Review

The consequences of refractory epilepsy and its treatment

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Abstract

Seizures in some 30% to 40% of patients with epilepsy fail to respond to antiepileptic drugs or other treatments. While much has been made of the risks of new drug therapies, not enough attention has been given to the risks of uncontrolled and progressive epilepsy. This critical review summarizes known risks associated with refractory epilepsy, provides practical clinical recommendations, and indicates areas for future research. Eight international epilepsy experts from Europe, the United States, and South America met on May 4, 2013, to present, review, and discuss relevant concepts, data, and literature on the consequences of refractory epilepsy. While patients with refractory epilepsy represent the minority of the population with epilepsy, they require the overwhelming majority of time, effort, and focus from treating physicians. They also represent the greatest economic and psychosocial burdens. Diagnostic procedures and medical/surgical treatments are not without risks. Overlooked, however, is that these risks are usually smaller than the risks of long-term, uncontrolled seizures. Refractory epilepsy may be progressive, carrying risks of structural damage to the brain and nervous system, comorbidities (osteoporosis, fractures), and increased mortality (from suicide, accidents, sudden unexpected death in epilepsy, pneumonia, vascular disease), as well as psychological (depression, anxiety), educational, social (stigma, driving), and vocational consequences. Adding to this burden is neuropsychiatric impairment caused by underlying epileptogenic processes (“essential comorbidities”), which appears to be independent of the effects of ongoing seizures themselves. Tolerating persistent seizures or chronic medicinal adverse effects has risks and consequences that often outweigh risks of seemingly “more aggressive” treatments. Future research should focus not only on controlling seizures but also on preventing these consequences.

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1. Risks of refractory or uncontrolled epilepsy

More than 50 million people worldwide suffer from epilepsy [1]. Each year, 16 to 134 new-onset epilepsy cases per 100,000 people add to the global burden of epilepsy [2,3]. In a population-based study conducted in Western Europe, the epilepsy in 22.5% of all patients was found to be drug-resistant [4]. Patients with drug-resistant epilepsy account for most of the burden of epilepsy in the population [5] because of the substantial frequencies at which they experience comorbid illnesses [6,7], psychological dysfunction [8], social stigmatization [9], reduced quality of life and increased risk of mortality [10–12], and, ultimately, a decreased life expectancy [6,13]. Therefore, treatment efforts must aim for full seizure control, especially for generalized tonic–clonic seizures. Diagnostic procedures and medical and surgical treatments are not without their own risks [14–19]. However, these risks are usually smaller than the risks of uncontrolled, progressive, or drug-resistant epilepsy. Moreover, these risks must be explained to patients carefully, such that informed treatment decisions can be made.

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1.1. Epidemiology

The incidence of epilepsy in developed countries is approximately 50 per 100,000 individuals per year, with the greatest rates for infants and the elderly [2,20]. In developing and resource-poor countries, where most people do not receive adequate treatment, the incidence is usually greater than 100 per 100,000 individuals per year [2,21]. A decline in the incidence of childhood epilepsy has been observed during the past 30 years in developed countries, but this has been paralleled by an increase in the incidence of epilepsy in the elderly [22,23]. The prevalence of epilepsy in developed countries ranges between 4 and 10 per 1,000 individuals per year [2,20,21], with much greater prevalence rates in developing and resource-poor countries [2], and some estimates at greater than 130 per 1000 individuals per year [3,24].

The seizures in approximately two-thirds of people with epilepsy can be successfully controlled with currently available antiepileptic drugs (AEDs), leaving one-third with uncontrolled epilepsy [25]. The temporal patterns of epilepsy, with a substantial number of patients following a relapsing– remitting course [26,27], can render early identification of patients with drug-resistant epilepsy a difficult task and may explain delays in referrals to epilepsy surgery centers [28,29]. Although up to 24% of patients with drug-resistant epilepsy can achieve remissions for more than 1 year [30–33], physicians should not withhold referral for presurgical evaluation, since two randomized controlled studies have clearly shown superiority of surgical treatment versus continuous medical treatment [34,35]. Based on these studies, the number of patients with temporal lobectomy needed to treat one patient completely seizure-free after years of chronic disabling seizures is $\leq 2$ [34,35]. A delay in referral increases the burden of epilepsy for the overall population, and reduces life spans and quality of life for individual patients.

1.2. Drug resistance and its clinical predictors

In 2010, the International League Against Epilepsy published a consensus definition of drug-resistant epilepsy that aimed to improve patient care and facilitate research, and which should ultimately lead to earlier identification of and better delineation of the syndromes associated with drug resistance [36]. The definition of drug resistance encompasses two hierarchical levels. Level 1 provides a general scheme to categorize response to interventions as seizure freedom, treatment failure, or undetermined, on the basis of standard criteria. Level 1 provides the basis for Level 2 determinations, which form the core definition of drug-resistant epilepsy “as a failure of at least two tolerated, appropriately chosen and used” AED regimens “to achieve sustained freedom of seizures [36].” According to the “rule of three” for calculating confidence intervals for zero events [37], “sustained seizure freedom” requires that the patient be seizure-free for at least three-times the longest interseizure interval before the intervention, or at least 12 months, whichever is greater [36]. This definition conceptualizes drug resistance as a dynamic phenomenon, also allowing for remission over time [26], which can be observed at an annual rate of 4% for adults in prospective series and at even greater rates for children [38–40].

