How much can medical management alone improve the outcome of adult drug-resistant epilepsy? An exploratory study on possibilities and limitations of combining multiple therapeutic actions

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Purpose: Failure to control epileptic seizures with two medications, adequately chosen and dosed, indicates drug-resistant epilepsy (DRE). The chance of pharmacologically controlling seizures is low for patients with DRE and uncontrolled seizures who are not candidates for surgery, who have already undergone surgery, or who already had a vagus nerve stimulator (VNS) placed. Patients experiencing these conditions must instead rely on medical management of their seizures, and there is no breakthrough solution on the horizon.

Medical care of DRE might be optimized by systematically considering factors that promote and inhibit breakthrough seizures. For example, seizure control could be enhanced through measures such as increasing the frequency of follow-up visits, tracking treatment plan compliance, treating sleep disorders, rational polypharmacy, adjusting drug administration to achieve higher levels when seizures are more likely and educating patients on seizure triggers. A systematic and simultaneous implementation of all of these measures is likely to yield a sizable, clinically relevant, improvement.

This paper presents an exploratory study on the effects of implementing such an approach, specifically evaluating this method's impact on seizure frequency.

Methods: I performed a retrospective chart review of 659 consecutive adult patients with epilepsy followed up at the University of Utah and at the Salt Lake City VA Medical center using the multimodal approach described above. I identified 27 patients who had DRE and uncontrolled seizures and in whom a medical management optimization protocol was implemented. I measured these patients' seizure frequency at the beginning and the end of the study period and compared the results with those of a matching control group of 48 patients.

Results: The optimization protocol did not increase the number of seizure-free patients with DRE; however, it was effective in minimizing seizure frequency in patients whose seizures remained uncontrolled. Among these patients, the median seizure frequency dropped by 64% in the optimization group but did not change in the control group.

Conclusions: Despite the high occurrence of DRE, there is no accepted protocol for the related medical management. This paper describes an effective approach that can be implemented in a clinically relevant and readily achievable manner.

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1. Introduction

Failure to control epileptic seizures with two medications, adequately chosen and dosed, indicates drug-resistant epilepsy (DRE) [21]. In patients with DRE and uncontrolled seizures who are not candidates for surgery, have already undergone surgery, or have had a vagus nerve stimulator (VNS) placed, the chance of seizure control is low [10, 9]. Many patients with DRE must rely solely on medical management. Among non-surgical approaches, a modified diet can result in seizure freedom in 13% of patients and a reduction of more than 50% in seizure frequency in 53% of patients [26]. However, diet modification, as a seizure treatment has been less studied in adults than in children.

Patients with DRE and uncontrolled seizures may experience increases in seizure frequency and severity, along with cognitive and psychiatric dysfunction, injuries, status epilepticus, and sudden unexpected death in epilepsy (SUDEP) [23]. New antiseizure drugs introduced in clinical practice throughout prior decades have
not improved the number of patients with DRE who become seizure free [9]. Antiepileptogenic drugs are not on the close horizon, either.

Providing patients with DRE who are not surgical candidates or who still experience seizures after surgery with superior medical care, involves leveraging all available therapeutic tools and resources. Thus, DRE medical care can be optimized by systematically considering as many factors as possible that facilitate or inhibit breakthrough seizures. Seizures’ control could be enhanced by systematically combining multiple therapeutic interventions: improving compliance, more frequent follow-up visits, treating sleep disorders, combining anti-seizure drugs with different mechanisms of action, adjusting drug treatment schedules to achieve higher peak blood levels when seizures are more frequent and improving patients’ education.

Each of these measures, when used independently, might yield only a limited therapeutic benefit. Clinical studies confirming the relevance of each would require a large sample size. Such research would be expensive and studying a modest therapeutic action would be of limited practical utility. In general, these measures tend not to be incorporated into the standards of care of patients with epilepsy and may thus be inconsistently implemented in clinical practice. Yet, at least in theory, a systematic and simultaneous implementation of all of the above measures is likely to yield a sizable, clinically relevant improvement by accruing the small therapeutic effect of each.

This paper presents empirical evidence and a proof of concept that the above approach (i.e., a systematic implementation of multiple therapeutic actions), yields a notable clinical improvement in DRE. This approach is relevant for DRE cases involving uncontrolled seizures in patients for whom no clinical alternative exists apart from medical management. The proposed approach is also valuable because it can be easily applied and offers further opportunity for refinement.

2. Methods

I performed a retrospective review of the charts of 659 consecutive, unselected adult patients seen at the epilepsy clinic of the University of Utah Health Sciences Center (2014–2016) and at the Salt Lake City VA Medical Center (2018–2020).

Per Kwan et al. [21] DRE is defined as the failure of adequate trials of two tolerated, appropriately chosen and implemented drug schedules to achieve sustained seizure freedom (for longer than 3-fold the longest inter-seizure interval and also for longer than 12 months). Cases involving remission shorter than 3-fold the longest inter-seizure interval and shorter than 12 months are defined as “indeterminate.” Breakthrough seizures due to non-compliance are not thought to reflect drug resistance.

The following exclusion criteria were applied consistently in all experimental groups: patients who (i) experienced nonepileptic seizures, irrespective of association with epileptic seizures; (ii) had less than three clinic encounters; (iii) exhibited low or no interest in adhering to the recommendations of the physician(s); (iv) had surgery (resection, VNS, and RNS) during the study period; (v) had a VNS placed within 3 years before the study period; (vi) their medical records did not provide a reliable definition of seizure frequency at baseline and/or during the observation time interval; (vi) their seizures at baseline, prior to the observation interval, were rare (<1 seizure per year) and relapsing-remitting with a variable, irregular occurrence: this seizure pattern could not reliably indicate the impact of optimization.

