Past, Present and Future in the Search for the Perfect Anti-epileptic Drug

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Past, Present, and Future
In the
Search for the Perfect Anti-epileptic Drug

Kristin Robinson

2002
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Course Paper

Abstract

This paper explores the development of anti-epileptic drugs, starting with the earliest forms of treatment, moving to the drugs currently in use and those recently approved by the FDA, and ending with the drugs (and devices!) that will likely be approved for use in the near future. It covers all aspects relating to such drugs, examining why the need for an effective drug is so significant, how a specific medication is chosen by a physician and his patient, the special considerations for anti-epileptic drug use in certain populations, the
problems with the current approval process for anti-epileptic drugs by the FDA, and the scientific advances that have been and continue to be made in the search for a safe and effective anti-epileptic drug.

Prologue: My Experience with Anti-epileptic Drugs

2.5 million people in the United States suffer from epilepsy. I am one of them.

I was diagnosed in January 2001, the middle of my first year of law school. I was preparing for my return to Cambridge following Christmas vacation when, without warning or precedent, I was struck by a generalized tonic-clonic seizure (popularly known as a grand mal seizure). In the emergency room I was prescribed the first of the several anti-epileptic drugs I would try. It was what I now know to be a standard “first-line” drug called Dilantin.

I went to a neurologist the following day, and over the next week took a series of diagnostic tests. Having hoped that this was just a random, isolated experience (many people have a seizure at some point in their lives, never to have one again), my parents and I were shocked and dismayed by my diagnosis: epilepsy.

Since that day, I have done my best to learn everything possible about epilepsy, both the condition in general and mine in particular. I have learned about the causes of epilepsy (like 70 percent of other sufferers, the cause of my seizures is unknown, or idiopathic), the typical age of onset (childhood or old age – neither of which describe me) and, through trial and error, the medications available to treat epilepsy.

1Natalie Frazin, White House-Initiated Conference on Epilepsy Emphasizes “no seizures, no side-effects” NINDS publications, at www.ninds.nih.gov. The NINDS (National Institute of Neurological Disorders and Stroke) is the primary Federal supporter of research on disorders of the brain and nervous system.
Finding the correct anti-seizure medication is a difficult task, and takes into account many factors. In the patient’s mind only two really matter: seizure control and side effects. My first medication, Dilantin, did an excellent job of controlling my seizures. Unfortunately it also had severe cognitive and psychological effects. I was unable to concentrate on my schoolwork, unable to put thoughts together in response to questions and, when a thought would come to me, unable to put it into words. I also found myself having tremendous mood swings and, though I have always had a very happy, optimistic and upbeat personality, I often felt depressed (though that could have been the diagnosis itself, the lifestyle changes that accompanied it, or simply the effect of my first winter in Boston). I even considered leaving Harvard Law School. Though my family and friends were consoling and my doctors told me that these side effects were normal, I had no idea how common they were or that other medications were available.

Complaints about my cognitive impairment finally led my doctor to change my medication, again to an older, well-established medicine called Depakote. Besides the patient insert, I was given no notice of the extreme side effects of this drug, and was not told of them until five months later when, after gaining 25 pounds, continuing to feel depressed, and having three more seizures, my doctor suggested that perhaps this was not the correct medication for me.

The next (and hopefully final) attempt at an effective, side effect-free medication was a new and promising drug called Lamictal. Though its long-term effects are not as well documented, clinical trials have demonstrated its efficacy in seizure control and its relative lack of side effects. Because of the possibility of a severe life-threatening rash or increased seizure frequency, it is necessary to start doses of Lamictal at a low level, slowly working up while weaning the patient off the former drug.

Fortunately, despite some recent setbacks associated with my final (and long awaited) removal from Depakote and increase in Lamictal dosage, we seem to have found the correct drug for me (though recent tests have not yet confirmed that finding and I may be switching again in the near future). Although we will not know
for two years whether it is truly effective (the length of time a person has to be seizure-free before a drug is generally concluded to be working), I feel confident that it will be, and that I will be one of the 80 percent of epilepsy patients who are able to achieve long-term relief from their seizures through modern medical treatments.

I chose to write my paper on the topic of anti-epilepsy drugs for two reasons. One, obviously, is my personal interest in the subject stemming from my own epilepsy. The other is a desire to teach others who, though well educated, know very little about this extremely common but often misunderstood problem, its causes, and the methods available to treat it. I was certainly one of those people a year and a half ago. Perhaps through the posting of this paper on the class website I will shine some light on the subject for someone who has never known somebody with epilepsy and has many misunderstandings about the disorder, someone who knows somebody with epilepsy and would like to increase his or her knowledge of the condition, or someone like me, who has epilepsy and derives a good deal of comfort from knowing that treatments and medications to eradicate the seizures are constantly being developed and improved.

This paper took me a good deal of time to write, much longer than anticipated. I am sorry if it is over-inclusive, but so much about epilepsy medication is tied to other aspects of the disorder that it was difficult to disentangle them. Each piece of information I found led me to other interesting facts. Reading about modern medications and their development, for example, led to books about the history of documented epilepsy and some of the older (horrific!) treatments used. Learning about the medications currently prescribed led me to question why a doctor might prescribe a certain one; because that decision is due partly to the type of seizure a person experiences, I began to research the causes for different types of seizures; and because certain causes of seizures are related to a person’s age, sex, or other unrelated illnesses, I wrote about special considerations in medicating women, the old and young, and those with heart, liver, blood, or

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other diseases. It all seemed so relevant to my life that I had a difficult time sifting out what was relevant to my paper.

In March of 2000, the White House convened a conference on the current state of epilepsy research and hopes for the future. The slogan adopted at the conference, which was attended by scientists, doctors, people with epilepsy, policy makers and volunteers, was to develop an epilepsy treatment with “no seizures, no side effects.” With adequate time, money and energy put into achieving that goal, the day is not too far off when people with epilepsy will be able to lead normal lives, free from frightening and dangerous seizures and free from frustrating and embarrassing side effects. A “miracle drug” is out there somewhere, just waiting to be discovered. Like all other epilepsy sufferers, I eagerly await that discovery.

**The History of Anti-epileptic Drugs**

“There is scarcely a substance in the world capable of passing through the gullet of a man that has not at one time or another enjoyed the reputation of being anti-epileptic”

— Edward H. Sieveking (1816 – 1904)

Epilepsy is an affliction as old as time. Prehistoric man most likely suffered from the condition; evidence of trephining (drilling holes in the skull to cure neurological disorders) has been found among fossilized bones.

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3. See Natalie Frazin, supra note 1.
Ancient Babylonian texts refer to seizure disorders, as do the texts of ancient Egypt, Greece, Rome, China and India. The Bible, too, contains description of maladies that could only be categorized under the modern definition of epilepsy. And, as with most diseases, along with the earliest descriptions of the disorder of epilepsy come the earliest recorded attempts at a cure.

The seizure prevention techniques used by the ancients may seem absurd, disgusting or profoundly disturbing today, but they represent an effort to combat what were seen at the time to be the causes of epilepsy. In ancient Greece, for example, where emotional disturbances, “auras”, and external factors such as temperature and humidity were viewed as causal, suggested remedies included a modification of one’s diet, an increase in exercise, rest and relaxation, or a change in location so as to avoid the external causes. While these remedies seem reasonable (indeed, doctors today prescribe dietary changes, the calming of emotional disturbances, and increased rest to reduce the frequency of epileptic occurrences), other Greek remedies, from 500 B.C. until 200 B.C., included the consumption of blood, the genitals of a seal, hippopotamus, and hare, and feces of the crocodile. Clearly reason did not always rule.

The Babylonian texts, which contain the earliest recorded accounts of epilepsy, also reflect a belief that a cause of epilepsy was possession of the afflicted by spirits, demons or ghosts. The primary cure resembled an exorcism. Those who lived in India saw epilepsy as resulting from a disturbance of the mind. The cure? Cleanliness. The ancient Chinese views represent their philosophy; to them, epilepsy resulted from

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6Scott, supra note 4, at 13, 21, 25, 26. For references by the Babylonians and Assyrians, see M. Stol, Epilepsy in Babylonia 3 (STYX Publications 1993).
7Temkin, supra note 5, at 91. See also Scott, supra note 4, at 26-27.
8Scott, supra note 4, at 18 - 21.
9Temkin, supra note 5, at 12, 22.
10Scott, supra note 4, 21-22.
11See Stol, supra note 6, at.3.
12Scott, supra note 4, 25.
a disturbance of the ying and the yang within the afflicted person’s body, best treated with herbs and acupuncture.\[^{13}\] The biblical view seems to equate epileptic seizures with lunacy, and notes the dangerous side effects associated with their occurrence.\[^{14}\] Unlike in most of the other cultures, many Romans did not see epilepsy as a disturbance of the mind, but as a disturbance of the body. Epileptics were viewed as unclean and were usually shunned and expelled from society for fear of contagion.\[^{15}\] Supposed remedies for the disorder were the blood or liver of a slain gladiator.\[^{16}\] In extreme cases amputation was seen as the only available cure.\[^{17}\] Later, in medieval times, astronomical phenomena or an imbalance in the bodily humors were believed to contribute to epilepsy; strange treatments included exorcisms, powdered human skull, vulture liver, and mistletoe.\[^{18}\] In the mid-nineteenth century, excessive masturbation was thought to cause epilepsy and a host of other neurological disorders.\[^{19}\] Again, the purported “treatment” reflected the supposed cause; in cases of incurable masturbation, castration or circumcision was suggested.\[^{20}\]

Fortunately for those who have epilepsy today, it has been a long time seizure disorders were treated with blood or exorcisms. Especially in the past sixty years (the Modern Era of epilepsy research), society has witnessed the development of many drugs that can control, or at least lessen the occurrence of, seizures in most people with a minimum of undesirable side effects. Unfortunately, people with epilepsy still face prejudice, biases, superstitions and prohibitions that can devalue their quality of life. India, for example, continues to maintain prohibitions against driving and marriage for those with epilepsy, preventing them

\[^{13}\text{Id. at 25} - 26.\]
\[^{14}\text{Id. at 27. See also Temkin, supra note 5, at 91.}\]
\[^{15}\text{Temkin, supra note 5, at.8.}\]
\[^{16}\text{Id. at 23.}\]
\[^{17}\text{Scott, supra note 4, 30.}\]
\[^{18}\text{Id. at 31.}\]
\[^{19}\text{Id. at 38.}\]
\[^{20}\text{Temkin, supra note 5, at 231-232. See also Scott, supra note 4, 38.}\]
from having a normal lifestyle. Here in America, people with epilepsy are often discriminated against in employment and educational pursuits, restricted from many recreational activities, and avoided by many misinformed people due to their uncontrolled seizures or the side effects of the drugs used in attempts to control them. To improve the quality of life of the 2.5 million Americans (and 50 million people worldwide) who have epilepsy, researchers and clinicians must put great effort into finding drugs that can render these people seizure-free with few or no side effects.

In this paper I will attempt to explore the transitions that have brought us from the days of castration and mistletoe to modern medicines, including well-known drugs such as phenytoin and carbamazepine, as well as newcomers like lamotrigine and oxcarbazepine. I will also examine how far we still need to go in the search for the perfect anti-epileptic drug. I will begin by explaining why an effective anti-epileptic is so essential in improving the lives of epilepsy sufferers, then will look at how a patient and his or her doctor choose from one of the currently available medications. I will do a short survey of the drugs currently on the market, listing their uses, side effects, and interactions with other prescription and nonprescription drugs. Special areas of consideration, such as drugs for pregnant women, children and the elderly, or those suffering from other ailments are also within the purview of this paper. As the preceding paragraphs have pointed out, we have come a long way in the treatment of epilepsy but there is still farther to go. “No seizures, no side effects” is not a reality yet.

