Marginal decision-making in the treatment of refractory epilepsy

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**ABSTRACT**

**Objective:** Epilepsy surgery is one of the most effective treatments in modern medicine. Yet, it remains largely under-utilized, in spite of its proven efficacy. The referrals for epilepsy surgery are often delayed until it is too late to prevent the detrimental psychosocial effects of refractory seizures. The reluctance towards epilepsy surgery is influenced by the perceived risks of the procedure by practitioners and patients. This review discusses how, in general decision-making processes, one faces a natural tendency towards emphasizing the risks of the most immediate and operational decision (surgery), at times without contrasting these risks with the alternative (uncontrolled epilepsy).

**Methods:** In the field of economics, this bias is well recognized and can be overcome through marginal analysis, formally defined as focusing on incremental changes as opposed to absolute levels.

**Results:** Regarding epilepsy surgery, the risks and benefits of surgery are considered separately from the risks of uncontrolled epilepsy. For instance, even though surgery carries an $\sim 0.1$–$0.5\%$ risk of perioperative mortality, the chance of sudden unexpected death with refractory epilepsy can be as high as $0.6$–$0.9\%$ per year. It is suggested that the inadequate way of phrasing clinical questions can be a crucial contributing factor for the under-utilization of epilepsy surgery.

**Significance:** It is proposed that examining decision-making for epilepsy surgery in the context of marginal analysis may enable providers and patients to make more accurate informed decisions.

**Introduction**

Epilepsy surgery is one of the most effective treatments in modern medicine\textsuperscript{1}. Up to three quarters of patients with medication refractory temporal lobe epilepsy that undergo surgery can achieve complete remission of seizures\textsuperscript{2}. In fact, any experienced epileptologist has the unparalleled satisfaction of having known numerous patients who achieved complete cure of seizures after lifelong disabling epilepsy. Some of them being eventually discharged from the clinic after surgery without the need for further anti-epileptic therapy.

It is well recognized that patients with epilepsy who do not achieve seizure freedom after the appropriate use of two anti-epileptic medications are unlikely to respond to other regimens\textsuperscript{2,4} and should be considered for surgery as soon as possible\textsuperscript{4}. For this reason, the American Academy of Neurology (AAN) recommends that the time between the diagnosis of refractory epilepsy and the referral for surgery should take no longer than 1 year\textsuperscript{3}.

Most states in the US have at least one Comprehensive Epilepsy Center capable of adequately performing the presurgical investigation and the surgical treatment of even the most complex cases of epilepsy. Taken together, given the proven efficiency of the surgical treatment and the availability of qualified centers, one would expect that patients with medication refractory epilepsy would often encounter timely access to surgical evaluation and treatment.

Unfortunately, this is still far removed from reality. In spite of the AAN recommendations, the average time between diagnosis of refractory epilepsy and the surgical referral still ranges between 10–20 years\textsuperscript{5}, even within states with the highest resources. Patients are typically referred for surgery only after several years of poorly controlled epilepsy, often when it is too late to prevent the detrimental psychosocial effects of refractory seizures. Dr Samuel Wiebe, in a commentary article published in the journal *Nature* in 2014, emphasized that epilepsy surgery remains one of the most under-utilized treatments in modern medicine, noting: “not enough doctors and patients opt for surgery to treat epilepsy, despite clinical evidence of the benefits\textsuperscript{1}.

It is still poorly understood why surgical referral rates remain sub-optimal. One important factor may be the reluctance from patients and practitioners towards surgical intervention. It is common sense that invasive procedures should be replaced by non-invasive treatments whenever possible. Nonetheless, the hesitancy towards epilepsy surgery remains out of proportion to its proven efficiency.

In this article, we discuss some factors that likely influence the process of making medical decisions in the context of epilepsy surgical evaluation and treatment. We discuss how, in general decision-making processes, we face a natural tendency towards emphasizing the risks of the most immediate and operational decision (surgery), at times without
contrasting these risks with the alternative that has become reality for the patient (uncontrolled epilepsy).

