiety disorders have the highest frequency [3], followed by psychosis. The resulting impact on quality of life for patients suffering both epilepsy and psychiatric illness is potentially profound, and the importance of frequent and regular consultation between neurologists and psychiatrists treating patients who have epilepsy cannot be overstated.
The relationship between epilepsy and psychopathology is poorly understood, and proposed mechanisms abound [4]. Although the role of excitation and inhibition in epilepsy probably involves complicated interactions [5], chronic epilepsy may be associated with increased cortical excitability, and abnormal inhibitory activity elicited in response to this excitability has been suggested to lead to the emergence of psychopathology [6]. While many studies have identified specific risk factors for psychopathology in the setting of epilepsy [7], a myriad of less quantifiable factors, such as the burden of social stigmatization and discrimination, may also contribute to produce a multifactorial setting in which epilepsy and neuropsychiatric conditions frequently coexist.

2.1. Mood disorders

Depression is a common and potentially underdiagnosed comorbidity of epilepsy. The prevalence of interictal depression may be highest for complex partial epilepsy [7], particularly of left temporal lobe origin [8,9]. The lifetime-to-date major depression rate in epilepsy has been reported to be almost 40% [10]. This may be nearly 60% for patients with complex partial seizures [11], although depression may be more difficult to diagnose in patients with the more severe epilepsies. Depressive disorders in epilepsy often do not fit the \textit{DSM-IV} criteria for major depression, and they may be more appropriately diagnosed as atypical depression [12]. Risk factors for depression in epilepsy have been identified (Table 2). A fascinating bidirectionality of depression and epilepsy has been noted, with reports of depression as a significant risk factor for a first unprovoked seizure [13,14].

Depression has also been noted as a side effect of antiepileptic agents [15], and conversely, the discontinuation of mood-stabilizing antiepileptic agents may contribute to the unmasking or provocation of an underlying mood disorder [4]. Ictal depression is noted to occur [15], particularly as a simple partial seizure manifesting as a brief, incongruent change in mood. Clearly, this seizure type may frequently go unrecognized as epileptic in origin.

The frequency of bipolar disorder does not appear to be increased in epilepsy [16], and mania is reported far less frequently than depression [17]. When mania does occur, it is often less severe than in typical bipolar I disorder [18], possibly because of the antimanic properties of many antiepileptic agents.

2.2. Anxiety disorders

The prevalence of anxiety disorders in epilepsy is high, particularly in intractable epilepsy (Table 1). Most common are panic disorder, generalized anxiety disorder, and obsessive–compulsive disorder [4]. In contrast to the less frequent ictal depression, fear is a common ictal aura [19], and it may contribute to interictal anxiety [20] or panic disorder [21]. Panic attacks may actually represent seizures, which may complicate the treatment of patients with epilepsy and comorbid anxiety disorders. Admission for continuous video/EEG monitoring to capture and characterize this type of event is often useful, although a simple partial seizure manifesting as fear or panic may not be apparent by surface EEG monitoring [22].

2.3. Psychosis

Psychosis as a comorbidity of epilepsy, also referred to as POE (psychosis of epilepsy), occurs in the interictal, ictal, and postictal states [23] (Table 1).
An additional category of “alternative psychosis,” related to the remission of seizures (sometimes referred to as forced normalization), has been proposed [23]. Many neurobiological theories as to the relationship between psychosis and seizures exist [24], as do comparisons between schizophrenia in the nonepilepsy patient and psychosis of epilepsy [25,26]. There is evidence that the interictal psychotic state is associated with fewer negative symptoms, less severe psychotic episodes, and rarer personality deterioration than is nonepileptic schizophrenia [27], although these findings have been disputed [28]. The clinical observation that interictal psychosis is increased in temporal lobe epilepsy (TLE) [29] correlates with recent anatomic data that demonstrated increased size of the bilateral amygdaloid volumes in patients with TLE and psychosis [30]. An interesting comparison between psychosis in temporal and frontal lobe epilepsy (FLE) demonstrated that hebephrenic symptoms (emotional withdrawal and blunted affect) predominated in FLE, while TLE patients tended to have more paranoid features [28]. The clinical observation that interictal psychosis is increased in temporal lobe epilepsy (TLE) [29] correlates with recent anatomic data that demonstrated increased size of the bilateral amygdaloid volumes in patients with TLE and psychosis [30]. An interesting comparison between psychosis in temporal and frontal lobe epilepsy (FLE) demonstrated that hebephrenic symptoms (emotional withdrawal and blunted affect) predominated in FLE, while TLE patients tended to have more paranoid features [28]. Risk factors for interictal psychosis include a family history of psychosis, younger age at onset of epilepsy, and borderline intellectual functioning [31].