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Why an Effective Anti-epileptic Drug is Essential

Epilepsy is a dangerous disorder with far-reaching effects on the lives of those afflicted. Uncontrolled epileptic seizures can be detrimental to a person’s physical, mental, and emotional health, social interactions, educational and vocational opportunities and quality of life. A recent estimate of the annual financial cost of epilepsy in the United States came to $4 billion, but to the individual epileptic the tolls taken on the body, mind, and psyche can seem much more important. Until a cure for epilepsy is discovered, medical treatment remains the only reliable means of relieving the effects of the disorder and averting the dangers and negative repercussions of uncontrolled seizures. An adult’s ability to cope with his or her epilepsy in social and everyday life is closely related to the degree of control exercised over his or her seizures. Medication is the option chosen by most epilepsy sufferers for seizure control. To enable them to lead active, normal lives, an effective anticonvulsant drug is essential.

Physical Dangers

The loss of consciousness that accompanies some seizures causes obvious immediate physical harms, such as falling, hitting one’s head or sustaining a concussion, and biting one’s tongue due to convulsions, all of which are good reasons to avoid seizures through effective treatment. The dangers of uncontrolled seizures, however, go far beyond the inconvenience of occasional bumps and bruises. In one study, people with

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23 Steven C. Schacter, MD, Epilepsy, Neurologic Treatment Vol. 19, No.1 (February 2001) 57, 57. The article was written for the Office of Clinical Trials and Research, and Department of Neurology, Beth Israel Deaconess Medical Center; and Department of Neurology, Harvard Medical School. He cites a 1996 survey by Murray et. al for that figure.

epilepsy reported a higher number of illnesses in general than those without the disorder. Further, it has been noted that people whose severe seizures are treatment resistant have, on average, a shorter life expectancy than people in the general population. The risk of deaths among people with epilepsy to those without is 2.3 to 1, meaning that a person with epilepsy is more than twice as likely to die at any given age than an identical person without epilepsy. The minor temporary injuries cannot be written off as mere inconveniences, but as potentially cumulative events that can lead to later problems and early mortality. The risk of a life-threatening condition called status epilepticus, in which a seizing person does not regain consciousness between a series of seizures or experiences seizures longer than several minutes in duration, is greatly increased in people with uncontrolled epilepsy. Sudden unexplained deaths also occur twice as frequently in those with epilepsy than among the general population, with medication by more than one anti-epileptic drug possibly being a contributing factor. The common perception that the only health risks associated with epilepsy are the minor ones due to falling during a convulsion is far from accurate. An effective treatment is necessary to combat both the major and minor hazards of seizures.

**Mental, Emotional and Psychological Effects**

Physical dangers are not the only harmful effects of epilepsy that demand immediate treatment. The disorder is also known to contribute to many mental, psychological, emotional, and social problems in those it affects. Prejudices and biases against people with epilepsy, usually perpetuated by misunderstandings, fear, and

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26Id. at 141.
27Lechtenberg, supra note 24, at 55.
28Seizures and Epilepsy: Hope Through Research, supra note 2.
29Id.
a lack of awareness of the medical (rather than psychological) nature of the disorder, can cause low self-esteem, depression and suicide. Cruel treatment or avoidance by others can lead to discomfort in and resistance to social settings and a constant fear of social interactions and pressures. Children are especially at risk for psychological injury due to the disorder because of their vulnerability to the cruelty of others and their inability to defend themselves from prejudice based on their condition. Teasing or tormenting by other students, the trauma or fear of having a seizure in the classroom, or the frustration and embarrassment caused by classroom manifestations of the cognitive side effects of many anti-seizure drugs (inhibiting concentration and learning) can lead to behavioral and emotional problems. The perpetual fear of having a seizure, especially in public or while in a dangerous setting, is difficult to handle even for adults. Effective anti-seizure medications would do much to allay that fear.

**Impairment of Educational and Vocational Activities**

The physical, psychological and emotional problems caused by epilepsy often lead to educational and vocational problems for those with the disorder. Though epilepsy is defined as a disability under the Americans with Disabilities Act, making denial of employment or access to any educational, recreational or other activity illegal, the effects of epilepsy and the medications currently available for its treatment, as well as the lifestyle changes that accompany the disorder, often make that legal protection less valuable. As noted above, the side effects of many epilepsy medications include drowsiness, difficulty concentrating and other cognitive problems, and behavioral issues in children. Frequent seizures also impair memory and contribute to poor academic performance. Problems associated with a child’s epilepsy can cause unwelcome absences from school. Though an equal education may be technically available to children with epilepsy, in reality it

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30 Id.
31 Id.
32 Id.
34 See Cornaggia and Beghi, supra note 25, at 140.
is difficult for them to keep up in their classes and maintain good grades. Though a patient, understanding and helpful teacher can do much to alleviate these problems, bullying and berating by other students who see the child with epilepsy as dumb or slow, or treat him or her as a pariah due to the seizures, can make the educational process very difficult and uncomfortable for an epileptic child. It is not surprising that people with epilepsy do not tend to go far in their schooling; in fact, one survey showed that only 56 percent of people with epilepsy finish high school and about 15 percent finish college.\(^{35}\)

The lack of higher education due to epilepsy also affects a person’s job opportunities, as do the typical biases and misunderstandings about epilepsy and the fact that many people with the disorder are unable to drive, making it difficult to get to and from work.\(^{36}\) As with students in school, adults with epilepsy reported higher numbers of absences from work in one study, making it difficult to attain and maintain steady employment.\(^{37}\) In fact, one out of every five adults with epilepsy sees their greatest challenge resulting from their disorder to be holding a job.\(^{38}\) Employer concerns about safety problems due to seizures, absenteeism from work, customer and co-worker reactions when a seizure takes place, and functional limitations on the ability of a person with epilepsy to perform a job lead to employment discrimination against those with the disorder.\(^{39}\) About 25 percent of working-age people with epilepsy are unemployed.\(^{40}\)

**Epilepsy’s Effects on the Patient’s Lifestyle**

Driving and other aspects of one’s lifestyle are also challenged by an epilepsy diagnosis, but can be brought nearly to normal with ongoing effective treatment. In most states a person with epilepsy is not allowed to

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\(^{35}\) Seizures and Epilepsy: Hope Through Research, supra note 2.

\(^{36}\) Id.

\(^{37}\) See Cornaggia and Beghi, supra note 25, at 140.

\(^{38}\) Lechtenberg, supra note 24, at 43.

\(^{39}\) Troxell, supra note 21, at 210.

\(^{40}\) Seizures and Epilepsy: Hope Through Research, supra note 2.
hold a driver’s license until it can be proven that he or she has been seizure-free for a specified length of time. Though some states have exceptions for people whose seizures follow a specific pattern (i.e. allowing day driving for people whose seizures occur only at night or during sleep, cautious driving for those whose seizures do not impair consciousness, or driving by those whose seizures have distinct warning signs that allow them time to get off the road if one is oncoming), the loss of independence associated with the freedom to drive is frustrating to many people with epilepsy. It has also been found that the risk of getting into a seizure-related car accident decreases as the length of time since the last seizure increases. Effective seizure control that can eliminate seizures entirely will therefore do much to give many seizure sufferers their freedom back.

Recreational Dangers

The final danger associated with uncontrolled seizures stems from recreational activities, and tends to deprive people of sports or games that they had previously enjoyed. Swimming, sailing, and other water-based activities, for example, should be done only with precautions or under supervision, while sports like scuba diving, skydiving, or motor racing must be avoided completely. Even sports in which a momentary loss of attention would not itself lead to injury (soccer, tennis or basketball, for example) can lead to other problems such as dehydration, overexertion and hypoglycemia, which put a person with epilepsy at an increased risk of seizures. While the diagnosis of epilepsy itself can be very distressing, the physical, mental and
emotional effects of the condition and the currently available treatments can cause more problems for sufferers of the disorder on a day-to-day basis. Furthermore, restrictions on driving and recreational activities, as well as a loss of educational and vocational opportunities, can lead to a very severe alteration in the quality of life of people with uncontrolled seizures. Effective and side effect-free anti-epileptic drugs could remove these barriers to living a normal life for people with the very common disorder of epilepsy. Discovery of such drugs must therefore be a scientific priority.

The Basics of Epilepsy and its Treatment

The call for the development and improvement of anti-seizure medications does not mean that none currently exist. In fact, there are over twenty medications on the market to treat epilepsy today, a tremendous improvement from just twenty-five years ago. Each has its strengths and weaknesses; no wonder drug has been discovered yet. While one drug might offer impressive seizure control in adults, it might cause dangerous rashes in children. The cognitive side effects of some drugs might make them unbearable to certain epilepsy patients, while other patients might be more disturbed by gastrointestinal or behavioral side effects. More importantly, each drug is particularly suited to treating one or more specific types of epileptic seizure; a drug that provides wonderful control for the patient with absence seizures might do nothing at all for the one with tonic-clonic seizures. The choice of the appropriate medicine for the specific patient from among the current arsenal is the most critical step toward deriving good seizure control with a minimum of side effects.

Doctors today have other considerations as well in prescribing medications for patients with epilepsy. The

\[46\text{See Scott, supra note 4, 88-89.}\]
current trend, due to reports of increased toxicity and long-term problems with use of multiple anti-epileptic
drugs, is toward monotherapy, the treatment of a patient with only one anti-epileptic drug. Finding that
drug and bringing it to a steady state in the patient’s blood may be a time consuming trial-and-error process.
In 20 percent of patients, despite all the drugs available and the best efforts of their physicians, adequate
seizure control cannot be attained even if more than one drug is used.

The fact that some epilepsy patients cannot derive adequate seizure control from any of the over twenty
anti-epileptic drugs on the market and the fact that other patients can do so only at the cost of troubling
side effects make it clear that the call for new anti-seizure drugs is not due to a lack in quantity, but a lack in
the quality. People with epilepsy should not have to choose between dangerous seizures and “tolerable” but
highly unpleasant side effects. The great advances that have been made in treating epilepsy in the recent
past are evidence that improvements continue to be possible, especially with our ever-increasing scientific
knowledge, our understanding of the nature of epilepsy itself, and our awareness of how anti-epileptic drugs
interact with the body to prevent seizures.

What are Seizures, and How and Why do they Occur?

Before it is possible to determine an effective treatment for epilepsy, it is essential to understand the mech-
anisms by which seizures occur. Epilepsy, generally, is a disturbance in the electrical activity of the brain
in which the neurons become disturbed and begin to signal abnormally, creating “spikes” in the person’s
brain waves.47 These spikes cause seizures, sudden interferences with behavior, perception, movement, con-

47Seizures and Epilepsy: Hope Through Research, supra note 2. See also Lechtenberg, supra note 24, at 4–5.
The disruption can occur due to an overly high level of excitatory neurotransmitters, which increase neuronal activity, or an abnormally low level of inhibitory neurotransmitters, which decrease neuronal activity.\textsuperscript{48} GABA (gamma-aminobutyric acid), an inhibitory neurotransmitter, may be tied to epilepsy; some anti-epileptic drugs are designed to change the amount of GABA in the brain or alter the brain’s response to it.\textsuperscript{49} All anti-epileptic medications act to control the errant brain waves that spike out of control when seizures take place.