In the field of economics, this bias in the decision-making process is well recognized and studied, and can be overcome through proper application of marginal analysis, formally defined as focusing on the incremental changes, as opposed to the absolute levels. In this article, we evaluate surgical referral in light of this knowledge from the field on economics. Importantly, this is not an analysis of the economics of surgical decision-making in a cost-benefit “financial” sense, but an application of fundamental decision-theory principles pioneered in economics to medical decision-making.

Marginal analysis

The introduction of marginal analysis into economic theory in the late 19th century is often referred to as the “marginal revolution” in economics. This major advance in economic science was pioneered by economists such as Jevons, Menger, and Walras; and further refined by Bohm-Bawerk, Marshall, and Pareto. It is responsible for economics becoming a true positive, predictive science, rather than a normative discipline.

Mainstream, or “Neoclassical”, economic theory is now founded in the idea that human decision-making is best characterized by, and made with, marginal analysis. Rather than just thinking generally about the costs and benefits of a decision, the theory provides a more precise estimation of the expected results by enabling a comparison between the marginal costs and the marginal benefits, where the term marginal signifies the change, or additional increments.

Consider how a person would view the following decision. At a restaurant, the person intended to get a $1 hamburger and a $1 drink, but sees a “value menu combo” of a hamburger, a drink, and fries for $2.25. Marginal decision theory would suggest the person best view the decision in the following terms “is it worth 25 cents for the French fries?” The change in the total cost from $2.00 for both individual items to $2.25 for the combo vs the change in the food items (adding the fries). Importantly, note that the identical marginal decision is present if we change the prices to $2 for the hamburger, $2 for the drink, and $4.25 for the combo. The relevant question is still whether the fries are worth the extra 25 cents. To some consumers the fries may be worth 25 cents, while to others they are not. The main point, however, is that, in the decision, only the marginal changes are relevant, and not the total amounts.

Now consider a second example: a person trying to decide between taking a bus or a plane from Miami to New York. Assume the bus takes 56 h and costs $100, while the plane takes 6 h and costs $300. The relevant decision is whether it is worth the extra $200 to save 50 hours. As both of these examples illustrate, it is the changes in the costs and benefits that reflect the proper decision-making criteria.

Similarly, in production theory, a business firm would produce another unit of output only if the marginal revenue (that is, the change in the total revenue) is greater than the marginal cost (the change in the total cost). Whether to change business hours to remain open an extra hour prior to closing at night would similarly be made by comparing the extra revenue in that hour to the additional costs of staying open. However, it is important to explicitly point out that again it is the changes that matter, not the totals. The business’ total costs and total revenues are not relevant in these decisions—only the additional costs and benefits.

Marginal analysis is similar in many ways to the notion of “sunk costs”. A sunk cost is a cost that has already been incurred. While many people may be tempted to consider sunk costs in decisions, they are not relevant and should be completely discounted. If you purchased a stock for $100 that has now fallen to $60, would the correct decision be not selling it until it gets back to $100? Probably not, as a better decision would be to sell it if you think the price will fall further, and hold it if you think the price will rise. The $100 originally paid for the stock is irrelevant to the current decision—it is a sunk cost. Only the future prospects matter.

Suppose an emergency procedure has a 60% survival rate. Whether the 40% chance of dying during the procedure is large or small depends on the alternative course of action. If the default option of not having the procedure means a person has a 75% chance of survival (a 25% chance of death), then the marginal increase in death risk with surgery is only 15%. Thus, the true marginal risk associated with the procedure is this increase of 15%, not the full 40%. A proper decision about the procedure is best made by considering only the 15% marginal risk, not the 40% total risk. If the medical personnel explain the risks as being 40% without clearly communicating the consequences without the procedure, the patient would be very unlikely to have the procedure. “This procedure will increase your risks of dying by 15 percentage points relative to not having it” is a much clearer and accurate exposition than “This procedure has a 40% risk of death”. While both can be explained, if the patient doesn’t understand that real risks without the procedure are present as well, they can easily be led to make a poor treatment decision. Table 1 provides a summary of various terms related to marginal decision-making.

Marginal analysis in medicine

A broad PubMed and Google Scholar search (with terms “marginal risks”, “marginal gains”, “marginal”, “risks”, “surgical risks”, “marginal costs”) revealed that terms such as marginal costs are frequently used to describe financial costs associated with cost-effectiveness calculations, with some specific examples related to surgical risks in the cardiac surgery literature. These are discussions related to additional financial costs associated with compounded co-morbidities or risk factors in specific populations.