### 2.4. Suicide

It is mandatory for clinicians who treat patients with epilepsy to be aware of the increased risk of suicide in this population. While suicide is a rare event, estimated to occur in 1 of 10,000 persons annually in the United States, the suicide rate in patients with epilepsy appears to be increased at least 5-fold [37]. There may be a 25-fold increase in the suicide rate for patients with TLE [38]. In addition, it has been reported that up to one-third of patients with epilepsy have attempted suicide [39]. As is the case with psychosis, suicide rates may increase after cessation of seizures [40]. It has been noted that suicide in epilepsy tends to occur precipitously, in a period of sudden, intense interictal depression or psychosis [40]. Risk factors for successful completion of suicide include psychosis with paranoid hallucinations and ictal command hallucinations [39].

### 2.5. Treatment considerations

Establishing a trusted psychiatry liaison is mandatory for any epilepsy practice. The combination of pharmacological therapy for psychiatric indications and for epilepsy is potentially complex, and a familiarity with both will reduce potential complications. As indicated in Table 3, some neuroleptics or antidepressants are implicated in lowering the seizure threshold, and certain anticonvulsants may unmask or worsen psychiatric conditions. Furthermore, either class of agents may affect metabolism. It is important to note that most complications of pharmacological therapy occur at higher doses of medication.

### 3. Sexuality and reproduction in epilepsy

The medical profession has long perceived an association between epilepsy and sexuality. In the second half of the 19th century, the belief that epilepsy was somehow an effect of an excess of sexual desire and the perceived similarity between seizures and orgasms made the application of bromides as antiepileptics plausible, as these compounds had been noted to cause impotence. It seemed reasonable to infer that a reduction in libido would lead to a corresponding reduction in the frequency of seizures [41].

---

**Table 3**

<table>
<thead>
<tr>
<th>Pharmacologic considerations and medications best avoided in psychiatric disorders and epilepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Increased risk of seizures</strong></td>
</tr>
<tr>
<td><strong>Emergence of psychosis</strong></td>
</tr>
<tr>
<td><strong>Potential for significant drug-drug interactions:</strong></td>
</tr>
<tr>
<td>Hepatic enzyme inducers that may increase metabolism of other agents</td>
</tr>
<tr>
<td>Hepatic enzyme inhibitors that may decrease metabolism of other agents</td>
</tr>
<tr>
<td><strong>Leukopenia</strong></td>
</tr>
<tr>
<td><strong>Hypertensive crisis</strong></td>
</tr>
</tbody>
</table>
By the 1950s, the perceptions of the medical profession had begun to migrate to the opposite pole. Gastaut and Collumb [42] described a lack of sexual interest in patients with complex partial seizures. The patient with epilepsy was now pictured as an individual marked by a paucity rather than an excess of sexual desire. Since that time, there has been a widely held view that hyposexuality, defined as “a global reduction in sexual interest, awareness, and activity” [43], is characteristically associated with epilepsy. There are numerous data in support of this view. For example, in a series of 54 patients drawn from general practices in London, only 43% had had sexual activity in the last month, as compared with 91% of controls [44]. This does not seem to hold true in all populations. A series of 86 Danish outpatients with epilepsy revealed low rates of sexual dysfunction that did not differ from control rates [45].

Recently, it has been argued that the sexual dysfunction of epilepsy should be framed as a “primarily physiological, not psychological” problem, as “in large part a disorder of arousal, not desire” [46]. Morrell et al. found that in a group of patients with temporal lobe epilepsy, both men and women developed significantly lower increases in genital blood flow in response to erotic videotapes than did controls, even when subjective assessment of arousal was normal [47]. Lack of spontaneous morning tumescence, anorgasmia, erectile difficulties and dyspareunia, vaginismus, and lack of vaginal lubrication have been reported to occur in more than one-third of male and female patients, respectively [46]. In one sense, Morrell and colleagues’ work completes the turn initially marked by Gastaut. While Gastaut sought to define the causes for the sexual dysfunction of epilepsy in physiological terms, its substrates too are now described in these terms. In another sense, Morrell and colleagues’ work marks a further change and broadening of perspective: both physiological and psychological causes for the changes in arousal patterns that are seen in epilepsy are sought.