Besides the number of failed AEDs (which is used as a definition criterion), the most consistent predictors of refractory epilepsy are a high frequency of seizures in the early phase of the disease, a neurologic deficit at disease onset, and a structural cause of the epilepsy, as evidenced by MRI [39,41–43]. However, uncontrolled epilepsy is not always drug-resistant [44], and pseudoresistance due to incorrect diagnosis, inappropriate AED, or inappropriate dosage must be ruled out before a patient’s seizures can be considered drug-resistant [45–50].

1.3. Burden of refractory epilepsy

The impact of epilepsy on an individual’s life is a combination of physical consequences of seizures, effects on social position, and psychological outcomes of both. An estimated 26% of the burden of neurologic disorders is caused by epilepsy, calculated in disability-adjusted life-years (DALYs) [51]. In 2011, the global burden of chronic epilepsy for women was greater than that of breast cancer, and was nearly four-times greater than the burden of prostate cancer for men [51]. This calculation includes premature deaths and the loss of healthy life because of disability. However, it does not factor the effects of stigma and social exclusion or their repercussions on families [9,52].

2. Epilepsy and mortality

Mortality is greater for those with epilepsy than for those without for many reasons, including sudden unexpected death in epilepsy (SUDEP), accidents, suicide, vascular disease, pneumonia, and factors directly related to the underlying causes (e.g., brain tumors, neurodegenerative disease). Within epilepsy, mortality is greatest for those with refractory disease. Although this excess mortality has been long-recognized, many large, high-quality studies (all published in 2013) have provided important details about the magnitude of the problem, consistent findings between countries, and specific causes [12,53–61]. Overall, people with epilepsy have a 1.6–to 11.4-times greater mortality rate than expected [55,56,62]. In childhood-onset epilepsy, the standardized mortality ratio (SMR) is 5.3–9.0 [59,63,64]. In a study of 245 children with epilepsy in Finland followed for 40 years, 24% had died (3 times the expected rate) [64]. Cumulative mortality was 37% for those with symptomatic epilepsy and 12% for those with idiopathic/cryptogenic epilepsy (Fig. 1) [64]. Of the 107 patients not in terminal remission (i.e., not seizure-free for the last 5 years), 48% had died. The only multivariate predictor of survival was 5-year terminal remission of seizures [64].

In an older study of 564 newly diagnosed patients from the United Kingdom, those with symptomatic epilepsy had up to a 10-year shorter life expectancy than those without epilepsy [6]. Further, those with epilepsy of unknown cause had up to a 2-year shorter life expectancy [6]. A later follow up of the same cohort for 20 to 25 years found a SMR of 2.55 overall, with a 3.68 SMR (3.05–4.42) for those with symptomatic epilepsy, and a 1.66 SMR (1.33–2.06) for those with idiopathic/cryptogenic epilepsy [65]. These SMRs remained significantly increased 20 to 25 years after diagnosis, despite greater than 70% of patients being in remission. In a very large study of 69,995 people with epilepsy in Sweden followed for an average of 9 years, 8.8% had died, with a median age of 34.5 years at time of death. The adjusted odds ratio for mortality was 11.1 versus the general population and 11.4 compared with unaffected siblings (Table 1) [55].

Fig. 1. Cumulative rate of death according to cause of epilepsy. Copyright © 2010 N Engl J Med. Reproduced with permission from Massachusetts Medical Society.


2.2. Sudden unexpected death in epilepsy

Sudden unexpected death in epilepsy is defined as “sudden, unexpected, witnessed or unwitnessed, nontraumatic, and nondrowning death, occurring in benign circumstances, in an individual with epilepsy, with or without evidence of a preceding seizure and excluding documented status epilepticus [72].” Definite SUDEP requires a postmortem examination that does not reveal an alternative cause of death. If no postmortem examination is performed, the cause is designated “probable SUDEP” [72].

The average incidence is 1 per 1,000 patients with epilepsy per year. In refractory epilepsy, the incidence is 6 per 1,000 patients per year, and the lifetime incidence is 7% to 35%, with the greater end of this range applying to childhood-onset refractory epilepsy [73].

Risk of sudden, unexplained death in those with epilepsy is approximately 16-times that of the general population, after adjustment for multiple factors, including age, sex, and psychiatric and neurologic disease [56]. Sudden unexpected death in epilepsy is most common in young adults, followed by adolescents. Approximately 2000 SUDEP deaths occur each year in the United States [73]. The estimate of “years of potential life lost” to SUDEP is 73,000 per year in the United States, greater than the values for multiple sclerosis, Alzheimer’s disease, and Parkinson’s disease [73].

Having uncontrolled seizures, especially convulsive and nocturnal seizures, is the greatest risk factor for SUDEP [74–77]. However, SUDEP has occurred in patients with seemingly well-controlled epilepsy (rare) and in those who had never had a convulsion (a significant minority of cases). For example, 20% of more than 150 patients who suffered from SUDEP had no history of convulsive seizures in one study [78]. In an older study of 20 SUDEP cases, 4 had no known convulsions in the prior year, and 2 had been reportedly seizure-free [79].