Specifically, I compared the outcomes between two groups. The first group, or study group, was labeled the “medical management optimization” group (hereafter “optimization group”) and consisted of patients who were followed up by this author and a supervised mid-level provider. The second group, the control, consisted of patients followed up by four other neurologists specialized in epilepsy. According to these patients’ medical charts, the neurologists adopted measures similar to those of the optimization group, albeit much less systematically.

The first part of the Results section presents a comparison of measures implementation between the optimization and control groups, as documented in patients’ records. The second part provides an overview of the groups’ outcomes. The main endpoint is the change in seizure frequency as reported in the chart in patients’ follow-up progress notes.

Diaries with specific dates of seizures were maintained by 45% of patients while in the remaining cases the seizure frequency adopted in the study represented the number provided by patients and/or caregivers and reported in patients’ progress notes. Attempts were made to speak with caregivers to assess for seizures of which a patient was unaware. Among 42 cases of Focal Impaired Awareness Seizures (FIAS) in the control group, in 26/42 (62%) related follow-up encounters, the epilepsy interval history was corroborated by a caregiver who accompanied the patient to the clinic. Of the remaining 16 patients, 12 reported living with family or housemates who would informs the patients of any seizures they had witnessed. The optimization group included 21 cases of FIAS; the epilepsy history of 14/21 (66%) was corroborated by an accompanying caregiver. The remaining 7 patients lived with family or housemates; at follow-up visits, we inquired with the patients whether their housemates had informed them of having witnessed breakthrough seizures. We also called the caregiver(s) whenever possible.

To assess the impact of optimization of the outcome I proceeded as follows. The seizure frequency at the end of the evaluation (POST-value) in the optimization group is assumed to reflect the optimization itself. To account for variability in baseline seizure frequency between different individuals, POST-values were normalized to PRE-values (baseline seizure frequency) to enable a statistical comparison of higher power with the control group. For each patient, I calculated the normalized seizure frequency as $R_{S_z}$ Frequency:

\[
R_{S_z}\text{Frequency} = \frac{\text{Seizure-frequency-after-optimization (POST)}}{\text{Seizure-frequency-at-baseline (PRE)}}
\]

(1)

Ratio values of $\sim 1$ indicate that no relevant changes occurred. Ratios of $>1$ and of $<1$ represent an increase and a decrease in seizure frequency, respectively.

Focal Impaired Awareness Seizures (FIAS) may occur without patients’ awareness of their occurrence [12] leading to an underestimate of the actual seizure frequency. In this study, $R_{S_z}$ Frequency represents the change in seizure frequency, rather than the absolute seizure frequency. Therefore, it should represent a fair estimate of the outcome, whether seizure frequency is improving or not, if the fraction of FIAS unreported by patients/caregivers, remains approximately constant throughout the study interval. The fraction of unreported FIAS may vary from month to month [11] and therefore $R_{S_z}$ Frequency values were calculated by using the reported seizure frequency throughout several months.

Terminology for seizures and epilepsy classification follows Fisher et al. [14] and Sfelfer et al. [33]. Statistical comparisons were performed through Wilcoxon test or Student’s t-test with Kaleidograph (Reading, PA) and through Squared Chi with an online version of GraphPad (https://www.graphpad.com/quick-calcs/contingency1/).
3. Results

I obtained a list of patients followed up in the epilepsy clinic at the University of Utah Health Sciences Center and at the Salt Lake City VA Medical Center. Based on this list, I reviewed the charts of 309 consecutive, unselected cases in the list of patients in the optimization group. I reviewed the charts of 350 additional consecutive, unselected cases in the control group; these individuals were followed up in the same clinic and at matching time intervals. Exclusion criteria (see Methods section) were applied consistently across both groups. After exclusions, in total, the study sample included 48 patients in the control group and 27 patients in the optimization group who exhibited DRE and uncontrolled seizures. These patients exhibited an epilepsy history with seizures occurring for many years, often for decades. For example, in the control group, 93% of patients had experienced seizures for more than 5 years; over the same time frame, 75% of patients in the optimization group had experienced seizures.

The control and optimization groups’ demographics, epilepsy history, features, and severity are summarized in Tables 1 and 2 and are detailed in Section 2. The same section addresses whether differences between the two groups may underlie the more favorable clinical outcome of the optimization group and describes the methodology used for statistical comparisons.

3.1. Medical management controls seizures in 15–18% of patients with DRE

Within the patient cohort in the current study, 11/62 patients (18%) with DRE in the control group and 5/34 (15%) patients in the optimization group achieved seizure control. This study focused on the remaining patients with DRE, in whom seizures remained uncontrolled. The first part of this subsection outlines the specific optimization steps and how these were pursued compared with the control group. The second part summarizes the effect of optimization on the frequency of patients’ breakthrough seizures versus the control group; potential confounding factors are also addressed.