The neuronal disturbance that leads to epileptic seizures can be caused by many things, including illness, brain damage stemming from head injury or stroke, brain tumors, poisoning, alcoholism, infectious diseases and abnormal brain development.\textsuperscript{50} Genetics also play an important role.\textsuperscript{51} Having a seizure does not mean that you have epilepsy; in fact, many people have a single seizure at some point in their lives, never to have one again. Though a single seizure might not indicate the disorder, somebody who suffers from multiple seizures is generally considered to have epilepsy.\textsuperscript{52}

The search for the correct anti-seizure medication begins with a determination of the type of seizure from which a person suffers because different seizure types indicate different methods of treatment. There are many types of seizures, each of which affects different parts of the brain in different manners.\textsuperscript{53} Simple \textbf{partial} seizures, for example, occur in only one area of the brain. Their indicators are strange sensations or sudden feelings of joy, sadness, or anger. The sufferer does not lose consciousness in this type of seizure.\textsuperscript{54} A more serious, though momentary, partial seizure is the \textbf{complex partial} seizure. Complex partial seizures are the most common of all the seizures in adults.\textsuperscript{55} They too occur in just one area of the brain, but in

\begin{footnotesize}
\begin{enumerate}
\item Lechtenberg, supra note 24, at 4 – 5.
\item Seizures and Epilepsy: Hope Through Research, supra note 2.
\item Id.
\item Id.
\item Comprehensive Epilepsy Center at Cornell Website at http://wo4.med.cornell.edu/cgi-bin/webobjects/pops-public.woa/wa/practice?name=Comprehensive+Epilepsy+Center
\item For a description of the various types of seizures, see Lechtenberg, supra note 24, at 21 - 35.
\item Seizures and Epilepsy: Hope Through Research, supra note 2.
\item Schacter, supra note 23, at 58.
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this case the person might lose consciousness to some degree, often seeming to be in a dreamlike state and displaying strange, repetitive behaviors called automatisms.[57]

**Absence** or petit mal seizures are yet another type of seizure. In this case the abnormal neuronal activity is not confined to one area of the brain, making these generalized seizures. Absence seizures are characterized by a loss of attention, in which the person stares off into space for five to ten seconds and certain body parts twitch or jerk. This type of seizure is very common among children with epilepsy.[58] Other generalized seizures include **tonic**, in which the person’s muscles and body become stiff and rigid, and **clonic** seizures, which are accompanied by jerking movements. When the characteristics of these two seizure types are mixed, the person is said to have **tonic-clonic** (or grand mal) seizures.[59] In tonic-clonic seizures the loss of consciousness is sudden and the person’s body becomes stiff, then begins to jerk or twitch, possibly leading to tongue biting and teeth grinding. These are the type of seizures most people associate with epilepsy. **Myoclonic** seizures cause the person to jerk or twitch body parts due to sudden muscle contractions, while and **atonic** seizures (drop attacks) cause a loss of muscle tone, leading to a sudden fall and possibly injury.[60]

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**The Goal of Anti-epileptic Drugs and the Mechanisms by which they Work**

The goal of an anti-seizure medication is to suppress the problematic brain waves by achieving what is known as a “steady state” of medication in the blood. This steady state is the level at which seizures are controlled

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[57] Seizures and Epilepsy: Hope Through Research, supra note 2.
[58] See Schacter, supra note 23, at 59. See also Seizures and Epilepsy: Hope Through Research, supra note 2.
[59] Schacter, supra note 23, at 59.
[60] Seizures and Epilepsy: Hope Through Research, supra note 2.
[61] Id.
[63] Seizures and Epilepsy: Hope Through Research, supra note 2. See also id.
or lessened, a level below which seizure control is ineffective and above which the side effects of the drug become intolerable.

Treatment begins with the oral administration of an anti-epileptic drug, whether in a pill, powder, or syrup form. The drug is then absorbed through the intestines; from there it enters the blood stream, where the plasma level rises. The blood then transports the drug to the person’s brain, where it crosses the blood/brain barrier. The brain concentration rises and the drug acts on neurotransmitters to prevent epileptic seizures, possibly causing toxic effects as well. During the last stages of the treatment process, metabolism and excretion are also occurring.

The amount of the anti-epileptic drug in the blood (and through the blood, the brain) is not constant, changing frequently due to its rate of absorption from the intestines, its distribution to different body parts, its metabolism, and its excretion. Checking blood levels is an essential part of the treatment of those on anti-epileptic medications to ensure that the amount of the drug in their bodies is maintained within the specified range (the steady state).

Achieving this steady state, and eliminating or lessening seizures, is preferably done with one drug (monotherapy), though difficult to control seizures often require two or more drugs (polytherapy). Approximately 60 percent of epilepsy patients derive good seizure control from one medication, usually (in descending order) phenytoin, carbamazepine, and valproate. Monotherapy allows for a larger therapeutic window, more effective seizure control, less potential for drug interactions, decreased risk of teratogenic effects (effects on a developing fetus during pregnancy), better patient compliance, and increased cost-effectiveness.

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64 Epilepsy Foundation of Victoria, Australia website at http://www.epinet.org.au/info/medication.html. See also Scott, supra note 4, 142.
65 Epilepsy Foundation of Victoria, Australia, supra note 64. See also Scott, supra note 4, 142.
66 Scott, supra note 4, 142.
67 Epilepsy Foundation of Victoria, Australia, supra note 64.
68 See The EpiCentre, supra note 33.
69 Lechtenberg, supra note 24, at 221.
70 Schacter, supra note 23, at 69.
apy is the less desired approach because many anti-seizure medications increase each other’s side effects or counteract each other’s therapeutic effects, making a perfect combination difficult to come by. Each drug may alter the absorption, metabolism, or excretion of any others taken, making a steady state difficult to find and maintain. The fact that each drug comes with its own set of side effects means that a person on polytherapy is often exposed to a vast array of undesirable problems. Even if the medications are controlling the patient’s seizures, this multitude of side effects is often enough to cause noncompliance with the doctor’s prescription, leading to further seizures.

It is hoped that, with further research, drugs might become available that can reach a steady state in a person’s bloodstream while being prescribed at lower levels than necessitated by the current arsenal of medications. This will increase the availability of monotherapy treatments for patients with previously hard to control epilepsy, decrease undesirable side effects, and bring about a higher level of compliance with doctors’ orders.

**How Does a Doctor Determine Which Medicine is Best?**

The doctor’s decision as to the medication of a specific patient is based primarily on which of the above-described types of seizure a person experiences. The type of seizure suffered by a particular patient is determined by diagnostic testing, usually performed after the initial seizure and definitely after a second. In ancient Greece, a potential method for determining whether or not a patient had epilepsy was to put the person with seizures into a goat’s skin, plunge him into the sea, and whether he floated or not determined if

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71 See *The EpiCentre*, supra note 33. See also Schacter, supra note 23, at 70.
72 See *Epilepsy Foundation of Victoria, Australia*, supra note 64.
73 Leichtenberg, supra note 24, at 8, 19.
he had epilepsy (those so unfortunate as to sink were positively diagnosed with the disorder). The primary diagnostic test today is the electroencephalogram (EEG), which can detect spiking in a person’s brain waves that may be characteristic of a specific type of epilepsy. A CT (computerized tomography) scan or an MRI (magnetic resonance imaging) test may also be ordered to determine if there are any internal injuries or lesions on the brain that may have caused the seizure. The results from these tests will help the doctor to determine whether to medicate a person who has had only one seizure, which is usually done if the benefits of doing so (preventing a potential second seizure) outweigh the risks (undesirable side effects).

Abnormal spiking in the brain waves of the patient or a noticeable problem detected in the patient’s CT scan usually indicate immediate medication, as there is a good possibility that the person will eventually have another seizure.

A second method of testing is through blood work, especially in childhood seizures. Blood tests can indicate metabolic or genetic disorders that can cause seizures, or can notify the doctor of underlying causal conditions such as infection, poisoning, anemia, or diabetes. These and spinal fluid tests can assist the doctor in ruling out other potential causes of nervous system disease.

The most important part of the diagnostic process may be a taking of the personal and family medical histories of the patient. The doctor must hear descriptions of the seizures from the patient, his or her family, and any witnesses to the events. These provide important information as to the bodily reaction to the neurological seizing, sometimes a definite indicator of the type of seizure involved. Past illnesses or injuries that may have affected the person’s brain or led to a lower seizure threshold must be disclosed, as should

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74 Temkin, supra note 5, at 26.
75 Lechtenberg, supra note 24, at 192.
76 See Lechtenberg, supra note 24, at 195, 196.
77 Seizures and Epilepsy: Hope Through Research, supra note 2.
78 Id. See also Fritz E. Dreifuss, Epilepsy: Standards of Medical Care in Epilepsy and Law 33, 38, supra note 21, at 38.
79 Lechtenberg, supra note 24, at 197.
80 Dreifuss, supra note 78, at 37. See also Schacter, supra note 23, at 58.
81 A doctor would know, for example, that a person who fell to the floor and whose body was rigid was not having an absence seizure, while a person who stared into the distance or performed automatisms was probably not suffering from a tonic-clonic fit.
any concurrent illnesses or changes in lifestyle, a family history of any neurological problems (due to the possibility of genetic causes) and any problems during birth (such as oxygen deprivation). By indicating the type of seizure involved, the descriptions contribute greatly to the choice of the proper medication.

In the end, the determination of which medicine is appropriate for a particular patient depends on a long process of trial and error in which the physician and the person with epilepsy work together to determine what level of seizure control is necessary (and attainable) and what types of side effects are unbearable (and avoidable). In the best case scenario, the first drug prescribed will work well for the patient, and after reaching a steady state the patient can remain on monotherapy for long-term treatment. In the worst case scenario, the doctor and patient try several drugs alone and then together, and still cannot achieve seizure control. For this reason the arsenal of anti-epileptic drugs must keep growing.

The Current Arsenal of Anti-epileptic Drugs

While the treatment of epilepsy has a long and varied history (discussed in the second section of this paper), the first effective anti-epileptic drugs were not introduced until 1857. It was then that Sir Charles Locock, an English physician, noticed that bromides had a sedative effect and decided to try them on his seizure patients. Because bromides were known to cause sexual impotence in men, Locock reasoned that they

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82 See Dreifuss, supra note 78, at 37.
83 I did not cite each piece of information in the following paragraphs because it is, for the most part, widely available. See generally Epilepsy Foundation of Victoria, Australia, supra note 64; The EpiCentre, supra note 33; Johns Hopkins Epilepsy Center website at http://www.neuro.jhmi.edu/epilepsy/meds.html; Epilepsy Meds at adhdguide.net website at www.adhdguide.net/pharmacy/epilepsy.
84 Seizures and Epilepsy: Hope Through Research, supra note 2.
might be useful as a treatment for seizures seemingly related to a woman’s menstrual cycle. Though the drugs had a fairly high level of toxicity, seizure relief was impressive.

The modern conquest of epilepsy, which really began in the 1930’s with the introduction of Dilantin, has been a triumph of modern medicine, but still has far to go. The development of medications like Tegretol and Depakote has provided seizure control to most patients with few unpleasant side effects. More recent additions, like those developed and approved in the past ten years or the promising new drugs that are currently being researched in clinical trials, have raised the standard even higher in terms of better seizure control with fewer side effects; hopefully in ten years even they will obsolete. The research and development of new anti-epileptic medications must continue until every case of epilepsy has a drug to match.