Approximately 80% of witnessed or recorded SUDEP cases are associated with seizures. Although earlier studies had suggested that polytherapy or specific medications were associated with SUDEP, this does not appear to be the case (with controlling for frequency of convulsions) [80,81]. In fact, adding an AED to therapy rather than placebo appears to lower the rate of SUDEP, at least in the short term, based on a meta-analysis of 112 randomized controlled trials of AEDs [82].

In that meta-analysis, the rate of SUDEP was 0.9 per 1,000-patient-years in the active AED arm vs. 6.9 in the placebo arm (odds ratio of 0.17 for SUDEP, p = 0.005, and odds ratio of 0.37 for all mortality). In addition, a study employing Medicaid claims data for 33,658 patients found that periods of nonadherence to AEDs were associated with a tripling of mortality, as well as increases in emergency department visits, motor vehicle accidents, fractures, and hospitalizations [83].

2.3. Causes of SUDEP

In most witnessed or recorded cases, respiratory issues appear to precede cardiac arrhythmias. Hypoxemia, mainly associated with central apnea, occurs with many seizures, and not just generalized convulsions. In one investigation, 35% of focal seizures without secondary generalization were associated with oxygen saturation below 90%, and 11% of these seizures fell below 80% [84]. Serotonin deficiency may play a role in pericardial apnea as has been found in sudden infant death syndrome [85,86]. In an animal model of SUDEP, boosting serotonin concentrations prevented seizure-related apnea and death [87,88]. Generalized EEG suppression, or “central shut down,” may also occur early. In one study, duration of postictal EEG suppression was strongly correlated with risk of SUDEP [89], but this was not found in another study [90]. Many cardiac and autonomic changes have been discovered in ictal and postictal settings. Recent data suggest that genes associated with ion channels expressed in both the heart and brain may predispose to seizure-related cardiac arrhythmias, and may be part of the combination of factors necessary to lead to SUDEP [91]. Other contributing factors may include acidosis, the prone position, rebreathing of CO₂, excessive adenosine or opioids, spreading depression, or laryngospasm [74–76,92–96].

An important recently published international study (MORTEMUS [97]) on mortality in epilepsy monitoring units (EMUs) identified 16 cases of SUDEP and 9 cases of near-SUDEP (successfully resuscitated) at 148 EMUs, mostly in Europe [97]. Fourteen of the 16 SUDEP cases occurred at night, and most patients were not directly supervised at

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Table 1

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio for Death Compared with Population Controls (95% CI)</th>
<th>Odds Ratio for Death Compared with Unaffected Sibling Controls (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>11.1 (10.6–11.6)</td>
<td>11.4 (10.4–12.5)</td>
</tr>
<tr>
<td>Natural causes</td>
<td>15.5 (14.6–16.4)</td>
<td>16.7 (14.9–18.7)</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>11.2 (10.3–12.2)</td>
<td>11.3 (9.4–13.7)</td>
</tr>
<tr>
<td>Nervous system</td>
<td>71.1 (57.3–88.4)</td>
<td>86.9 (543–139.1)</td>
</tr>
<tr>
<td>External causes</td>
<td>3.8 (3.3–4.0)</td>
<td>3.2 (2.7–3.7)</td>
</tr>
<tr>
<td>Suicide</td>
<td>3.7 (3.2–4.2)</td>
<td>2.9 (2.4–3.6)</td>
</tr>
<tr>
<td>All accidents</td>
<td>3.6 (3.1–4.1)</td>
<td>3.6 (2.9–4.5)</td>
</tr>
<tr>
<td>Vehicle</td>
<td>1.4 (1.1–1.8)</td>
<td>1.5 (1.1–2.2)</td>
</tr>
<tr>
<td>Other</td>
<td>5.5 (4.7–6.5)</td>
<td>6.3 (4.6–8.8)</td>
</tr>
<tr>
<td>Drug poisoning</td>
<td>5.1 (3.9–6.5)</td>
<td>5.7 (3.3–9.7)</td>
</tr>
<tr>
<td>Fall</td>
<td>8.5 (5.3–13.7)</td>
<td>10.0 (2.9–33.8)</td>
</tr>
<tr>
<td>Drowning</td>
<td>7.7 (4.7–12.7)</td>
<td>9.5 (3.5–25.7)</td>
</tr>
<tr>
<td>Other and unspecified</td>
<td>4.9 (3.6–6.5)</td>
<td>5.2 (3.2–8.5)</td>
</tr>
<tr>
<td>Assault</td>
<td>2.8 (1.6–4.8)</td>
<td>1.7 (0.9–3.3)</td>
</tr>
</tbody>
</table>

Data are adjusted odds ratios (aOR) of external deaths compared with population controls (matched for age and sex, and adjusted for income, and marital and immigration status) or unaffected sibling controls (adjusted for age and sex).

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time of death. Fourteen of the 16 cases occurred with patients in the prone position, and all were preceded by a convulsive seizure. Seven of the 9 near-SUDEP cases also followed a convulsion. All successful resuscitations began within 3 minutes of arrest, whereas all unsuccessful ones began after at least 10 minutes [97]. In the 10 cases with adequate cardiac, respiratory, and video monitoring, a consistent but complex pattern was detected consisting of postictal tachypnea, followed by an early, centrally mediated, parallel collapse of both cardiac function and respiratory function within 3 minutes postictically [97]. This was terminal in one-third of the cases, but transient recovery occurred in the rest. In the cases with transient recovery, gradual failure of respiration developed, with terminal apnea always preceding terminal asystole [97].