1. Medical management optimization of patients with DRE by systematically combining multiple therapeutic actions

| Table 1 | Seizures are controlled in 15–18% of patients with drug-resistant epilepsy. |
|---------|-------------------------------------------------|
|          | Control | Optimization |
| Patients whose charts were reviewed | 350     | 309          |
| Number of patients after exclusions | 131     | 94           |
| Patient not with DRE | 61/131 (47%) | 54/94 (57%) |
| Patients with indeterminate DRE | 8/131 (6%) | 6/94 (6%) |
| Total patients with DRE | 62/131 (47%) | 34/94 (36%) |
| Subgroups of patients with DRE | | |
| Patients with DRE and controlled seizures | 11/62 (18%) | 5/34 (15%) |
| Patients with DRE and indeterminate seizures’ control | 3/62 (5%) | 2/34 (6%) |
| Patients with DRE and uncontrolled seizures | 48/62 (77%) | 27/34 (79%) |

| Table 2 | Demographics and frequency of the epileptic seizures of patients and potential confounding factors. |
|---------|-------------------------------------------------|
|          | Control | Optimization |
| Patients with DRE and uncontrolled seizures | 48 | 27 |
| Age (years) | μ ± SE | 45.6 ± 2.3 ns | 46.7 ± 3.0 |
| Gender (F:M) | 20:28 (42:58%) ns | 8:19 (30:70%) |
| FIAS without generalization | 17/48 (35%) | 15/27 (56%) |
| FIAS with generalization | 25/48 (50%) | 6/27 (22%) |
| FAS | 4/48 (8%) | 5/27 (19%) |
| IGE | 1/48 (2%) | 1/27 (4%) |
| Atonic | 2/48 (4%) | – |
| Developmental delay | μ ± SE | 22/48 (46%)** | 3/27 (11%) |
| Seizures’ onset age | Median | 15 ± 3* | 25 ± 4 |
| Years with seizures | μ ± SE | 10 | 19 |
| Seizures/month at baseline | μ ± SE | 4.54 ± 0.87 ns | 13.67 ± 4.84 |
| Abbreviations. DRE: drug-resistant epilepsy. FIAS: focal impaired awareness seizures. FAS: focal aware seizures. IGE: idiopathic generalized epilepsy. |

Drug-resistant epilepsy was defined based on Kwan et al. [21] (see Methods and Results). Note that in the control group, one patient had both FIAS with secondary generalization and atonic seizures. Of the four patients with FAS in the control group, one had secondary generalization; the remaining three had focal seizures. Thus, in the control group, the total number of patients with focal seizures and secondary generalization was 26 (25 with FIAS and one with FAS). Twenty control patients had focal seizures without secondary generalization (17 with FIAS and three with FAS).

None of the five patients with FAS in the optimization group had secondary generalization.

* P < 0.05. ** P < 0.01, Wilcoxon test. ns not statistically significant.
Optimization included the following steps: (A) attempts to improve compliance; (B) increasing the frequency of follow-up visits; (C) screening for possible sleep disorders; (D) applying rational polypharmacy; (E) assessing for a temporal pattern of breakthrough seizures and adjusting drugs’ schedule accordingly; (F) counseling on preventable seizure triggers; and (G) administration of rescue medication in cases of seizure clustering.

A. Optimization of DRE medical management: attempts to improve compliance

Low compliance is a common cause of treatment failure and is due to multiple contributing factors [32], such as (i) inadequate communication with healthcare providers, (ii) side effects of antiseizure drugs, (iii) forgetfulness, and (iv) low motivation due to depression. Effort to improve compliance should address as many of these contributing factors as possible.

(i) Adequate/inadequate communication with healthcare providers. Nearly all patients in the optimization group had documented assessment and treatment planning involving themselves and their families. In contrast, in the control group, about 10% of patients did not have these discussions documented in their charts.

(ii) Side effects of antiseizure medications. Patients with DRE generally take multiple medications at relatively high doses and are therefore more susceptible to medications’ side effects. In the optimization group, side effects were more frequently discussed with patients, leading to better understanding and management.

(iii) Forgetfulness. Cognitive difficulties are common in patients with epilepsy. Bedside testing for cognitive difficulty was implemented in the optimization group, resulting in higher documentation of cognitive impairment.

(iv) Low motivation due to depression. The optimization group received more frequent counseling on seizure triggers, which helped improve motivation and adherence.
documented in more patients of the optimization group (Fig. 1A, third histogram from the left) but in fewer control patients. Identifying cognitive impairment prompted compensatory measures, such as cognitive rehabilitation, family involvement, and, if indicated, referral to visiting nurse services.

(iv) Low motivation related to depression. Depression may contribute to poor compliance. Bedside testing for depression was documented in most optimization patients (Fig. 1A, fourth histogram from the left) but in notably fewer control patients. Patients exhibiting symptoms of depression were referred to the Psychiatry department and were followed up more closely to ascertain their compliance.

B. Optimization of DRE medical management: Increasing the frequency of follow-up visits

Increasing the frequency of follow-up can lead to better monitoring of patients’ therapeutic responses and adverse side effects while enhancing patient–provider communication.

The intervals between follow-up visits tend to vary widely between patients. The type(s) and severity of seizures along with their frequency determine how often patients should attend follow-up visits. Therefore, seizures are a main source of the variability in patients’ follow-up visit intervals. To facilitate statistical comparison, it is convenient to first select a specific type of seizure to obtain a more homogeneous sample and then calculate an index reflecting the duration of follow-up intervals on the basis of seizure frequency.

FIAS, previously known as complex partial seizures, represented the most common type of seizure in the study cohort; therefore, to have a larger sample size, this seizure type was chosen for statistical comparison. To normalize inter-visit intervals by accounting for seizure frequency, the normalized follow-up interval (i.e., the ratio $R_{\text{follow-up}}$) can be calculated as follows:

$$R_{\text{follow-up}} = \frac{\text{Average-inter-visit-interval}}{\text{Average-inter-seizure-interval}}$$

The average inter-visit and inter-seizure intervals were measured in days. The index $R_{\text{follow-up}}$ is a ratio between two measures expressed in days (average inter-visit and average inter-seizure intervals, respectively) and therefore is a pure number. It enables statistical comparison between follow-up visits in cases of heterogeneous seizure frequencies.