There are several considerations in choosing between the various drugs on the market today. Seizure type is the first; carbamazepine, for example, is a very good drug for tonic-clonic and partial seizures, but useless if you have absence seizures. Vigabatrin, in fact, can make myoclonic epilepsy worse. Side effects are also a consideration; phenytoin, for example, is not the proper drug for people whose job or educational pursuits demand that they be especially awake or alert. There are considerations of the individual patient: youth (lamotrigine should not be used), pregnancy (valproate may cause birth defects), or other illnesses (those with liver disease should avoid felbatol). Use with MAO Inhibitors or tricyclic antidepressants increases the toxicity of most of the anti-epileptic drugs.

The oldest of the first-line drugs (principal drugs of first choice) still prescribed today is phenytoin (Dilantin®). It was introduced in 1938, and remains the primary choice for monotherapy seizure control. Phenytoin is used to control generalized tonic-clonic and complex partial seizures, but is ineffective against

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85 Temkin, supra note 5, at 298.  
86 Id. at 299.  
87 The EpiCentre, supra note 33.  
88 Epilepsy Foundation of Victoria, Australia, supra note 64.
absence seizures. It is also used to prevent and treat seizures related to neurosurgery. Though the drug offers very good seizure control, it has a variety of short-term side effects including blurred or double vision, drowsiness, unsteadiness, decreased coordination, mental confusion and slurred speech (symptoms similar to, and potentially confused with, drunkenness). It also can slow thought processes and reduce memory.

More troubling, however, are the long-term side effects that accompany the chronic use of phenytoin, such as the coarsening of facial features, overgrowth of gums, increase in body hair, and acne. Women with a dark complexion should not use it. Though these are merely cosmetic (except for the gum overgrowth, which can lead to serious problems), they represent a true hardship for those on the medication and are a possible reason for noncompliance with a doctor’s instructions. Phenytoin should not be used if the patient is taking thyroid hormones, tricyclic antidepressants, and various other drugs, including the anti-epileptic drug valproic acid. The efficacy of some birth control pills can be reduced if used with this drug.

Another commonly used first-line drug is carbamazepine (Tegretol®). Like phenytoin, it is very effective against generalized tonic-clonic and simple and complex partial seizures, but not against absences. If the initial dose is too high, the short-term side effects are similar to those for phenytoin, with nausea, dryness of the mouth and giddiness a possibility as well. Most side effects disappear within the first two weeks of use as the patient’s body adjusts to the drug. Reduction of the dose can lead to a reduction in the “drunk-like” side effects, and a gradual introduction of the drug into the system may avoid them altogether. Serious side effects, though rare, are jaundice and a lowering of the white cell count of the blood. A person should

89 Johns Hopkins Epilepsy Center, supra note 83.
90 See The EpiCentre, supra note 33.
91 See id.
92 Id.
93 Id.
94 Id.
discuss any liver disease, blood cell or bone marrow problems, a drinking habit of over two drinks a day, or depression with his doctor before taking the drug. Several drugs either affect or are affected by the presence of carbamazepine in the patient’s system, including birth control pills; as with all anti-epileptic medications, it is essential for the patient to speak to his or her doctor or pharmacist about possible drug interactions before taking the drug. Interactions with MAO inhibitors can be fatal.

**Valproic Acid/Valproate** (Depakote®) is a third drug that is prescribed as monotherapy in newly diagnosed cases of epilepsy. It acts by increasing the brain’s levels of the neurotransmitter GABA. It is useful in combating generalized tonic-clonic seizures and partial seizures, as well as absences and myoclonic seizures. Gastrointestinal side effects, such as diarrhea, abdominal pain, nausea, and vomiting are possible accompaniments to this drug, as is weight gain. Drowsiness, tremor and hair loss may occur. Dizziness, imbalance, and sedation are also possible if valproic acid is used with other drugs. Most serious but least common are the liver damage, blood disorders (bleeding or bruising), or severe pancreatitis that can occur. Common over-the-counter drugs, such as aspirin and antihistamines, can increase the valproic acid levels in the blood, causing toxicity. Several other anti-epileptic drugs, such as Felbamate, can affect or be affected by valproic acid, making it difficult to include this drug as part of a polytherapy regimen. Carbonated beverages should be avoided while on this medication due to possible irritation of the mouth and throat.

**Ethosuximide** (Zarontin®) is the drug of choice for absence seizures, and is effective only in that type. Side effects for the drug are behavioral disturbances, nausea and drowsiness, hiccups, headache, rash, decrease in appetite, abdominal pain, and an unsteady walk. Sometimes it prevents absence seizures at the cost of

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95 For full information on Depakote, see patient prescription insert (Abbott Hospital).
96 A chat room I visited at adhd.net, supra note 83, more than confirmed people’s unhappiness with the side effects of Depakote. Among the complaints I witnessed were mood changes, nausea and heartburn, sleepiness, and confusion. They are all dissatisfied, as was I, with the results of Depakote.
97 See patient prescription insert for Depakote, supra note 95.
98 Id.
allowing, or maybe even causing, more serious tonic-clonic seizures.\textsuperscript{99}

Some of the drugs used as adjunctive, or add-on, therapy include clonazepam (Klonopin\textsuperscript{®}), clobazam (Frisum\textsuperscript{®}), clorazepate (Tranxene\textsuperscript{®}), and diazepam (Valium\textsuperscript{®}). Their effectiveness is wide-ranging: clonazepam works against drop attacks, myoclonic, partial seizures and absences; clobazam against drop attacks, generalized tonic-clonic, and partial seizures; and clorazepate works, along with Tegretol or Dilantin, against complex partial seizures. Diazepam is recommended only for intermittent or emergency use for managing status epilepticus. A problem with clonazepam, clobazam, and diazepam is that tolerance often develops, requiring a higher dosage to get the same therapeutic effects. They usually are used on fairly weak cases of epilepsy. Side effects for these drugs include drowsiness, sedation, poor coordination, depression, weight gain, nausea, unsteadiness and slowing of mental performance. These sedative and dependency-producing side effects limit their usefulness.

Primidone (Mysoline\textsuperscript{®} - introduced in 1954), along with Phenobarbital, the first synthetic drug used to treat epilepsy (introduced in 1912), was used mostly in the 1950’s and 1960’s.\textsuperscript{100} The original idea behind the use of Phenobarbital stemmed from the realization that bromides worked to control epileptic seizures partly due to their sedative nature.\textsuperscript{101} Phenobarbital, another sedative, was found to have the same anti-epileptic effects, and when it was introduced it was the first drug to provide a significant degree of seizure control to many people.\textsuperscript{102} It could not treat all seizure types, however, and had high levels of side effects, such as inducing dependency, so the newer drugs gradually replaced it.\textsuperscript{103} Phenobarbital can treat generalized seizures and some simple partial seizures. In high doses the side effects include lethargy, irritability, slurred speech, and imbalance. Several drugs, including anti-epileptics and oral birth control pills, either affect or are affected by Phenobarbital. Primidone works to control complex partial seizures. Once inside the body, it

\textsuperscript{99}Scott, supra note 4, 99.
\textsuperscript{100}Id. at 58.
\textsuperscript{101}See id. at 59
\textsuperscript{102}See Lechtenberg, supra note 24, at 224. See also Scott, supra note 4, at 59.
\textsuperscript{103}Lechtenberg, supra note 24, at 224.
is metabolized as Phenobarbital and thus the side effects are similar to phenobarbital’s, including drowsiness and hyperirritability, dizziness, double vision, sexual impotence and skin rash. Primidone also interacts with several other anti-epileptic medications.

**Vigabatrin** (Sabril®) is used to control partial or focal epilepsies and infantile spasms. It suppresses epileptic seizures by enhancing the activity of the neurotransmitter GABA. SIDE EFFECTS FOR THE DRUG ARE DROWSINESS, DIFFICULTY CONCENTRATING, MOOD CHANGES, AND POSSIBLY DOUBLE VISION, WEIGHT GAIN, ANDNAUSEA. Fortunately the side effects tend to be short-lived. Care must be exercised in prescribing vigabatrin to those with preexisting psychiatric problems (one of the reasons it is essential to give the doctor a full health history when deciding upon medications) because it is apt to cause psychotic episodes.

There are several drugs, released within the past decade, that show great promise in their ability to control seizures with fewer side effects than their predecessors. They include felbamate, gabapentin, and lamotrigine.

**Felbamate** (Felbatol® - approved by the FDA in 1993) is a drug used as monotherapy and add-on therapy to treat secondarily generalized complex partial and tonic-clonic seizures in adults ages fourteen and over, as well as Lennox-Gastaut syndrome in children two to fourteen years old. IT IS ABSORBED PRIMARILY THROUGH THE GASTROINTESTINAL TRACT AND WORKS BY ALLOWING GABA FUNCTIONING AND BLOCKING VOLTAGE-DEPENDENT SODIUM CHANNELS. IT HAS THE VERY SERIOUS POTENTIAL SIDE EFFECTS OF REDUCING THE BODY’S ABILITY TO MAKE BLOOD CELLS (APLASTIC ANEMIA) AS WELL AS CAUSING LIVER FAILURE. A DOCTOR MUST BALANCE THE RISKS AND BENEFITS OF USING THE DRUG, AND ONLY DO SO IF THE EPILEPSY IS SO SEVERE THAT THE RISK OF APLASTIC ANEMIA IS WORTH TAKING FELBAMATE IN
order to treat it.\textsuperscript{108} Other problems with felbamate are its interactions with many other anti-epileptic drugs, such as Dilantin, Tegretol, or Depakote. When combined with those drugs, side effects include headache, nausea, vomiting, sleepiness, dizziness, and insomnia. Because of the interactions, it is essential that a person on polytherapy using felbamate with other anti-epilepsy medications get frequent blood tests to ensure maintenance of a steady state with each of the drugs.

**Gabapentin** (Neurontin\textsuperscript{®} - approved by the FDA in 1993) is recommended for use in treating difficult-to-control complex partial seizures with or without secondary generalization in adults and partial seizures in children between three and twelve years of age.\textsuperscript{109} The drug is structurally related to GABA, but it is not known how it functions to control seizures.\textsuperscript{110} The side effects that were reported in trials include sedation, dizziness, fatigue, unsteadiness, nausea and terror. In children ages three to twelve, other effects were viral infection, somnolence, and hostility.\textsuperscript{111} According to the information booklet produced by its manufacturer, Pfizer Inc., Neurontin is the most frequently prescribed adjunctive anti-epileptic drug (beating out lamotrigine, topiramate, levetiracetam, tiagabine, and zonisamide, in that order).\textsuperscript{112} Gabapentin does not metabolize and is not bound to plasma proteins, making it useful as add-on therapy because interactions with other anti-epileptic drugs do not seem to be significant.\textsuperscript{113} It does not counteract the effects of oral contraceptives and the fact that its titration can be rapid without toxic side effects should lead to increased compliance with a doctor’s prescription.\textsuperscript{114}

\textsuperscript{108}Id. at 62. Because of these risks, the drug is usually only used in cases of Lennox-Gastaut syndrome, where the severity of the seizures and the need for control justifies the risk.

\textsuperscript{109}For complete information, see Neurontin booklet (Pfizer Inc. 2001).

\textsuperscript{110}See The EpiCentre, supra note 33. See also Neurontin booklet, supra note 109, at 26.