The psychological factors that can contribute to impaired arousal include reduced self-esteem as a consequence of having seizures. When sexual activity precipitates seizures or becomes associated with the aura, seizure or postictal period arousal may be negatively reinforced [46]. At the same time, epilepsy can potentially result in changes in arousal through a number of physiological mechanisms: epileptic discharges involving the limbic system may alter arousal patterns directly [48] as well as indirectly through changes in hypothalamic–pituitary function. Antiepileptic drug-induced limbic and hormonal and end-organ changes may also play a role. It is important for the clinician to screen for sexual dysfunction and to refer appropriately. While in particular cases the etiology may remain obscure, often this does not preclude successful treatment [121].

A number of large surveys have demonstrated that epilepsy also has a significant impact on fertility. Decreases in fertility rates as compared with the nonepileptic population are on the order of one-third [49,50], although this is not reported in all studies [51,52]. While reduced rates of sexual activity contribute to part of the decrease in the fertility rate, reductions in the conception rate probably play a role, as well. In men, decreased potency and abnormal sperm structure are both present in epilepsy; antiepileptic drug (AED) use is a factor, although untreated men are also affected [53]. There are reports of reversible ejaculatory failure in patients taking carbamazepine [54] or gabapentin [55]. Menstrual dysfunction, resulting in both anovulatory cycles and amenorrhea, occurs in up to 50% of women with epilepsy [56]. Both men and women with epilepsy have altered hypothalamic–pituitary–gonadal function, which has consequences for both arousal and conception rates.

While the relative contributions of epilepsy itself and antiepileptic medications are disputed, one study found that levels of follicular phase luteinizing hormone (LH) and luteal phase estradiol were significantly lower in women with epilepsy than in controls, while prolactin and steroid hormone-binding globulin (SHBG) were higher. In the same study, men with epilepsy had lower levels of 17α-hydroxyprogesterone and free testosterone than controls, while LH, follicle-stimulating hormone (FSH), and SHBG were significantly higher [57].

Finally, the marriage rate of people with epilepsy without other neurological problems is significantly lower than that of the general population: one study found that the probability of being single was 3.7 times that of controls [58].

3.1. The polycystic ovary syndrome

The polycystic ovary syndrome is an important medical concern in epilepsy. Polycystic ovary syndrome (PCOS) is characterized by a menstrual disorder (amenorrhea, oligomenorrhea, abnormal cycle intervals, or menometrorrhagia) and signs of hyperandrogenism, including hirsutism, acne, and alopecia. Obesity is common in PCOS but not universal. Biochemical evidence of PCOS includes elevated serum concentrations of androgens, along with abnormally low midluteal phase levels of progesterone. Typically, elevated levels of LH and normal or low levels of FSH are present. The finding of polycystic ovaries on ultrasound is typical but neither essential nor sufficient for the diagnosis [59].

The syndrome may have neurological consequences: anovulatory cycles are associated with more frequent seizures. In addition, anovulatory cycles may be associated with a higher frequency of migraine [60]. Crucially, the unopposed mitogenic effects of estrogen have been linked with higher rates of endometrial carcinoma.
PCOS has also been associated with insulin resistance and hyperlipidemia, important risk factors for cardiovascular disease [61].

A number of studies have shown that PCOS is overrepresented among women with epilepsy. An association between PCOS and AED treatment has not always been demonstrated [62]. The view that AEDs, and in particular valproic acid (VPA), play a more prominent role in the development of PCOS than epilepsy itself is based on experience from several other series, clinical improvement after switching from VPA to lamotrigine, and recent experimental animal data [63].