2.4. SUDEP prevention

Maximizing seizure control is the only proven method of decreasing the risk of SUDEP. Besides the evidence for this method observed in studies on medication noncompliance and the placebo arms of the AED studies described above, additional supporting evidence comes from several studies demonstrating that SUDEP risk for those rendered seizure-free after epilepsy surgery is markedly decreased [76,98–102]. However, the evidence that surgery itself is what lowered the risk is not definitive, as these data were not from randomized trials, and intrinsic differences in SUDEP risk between patients amenable to surgical cure and those who are not may confound the results.

Nocturnal supervision appears to be protective-based on three studies: MORTEMUS [97], during which most deaths in EMUs occurred at night with inadequate supervision (by medical staff in this case); a case-controlled study showing a reduced risk of SUDEP with nighttime supervision (room sharing or listening device) [78]; and a study of children with severe epilepsy living in a residential school, with all 14 deaths occurring during breaks outside the school, rather than when children were closely supervised in school [103]. Most of these deaths were unwitnessed. Discussing the risk of SUDEP with patients and families is strongly recommended for virtually all people with epilepsy, as it will likely help patients maximize compliance and avoid seizure triggers such as sleep deprivation and alcohol use. Seizure alarms are beginning to be investigated scientifically, with technical improvements and further data likely to emerge quickly [74,104,105]. Rapid advances in SUDEP research should help elucidate risk factors, mechanisms, and other preventive strategies.

3. Epilepsy as a progressive disorder

Epilepsy progression may be considered the worsening over time of seizure control, cognition, behavior, structural abnormalities, EEG patterns, or social interactions in patients who do not have underlying progressive brain disorders. This is a controversial area, with evidence for and against epilepsy as a progressive disease. The heterogeneity and difficulties in classifying seizures and different forms of epilepsy [106], and in characterizing resistance to AEDs [36,43,107], are additional obstacles to defining when and how epilepsy progression occurs [27,108–111].

Some types of epilepsy progress over time [112,113], while others most likely do not (e.g., childhood absence and juvenile myoclonic epilepsy [106,114,115]). However, high-seizure frequencies may be related to worse social adjustment outcomes [116]. In addition, one study of patients with idiopathic generalized epilepsies with only tonic–clonic seizures found that reductions of thalamic volumes and fronto-central and limbic cortices occurred faster in patients with poorer seizure control [117]. It is unclear if the progression of damage with some focal epilepsies depends on underlying etiologies, prolonged focal seizures, frequencies of secondary generalized seizures, durations and frequencies of focal seizures, genetic predisposition, other environmental factors (e.g., viral infections, head trauma), or a combination of these factors [111,118–124]. Whether some epilepsy syndromes are progressive but not medically refractory is still unclear. However, preliminary evidence indicates that, in the context of familial mesial temporal lobe epilepsy (TLE), patients experience hippocampal volume reductions over time independent of seizure frequency [125]. Furthermore, structural and functional damage occurs in patients achieving good response to AEDs [126], and in patients with new-onset TLE [127].

3.1. Neuroimaging and structural damages

Evidence that some types of epilepsy do progress over time is derived from neuroimaging studies. Different studies have demonstrated structural damage to be more pronounced in individuals with longer durations of epilepsy, and others have been able to quantify this progression over time. However, other studies have failed to demonstrate progression, possibly because of the heterogeneity of the individuals evaluated [109].

Neuroimaging studies have shown widespread extrahippocampal neuronal damage and dysfunction in patients with mesial TLE with and without hippocampal sclerosis [124,128–132]. This damage progresses over time [133–138] and improves after successful surgical treatment [139–141]. However, it is still unclear why, when, and how brain damage occurs in TLE. Seizure frequency is considered the most important factor for progression in mesial TLE. However, it is possible that not all types of seizures induce damage, or that some individuals are more resistant to seizure-induced damage [136,142,143]. Genetic background, age, type of initial brain insult, and other environmental factors most likely interact in several ways, making it difficult to determine the underlying mechanisms of damage progression in TLE [136].

Mechanisms responsible for or that influence the development of chronic epilepsy differ from those that actually precipitate acute epileptic seizures [108]. Another variable is that seizure-related damage may be expressed in many ways, and does not necessarily represent neuronal loss or atrophy. For example, patients with mesial TLE often have progressive memory loss and, sometimes, cognitive impairment, as well as progressive increases of bilateral epileptiform discharges on EEG [112,113,142,144–149]. These observations suggest that focal epilepsy may lead to neuronal dysfunction remote from the seizure foci.

3.2. “Seizures beget seizures”

The concept introduced by Dr. William Gowers (1881) that “seizures beget seizures” indicates the implicit concept that epilepsy may be a progressive disorder related to the occurrence of seizures [150]. Since then, or maybe even before, the “cause–of–consequence” issue of repeated seizures and brain damage (and, more specifically, hippocampal sclerosis in TLE) has been debated [111,142,151–155].

Descriptions of SE leading to neuronal changes in rats and humans abound, especially in the hippocampus, which clearly indicate that seizures in the context of SE can cause hippocampal sclerosis and further TLE [111,156–159]. However, there is also evidence for the occurrence of MRI signs of hippocampal sclerosis in people without epilepsy or preceding the onset of seizures, clearly indicating a strong genetic influence in the development of hippocampal sclerosis [160–162].