\textsuperscript{111}See Neurontin booklet, supra note 109, at 7.

\textsuperscript{112}Id. at 6, citing December 2000 Scott-Levin audit of uses by diagnosis.

\textsuperscript{113}Schacter, supra note 23, at 63.

\textsuperscript{114}See Neurontin booklet, supra note 109, at 7 - 9.
**Lamotrigine** (Lamictal® - approved by the FDA in 1994) is most effective in treating adults with partial seizures and refractory generalized epileptic seizures. It may also work for treating the seizures associated with Lennox-Gastaut syndrome. Lamotrigine works in just the opposite manner of vigabatrin, reducing the activity of the excitatory neurotransmitter glutamine by preventing its release from nerve endings. It is quickly and totally absorbed following oral administration. Slow and careful titration (increase in dosage) is necessary when starting the drug to avoid a serious and potentially fatal rash or other allergic reaction, which is most likely to appear in the early weeks of treatment. The possibility of a rash beyond that time exists if a person exceeds the dosage prescribed by his or her doctor. The risk of rash is significantly greater in children than in adults. Valproic acid and lamotrigine counteract each other, with valproic acid levels decreasing with the increase of lamotrigine. Taking valproic acid along with lamotrigine also increases the risk of a dangerous rash. A further dermatological problem is rash caused by excessive exposure to sunlight, so it is recommended that a person using the drug wear sunscreen or protective clothing when outdoors. Side effects besides rash include nausea, dizziness, sleepiness, lack of coordination, nausea, and blurred or, double vision. When taken with other drugs, drowsiness and sleepiness may occur. Lamotrigine also causes problems with folic acid synthesis, so women using the medication who plan to become pregnant should take a folate supplement.

There are several other very recent additions to the anti-epileptic drug arsenal. **Topiramate** (Topamax® - Approved by the FDA in 1996) acts by evening out the brain’s electrical activity while blocking substances

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115 For more information about lamotrigine, see Lamictal Patient Prescription Insert (Glaxo Pharmaceutical).
116 Schacter, supra note 23, at 64.
117 See The EpiCentre, supra note 33.
118 Schacter, supra note 23, at 64.
119 See Lamictal Patient Prescription Insert, supra note 115.
121 See Lamictal Patient Prescription Insert, supra note 115.
122 Id.
123 An additional side effect, known from personal experience and conversations in chat rooms at adhd.net, is a loss of short-term memory, including words and names.
that increase that activity, and in doing so significantly reduces refractory partial and other seizures.\footnote{124}{See The EpiCentre, supra note 33.}

Topamax was approved as adjunctive therapy for adults with partial onset seizures in December 1996.\footnote{125}{Topamax Antiepileptic Drug Cleared by FDA (December 27, 1996) at Doctor’s Guide website, \url{http://www.docguide.com}.}

In September 2001 the FDA also approved the drug as add-on therapy for dealing with seizures in adults with partial onset seizures and children with Lennox-Gastaut syndrome.\footnote{126}{Foundation Welcomes FDA Approval of Drug for Severe Epilepsy Syndrome (September 4, 2001) at \url{http://www.epusa.media}. See also FDA Approves Topamax (Topiramate) as Adjunctive Therapy for Lennox-Gastaut Syndrome (September 4, 2001) and FDA Approves Topamax for Pediatric Epilepsy at Doctor’s Guide website, \url{http://www.docguide.com}.}

When tested with other anticonvulsants, patients reported poor coordination, slowed functioning, mood disorders, and slurred speech. Topamax has interactions with several anti-epileptic drugs, making polytherapy difficult. It is important to have high fluid intake while taking the drug due to the slightly increased risk of kidney stones. It is also important to note that topiramate does reduce the effectiveness of some birth control pills.

**Tiagabine hydrochloride** (Gabitril\textregistered) - Approved by the FDA in 1997) controls partial seizures. It seems to function on the brain to prevent seizures by inhibiting the neuronal reuptake of GABA, prolonging the amount of time it is available at receptor sites.\footnote{127}{See The EpiCentre, supra note 33. See also Schacter, supra note 23, at 65.}

Possible side effects are lightheadedness, lack of energy, nausea, nervousness, tremor, abdominal pain, or difficulty concentrating. The drug does interact with other anti-epileptic medications, and polytherapy should be planned accordingly.

The newest drugs with high potential are **levetiracetam** (Keppra® - Approved by the FDA in 1999), **zonisamide** (Zonegran® - Approved by the FDA in 2000), and **oxcarbazepine** (Trileptal – Approved by the FDA in 2000), which is similar to carbamazepine but with fewer side effects.\footnote{128}{Seizures and Epilepsy: Hope through Research, supra note 2.}

Levetiracetam offers control of refractory partial-onset seizures and perhaps generalized seizures as well.\footnote{129}{Schacter, supra note 23, at 66.}

After oral administration the drug, like lamotrigine, is rapidly and almost totally absorbed into the sys-
Side effects associated with levetiracetam include fatigue, dizziness, and infection. There is very little potential for adverse interaction between this and other anti-epileptic drugs, and it does not affect the efficacy of oral birth control pills.

Zonegran was approved by the FDA in March of 2000 as add-on therapy for partial onset seizures, but it may also be effective in treating generalized seizures, infantile spasms, the mixed seizure types associated with Lennox-Gastaut syndrome, and myoclonic seizures. It lessens seizure activity by blocking presynaptic voltage-sensitive sodium and calcium channels in neurons. The drug’s safety and efficacy was established in three multicenter placebo-controlled double-blind trials treating those with refractory partial onset seizures. Reported side effects include drowsiness, lack of coordination, appetite loss or anorexia, and impaired thinking and confusion. Two positive aspects of the drug that might improve patient compliance with a doctor’s prescription are its faster results (potentially reaches a steady state within two weeks) and the need to take fewer pills (no difference found between those who took one dose daily and those who took two).

The FDA also recently approved oxcarbamidine (Trileptal®) in January 2000. The drug functions by blocking voltage-sensitive sodium channels, stabilizing hyper-excited neural membranes, and inhibiting repetitive neuronal firing. It can be used as monotherapy in adults with partial seizures or as adjunctive

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130 Id. at 66.
131 Id. at 66-67.
132 Id. at 66. See also Keppra (levetiracetam) Safe, Effective in Elderly with Epilepsy, Doctor’s Guide at www.docguide.net.
133 FDA Clearance of Zonegran Helps Meet Critical Need for New Therapies (March 28, 2000) at http://www.epusa/media. See also Schacter, supra note 23, at 68.
134 Internet Drug Index, supra note 120.
135 FDA Clearance of Zonegran Helps Meet Critical Need for New Therapies, supra note 133.
136 Internet Drug Index, supra note 120.
137 Internet Drug Index, supra note 120.
138 For complete information on Trileptal, see Trileptal Informational Pamphlet (Novartis Pharmaceuticals 2000) and included patient insert (Rev. January 2000).
140 See Tripetal patient insert, supra note 138.
therapies in adults and children.\textsuperscript{141} Trials have shown its long-term safety and efficacy in treating children with partial seizures, significantly reducing seizure frequency with only mild and short-lived side effects.\textsuperscript{142} According to the informational booklet published by the drug's producer, Novartis Pharmaceuticals, the reported side effects in clinical trials of the drug included dizziness, sleepiness, vision and gastrointestinal problems, and a lack of coordination, but were often no different in the drug-treated population and the placebo-treated population.\textsuperscript{143} Safety has been demonstrated in twenty-nine clinical studies with over three thousand subjects and by use of the drug in other countries for more than ten years.\textsuperscript{144} It may soon be approved for monotherapy use in children as well as adults.\textsuperscript{145} The drug should be used with care when dealing with a patient who has a history of hypersensitivity to carbamazepine because they are chemically and structurally similar.\textsuperscript{146} The drug may also reduce the effectiveness of oral contraceptives.\textsuperscript{147}

Why Hasn’t an Effective, Side Effect-free Anti-epileptic Drug Been Developed?

The reason for the current lack of side effect free anti-epilepsy medications that provide adequate seizure control for every person with epilepsy may have less to do with the limits on modern science or the incapacity of researchers to discover such a cure than with the difficulties inherent in receiving approval for a new anti-epileptic drug, first as an add-on therapy, and later for use as a monotherapy. Despite the fact that international pharmaceutical companies are striving to find safer, more effective treatments for epilepsy

\begin{footnotes}
\item[141]Epilepsy Foundation Says New Medication Brings Hope for Thousands Who Struggle with Seizures, Side Effects, supra note 139. See also Trileptal Informational Pamphlet, supra note 138.
\item[142]Sustained Benefits Seen with Tripletal (Oxcarbazepine) as Adjunctive Therapy in Pediatric Partial-onset Seizures (December 5, 2001), Doctor's Guide website at http://www.docguide.com.
\item[143]Trileptal Informational Pamphlet, supra note 138.
\item[144]Id.
\item[145]Sustained Benefits Seen with Tripletal (Oxcarbazepine) as Adjunctive Therapy in Pediatric Partial-onset Seizures, supra note 142.
\item[146]See id. See also Trileptal Informational Pamphlet, supra note 138; Schacter, supra note 23, at 67.
\item[147]Schacter, supra note 23, at 67.
\end{footnotes}
that will succeed in the current twenty-five drug marketplace, new drugs are not cascading onto the market because of the high cost of research, development and marketing (more than $150 million per drug).\textsuperscript{148} Though it would seem that, because doctors ardently support monotherapy as opposed to polytherapy, new drugs approved for monotherapy would be pouring onto pharmacy shelves, that is not the case. The clinical, procedural, and ethical limitations placed on researchers in getting such drugs approved slow the process significantly. Most drugs that are currently on the market are approved only for add-on therapy use.\textsuperscript{149} An individual doctor who realizes that one of these medications would be effective and safe for his patient as a primary, monotherapy drug may not prescribe the drug as such, but must do so “off-label”, which leads to problems with legal liability and insurance reimbursement.\textsuperscript{150}

Before a drug can be approved at all (either for mono or polytherapy), there must be extensive and expensive clinical testing. The tests must first be done on animals to prove the drug’s safety, efficacy, and its effects on reproduction.\textsuperscript{151} Only after those factors have been positively established can the investigational drug trials, with humans afflicted with the disorder as the subjects, be commenced.\textsuperscript{152} At that stage the drug is tested for safety and long-term effectiveness under testing conditions carefully monitored by the FDA.\textsuperscript{153} For an anti-epileptic drug to obtain approval from the FDA, researchers must prove a difference in treatment effect between the drug being tested and a placebo (an inert substance or sugar pill not intended to provide any positive effect).\textsuperscript{154} For this reason, new drugs are usually approved only as add-on medications so that patients can stay on their normal treatment regimen while completing the trial, instead of forcing half of the study population to rely only on a placebo to ensure seizure control.\textsuperscript{155} Receiving approval of

\textsuperscript{148}The EpiCentre, supra note 33
\textsuperscript{149}Workshop on Antiepileptic Drug (AED) Monotherapy Indication (March 8-9 2001), sponsored by the National Institute of Neurological Disorders and Stroke, National Institute of Health (NINDS/NIH), the American Epilepsy Society (AES), Citizens United for Research in Epilepsy (CURE), and the Epilepsy Foundation (EF), available at www.nih.com.
\textsuperscript{150}Id.
\textsuperscript{151}See Comprehensive Epilepsy Center at Cornell, supra note 53, section on Investigational Drug Trials.
\textsuperscript{152}Id.
\textsuperscript{153}Id.
\textsuperscript{154}Workshop on Antiepileptic Drug (AED) Monotherapy Indication, supra note 149.
\textsuperscript{155}Id.
a new epilepsy drug (or one currently approved only for add-on therapy) for use as monotherapy is more problematic because trials that use a placebo as the only treatment for a person with epilepsy increase the danger of seizures and may cause the trial participant harm, which is ethically unjust. When a placebo controlled monotherapy trial does occur, it is essential that the researchers are prepared for any emergency that might result from a lack of treatment in the placebo population, and have appropriate safety mechanisms in place. If it is hoped that the drug will control a certain type of seizure, such as the relatively benign brief absence, myoclonic, or simple partial seizures, and only patients with those type of seizures are involved in the study, the risk is not as great that harm will be done to the patient if seizures occur during placebo use as it is with populations with more severe seizures. One option is to use a “pseudo-placebo” (an active medication, but given in doses significantly lower than those needed for patient treatment) to get the blind trial effect without entirely depriving epilepsy patients of active drugs. This method was used in the trials to gain monotherapy approval for the drug felbamate; Valproate was used as a pseudo-placebo to show efficacy.