Epilepsy itself may be related to PCOS via epileptic discharges disrupting normal hypothalamic function. The mechanism by which VPA may precipitate PCOS has not been entirely elucidated. There is evidence supporting the view that hyperinsulinemia, mediated either by VPA-induced weight gain [64] or by a direct effect of VPA on pancreatic islet cells [65], underlies the association between VPA and PCOS. This is unlikely to be the complete explanation, as hyperinsulinemia is not detected in all cases of women taking valproate who have PCOS, and VPA-treated nonepileptic rats develop increased numbers of ovarian cysts and changes in sex steroid hormone levels without associated changes in insulin levels [63]. VPA-mediated changes in androgen metabolism may play a key role. VPA, an inhibitor of the P450 system, has been associated with elevated serum levels of free androgen levels in both sexes. By contrast, strong inducers of the P450 system, such as carbamazepine, reduce biologically active androgen levels by increasing rates of both androgen metabolism and the production of SHBG [66].

3.2. Catamenial seizures

Between 30 and 50% of women with epilepsy have predictable changes in seizure frequency in concert with the menstrual cycle [67]. Estrogen is known to have proconvulsant effects, while progesterone has anticonvulsant properties [46]. Elevations in the estrogen/progesterone ratio, which is maximal at ovulation, and falling progesterone levels at the end of the luteal phase may be responsible for these fluctuations in seizure frequency. Progestosterone supplementation and estrogen antagonists have been studied in small series with encouraging results [68,69]. The long-term safety and efficacy of these approaches are not known.

Cyclic fluctuations in seizure frequency may also be related to changes in AED levels. The serum levels of certain anticonvulsants metabolized by the P450 system (e.g., phenytoin and carbamazepine) have, in some series, been shown to decrease in the premenstrual period, apparently as a result of declining levels of gonadal steroids and decreased competitive inhibition [70]. It may be helpful to check trough AED levels at the time of menses in women with perimenstrual seizure exacerbations [70].

3.3. Contraception and AEDs

Contraceptive failure occurs in up to 7% of patients with epilepsy who are on birth control pills, as compared with a failure rate of 1 to 2% in the general population. Enzyme-inducing AEDs increase the metabolism of contraceptive hormones. Nonenzyme-inducing drugs, such as gabapentin, lamotrigine, and VPA, are not associated with contraceptive failure. Breakthrough bleeding does not necessarily signal contraceptive failure. Selection of a contraceptive agent containing 50 μg or more of the estrogenic component is recommended in this setting [71].

3.4. Pregnancy and AEDs

A full exploration of the interactions between epilepsy and pregnancy is beyond the scope of this article; our discussion is limited to an outline of some of the key issues. While 90% of women with epilepsy have normal pregnancies, factors to consider include the risk that seizures pose to the fetus and the mother, the teratogenic risks and long-term developmental effects associated with AED treatment, and adverse neonatal effects of AEDs.

It is clear that generalized tonic–clonic seizures are associated with adverse fetal outcomes, including stillbirths and fetal bradycardia [72]. The effects of other seizure types are less well understood. Both free and unbound AED levels drop during pregnancy. Monitoring free AED levels is therefore important to minimize seizure frequency.

There is evidence that the incidence of fetal malformations is higher in women with epilepsy not receiving AEDs than in the general population, although it is unclear to what extent this risk is attributable to seizures or genetic predisposition [72]. Virtually all studies, however, have supported an increase in fetal malformation rates in association with in utero exposure to AEDs; with AED treatment, the incidence of fetal malformations is on the order of 4 to 11%, as compared with a rate in the general population of 2 to 4% [73]. Teratogenic risks are minimized by the initiation of AED monotherapy at the lowest effective dose, with folate supplementation, prior to and during pregnancy.

Numerous case reports suggest that hepatic enzyme-inducing antiepileptic drugs increase the risk for neonatal hemorrhage, although a recent large series has questioned this association [74]. Antenatal administration of vitamin K to mothers and postnatal administration to infants exposed to AEDs in utero are widely recommended [72].
A variety of disturbances attributed to AED withdrawal have been seen in newborns exposed to AEDs during pregnancy, including hyperexcitability, tremors, myoclonus, and seizures. These usually occur in the first 72 hours of life [72]. The mother should receive guidelines for infant care to minimize the risk that maternal seizures pose to the infant. Finally, changing maternal AED dosage requirements in the postpartum period should be monitored.