The 1954 Meyer’s hypothesis [163,164] that hippocampal sclerosis is both a cause as well as a consequence of epileptic seizures in TLE has been supported by more recent investigations [153,165]. By expanding the concept of initial precipitating injury (IPI) to include any significant medical event likely to injure the brain before the onset of epilepsy, such as prolonged focal seizures, trauma, hypoxia, and intracranial infection, studies of surgical series of mesial TLE have found a strong association between hippocampal sclerosis and IPI [153]. These studies support the concept that hippocampal sclerosis is likely an acquired pathology, and most of the neuronal loss occurs with the IPI. However, ongoing frequent seizures do cause additional progressive hippocampal damage [133–135,137,138,153,166].
The main limitation of studies investigating effects of seizure frequency on progressive epilepsy damage is reliance on patients’ and observers’ accounts, which are well-known to be inaccurate [166]. In addition, many patients have seizures that go unnoticed or are not remembered, particularly in TLE.

Another chicken-or-the-egg dilemma is whether more extensive structural damage induced by IPI causes more frequent seizures or more frequent seizures cause more widespread damage [124,167]. Patients with refractory epilepsy seem to have frequent seizures from the beginning of their epilepsies, have seizures that fail to respond to AEDs early in their disease courses, and may have widespread damage from onset of epilepsy [27,43,124,127]. In contrast, patients with good response to AEDs tend to have well-controlled seizures and perhaps even achieve remission [126,163,167].

Some studies support the hypothesis that generalized seizures and not focal seizures are the main cause of progressive damage [122,168]. In contrast, some community-based studies or other studies with very heterogeneous groups of individuals failed to associate seizures with further injury in individuals with epilepsy [151,169,170]. This suggests that most of the brain damage occurs before the onset of seizures or develops insidiously over a more prolonged period [121].

### 3.3. Duration of epilepsy

Duration of epilepsy, independent of seizure frequency, has also been associated with epilepsy progression, in the region of putative seizure onset [171,172] and in remote areas [137,172]. Earlier age of epilepsy onset has also been related to worsening of structural damage in TLE [172,173], as well as to an adverse neurodevelopmental impact on brain structure and function [173].

### 3.4. Epilepsy progression and response to antiepileptic drugs

Community-based studies of patients with several years of delay before starting AED therapy show patterns of response similar to those for patients with newly diagnosed epilepsies [174,175].

The influence of AED exposure in epilepsy progression is also not well-understood. One study [169] showed generalized brain atrophy more commonly in patients with increased exposure to AEDs, independent of seizure control. However, no large conclusive data set investigating the different types and mechanisms of various AEDs has been published, rendering this a difficult issue to address. The majority of individuals with refractory epilepsies (i.e., those more susceptible to epilepsy progression) are exposed to greater dosages/regimens of AEDs, compared with those with good seizure control (i.e., those less susceptible to damage progression also tend to receive lesser AED dosages, and less frequently receive polytherapy). Therefore, with the relationship between widespread brain damage (at least in part, preceding seizure onset) and high frequency of seizures, one of the best prognostic factors appears to be response to the first AED tried. Approximately 60% of patients with epilepsy will become seizure-free with the first one to two AEDs, and approximately 4% with further AED trials [43].

Despite the controversial views of the results of different studies (Table 2) — which may be related to the heterogeneity of the patients included — most current evidence indicates that TLE is often a progressive disorder. In this context, for patients with refractory seizures, resistance to AEDs must be defined early, and surgery or other alternative treatments must be considered as soon as possible. Early control of seizures may decrease the risk of progressive structural, cognitive, and behavioral damage related to repeated seizures.

Secondary epileptogenesis is the concept that an initial seizure focus over time can generate a secondary focus that, with additional seizures and time, will become independent of the initial focus. Secondary epileptogenesis is readily demonstrated in animals by kindling [177,178], but its presence in humans is controversial. Morrell [149,179] studied a series of patients with tumor-related epilepsy and found clinical, EEG, and/or pharmacologic evidence of secondary epileptogenesis in 34% of these patients. Unlike epilepsy secondary to trauma, infection, or vascular disease, tumors present an etiology for which the development of additional ictal foci would be highly unlikely. Morrell concluded that the more frequent the seizures and the longer the epilepsy duration, the more likely a secondary focus would be to become permanent and independent of the initial inciting focus [149,179]. This is in keeping with the observation that bitemporal spiking occurs frequently in patients with unilateral temporal-lobe seizure onsets [180]. However, the contralateral spikes tend to decrease or disappear after successful surgery [181].

The data on the “pros” and “cons” of the progression of damage in epilepsy presented above clearly indicate that the issue is complex and heterogeneous and needs to be examined further in more homogeneous groups of patients. Therefore, until we have more robust evidence, it is up to readers to decide whether epilepsy is a progressive disorder or not on the basis of the available data and the readers’ own judgments.