Regarding FIAS in this study, patients’ median inter-visit intervals as denoted by $R_{\text{follow-up}}$ were 3.3 and 10.1 in the optimization and control groups, respectively ($P = 0.015$, Wilcoxon test) (Fig. 1B). As an example, to illustrate the insight obtained by calculating $R_{\text{follow-up}}$ with FIAS occurring every 9 days, follow-up would occur in 28 days and 90 days in the optimization and control groups, respectively.

The duration of intervals between subsequent follow-up visits involves two conflicting considerations: the interval should be short enough to limit breakthrough seizures as much as possible but long enough to indicate whether the treatment is effective. A follow-up interval of $\sim$3-fold the average inter-seizure interval, similar to the median of the optimization group, could represent the best option for several patients. The final decision on how often a patient should be seen in follow-up is to be individualized to the specific clinical context. Overall, however, more frequent follow-up encounters allow for more efficient implementation of optimization measures.

Increasing the frequency of follow-up visits does not change the general principles of DRE medical management. However, more frequent encounters allow closer monitoring and continuity of care: among the others, a more rapid adjustment/change of management, more time with the patient to establish rapport and a more thorough grasp of the overall social, psychiatric and medical conditions of each patient.

The advantages of increasing the frequency of follow-up visits, for example, are evident in case of side effects from a medication: the physician would decrease the dose and attempt a slower titration, as well as explain the importance of compliance, regardless of the frequency of visits. However, shorter inter-visit intervals, decreases the risk of the patient ceasing to take the medication(s), at least for long times, resulting in more breakthrough seizures in between appointments. In the optimization group, inquiry and counseling on medications’ side effects were typically pursued at each follow-up visit: pharmacological regimen was promptly adjusted, whenever indicated.

C. Optimization of DRE medical management: assessing for sleep disorders

Screening for sleep disorders was documented in 6/48 patients in the control group; 2/48 were tested. Of the 2/48 (4%) who were diagnosed, only 1/48 (2%) complied with treatment. Among patients in the optimization group, screening for sleep disorders was documented in 18/27 patients (67%) ($P = 0.0001$, Fisher’s exact test vs. corresponding value of control group), and all of them (18/27) were referred for sleep laboratory testing. In this group, 13/27 patients were diagnosed with a sleep disorder ($P = 0.0001$, Fisher’s exact test vs. corresponding value of control group). Of these, 12/27 patients had obstructive sleep apnea (OSA) and one patient had restless leg syndrome. Of the diagnosed patients, only 8/27 (30%) complied with treatment through wearing a CPAP at night ($P = 0.0011$, Fisher’s exact test vs. corresponding value of control group); the other 4/27 declined it and/or did not tolerate it.

In sum, in patients in the optimization group, bedside screening, formal testing, as well as diagnosis and treatment of sleep disorders were obtained more frequently than in the control group. In the optimization protocol, higher screening and testing for sleep disorders led to diagnosing OSA in 12/27 (44%) of individuals with DRE and uncontrolled seizures, a notably large number.

D. Optimization of DRE medical management: Avoid combining drugs with similar mechanisms of action (rational polypharmacy)

I assessed the number of patients who were simultaneously taking antiseizure drugs with similar mechanisms of action during the observation interval. Antiseizure drugs can be classified on the basis of their mechanism of action [34]. A sizable number of anti-seizure drugs are inhibitors of voltage-gated sodium channels. These types of drugs include inhibitors of “fast-inactivated state” sodium channels (phenytoin, carbamazepine, oxcarbazepine, lamotrigine, rufinamide) and inhibitors of “slow-inactivated state” sodium channels (eslicarbazepine and lacosamide), respectively [8].

Studies on experimental models and on human subjects indicate that a greater therapeutic effect can be obtained by combining drugs with distinct mechanisms of action. Thus, I counted the number of patients who were prescribed drugs with a similar mechanism of action at the same time. In the control group, 5/48 (10%) of patients were taking two “use-dependent” sodium channel blockers simultaneously; in the optimization group, no patients (0/27) were taking two “use-dependent” sodium channel blockers prescribed at the same time. The difference between these groups in terms of combining use-dependent sodium channel blockers was not statistically significant ($P = 0.1527$, Fisher’s exact test).
No other patients were taking a combination of antiseizure drugs with a similar mechanism of action at the same time in either the control or optimization group.

E. Optimization of DRE medical management: Guiding of antiseizure drug schedules through seizures’ temporal patterns

Breakthrough seizures exhibit a circadian rhythm [20]. Patients of the optimization group were asked about when breakthrough seizures occurred over the course of the day. Medical records documented a temporal occurrence of breakthrough seizures in 2/48 (4%) control group patients and in 9/27 (33%) optimization group patients ($P = 0.0001$, Fisher’s Exact test). Of the latter, 5/27 (18%) corresponded to occurrences in sleep, typically at night, while the remaining 4/27 (15%) corresponded to occurrences in mid-late afternoon.

The schedule and dose of antiseizure medication was changed in 7/27 (26%) to yield higher levels at the times of breakthrough seizures. To improve night-time breakthrough seizures, the bedtime dose was increased; to prevent mid-late afternoon breakthrough seizures, an add-on dose was prescribed in the early afternoon. Representative examples are discussed in the legend of Fig. 2.