The approval process as it currently stands makes it very difficult for new anti-epileptic drugs to reach the market, both initially as add-on drugs and later as drugs for monotherapy. The trials are costly and time consuming, replete with ethical issues of patient treatment and its deprivation in the name of science, and have a high likelihood of subject withdrawal from the trial. The FDA has recently indicated some degree of willingness to consider using a testing mechanism favored in Europe, whereby new medications for

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156 See Joyce A. Cramer, Ethical Issues in the Planning and Conduct of Clinical Drug Trials 13, 16 in Epilepsy and Law, supra note 21. See also Workshop on Antiepileptic Drug (AED) Monotherapy Indication, supra note 149.

157 Cramer, supra note 136, at 15. Such trials often occur in hospital settings, for example. See also Workshop on Antiepileptic Drug (AED) Monotherapy Indication, supra note 149.

158 Cramer, supra note 136, at 16.

159 Id. See also Workshop on Antiepileptic Drug (AED) Monotherapy Indication, supra note 149.


161 Workshop on Antiepileptic Drug (AED) Monotherapy Indication, supra note 149.
monotherapy are tested through “control equivalence trials”\textsuperscript{162} This type of trial involves comparing a potential new anti-epileptic drug with a well-established drug that is generally considered to be effective\textsuperscript{163} This testing format would promote the development of new anti-epileptic drugs for monotherapy by eliminating the safety and ethical concerns about placebo-controlled monotherapy drug trials\textsuperscript{164}

**Special Considerations in Treating Women with Epilepsy**

Women with epilepsy face a number of problems specific to their sex and the situations connected with it. Hormones, for example, are known to play an important role in the triggering of seizures in many women. This can explain why many women’s initial seizures occur during the teenage years, during pregnancy or upon entering old age (and menopause), all times when hormone levels are surging, dipping, and changing day-to-day. The same hormonal fluctuations can lead to breakthrough seizures in teenage or pregnant women whose epilepsy had previously been controlled, requiring a reevaluation of their treatment strategy\textsuperscript{165} It has also been noticed that, for many women, the menstrual cycle and the hormonal changes that accompany it are responsible for triggering seizures. Seizures that occur around the time of menstruation are called catamenial seizures\textsuperscript{166} This can be diagnosed by obtaining blood tests to detect hormone levels as soon after a seizure as possible, or by a woman simply keeping a journal of where she was in her monthly cycle when a seizure occurred. The knowledge of whether her seizures are hormonally triggered can be very useful to a woman in her daily lifestyle choices; she might refrain from driving or other potentially dangerous activities,

\textsuperscript{162}Id.

\textsuperscript{163}Id.

\textsuperscript{164}Id.

\textsuperscript{165}Dreifuss, supra note 78, at 40.

\textsuperscript{166}Lechtenberg, supra note 24, at 11.
for example, during the time in the month when her seizures usually occur, and rest easy throughout the rest of her cycle. Medication considerations might also be affected if a woman suffers these menstrual-based seizures; changing the dosage of her regular medication or adding an adjunctive therapy during specific points in her cycle may control the seizures.\textsuperscript{167}

A major concern for women with epilepsy is pregnancy. Both the ability to get pregnant, the desire not to get pregnant and the ability to carry a healthy baby to full term may be affected by the disorder and the medications used to control it. The ability to get pregnant is, again, tied to hormones. The disturbance in hormonal activity that can trigger many women’s seizures can also result in a failure to ovulate and a condition known as polycystic ovarian syndrome (PCOS), making pregnancy very difficult. Furthermore, some seizure medications and some types of epilepsy can reduce a person’s interest in sexual activity, which is an obvious hindrance to becoming pregnant.\textsuperscript{168} These concerns, along with an actual choice among women worried about passing on the disorder or the inability to find a suitable marriage partner, contribute to the fact that women with epilepsy have fewer pregnancies than women in the general population.\textsuperscript{169} The desire not to get pregnant is also affected, as many anti-epileptic drugs counteract the effects of birth control pills, rendering them useless against preventing conception.

For a woman who does desire to be a mother, the problems do not end with conception. She must first find a neurologist and an OB/GYN who are willing to work together and with her to ensure that the pregnancy goes as smoothly as possible. Many doctors still have the outdated belief that an epileptic woman should not get pregnant at all, as it is seen as dangerous for both the baby and the mother. However, most doctors

\textsuperscript{167}Id.
\textsuperscript{168}See Seizures and Epilepsy: Hope Through Research, supra note 2, section on Pregnancy and Motherhood.
\textsuperscript{169}Lechtenberg, supra note 24, at 86.
today see no obstacles to having a healthy baby as long as the pregnancy is carefully planned and carefully monitored.

The key considerations in dealing with an epileptic woman’s pregnancy are whether she will take medication(s), which medication(s) she will take, and at what dosage. Most doctors are in agreement that the most important thing in producing a healthy baby is preventing seizures altogether, and if medication is needed to produce that result, than medication should be taken.\textsuperscript{170} A fetus is at great risk of harm due to a lack of oxygen if severe seizures during pregnancy are not prevented\textsuperscript{171}. Epilepsy is associated with an increased number of miscarriages in early pregnancy, a greater chance of premature labor, and the possibility of injury due to a seizure\textsuperscript{172}. Severe, or even minor, seizures during pregnancy can harm the developing baby and trauma associated with them can cause late-term miscarriage\textsuperscript{173}. However, not all epileptic women will need to take medications during pregnancy, and it may be decided that the risk of having a seizure during the pregnancy is outweighed by the risks of drug related fetal side effects, especially if the woman has only mild seizures or has not had any at all in a long time\textsuperscript{174}.

The goal in medicating a pregnant woman is to have the mother on monotherapy (one medication) throughout the pregnancy, as more than one medication can have increased side effects (and possibly damaging effects on the fetus) and make dosage more difficult to monitor. The rate of birth defects among the unaffected population is 2 to 3 percent\textsuperscript{175}. That risk is two to three times greater among women taking one anti-epileptic drug during pregnancy, and even more complications occur if the woman is on polytherapy instead

\textsuperscript{170}National Study to Assess Impact of Anti-seizure Medications on Unborn Children (2001), Medical College of Georgia news brief, available on their website at www.mcg.edu/news/2001newsrel/meador.htm.  
\textsuperscript{171}The EpiCentre, supra note 33, section called How Safe are Anti-epileptic Drugs in Pregnancy? See also Lechtenberg, supra note 24, at.91.  
\textsuperscript{172}The EpiCentre, supra note 33, section called How Safe are Anti-epileptic Drugs in Pregnancy?  
\textsuperscript{173}Seizures and Epilepsy: Hope Through Research, supra note 2, section on Pregnancy and Motherhood. See also National Study to Assess Impact of Anti-seizure Medications on Unborn Children, supra note 170.  
\textsuperscript{174}The EpiCentre, supra note 33, section called How Safe are Anti-epileptic Drugs in Pregnancy?  
\textsuperscript{175}National Study to Assess Impact of Anti-seizure Medications on Unborn Children, supra note 170.
of monotherapy. \(^{176}\) Whereas normally drugs may be taken twice daily, it is better to avoid blood levels peaking too high by administering drugs (especially valproic acid) more frequently (3 or 4 times a day) in smaller doses.\(^{177}\)

Another goal is to have the mother on the lowest dosage possible that can still provide adequate control of her seizures.\(^{178}\) Because the drugs pass through the placenta from mother to baby, it is obvious that, the lower the dose, the less risk of a harmful effect on the fetus.\(^{179}\) Because a woman’s hormone levels are changing almost constantly during pregnancy and drugs are metabolized differently, however, maintaining a steady state and keeping her at the lowest possible dose require frequent blood testing, as does the fact that a woman’s increased blood volume may dilute her medication.\(^{180}\) An increase in total daily dosage is often required as the mother’s size increases, but the dose must be lowered again immediately after delivery.\(^{181}\) Again, a neurologist and OB/GYN willing to work together are essential in ensuring the mother’s and fetus’s safety.\(^{182}\) Women with epilepsy may notice a change in seizure frequency during their pregnancies; 24 to 40 percent experience an increase, while others notice a decrease.\(^{183}\)

Each year over 24,000 babies are born to women with epilepsy, but there is still no anti-epileptic drug known to be entirely safe during pregnancy.\(^{184}\) The decision about which drug to take is very important. For a

\(^{176}\) Lechtenberg, supra note 24, at 95. See also The EpiCentre, supra note 33, section called How Safe are Anti-epileptic Drugs in Pregnancy?

\(^{177}\) Lechtenberg, supra note 24, at 95.

\(^{178}\) Id.

\(^{179}\) See National Study to Assess Impact of Anti-seizure Medications on Unborn Children, supra note 170.

\(^{180}\) See Lechtenberg, supra note 24, at 89. See also Seizures and Epilepsy: Hope Through Research, supra note 2, section on Pregnancy and Motherhood.

\(^{181}\) Seizures and Epilepsy: Hope Through Research, supra note 2, section on Pregnancy and Motherhood. See also Lechtenberg, supra note 24, at 91.

\(^{182}\) See Lechtenberg, supra note 24, at 89.

\(^{183}\) See Lechtenberg, supra note 24, section on Pregnancy and Motherhood.