### 4. Neuropsychiatric comorbidities of refractory epilepsy: the chicken or the egg?

As the foregoing sections suggest, most of the mortality and morbidity of epilepsy is borne by patients with chronic refractory seizures. Therefore, it has often been assumed that seizure activity itself is the primary cause of the cognitive, emotional, and behavioral comorbidities that commonly occur. The extensive literature on the topic, going back many decades, shows that patients with chronic seizures experience greater rates of cognitive deficits, emotional problems, physical and psychiatric disease, health care utilization, educational and occupational underachievement, failure in fulfilling normal social roles, and reduced quality of life [115,182–191]. Many psychosocial problems improve when chronic seizures remit [34,35,192–194]. For example, 31% of young adults in one longitudinal cohort continued to have seizures 15 years after diagnosis. Approximately 45% of these were employed, compared with approximately 88% of patients who had been in remission at least 5 years [192]. It is, therefore, not surprising that efforts to understand and treat comorbidities have historically focused on determining the mechanisms by which seizures become refractory and developing treatments to suppress them. However, it is increasingly apparent that the effects of refractory epilepsy go beyond the effects of seizures themselves. A growing body of literature suggests a more complex set of causal relationships than has previously been considered. In a nutshell, it is increasingly clear that neuropsychiatric comorbidities are evident prior to the onset of observable seizure activity, or sufficiently soon after onset that they are unlikely to have been caused by seizure activity itself. They, therefore, are likely to reflect pre-existing, otherwise “clinically silent,”

Table 2
Natural history of epilepsies: controversies.

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<tr>
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<tbody>
<tr>
<td>Tendency toward progressive reduction of seizure-free intervals in populations without treatment</td>
<td>Untreated population: no unfavorable evolution</td>
</tr>
<tr>
<td>Worse prognosis of seizure control related to the number of seizures prior to treatment</td>
<td>Tendency of worsening over time related to inherent severity of the disease</td>
</tr>
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</table>
structural or functional abnormalities that eventually evolve into clinical seizure foci.

Epidemiologic studies have provided the first clues that comorbidities can precede the onset of seizures. In two large, independent population cohorts followed prospectively, those who ultimately developed idiopathic or cryptogenic epilepsy were more likely than controls without epilepsy to have had prior diagnoses of the inattentive type of ADHD, depression, and suicide attempts [195–197]. Because these studies were limited to idiopathic (presumed genetic) or cryptogenic (presumed developmental) cases, the associations cannot be explained by pre-existing (e.g., remote-symptomatic) neurologic insults. Developmental, stress-related, hypothalamic–pituitary–adrenal axis dysfunction and associated abnormalities in hippocampal neurogenesis and cell death may underlie the comorbidity of some forms of refractory epilepsy and depression [198]. Of children with idiopathic or cryptogenic epilepsy who had received special education services in a longitudinal, population-based study, 31% had begun receiving services before the onset of clinical seizures [188].

Studies of recently diagnosed patients are necessarily confounded by retrospective assessment, medications, and recent seizures. Nevertheless, they provide the best estimates of antecedent functional and structural deficits in the absence of large prospective studies of at-risk persons. Children with first-recognized seizures were 2.8–times more likely than their siblings to be perceived by their parents as having had clinically significant attention problems in the preceding 6 months [199]. Cognitive deficits compared with those of controls have been evident within 3 to 12 months of diagnosis, even in nonmedicated patients [200–202]. Children diagnosed with localization-related epilepsy within the previous year had greater cortical gray-matter volumes in various brain regions compared with cousin controls [173]. Children with idiopathic generalized epilepsies had greater gray-matter and lesser white-matter tissue volumes throughout the frontal, parietal, and temporal regions, including subcortical structures with lesser gray-matter tissue volumes in the medial orbitofrontal region [173].

Although these findings suggest that structural and functional abnormalities often precede the onset of seizures and medication use, they remain inconclusive. Stronger evidence for antecedent functional and structural abnormalities could come from studies of unaffected probands in highly familial forms of epilepsy. For example, frontothalamic networks that support executive function are deficient in juvenile myoclonic epilepsy [203]. Unaffected siblings of these patients performed better on a task of executive function than probands, but performed worse than unrelated healthy controls [204].

In summary, persisting seizures place a large psychosocial burden on patients, families, and society. However, many “essential comorbidities” precede seizure onset and the refractory state in “epilepsy-only” patients (Table 3), account for many psychosocial consequences, and may persist even when seizures become controlled. In light of these new studies, it is important to consider that refractory seizures are just one of a number of signs and symptoms of a heterogeneous set of genetic, developmental, and acquired refractory epilepsy syndromes. At the basic scientific level, this implies that epileptogenic processes may share common vulnerabilities and etiologic processes with these comorbid conditions. At a clinical level, it implies that the aim of “no seizures, no adverse effects” is a necessary but insufficient waypoint toward the goal of significantly improving the quality of life of those with refractory epilepsy. Therefore, concepts of aggressive treatment must take a broader scope by incorporating early diagnosis and treatment of comorbidities.