F. Optimization of DRE medical management: counseling on preventable seizure triggers, such as alcohol use and medications that lower the seizure threshold

Alcohol drinking is a known, recurrent, and preventable trigger of seizures [3]. Medications such as antibiotics can facilitate seizures [36], as can bupropion and tramadol. Therefore, counseling on these seizure triggers can decrease seizure recurrence. Nearly all (26/27) of optimization patients received counseling on such triggers compared to only 4% (2/48) of control patients ($P = 0.0001$, Fisher’s Exact test) (Fig. 1F).

In the optimization group, screening was pursued for other potential seizure triggers such as flashing lights, fever/infection, and menstruation. Increased seizure frequency after exposure to flashing lights was documented in 3/48 and 3/27 patients in the control and optimization groups, respectively. With the exception of one patient in the control group who wore tinted glasses, flashing lights appeared to be a rare/minor trigger such that no preventative action was taken. An increase in seizure frequency related to fever/infections was also reported in 2/48 and 3/27 patients in the control and optimization groups, respectively. Increased seizure frequency during menstruation was reported in 5/21 and 5/8 women in the control and optimization groups, respectively. The higher percentages reported in the optimization group for

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**Fig. 2.** In patients with DRE and uncontrolled seizures, medical optimization decreased the frequency of seizures by 64%.

Panel A is a scatter plot of the values of $R_{freq}$ (see Results section). Dotted lines represent median values. Data showed that the seizure frequency improved in the optimization group. The wide range of seizure frequency values at baseline made it difficult to appreciate whether, at the end of the observation interval, optimization changed seizure frequency. Therefore, seizure frequency at the end of the observation interval (POST-value) was normalized to (divided by) the seizure frequency at baseline (PRE-value) (see Results). $R_{freq}$ values close to 1 indicate that the seizure frequency did not change substantially, whereas values markedly higher and lower than 1 indicate a worsening or an improvement, respectively. The median was 1 in the control group and 0.36 in the optimization group, corresponding to a 64% improvement. This difference is statistically significant ($P = 0.00014$, Wilcoxon test). A sizable fraction of patients improved in the control group. The difference between the optimization and control groups was that fewer individuals in the optimization group fared worse.

Panel B presents three cases representative of success in the optimization group. In all three cases, I assessed for consistency in baseline seizure frequency for at least 12 months. In two cases (Patient #1, corresponding to purple dots and lines; Patient #2, corresponding to green dots and lines), available data on the baseline seizure frequency spanned years before implementing the optimization. Patient #1 (purple dots and lines) had undergone a temporal lobectomy and implantation of a vagus nerve stimulator. He experienced attacks with confusion and oro-buccal and manual automatisms, typically in the mid- to late afternoon. Baseline drug regimen was lacosamide 400 mg in am and 600 mg at bedtime. Optimization drug regimen was lamotrigine 300 mg in am; 400 mg in early pm, 300 mg at bedtime; lorcazepam 1 mg prn clustered seizures. At baseline, patient would experience a cluster of 4–5 seizures every 2–3 weeks. After optimization, patient would experience a cluster of 2–3 seizures every 8 weeks. Patient #2 (green dots and lines) had undergone frontal lobe surgery and at baseline was experiencing 2–3 daily attacks with facial twitching and throat spasms, typically after falling asleep. Baseline drug regimen was Vimpat 50 mg bid, Tegretol XR 400 mg am, 200 mg bedtime; levetiracetam 1000 mg bid. Optimization drug regimen was Vimpat 50 mg am and 200 mg bedtime; Tegretol XR 400 mg am, 200 mg bedtime; levetiracetam 1500 mg am, 3000 mg at bedtime. At optimization, patient would experience two attacks per week, and the attacks were shorter and less severe. Patient #3 (red dots and lines) had attacks of staring, confusion, and manual automatisms, typically between 3 and 6 pm. At baseline, seizures would occur with a cluster of four seizures about once a month. During this period, surgical option was deferred. Baseline drug regimen was lacosamide 150 mg bid; topiramate 200 mg bid; Tegretol XR 200 mg bid; lorazepam 1 mg prn clustered seizures. Optimization drug regimen was lacosamide 100 mg am, 200 mg early afternoon, 100 mg bedtime; Tegretol XR 200 mg am, 200 mg early afternoon; topiramate 100 mg am, 200 mg early afternoon, 100 mg bedtime; lorazepam 1 mg prn clustered seizures. After optimization, patient would experience a seizure cluster every 4 months.
fever/infection and menstruation as potential triggers might reflect the screening on a higher number of patients, rather than concrete differences in these patient populations. Fever/infection and menstruation are not easily preventable or actually preventable respectively, triggers. Rather, in such circumstances, seizure clusters can be managed through rescue medications rather than with preventative measures.

G. Optimization of DRE medical management: rescue medications when seizures occur in clusters

Seizures can occur in clusters [22]. In such cases, a rescue medication such as a benzodiazepine can decrease the number of seizures in the cluster. Seizures occurred in clusters in 10/48 (21%) patients in the control group, 7 of whom were treated with a benzodiazepine (diazepam or lorazepam). Clustered seizures occurred in 4/27 (15%) patients in the optimization group; 2 received lorazepam as rescue medication. Rescue medications were administered to some patients in both the control and optimization groups and do not explain differences in seizure frequency outcomes between these groups. However, rescue medication for clustered seizures is an essential aspect of an optimization protocol that can operate in synergy with other optimization interventions to enhance the chances of success.