The concept of marginal gains has also been used to describe risks associated with therapeutic options that are costly, albeit debatable regarding their efficacy, for example, related to some forms of chemotherapy for advanced or incurable types of cancer. Moreover, marginal risks of complications have been reported in relation to additional hours of operative time. Marginal risks have also been reported in...
relation to an increased likelihood of occurrence of a genetically determined diseases when combined with environmental exposure\textsuperscript{13} (e.g. marginal risk of macular degeneration conferred by smoking when combined with genetic predisposition\textsuperscript{14}).

The theoretical framework of marginal-decision making has been more directly discussed in Torgerson and Spencer\textsuperscript{15} when comparing the added costs with the added benefits of screening for Down’s syndrome during pregnancy\textsuperscript{15}. In their article, they discuss how marginal (additional) costs and benefits should be taken into account when adopting new policies for screening procedures.

Interestingly, the concept of marginal risks has been seldom reported when comparing the cumulative risk of conservative treatment vs surgery (either for epilepsy or for other diseases), with one notable and interesting exception: in 2015, Thiessen et al.\textsuperscript{16} described how the explanation of surgical risks (related to liver transplantation) could be aided by visual diagrams where survival and death rates are more clearly reported. Moreover, they argue that framing the discussion with visual aids could counter the tendency to “overestimate the risk of high-magnitude, low-probability event”. Their article did not discuss the theoretical framework of marginal risks in a more extensive manner, but their approach is similar in concept to what we describe in our manuscript.

### Marginal analysis applied to epilepsy surgery

In the context of epilepsy surgery, it is common practice, for example, to ask, “What is the risk of death associated with this surgery?” or “What is the risk of having memory problems if I have this surgery?” Providers may consider the benefits of surgery by asking, “What are the chances of becoming seizure free with surgery?”

We suggest that the common, and inadequate, way of phrasing clinical questions is a key contributing factor to the under-utilization of epilepsy surgery. We propose that we can greatly improve our approach to the treatment of refractory epilepsy by reframing choices in the context of marginal decision-making.

### Marginal risk of death

When making a decision about epilepsy surgery, one should not consider the risk of surgery in isolation. The overall risk of death from epilepsy surgery is extremely low, estimated to range from 0.1–0.5%\textsuperscript{17,18}. The risk of permanent morbidity from epilepsy surgery is also exceptionally low, at \textasciitilde{}2%\textsuperscript{17}. Nonetheless, committing to an endeavor such as surgery that hypothetically carries a chance of death is certainly daunting. A basic precept of medicine is \textit{Primum non nocere}, or “first, do no harm”. However, it is vitally important to consider that the patient is exposed to risk of death or progressive morbidity by avoiding surgery. Uncontrolled or “medically refractory” epilepsy carries a risk of death due to accidents, drowning, trauma, status epilepticus, adverse reactions to medicines, and sudden unexpected death in epilepsy (SUDEP)\textsuperscript{19–21}. In reality, mortality rates are 4–7-times higher in individuals with refractory seizures\textsuperscript{22}, with the chance of SUDEP being as high as 0.6–0.9% per year for individuals with refractory epilepsy\textsuperscript{23}. Therefore, the appropriate comparison should contrast the mortality with surgery vs the mortality from the absence of surgery, which is likely associated with uncontrolled epilepsy. While surgery carries an inherent mortality rate, in reality the risk of death is lower with surgery, which carries a marginal reduction in risk.

The same logic from SUDEP applies to cognitive problems associated with epilepsy. Progressive cognitive decline and accelerated long-term forgetting are common and now well recognized among subjects with uncontrolled epilepsy\textsuperscript{24–26}. Importantly, the marginal risk is the additional risk (or risk reduction) that arises from a specific intervention, compared to the risk without the intervention. In this context, surgery is clearly less risky than avoiding surgery.