### 5. Risks of antiepileptic drug treatment

Patients with chronic epilepsy usually require long-term treatment with AEDs, and those with refractory epilepsy often receive polytherapy. Potential treatment outcomes and subsequent decisions are outlined in Fig. 2 [205]. Adverse effects of AEDs have been reviewed in detail elsewhere [206–208]. In general, the adverse effects of AEDs can be divided into the following categories: (1) dosage-related for that individual patient (there is considerable overlap of central nervous system adverse effects characterized by lethargy, dizziness, and behavioral and cognitive impairment. These symptoms are mostly dosage-related and are more prevalent with certain AEDs [e.g., topiramate: word-finding difficulties and confusion, and levetiracetam: behavioral changes]); (2) hypersensitivity reactions, usually within 2 to 3 months of initiating a specific agent for many AEDs, but specific guidelines for use (age, coadministration, and dosage-increase rate) have obviated the occurrence in many patients; (3) long-term adverse events (e.g., cerebellar atrophy, retinal dysfunction, aplastic anemia, and lymphoma), greater awareness of which has led physicians to switch to AEDs with more favorable long-term safety profiles; (4) adverse drug–drug interactions, which are much more common with first-generation AEDs; (5) long-term, adverse hormonal and metabolic adverse effects related to use of P450–inducing agents (e.g., exacerbation of osteoporosis and acceleration of vascular disease) [209]; and (6) structural and cognitive teratogenicity, including lower intelligence quotients, which are most specifically associated with use of sodium valproate. These effects are not mutually exclusive. For example, valproate-related tremor may be both idiosyncratic and dosage-related for an individual patient.

All AEDs may potentially have adverse effects. Some of these may be subtle, or may be only apparent retrospectively (i.e., after discontinuing a particular drug after its long-term use). Behavioral and mood effects may be particularly problematic in determining a true cause–effect relationship. However, a careful analysis of the temporal relationship between the onset or worsening of symptoms and the initiation of a particular drug usually informs a reasonable clinical decision to either continue or stop treatment. Not infrequently, AED choice is determined by the presence of comorbid conditions for which a particular AED may also be effective (e.g., migraine: topiramate and valproate; mood stabilization: lamotrigine and valproate). Advances in pharmacogenomics are beginning to yield clinical relevance. For example, carbamazepine hypersensitivity may be predicted by the presence of the HLA-B*1502 allele in Han Chinese [210], and by that of the HLA-A*3101 allele in Caucasians [211]. Further collaborative study in pharmacogenomics (e.g., EpivPGX [212]) may uncover other genomic markers to help predict serious adverse effects and, thus, allow for more tailored and safer treatment decisions for patients.

Valproate teratogenicity is now well-recognized, and is a significant limiting factor in prescribing valproate to women of child-bearing age. This can pose difficult risk–benefit decision-making, particularly for young women with idiopathic generalized epilepsy, and especially for those with more refractory disease. In addition, recent evidence is accumulating that children born to mothers receiving sodium valproate are more likely to experience learning difficulties and autistic spectrum disorders compared with children exposed in utero to other AEDs, such as carbamazepine, lamotrigine, and levetiracetam [213,214].

Some very effective AEDs are also limited by idiosyncratic adverse drug reactions. For example, vigabatrin, which can be an effective drug for a variety of epilepsies, may cause a peripheral retinopathy leading to (an often asymptomatic) visual field constriction in approximately
one-third of patients [215]. For this reason, the drug is uncommonly used, especially in adult patients, including those with refractory disease who may benefit from therapy. The mechanism of this retinopathy is unclear. It may have a pharmacogenomic basis, but studies to date have been unrevealing [216].

6. Risks of nondrug treatments

6.1. Surgery

Surgery candidacy is a quantitative rather than a binary variable. Risk–benefit analysis for surgery includes not only the risks, but also the realistic expectations (e.g., seizure freedom vs. seizure reduction). For example, the risks associated with a temporal resection are greater than the risks associated with neurostimulation. However, if the goal is a seizure-free outcome, the analysis will favor surgery over neurostimulation.

6.1.1. Resective surgery

Temporal lobe resections are the safest, with a serious complication rate of <5%, and with continually improving techniques [217]. Nonlesional extra-temporal resections have a greater rate of complications and a lower rate of seizure freedom. Invasive EEG is often used for extra-temporal resection, and that carries its own risks [218]. Lesional extratemporal resections are somewhere in-between. The most frequent adverse effects of temporal lobe surgery are superior quadrant visual field defects (~8% for temporal lobectomies and rare for selective resections), wound infections (~5%) [217], and mild verbal memory decline with dominant resections (~8%) [18]. These are usually acceptable risks, given the probability of obtaining a seizure-free outcome.

6.1.2. Corpus callosotomies

These are palliative (not aiming at seizure freedom), and are performed for “drop seizures” and other severe motor seizures in refractory, symptomatic, generalized epilepsy. Surgical complications are rare with two-phase surgeries (anterior two-thirds possibly followed by the posterior third). The control of drop attacks with a callosotomy can be life- and injury-saving. Because these patients almost always have major pre-existing neuropsychological deficits, cognitive complications are generally minimal [219].

6.1.3. Hemispherectomies

These are performed in young patients with severe epilepsy, usually with hemispheric lesions and deficits (hemiplegia and visual field cuts). Therefore, they are usually well-tolerated from a neurologic deficit point of view. Surgical complications, such as hydrocephalus, which may necessitate a shunt, may occur. Rates and outcomes of surgical complications have improved over time, with refinements in techniques, and use of functional rather than anatomic procedures [220]. A seizure-freedom rate of 60%–65% is an important part of the risk–benefit analysis [221].