2. Combining multiple therapeutic actions improves clinical outcome of patients with DRE

In the medical management optimization protocol proposed here, the therapeutic measures or steps described in prior sections were implemented much more frequently than in the control group. I then evaluated whether the proposed protocol led to clinical improvements. In theory, each of the adopted measures (see Section 1), should exert a therapeutic effect. Combining them should hence yield a higher therapeutic improvement than that when adopting none, or one individually, or a few simultaneously.

1. Medical management optimization decreases the frequency of seizures.

For each patient, I defined two contiguous intervals: the baseline and the observation period (test period), separated by the observation start time. Based on patients’ reports during clinical encounters in both groups, I determined the seizure frequency as a measure reflecting the effectiveness of the medical management protocol. Here I present the values of seizure frequency at baseline and during observation, as well as the interval durations in which measurements were obtained.

The seizure frequency preceding the observation start time (PRE-value) was determined as follows. A minority of patients (6/27 patients in the optimization group and 4/48 patients in the control group) were new to the practice. Their baseline seizure frequency was determined solely based on information provided by each patient and/or the caregiver during the initial clinical encounter. In the remaining patients, medical record information on seizures dated back to 2 - 408 (median: 70) months before the observation start time. Among these, in 80% of patients, epilepsy histories documented in progress notes spanned time windows longer than 10 months. In the latter, I calculated the average seizure frequency during the 10 - 12 months preceding the observation start time. For cases in which medical record documentation was shorter than 10 months, I calculated the average seizure frequency in an interval longer than three-fold the average seizure frequency.

The number representing seizure frequency was smaller than 1, for seizures occurring at intervals longer than a month, on average. Thus, for seizures occurring on average every 2, 4, and 12 months, average seizure frequencies were 0.5, 0.25, and 0.08, respectively.

The baseline PRE-value in the control group was 4.5 ± 0.9 (0.08 ± 0.30; median: 2) seizures per month, and about 93% of values were higher than 0.25 (i.e., seizures were more frequent than an average of one every 4 months). In comparison, in the optimization group, the baseline PRE-value was 13.7 ± 4.9 (0.08 ± 0.105; median: 3.7) seizures per month, and about 88% of values were higher than 0.25.

The intervals of observation were (μ ± SE) 19 ± 2 (9 ± 38; median: 17) months in the optimization group and 34 ± 2 (8 ± 80; median: 36) months, in the control group. The observation time for the control group was longer, reflecting availability of more clinical encounter data. Still, in the control group, management changes were typically rare throughout the observation period. In the optimization group, even as available observation intervals were shorter, 80% of interval values (21/27 cases) were still longer than 12 months. Section 2.2 shows that in the few cases with shorter observations, the effect of optimization was similar to cases with longer observations.

The median Rsz Frequency Value in the optimization group was 0.36, indicating a decline in seizure frequency of ~64%. Most values corresponded to a distribution centered on 0.36. Only four cases were distributed at ~1, and only two cases exhibited values higher than 1. The control group’s median Rsz Frequency Value was 1, and most values were distributed around 1. At least eight patients out of 48 (17%) exhibited values above 1, consistent with a progression.

When classifying control patients into subgroups based on the physician following them, the median values of Rsz Frequency for each subgroup ranged between 1 and 3.2. The difference of each subgroup versus the optimization group was always statistically significant.

Visits to the emergency department and hospitalizations related to epilepsy (increased seizures, injuries, or status epilepticus) were documented in 10/48 patients in the control group, compared to 1/27 in the optimization group. This difference was not statistically significant (P = 0.0849. Fisher’s exact test). No cases of SUDEP occurred in the control or optimization groups during the observation interval.

2. Assessing potential confounding factors

The optimization and control groups featured differences in (i) gender distribution, (ii) secondary generalization of seizures, (iii) the number of individuals with a developmental delay; (iv) base-line seizure frequencies; (vi) the number of years with seizures; (vii) the age of seizure onset (Table 2) and also (vii) the length of the observation times. The differences between the two groups were not statistically significant for each and all of these factors. However, it was still important to assess whether any of them could possibly contribute to the therapeutic effect of the optimization group, exemplifying potential confounding factors.

Thus, I stratified cases based on each of these factors (Table 3). When classifying Rsz Frequency values, based on gender, occurrence of generalized seizures, occurrence of developmental delay, Rsz Frequency values spread did not deviate from that of the entire dataset. In none of these cases, the stratification revealed obvious differences between subgroups that could underlie the Rsz Frequency of Optimization.

Last, as the observation time was shorter in the optimization group, I assessed whether the duration of the observation interval influenced this group Rsz Frequency. In particular, I compared values with observations longer than 12 months (21 cases) vs those with shorter observations (6 cases). For observation intervals of ≤12 months, Rsz Frequency values were 0.75 ± 0.39 (0.25 ± 2.7; med-


#### Table 3
Optimization of therapeutic effect is not driven by confounding factors.

|                          | Control                  | Optimization             |
|--------------------------|--------------------------|--------------------------|
| Not stratified (48)      | Not stratified (27)      |
| Median 1                 | Median 0.34              |
| Baseline seizures’       |                          |
| frequency (>4 sz/mo)     |                          |
| Median 1.23              | Median 1.08              |
| Female                   | Male                     |
| Median 1                 | Median 0.58              |
| Sexual gender            |                          |
| GTC                      |                          |
| No GTC (20)**            | No GTC (20)**            |
| Median 1                 | Median 1.24              |
| Developmental            |                          |
| No Dev Delay (26)**      | No Dev Delay (24)**      |
| Median 1                 | Median 1.12              |
| Seizure onset age        |                          |
| <4 yrs old (16) ns       | >4 yrs old (31)**        |
| Median 1                 | Median 1.2               |
| Years with seizures      |                          |
| <20 yrs (14) *           | >20 yrs (33)**           |
| Median 1                 | Median 1.2              |
| Years with seizures      |                          |
| <5 years (2)             | >5 years (45)**          |
| Median 1                 | Median 1.2              |

Abbreviations: GTC: generalized tonic-clonic seizures. Sz: seizures. Mo: month.