\(^{184}\) See National Study to Assess Impact of Anti-seizure Medications on Unborn Children, supra note 170.
woman with complex partial seizures, carbamazepine is a good drug choice during pregnancy.\textsuperscript{185} Between carbamazepine, Depakote, and phenytoin, however, it is not known which carries the greatest risk of creating fetal abnormalities.\textsuperscript{186} There is some evidence that where there is a family history of neural tube defects, phenytoin is the safest of the three.\textsuperscript{187} Reports that valproic acid causes disturbances in neural tube closure, however, have been somewhat contradicted by the many women who have had healthy babies after taking the drug during pregnancy.\textsuperscript{188} Regardless of whether a woman takes phenytoin, carbamazepine, or valproic acid to control seizures during pregnancy, it is essential that she also take folate supplements to reduce the risk of neural tube defects, the negative effects of which range from trivial abnormalities of the vertebrae to major abnormalities like maldevelopment of the spinal cord and spina bifida.\textsuperscript{189} 190 Carbamazepine and valproic acid are possibly linked to spina bifida, while face or skeletal problems may appear in babies whose mothers took phenytoin during the first trimester of pregnancy.\textsuperscript{191} Valproic acid, Trimethadione, and phenytoin are known to also increase the risk of a child having birth defects such as cleft palate, heart problems, or finger and toe defects.\textsuperscript{192} A woman’s doctor may advise her to switch to other medications during pregnancy.\textsuperscript{193}

It is essential to note that the listing of the possible adverse reactions during pregnancy for the older drugs does not indicate that the newer drugs do not present similar problems; it is yet unknown what effects on the fetus many of them will have.\textsuperscript{194} All anti-epileptic drugs have some risks accompanying their use during pregnancy; the doctor and patient should carefully balance the risk to the fetus should a seizure occur with the risks of birth defects associated with a particular drug, and only use the medication if the first risk

\textsuperscript{185}Lechtenberg, , supra note 24, at 94.
\textsuperscript{186}The EpiCentre, supra note 33, section called How Safe are Anti-epileptic Drugs in Pregnancy?
\textsuperscript{187}Id.
\textsuperscript{188}Lechtenberg, , supra note 24, at 94.
\textsuperscript{189}The EpiCentre, supra note 33, section called How Safe are Anti-epileptic Drugs in Pregnancy?
\textsuperscript{190}Lechtenberg, , supra note 24, at 96. See also The EpiCentre, supra note 33, section called How Safe are Anti-epileptic Drugs in Pregnancy?
\textsuperscript{191}Lechtenberg, supra note 24, at 96.
\textsuperscript{192}Seizures and Epilepsy: Hope Through Research, supra note 2, section on Pregnancy and Motherhood.
\textsuperscript{193}Id.
\textsuperscript{194}Lechtenberg, supra note 24, at 96.
outweighs the second.

Careful planning is one of the most important aspects of a healthy pregnancy for an epileptic woman. It is essential that a woman provide her doctor with enough notice of her desire to get pregnant that he will be able to switch her to a medication more compatible with pregnancy if necessary or make the decision to take her off of medication entirely.\(^{195}\) Both decisions should be considered as far in advance of the pregnancy as possible. Switching medications often requires time to slowly remove a patient from one and reach a steady state on another, usually with some trial and error. In terms of taking the woman off medication completely, it is important to know whether she will have rebound seizures or be able to handle the frequency of the minor seizures she had been controlling up to that point. Clearly it is better to figure these things out prior to the pregnancy. It is also important for the mother begin prenatal vitamin supplements, especially folic acid, well before pregnancy. This can counteract or reduce the possibility of birth defects due to anti-epileptic drugs.\(^{196}\) Careful planning makes this possible.

The birth itself is not usually a problem for epileptic women, although there is a slightly increased risk for hemorrhage, eclampsia, premature labor and cesarean section.\(^{197}\) Doctors can administer anti-epileptic drugs intravenously if labor triggers a seizure.\(^{198}\) Babies sometimes have symptoms of withdrawal from the mother’s seizure medications after they are born, but these problems wear off soon and do not usually cause long term side effects.\(^{199}\)

The dangers associated with women and epilepsy do not stop at the birth of a healthy child. Having a baby, even a healthy one, entails a lot of stress and frequent sleep deprivation, both triggers for epileptic seizures. Many new mothers whose seizures are not completely controlled worry about having a seizure while

\(^{195}\) Seizures and Epilepsy: Hope Through Research, supra note 2, section on Pregnancy and Motherhood.

\(^{196}\) Id. See also National Study to Assess Impact of Anti-seizure Medications on Unborn Children, supra note 170.

\(^{197}\) Seizures and Epilepsy: Hope Through Research, supra note 2, section on Pregnancy and Motherhood.

\(^{198}\) Id.

\(^{199}\) Id.
holding their child. Furthermore, breastfeeding may be an issue, depending on the drug that the mother is
taking. Many of the currently available drugs can be excreted through breast milk, but the minor amounts
are less than the baby was exposed to in the womb. Though the baby may become overly drowsy or
feed poorly, which should be closely monitored, in most cases doctors believe the benefits of breastfeeding
outweigh the risks. Again, a doctor must closely monitor the levels of the drug in the mother’s body to
determine whether such excretions would be harmful to the baby and perhaps require bottle-feeding or a
change in the mother’s medication. Some drugs are not recommended at all for breast-feeding mothers (i.e.
lamotrigine).

Despite the fears and precautions involved, the vast majority of epileptic women who become pregnant have
uneventful pregnancies and produce happy, healthy babies. In total, women with epilepsy have only a 4-6%
chance of having a baby with birth defects. Furthermore, the risk that the child of a parent with epilepsy
will develop epilepsy his or herself is only about 5%, unless the parent has a clearly hereditary form of
the disorder. With careful planning and monitoring, there is no reason for the birth of a healthy infant
not to occur. Working toward this goal are a number of national registries that have been set up, through
which women who are taking anti-epilepsy medications while pregnant can provide information on the health
of their children in return for being given information on proper planning for an epileptic pregnancy and
information on the anti-epileptic medications available for mothers. One such registry is at the Massachusetts
General Hospital. Together, women, their doctors, and researchers in these registries can help to find safe

\footnote{200}{Id. See also Lechtenberg, supra not 24, 98.}
\footnote{201}{Seizures and Epilepsy: Hope Through Research, supra note 2, section on Pregnancy and Motherhood.}
\footnote{202}{See Lamictal Patient Insert, supra note 115. See also Internet Drug Index, supra note 120.}
\footnote{203}{Seizures and Epilepsy: Hope Through Research, supra note 2, section on Pregnancy and Motherhood.}
\footnote{204}{Id.}
\footnote{205}{Id.}
and effective drugs to treat the woman-specific aspects of epilepsy.

Special Considerations in Treating Children or the Elderly

As many as one out of fifty children is believed to have epilepsy. The causes of epilepsy in children may be related to injury as fetuses or during birth. The developing brain is very sensitive and problems such as maternal infections, poor nutrition, or oxygen deficiencies can affect the fetus' brain and make him or her susceptible to seizures. Genetics often play a role as well.

An epilepsy syndrome that is frequent in childhood is absence epilepsy, in which the child has repeated absence seizures that cause a momentary lapse of consciousness. Teachers and parents often think the child is just daydreaming or not paying attention. Though this may cause problems in school, the seizures usually stop at puberty and cause no lasting damage. Ethosuximide, a drug made specifically for absence seizures, offers a red syrup form for children due to the prevalence of this type of seizure in that age group. Temporal lobe epilepsy with partial seizures also frequently begins in childhood, but is not harmless like the aforementioned absence seizures. Over time it can cause the hippocampus to shrink, having lasting effects on learning and memory, so it is essential to have early and effective treatment for this type of epilepsy. Following a double-blind, randomized, placebo-controlled trial in which researchers found a 33 percent seizure

\[\text{References:}\]
\[\text{Schacter, supra note 24, 57.}\]
\[\text{Seizures and Epilepsy: Hope Through Research, supra note 2.}\]
\[\text{“Understanding Epilepsy” by Epstein.}\]
\[\text{Seizures and Epilepsy: Hope Through Research, supra note 2.}\]
\[\text{See The EpiCentre, supra note 33.}\]
\[\text{Seizures and Epilepsy: Hope Through Research, supra note 2.}\]
reduction rate in pediatric patients, the FDA approved Topamax as adjunctive therapy to threat childhood partial seizures.\textsuperscript{212} Reported side effects were drowsiness, loss of appetite and corresponding weight loss, and difficulty concentrating.\textsuperscript{213} The FDA also recently approved a new drug called oxcarbazepine (Tripetal) to treat such partial seizures in children, currently only as adjunctive therapy, but possibly as monotherapy in the future.\textsuperscript{214} It has been shown to be safe, effective, and tolerable as add-on therapy for children with hard-to-control seizures.\textsuperscript{215} Monotherapy would be an even better approval because children’s monotherapy options are very limited (only five other anti-epileptic drugs are approved for monotherapy use in children) and polytherapy creates problems with drug interactions and increased side effects.\textsuperscript{216}

Lennox-Gastaut syndrome is an even more devastating type of childhood epilepsy. Children afflicted with it have a wide combination of seizure types, making treatment very difficult.\textsuperscript{217} They are subject to a high risk of cognitive and behavioral disabilities.\textsuperscript{218} The disease usually is diagnosed between the ages of three and five years old, with more than 1,400 new cases diagnosed each year.\textsuperscript{219} Felbamate is one drug used in its treatment, as is a newer option called topiramate, which was approved as add-on therapy for treatment of the condition in September 2001.\textsuperscript{220, 221} In clinical trials, the most common side effects seen in children taking the drug along with their current anti-epileptic drug regimen were excessive drowsiness, loss of appetite, fatigue, nervousness, difficulty with concentration, weight loss, aggressive reaction, and memory.

\textsuperscript{212}FDA Approves Topamax (Topiramate) as Adjunctive Therapy for Lennox-Gastaut Syndrome (September 4, 2001), Doctor’s Guide website at \url{http://www.docguide.com}.
\textsuperscript{213}Id.
\textsuperscript{214}Sustained Benefits Seen with Tripetal (Oxcarbazepine) as Adjunctive Therapy in Pediatric Partial-onset Seizures (December 5, 2001), Doctor’s Guide website at \url{http://www.docguide.com}.
\textsuperscript{215}“Trileptal (oxcarbazepine) Safe in Children With Inadequately Controlled Seizures” at Doctor’s Guide.com.
\textsuperscript{216}Sustained Benefits Seen with Tripetal (Oxcarbazepine) as Adjunctive Therapy in Pediatric Partial-onset Seizures, supra note 214.
\textsuperscript{217}Seizures and Epilepsy: Hope Through Research, supra note 2.
\textsuperscript{218}Foundation Welcomes FDA Approval of Drug for Severe Epilepsy Syndrome (September 4, 2001), FDA website at \url{http://www.efa.org/epusa/media}.
\textsuperscript{219}Id.
\textsuperscript{220}Johns Hopkins Epilepsy Center, supra note 83.
\textsuperscript{221}Foundation Welcomes FDA Approval of Drug for Severe Epilepsy Syndrome, September 4, 2001 at supra note 218. See also FDA Approves Topamax (Topiramate) as Adjunctive Therapy for Lennox-Gastaut Syndrome, supra note 212.
difficulties. Rasmussen’s encephalitis is also a very severe disorder in which half of the child’s brain shows continual inflammation, sometimes requiring the radical surgical treatment of a hemispherectomy.

Other types of childhood epilepsy begin in infancy, such as infantile spasms. This syndrome does not respond to conventional anti-epileptic drugs.

Children with epilepsy are subject to many hardships beyond those that adults with epilepsy suffer. Difficulty in concentrating, lack of memory, or hyperactivity are side effects of many anti-epileptic medications, making schoolwork difficult. Children are generally more subject to cruel treatment by their peers than adults are, and it is apt to affect them more significantly. The special restrictions, constant administration of anti-epileptic drugs, and learning or behavior disorders associated with childhood epilepsy may make parents overly-protective of their child, with this sheltering leading to further problems in social interactions.

Overall, children with epilepsy are subject to more behavioral and learning disorders than children in the general population. They also sometimes exhibit violent, destructive behavior not common in other children.