6.2. Neurostimulation

6.2.1. Vagus nerve stimulation

Available in the United States since 1997, VNS typifies the “low-risk, low-reward” paradigm. As an extracranial procedure, VNS carries minimal surgical risk and minor tolerability symptoms (i.e., hoarseness, cough, voice change) during stimulation [222]. Infections of the generator or lead sites (as with any surgery) are possible but uncommon, occurring in 3% to 5% of patients in one report [223]. Reports of arrhythmias are also uncommon [223].

6.2.2. Deep-brain stimulation

Deep-brain stimulation uses intracranial electrodes to stimulate brain structures presumed to restrict seizure activity. The one and only pivotal trial employed stimulation of the anterior nucleus of the thalamus (N = 110), and no deaths were reported related to the device or procedure. There were five reports of hemorrhage (none symptomatic), and 14 infections (none parenchymal — generator pocket, lead track, burr hole, meningeal) [224]. Deep-brain stimulation is approved in many countries but not in the United States.
6.2.3. Responsive neurostimulation

Responsive neurostimulation employs subdural and/or intraparenchymal electrodes in a closed-loop approach to seizure control. The device detects the onset of seizure activity in the implanted electrodes and then sends back an electrical stimulation to the seizure focus. In a pivotal trial (N = 191), no deaths related to the procedure or device occurred. Five percent of patients experienced hemorrhage. None had permanent neurologic deficit. There was a 5% infection rate (all of soft tissue only), with 4 device explanations [225]. Responsive neurostimulation was approved in November 2013 by the U.S. Food and Drug Administration and will likely become available elsewhere in the near future. Responsive neurostimulation has the capacity to treat two epileptogenic foci, and provides useful diagnostic information as well, including documentation of seizures and onset sites.

Neurostimulation treatments may limit the availability of body MRI once they are implanted, which is a disadvantage. Interestingly, there are no dramatic differences in efficacy between the three neurostimulation treatments above, but the complications are greater for the two intracranial techniques. At present, VNS may be the preferable option, by virtue of its risk–benefit ratio. Opinions on the use of neurostimulation techniques vary widely among Level-4 centers [226,227].

6.3. Diet

The ketogenic, modified Atkins, and other related diets have been shown to have some efficacy in seizure reduction, with the ketogenic diet being the most effective but the least well-tolerated. When used properly, each has fairly minimal risks. Constipation, nausea, and other gastrointestinal symptoms can occur initially. Nutritional deficiencies may occur and necessitate the use of vitamin, mineral, and calcium supplements. The ketogenic diet is more strict and, therefore, often used in young children. The initial risks of dehydration and hypoglycemia are mitigated by initiation in the hospital. Neither the ketogenic nor the Atkins diets appear to significantly increase long-term cardiovascular risks. For seizures, they are usually used only for a short time. Late-onset complications during maintenance therapy for chronic illness can be monitored and avoided for the most part [228].

7. Conclusions

In presenting a treatment option, a clinician will typically review with the patient the various pros and cons of the treatment. In epilepsy, a physician typically discusses the probability of complete seizure control or significant improvement versus the AE profile associated with the treatment. We believe that the risks of doing nothing or making no changes are rarely discussed with patients, especially the consequences of continued seizure activity, including the risks of mortality and morbidity. For patients with refractory epilepsy, the risks of continued seizures may outweigh the risks of treatments, including those with possible serious adverse effects. Yet, in discussions with patients, those treating epilepsy typically should balance the discussion between improving seizure control and the potential for experiencing AEs. Highly efficacious epilepsy treatments associated with increased risks, such as vigabatrin (vision loss) or felbamate (aplastic anemia), or more invasive procedures (callosotomy, DBS) are probably rarely discussed. As this review clearly outlines, the risk of continuing seizures is associated with significant mortality and morbidity and needs to be included in any discussion of treatment options. The risk of doing nothing or avoiding an efficacious treatment associated with an increased risk must be included in the risk–benefit discussion. Clearly, for some patients, the risk of a potentially high-risk treatment is significantly less than the risk of a potential AE from ongoing seizures. Clinicians need to include assessments of loss of life, quality of life, and epilepsy morbidities as part of any treatment discussion.

Author contributions

Dr. Eugen Trinka drafted the introduction on risks of refractory and uncontrolled epilepsy; Dr. Lawrence J. Hirsch drafted the section on epilepsy and mortality; Dr. Fernando Cendes wrote the section on progressive epilepsy; and Dr. John Langfitt prepared the section on neuropsychological, educational, and vocational consequences. In addition, Drs. Norman Delanty and Trevor Resnick developed the section on the risks of drug therapies, and Dr. Selim R. Benbadis contributed the section on nondrug treatments. Dr. Kenneth D. Laxer prepared the conclusions and served as the overall scientific editor for the review.

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References


Bell GS, Galtariz A, Bell CL, Johnson AL, Sander JW. Suicide in people with epilepsy: how great is the risk? Epilepsy 2009;50:1933–42.


Bell GS, Galtariz A, Bell CL, Johnson AL, Sander JW. Suicide in people with epilepsy: how great is the risk? Epilepsy 2009;50:1933–42.


Bell GS, Galtariz A, Bell CL, Johnson AL, Sander JW. Suicide in people with epilepsy: how great is the risk? Epilepsy 2009;50:1933–42.


Bell GS, Galtariz A, Bell CL, Johnson AL, Sander JW. Suicide in people with epilepsy: how great is the risk? Epilepsy 2009;50:1933–42.