Data shown in each cell are µ ± SE on the top and the median on the bottom.

The first row shows RSz Frequency in the control and optimization groups for the whole dataset (i.e., for non-stratified data). All subsequent rows show the values of RSz Frequency in the control and optimization groups when these were stratified into subgroups. The control and optimization groups differed from each other in their baseline seizure frequency, ratio of females:males, occurrence of secondary GTC, occurrence of developmental delay, age of seizure onset, and number of years with seizures. In theory, one or more of these factors could potentially contribute to the observed difference in RSz Frequency between the control and optimization groups. If so, the apparent improvement in seizure control would not be due to the therapeutic effect of optimization but to a confounding factor. Data showed that the difference between the control and optimization groups was maintained even when values were stratified in subgroups that could represent potential confounding factors.

In each row, statistical comparisons were run between the corresponding values of the stratified control and optimization groups. For example, in the row of the stratification according to seizure frequency, I compared the RSz Frequency with <4 seizures/month in the control group versus the RSz Frequency with >4 seizures/month in the control group. I then compared the RSz Frequency with >4 seizures/month in the control group versus the RSz Frequency with <4 seizures/month in the optimization group.

Note that, in the optimization group, there was no obvious difference in the therapeutic effect of implementing the optimization protocol between patients with seizures for <5 years versus those with seizures for >5 years: the protocol was effective even when implemented at a chronic stage of epileptic disease.

In one patient in the control group, age of seizure onset was not documented in the chart.

#### Table 4
Optimization of medical management does not require an increase in the doses of antiseizure drugs.

| Medication    | Control       | Optimization  |
|---------------|---------------|---------------|
| Valproate     | 1955 ± 239   | 1500 ± 408    |
| Lamotrigine   | 533 ± 80     | 525 ± 113     |
| Levetiracetam | 2843 ± 244   | 3029 ± 237    |
| Lacosamide    | 466 ± 35*    | 288 ± 45      |

Data are the µ ± SE of grand-total daily doses expressed in milligrams for four prescribed antiseizure medications. These medications were selected for statistical comparison because they were most common. Data showed that, on average, doses of antiseizure medications were similar between the optimization and control groups. Doses of lacosamide prescribed in the optimization group were lower than in the control group. *P < 0.05 Student's t-test

The coefficient of variation was 1.23. For observation intervals of >12 months, RSz Frequency values were 0.55 ± 0.12 (0.03 ± 2.3; median 0.32) and the coefficient of variation was 1. Therefore, RSz Frequency values obtained with shorter observation intervals are homogeneous with those obtained with longer observation times; the observation interval is not a confounding factor that underlies the therapeutic effect of Optimization.

#### 3. Therapeutic effect of optimization is not related to antiseizure medication doses

Drug dosage is another potential confounding factor, specifically if patients in the optimization group happened to have received higher medication doses. I identified the highest grand-total daily dose of several antiseizure drugs: lacosamide, valproate, levetiracetam, and lamotrigine.

On average, the grand-total daily doses of levetiracetam, valproate, and lamotrigine were similar between the optimization and control groups. In the optimization group, lacosamide was prescribed at a lower dose rather than at a higher dose (Table 4); upon review of the related charts, these patients’ lacosamide doses were increased gradually in an attempt to improve seizure control.

Thus, the therapeutic effect of optimization was not due to higher antiseizure medication doses. In addition, an optimization approach enabled a clinical improvement even without excessive antiseizure medication dosages that could lead to side effects.

#### 4. Discussion

1. Summary of the main findings of this study

   I presented a protocol for medical management optimization of DRE. In comparison with the control group, patients in the optimization group (a) were followed up in a manner meant to enhance compliance; (b) had more frequent follow-up visits; (c) were screened, tested, and treated more frequently for sleep disorders; (d) did not receive combinations of two sodium channel blockers; (e) were assessed for temporal patterns of breakthrough seizures to adjust drug schedules; and (f) were counseled more frequently about common and prevalent seizure triggers. The
medical optimization protocol did not apply these measures in isolation but rather attempted to combine them systematically in every patient with DRE.

Ultimately, roughly 16.5% (15–18%) of patients with DRE became seizure free with or without an optimization protocol. Among patients in whom seizures persisted, implementing an optimization protocol decreased the seizure frequency to 34% compared to no change, on average, in the control group.

2. A protocol of medical management optimization of DRE is necessary

Many patients with DRE must rely on medical management only. DRE medical management is generally thought to involve lifestyle and drug modifications (both choice and dosage). Adjusting medications can even lead to prolonged remission in a subset of DRE cases [30]. Yet debate persists among epilepsy specialists regarding an ideal protocol for DRE management.