3.5. Menopause, hormone replacement, and epilepsy

The effects of menopause on seizure frequency are variable. New-onset epilepsy and increases in decreases in seizure frequency have been documented [75–77]. Estrogen replacement would be expected to increase seizure frequency, and progesterone supplementation would be expected to mitigate this effect; experience in the series cited above was inconclusive.

4. General medical conditions

Nearly every patient with epilepsy will experience a comorbid medical condition at some point during the course of treatment. For some patients, this will be an uncomplicated infection treated with antibiotics or nonprescription agents. For many patients, and more commonly with age, one or more chronic medical conditions will coexist with epilepsy. The impact of these comorbidities is centered on pharmacological therapy. Many of the AEDs have prominent metabolic effects on other drugs or are metabolized differently depending on other drug interactions. Given that AEDs tend to require a stable level for maximal safety and efficacy, the need to consider and adjust for potential drug–drug interactions is constant. The potential of other medications to lower the seizure threshold must similarly be a consideration.

AED therapy is typically chronic. The choice of agent must consider potential long-term adverse effects. Among the adverse effects of increasing concern is AED-related bone loss.

4.1. Osteoporosis

Loss of bone mineral density (BMD) in the setting of chronic AED therapy, which was first described some decades ago [78], has recently reemerged as a major area of clinical concern. In the United States, 1.5 million fractures occur annually [79]. Osteoporosis, which is estimated to affect up to 40% of women and 12% of men in the general population, is a key factor contributing to fracture and to the extent of the resulting disability. The risk of hip fracture in white women appears to be doubled by use of AEDs [80], and numerous studies document a decrease in BMD in patients who are on chronic AED therapy [81], including even young men who otherwise would be at extremely low risk for bone loss [82].

Recent work has examined the differential risk between enzyme-inducing and nonenzyme-inducing agents. Initial reports suggested an increase in vitamin D metabolism by the hepatic enzyme-inducing AEDs [83]. The resulting vitamin D deficiency was thought to cause a secondary hypoparathyroidism leading to increased bone turnover. It has been demonstrated, however, that bone density is similarly reduced with chronic use of valproate, a hepatic enzyme inhibitor [84]. Reports of decreased BMD with use of the newer nonenzyme-inducing AEDs further obscure this proposed mechanism [85]. Another hypothesis suggests that an AED-mediated decrease in intestinal calcium, absorption underlies bone loss. Overall, however, studies measuring vitamin D, calcium, and PTH concentrations have reported conflicting results [85,86].

What is clear from the accumulating evidence is that a decrease in bone mineral density meeting criteria for osteopenia or osteoporosis is not uncommon in the setting of chronic AED therapy. This may occur more frequently when older AEDs [83,87] or multiple AEDs [86] are used. For some patients, decreased physical activity due to focal neurological deficits may be an additional contributing factor [88]. Bone density screening, bisphosphonates, vitamin and calcium supplementation, and occasionally hormone replacement therapy are potentially important tools for treatment. The role of preventive therapy has yet to be addressed.

4.2. Coronary artery disease

Cardiac conduction abnormalities have occasionally occurred in patients taking carbamazepine [89]. There are case reports of accelerated atherosclerosis in children receiving carbamazepine [90], but this appears to be very rare. Elevated plasma concentrations of homocysteine, an established risk factor for atherosclerosis, have been associated with the use of enzyme-inducing AEDs [91,92].

Interactions between aspirin or warfarin and AEDs are often of concern. The potential interactions of clinical importance are listed in Table 4. Close monitoring of antiarrhythmic drug concentrations and digoxin levels may be indicated when these medications are administered with enzyme-inducing AEDs.

4.3. Hypertension

Oral AEDs generally do not affect blood pressure, except in the setting of massive overdose, although there are rare case reports of hypertension with the initiation of treatment with carbamazepine [93]. Adverse inter-
actions between some calcium channel blockers and the AEDs phenytoin and carbamazepine have been reported [94]. An interaction between phenytoin and isradipine causing severe neurological toxicity has been described [95].

4.4. Hyperlipidemia

There are numerous reports associating the use of enzyme-inducing AEDs with deterioration in the lipid profile, although the details of these changes are controversial [96]. Elevations in total cholesterol and low-density lipoprotein levels along with elevations in lipoprotein a levels are of particular concern [96–99]. Although much work remains to be done, particularly with the newer AEDs, periodic monitoring of the lipid profile may be of value in patients taking anti-convulsants.