When choosing a medication for a child or elderly person with epilepsy, the doctor must consider the mode of administration. Among both children and the elderly, many people with epilepsy cannot (or will not) swallow a pill or capsule, especially since many epilepsy medications (such as Depakote) are rather large. It is essential, then, to choose an anti-epileptic drug that comes in syrup or powder form (powders can be either water soluble or sprinkled on food). The older first-line drugs, such as phenytoin, carbamazepine, sodium valproate, and ethosuximide come in syrup form; some newer medications, such as vigabatrin, come in an oral powder. The makers of Topamax, recently approved by the FDA as a treatment for Lennox-Gastaut

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222 FDA Approves Topamax (Topiramate) as Adjunctive Therapy for Lennox-Gastaut Syndrome, supra note 212.
223 Seizures and Epilepsy: Hope Through Research, supra note 2.
224 See id.
225 Lechtenberg, supra note 24, at 2, 3.
226 Id. at 125 – 126.
227 Id. at 126.
228 See Epilepsy Foundation of Victoria, Australia, supra note 64.
syndrome (commonly associated with childhood) took this into account in making their medication in capsules that can be opened and sprinkled onto food for ease in swallowing.\textsuperscript{229} Neurontin (gabapentin), which is approved for adjunctive treatment of partial seizures in children, offers a child-friendly oral solution with a “cool strawberry-anise flavor.”\textsuperscript{230} This makes administration much easier for a parent or caretaker, less of a problem for the person with epilepsy, and increases the likelihood of maintaining the prescribed drug regimen.

Certain drugs pose distinctive problems for children. Valproic acid, for example, has been known to cause acute liver disease, and even failure, in children who have severe seizures along with mental retardation, are on polytherapy, and/or have metabolic problems or brain disorders.\textsuperscript{231} These risks are increased if the child is under two years of age.\textsuperscript{232} The benzodiazepines group of drugs (including clorazepate and clonazepam), though they cause sedation in adults, can cause hyperactivity and drooling in children.\textsuperscript{233} Clonazepam can also cause withdrawn behavior, mood swings, and auditory hallucinations.\textsuperscript{234} Phenobarbital (and also myso-line, which is metabolized as Phenobarbital), can cause a severe hyperirritability syndrome in children.\textsuperscript{235} Ethosuximide, which is used to treat the generalized absence seizures that affect many children, can also cause irritability, interference with sleep patterns, and night terrors in young children.\textsuperscript{236} Lamotrigine’s risk of a serious, life-threatening rash is much higher among children than adults, and therefore the drug is not available for children under sixteen years old except for treatment of Lennox-Gastaut syndrome.\textsuperscript{237}

The elderly are another population prone to epilepsy and special consideration must be given to their specific

\textsuperscript{229} See FDA Approves Topamax (Topiramate) as Adjunctive Therapy for Lennox-Gastaut Syndrome, supra note 212
\textsuperscript{230} See Neurontin Pamphlet, supra note 109, at 21.
\textsuperscript{231} See The EpiCentre, supra note 33. See also Depakote Patient Prescription Insert, supra note 95.
\textsuperscript{232} See Depakote Patient Prescription Insert, supra note 95.
\textsuperscript{233} Johns Hopkins Epilepsy Center, supra note 83.
\textsuperscript{234} Lechtenberg, supra note 24, at 131.
\textsuperscript{235} Johns Hopkins Epilepsy Center, supra note 83. See also Lechtenberg, supra note 24, at 131; Scott, supra note 4, at 67.
\textsuperscript{236} Lechtenberg, supra note 24, at 131.
\textsuperscript{237} Internet Drug Index, supra note 120.
anti-epileptic drug needs. There are currently 555,000 elderly people with seizure disorders, so doctors must know of the specific medicating needs of that population. When evaluating an elderly person with epilepsy and determining which medication might be most effective in his or her treatment, it is again important to consider that the causes of their epilepsy may differ significantly from those of a younger patient. Stroke and heart attacks, which deprive the brain of oxygen, are causes of epilepsy more common among the elderly.

About 32 percent of recently developed epilepsy in the elderly population seems to be related to another condition that reduces the availability of oxygen to the brain cells called cerebrovascular disease. Finally, Alzheimer’s disease, which occurs among the elderly, can also cause epileptic seizures to begin.

A consideration when dealing with the elderly, regardless of the cause of their seizures or the medication they use to control them, is the fact that people become more sensitive to medications as they get older, requiring frequent blood tests to be certain that a steady state is maintained.

Selecting the correct anti-epileptic drug for an elderly patient is essential. Adequate seizure control is very important in this group of individuals because the average elderly patient tends to be more physically fragile than a younger patient. Severe grand mal seizures, for example, can harm the elderly by causing spine fractures due to the force of spinal muscle contractions. A fall might cause an older person to break a bone or fracture a hip. Seizure control is necessary to prevent the physical injuries extending beyond the seizure itself.

238 New Epilepsy Treatment Guidelines Reflect Significant Changes in Drug Choices (11/26/01), Doctor’s Guide at www.docguide.com
239 Seizures and Epilepsy: Hope Through Research, supra note 2.
240 Id.
241 Id.
242 Id.
243 Lechtenberg, supra note 24, at 23.
Some medications have more harmful effects in the elderly than in the general population. Not only do the elderly tend to have a higher percentage of other treated or untreated conditions which use of the wrong anti-epileptic drug could exacerbate, but they also seem to suffer increased side effects from normally prescribed drugs. Phenobarbital, for example, is known to cause depression in the rest of the population, but its effects are even greater among the elderly. Neurontin should also be used with great care among the elderly due to a higher frequency of decreased hepatic, renal, or cardiac function, the possibility of other concurrent illnesses, and interactions with the medications used to treat these conditions. Fortunately drugs like Keppra, which was recently approved by the FDA as add-on therapy for epilepsy treatment in the elderly, has a very low risk of the drug/drug interactions that often make prescribing anti-epileptic drugs to the elderly difficult. Also, the side effects of the drug, such as sleepiness, confusion, hostility and insomnia, were not much greater in the elderly than in other age groups taking this medication.

Special Considerations in Treating Patients with Other Ailments

This section is obviously closely related to the prior section in dealing with limitations placed on doctors in prescribing medications to those with other physical problems, except in this section the problems apply to all age groups. People with illnesses other than epilepsy must be careful and work closely with their doctors when selecting an anti-epileptic drug. Not only do many anti-epileptic drugs counteract the medicinal effects

244Keppra (levetiracetam) Safe, Effective in Elderly with Epilepsy, supra note 132.
245Scott., supra note 4.
246See Neurontin Pamphlet, supra note 109, at 29.
247See Keppra (levetiracetam) Safe, Effective in Elderly with Epilepsy, supra note 132.
248Keppra (levetiracetam) Safe, Effective in Elderly with Epilepsy supra note 132.
of drugs used to treat other ailments, but several of the epilepsy medications themselves are dangerous to someone with an underlying medical condition.

Because most epilepsy medications are processed through the liver and the blood, those with problems related to either must be wary in choosing a drug. Carbamazepine can cause a lowering of the white blood cell count and jaundice due to liver impairment. Sodium valproate is known to cause acute liver failure in some cases, and should be avoided entirely by those who have a history of liver disease. Lamotrigine should also be used with care in any patient with renal, hepatic, or cardiac problems because any functional impairment could change the way the body metabolizes or eliminates the drug, causing decreased effectiveness or toxicity.

Future Developments in the Search for a Miracle Drug

The NINDS sponsors research on the development, causation, and treatment of seizures and epilepsy’s effects on brain activity and development. It also plays a significant role in the search for and development of new anti-epileptic drugs through its Epilepsy Therapeutics Research Program, which has screened 22,000 compounds in its 25-year history and has contributed to the development of five drugs now approved for use in the United States. The search continues for new drugs that can be taken less frequently and control seizures with fewer unpleasant side effects.

249 The EpiCentre, supra note 33.
250 Id.
251 See Internet Drug Index, supra note 120.
252 Seizures and Epilepsy: Hope Through Research, supra note 2.
253 Id.
254 Lechtenberg, supra note 24, 216.
In creating new anti-epileptic medications, researchers continue to examine the roles neurotransmitters, such as GABA and glutamate, as well as injuries to cell membranes play in causing seizures.\textsuperscript{255} NMDA receptors and potassium channels are also potential neural targets for anti-epileptic drugs; research is currently being done in this innovative area.\textsuperscript{256} Researchers are studying the contribution of glia and other non-neuronal cells in the brain to seizures, hoping that this will lead to new treatments.\textsuperscript{257} Gene research is also a major factor in determining why some people are more susceptible to seizures and perhaps why some are more resistant to anti-epileptic medications.\textsuperscript{258} Identifying genes that influence epilepsy could help in the development of new anti-epileptic drugs, and so-called “gene chips” that allow a doctor to determine a patient’s genetic makeup might make the choice of medications simpler and faster.\textsuperscript{259} Each of these lines of research is leading to new information and new understandings about the very makeup of the human brain, what makes it susceptible to epilepsy, and what can alleviate that susceptibility.

One innovative treatment option currently being pursued is the use of stem cell transplants to bring GABA producing neurons into the brains of those with seizures. Another is a potential device that could detect changes in the brain that precipitate a seizure, thus allowing the patient to move to safe place or, even better, release a drug or electric impulse into the brain to avoid the seizure altogether.\textsuperscript{260} A recently approved device called the vagus nerve stimulator (approved by the FDA in 1997) is a further glimpse into the future of epileptic treatment.\textsuperscript{261} For those whose seizures are not controlled by anti-epileptic medications, using this device as add-on therapy may provide a good deal of relief. The device is implanted in the patient’s left upper chest with a connection to the left vagus nerve in the person’s neck. The generator can then

\textsuperscript{255}Seizures and Epilepsy: Hope Through Research, supra note 2.  
\textsuperscript{256}Natalie Frazin, supra note 1, referring to comments by Dr. Raymond Dingledine of Emory University.  
\textsuperscript{257}Seizures and Epilepsy: Hope Through Research, supra note 2.  
\textsuperscript{258}Id.  
\textsuperscript{259}Id.  
\textsuperscript{260}Seizures and Epilepsy: Hope Through Research, supra note 2.  
\textsuperscript{261}Id.  
\textsuperscript{262}For a description of the device and its functions, see Schacter, supra note 23, at 72.  
\textsuperscript{263}See also Audrey T. Hingley, Epilepsy: Taming the Seizures, Dispelling the Myths, the FDA website at www.fda.gov/fdac/features/1999/199_epil.html.
deliver intermittent stimulation to the brain to prevent, interrupt, or reduce the severity of a seizure. The side effects of the implantation are only those usually associated with a chest surgery, such as incisional pain, coughing and nausea. Besides that, however, the device reduces seizures without the side effects that usually accompany anti-epileptic drugs. The treatments that researchers can imagine and modern science can produce have almost no limit. One doctor at the White House conference on epilepsy envisioned a device which, when implanted in the brain, could attract axons and actually alter the brain’s circuiting. This device, though it may not be a reality yet, demonstrates the extents to which scientists will go in trying to eliminate seizures.

Although some of the aforementioned treatments are not new anti-epileptic medications, they would certainly be a welcome addition to the arsenal with which researchers, doctors, and patients continue to battle the crippling effects of uncontrolled epileptic seizures and the troublesome effects of the medications that attempt to control them. The search for the miracle cure for epilepsy continues and if the pace of discovery in the past ten years is any indicator, it will not be long before an effective, side effect-free treatment for epilepsy will be available to offer true seizure relief for the millions who suffer from this very common disorder.

\[262\] See Natalie Frazin, supra note 1, referring to comments by Dr. Daniel Lowenstein from the University of California, San Francisco.