### Marginal analysis of benefit

The overall published chance of seizure freedom with resective surgery for TLE ranges from 60–70%\textsuperscript{3}. While there is some decrease in efficacy at 5 years compared to 1 year, the seizure free rate at 5 years is still \textasciitilde{}50% at 5 years\textsuperscript{27}. To some providers, or patients, this may sound like a surprisingly low chance of success. However, as with risks, the benefit should be viewed compared to chances without surgery. Numerous studies have explored the chances of seizure freedom once 2–3 medicines have failed. Most data suggest that only 4–8% of patients achieve seizure freedom with medicines once 2–3 medicines fail\textsuperscript{3}. Taking an overall estimate of \textasciitilde{}5% chance of freedom with medicines, and 55% chance of seizure freedom with surgery, a marginal analysis shows that surgery is \textasciitilde{}10-times more effective than medical management after initial failures of appropriate medicines. Considering other therapies such as vagus nerve stimulation, with overall

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Marginal & Marginal: Additional, difference, or “change in” \\
\hline
Marginal analysis & The fundamental idea underlying most of economics that proper decisions are based on a comparison of the incremental changes in costs and benefits resulting from choosing one option over another. This is in contrast to a consideration of the absolute levels of cost and benefits of a single option. \\
Marginal benefit & The difference (or change) in the expected benefits from one course of action vs another course of action. For example, the marginal benefit of surgery would be the chance of seizure freedom with surgery minus the chance in seizure freedom from medicine alone, which is the change in the chance of seizure freedom. \\
Marginal cost & The difference (or change) in the expected cost from one course of action vs another course of action. For example, the difference or change in the risk of death from surgery vs the risk of death inherent in refractory epilepsy. \\
\hline
\end{tabular}
\caption{Definition of terms related to marginal decision-making.}
\end{table}
average seizure-free rates of ~6%\(^28,29\), the marginal benefit of surgery remains high (~10-fold).

### Incorporating marginal decision-making into epilepsy surgery decisions

In this manuscript, we have highlighted a key limitation in common decision-making that we believe strongly contributes to the under-utilization of epilepsy surgery. Risk and benefits are often considered in isolation. The baseline inherent risks of refractory epilepsy are often overlooked, when in fact therapeutic risks should be viewed in the context of the changes in risk, i.e. the marginal risk. A summary of the various factors to be considered in the marginal decision-making process for epilepsy surgery is presented in Table 2.

Prudent medical decisions consider not only the risks, but also the potential benefits of an intervention. The marginal benefit of epilepsy surgery is approximately a 10-fold better chance of long-term seizure freedom. It is quite uncommon for neurology providers to be able to offer patients two therapies, one of which has a lower risk and is 10-times more effective than the other choice. In fact, we propose that the concept of marginal analysis should be incorporated into research assessing the efficacy of novel epilepsy treatments in order to improve the understanding of the changes in risk yielded by new approaches.

This manuscript does not provide absolute quantitative criteria for decision-making, and this limitation is related to the fact that risks and benefits of surgery vs no surgery are not always absolute, or fully quantified in the literature. Nonetheless, the development of quantitative criteria would be an informative approach to better guide clinical practice in the future. For this reason, we believe that: (1) this manuscript intends to bring to light the issue of marginal risks in the context of epilepsy surgery, raise attention to this clinically relevant topic, and (2) encourage the reporting of quantitative variables related to risks of prolonged epilepsy and surgery in order to enable more formal quantitative analyses in the future.

In summary, our hope is that examining decision-making for epilepsy surgery in the context of marginal analysis may enable providers and patients to make a more accurate and informed decision. Considering surgery’s risks and benefits against real alternatives may have a profound impact in remedying the under-utilization of this vital treatment.

### Summary

- In spite of its unquestionable efficacy, epilepsy surgery remains under-utilized, and many patients lose the opportunity to achieve timely access to a cure.
- The reluctance towards surgery is, in part, related to the perceived risks of the surgical procedure.
- Nonetheless, uncontrolled epilepsy carries a much higher cumulative risk compared with surgery.
- In economics, marginal decision making assesses the natural tendency to emphasize immediate (surgery) vs alternative (uncontrolled epilepsy) risks.
- In this review, we discuss how marginal decision making could be applied to surgical decisions in epilepsy.

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