4.5. Diabetes

Some AEDs may have potentially beneficial side effects in this setting. Both topiramate and zonisamide are frequently associated with weight loss [100,101]. There are reports of improved glycemic control in patients with type II diabetes taking topiramate [102].

The association between valproate and weight gain raises the question of whether this drug would confer a risk with deteriorating glycemic control in type II diabetes. A recent evaluation of patients with type II diabetes receiving valproate did not demonstrate this association [103]. Gabapentin and carbamazepine have also been associated with weight gain [104], but the weight gain seen in patients treated with these drugs has not been associated with compromised glycemic control. Phenytoin is known to induce hyperglycemia [105]. Close monitoring may be indicated when these medications are used in patients with diabetes or risk factors for diabetes.

4.6. Renal insufficiency

Seizures occur in renal disease in several contexts, including uremia, the dialysis disequilibrium syndrome, and, occasionally, the setting of chronic dialysis (the dialysis encephalopathy syndrome). Refinements in dialysis techniques and the elimination of aluminum-rich dialysates have made the latter two syndromes less common. Patients taking AEDs may have seizures after dialysis because of rapid drug clearance during dialysis. At times, the cause of seizures may be multifactorial [106]. Medications associated with reductions in the seizure threshold may be more likely to cause seizures in the setting of renal failure. The neurologist is often asked for advice in the selection and dose adjustment for patients with renal insufficiency who are undergoing dialysis. Renal dysfunction can alter multiple aspects of AED pharmacokinetics, including absorption, protein binding, and renal and hepatic clearance [107].

The extent to which a drug undergoes renal excretion depends in large part on its water solubility. Thus, a decrement in the glomerular filtration rate will decrease dosage requirements for a water-soluble drug, such as gabapentin, and will have little effect on a lipid-soluble drug, such as carbamazepine. Also, because of changes in protein binding that occur in renal insufficiency, the free fraction of a largely protein-bound drug, such as phenytoin, often increases, resulting in higher rates of hepatic metabolism. Thus, the total level of the AED may decrease, while the free level remains nearly unchanged [107].

AEDs are cleared in dialysis principally by diffusion down their concentration gradient from the blood to the dialysate. The factors that determine how efficiently a drug is cleared include the molecular weight of the drug, its water solubility, the extent to which it is protein bound, and its volume of distribution. All AEDs in current use are small molecules, and, therefore, size is not an issue for the dialysis of AEDs. In practice, drugs that have high lipid solubility, high protein binding, and large volumes of distribution are difficult to remove by dialysis, while drugs with high water solubility, low protein binding, and small volumes of distribution are readily dialyzed. These principles apply to both peritoneal and hemodialysis [107]. Information guiding the dosage adjustment of AEDs in renal failure and dialysis is presented in Table 5.
5. Stigma

We conclude this review with a nonmedical but no less important comorbidity of epilepsy—the stigma associated with the disorder. Negative attitudes toward epilepsy have spanned centuries and cultures [108]. These attitudes have a significant impact on quality of life, leading to low self-esteem, helplessness, anxiety, and depression [108,109]. Even patients with new onset of epilepsy report feeling stigmatized [110], suggesting that the diagnosis alone creates an expectation of being treated differently. The barriers to overcoming the stigma of epilepsy are daunting. While laws forbidding marriage or mandating sterilization for persons with epilepsy are now part of the past, subtle prejudices continue to operate. Discrimination in the workplace is still common, and despite improvements over time, depictions of epilepsy in the popular media are frequently disparaging [111]. Furthermore, there is a suggestion that the negative attitudes found in the general public may also be detected in health care providers, who then reinforce the negative self-image of their patients [108]. Fortunately, recent trends promoting better education and awareness of epilepsy have begun to reduce this burden, although the road ahead is long. We hope improvements in the quality of life, reduction of the stigma, and better management of the many comorbidities of epilepsy will parallel the ever-increasing advances in the treatment of seizures.

References


Andress DL, Ozuna J, Tirschwell D, et al. Antiepileptic drug- 


Richens A, Rowe D. Calcium metabolism in patients with 

McAuley JW, Koshy SJ, Moore JL, Peebles CT, Reeves AL. 