3. Medical management does control seizures in a sizable minority of patients with DRE: Speculations on how and why

Medical management of DRE results in 15–18% of patients achieving remission regardless of whether an optimization protocol is implemented. The finding that a sizable minority of patients with DRE can achieve remission is not novel, though it is not always adequately acknowledged (for a more detailed discussion, see [5]). Therefore, it is important that this finding is reproduced, discussed, and divulged.

The fact that a medical management optimization protocol does not increase the number of patients with DRE who achieve remission reflects the limited efficacy of this approach, even when carefully implemented. Surprisingly, optimization may lower seizure frequency without improving the total number of patients who become seizure free. A possible explanation is as follows. Drug-resistant epilepsy and drug-responsive epilepsy, rather than embodying a gradual continuum, may in fact represent two distinct stages along the disease spectrum (i.e., severe and mild, respectively). The lack of seizure control to two medications separates the two stages, albeit imprecisely: the 15–18% of patients whose seizures are in remission at the third or fourth medication and who are considered DRE cases may still correspond to the mild stage of epilepsy. In these patients, seizure control could be achieved much more easily, even without an optimization protocol. By contrast, patients in the severe stage are unlikely to achieve remission, and the best possible outcome would be a marked decrease in seizure frequency in a large number of individuals.

4. Optimization consists of systematically accruing multiple small therapeutic increments

The beneficial effect of each or most of the components of the optimization group has been generally acknowledged. However, the extent of these components’ impacts is debated, and the interventions may not always be applied consistently. The goal of the present study therefore was not to restate their value but rather to measure the therapeutic effect that follows from implementing all of them systematically. In the following sections, I briefly discuss four therapeutic components integrated in the optimization protocol.

4.1. Improving compliance

Poor compliance is a major cause of treatment failure in patients with epilepsy [32, 27]. Low compliance can be challenging to address because it arises from multiple causes. A protocol designed to optimize the medical management of DRE with uncontrolled seizures requires a strategy and an effort to improve compliance. I have tackled several common drivers in this paper.

A key component of low compliance is forgetfulness [19], and reminders appear to be effective [2]. Patients in the present study were screened for cognitive impairment and depression. If indicated, patients were referred for psychotherapy and/or physicians engaged with patients’ families to remind patients to take their medications. If patients were socially isolated, then they were enrolled in a visiting nurse program. Finally, the frequency of follow-up visits was increased, and assessment and treatment plans were reviewed with patients/families at every visit.

Side effects from medications also contribute to poor compliance. In the 2011 American Academy of Neurology (AAN) guidelines on the quality of care of patients with epilepsy [16], the fifth measure required physicians to inquire about side effects, to educate patients about them, and to do so at every encounter. DRE treatment typically involves prescribing multiple antiseizure medications and at high doses. Thus, assessing for medications’ side effects is essential to DRE medical management, at least to enhance compliance.

4.2. Inquiring about, testing for, and treating sleep disorders

Sleep disorder screening is not incorporated into standard epilepsy care. However, inadequate sleep is a known trigger of breakthrough seizures, and untreated sleep disorders can lower the seizure threshold. Obstructive sleep apnea occurs in 30% of patients with epilepsy, a higher proportion than in the general population [15, 25].

In a pilot clinical trial [28], a 50% or greater reduction in seizures was observed in 28% of subjects in the therapeutic group, compared with 15% of those in the sham group. The therapeutic effect on DRE of screening/treating sleep disorders as a standalone measure would ultimately benefit only a minority of patients and would be only partial. The value of its impact can be better appreciated when combining it with several other therapeutic measures.

4.3. Rational polypharmacy

Combining antiseizure drugs with different mechanisms of action can yield a higher therapeutic effect, and a lower incidence of adverse side effects, than combining drugs with the same mechanisms of action. This principle has been termed “rational polypharmacy” [17, 35, 24, 7, 1, 31] and can be studied more extensively in epilepsy animal models (i.e., in homogeneous biological preparations).

In human subjects, combining two drugs with distinct mechanisms of action [6], results in a synergistic therapeutic effect, decreased hospitalizations and emergency department visits [29]. By contrast, in human patients with epilepsy, combining two drugs with similar mechanisms of action (e.g., two sodium channel blockers) enhances toxicity [4]. Overall, empirical evidence on the effectiveness of rational polypharmacy is difficult to confirm in humans. Its clinical relevance for human patients with epilepsy remains contested. In the current study, rational polypharmacy is only assumed to be effective and taken as a component of the optimization protocol.

4.4. Match the schedule of antiseizure medications to temporal patterns of seizure occurrence

Seizures manifest through a circadian rhythm [20], such that knowledge of temporal patterns of seizure occurrence can dictate schedules for antiseizure medications individualized to each patient. (e.g., [13], p. 503; see [20], for a more detailed discussion).
To the best of my knowledge, this approach is not always utilized in clinical practice.

Many breakthrough seizures occur at night and/or are related to sleep. Drowsiness is a common side effect of antiseizure medications: increasing bedtime medications' doses leads to lower impairment than increasing daytime doses. Thus, seizures' drug management can be less difficult with night-time seizures [18].

For breakthrough seizures in the middle-late afternoon, an additional medication dose in the early afternoon can boost serum levels when seizures are more frequent, thereby reducing attacks' frequency with a simple action and with a limited increase in the grand-total daily dose of antiseizure medications.

5. Study limitations

This study has at least five major limitations: (i) it was run on a small number of patients; (ii) it was carried out in a non-blinded fashion; (iii) it was based on a retrospective chart review; (iv) among the components of the optimization group, results cannot distinguish the contribution of each in improving seizure frequency; (v) the follow-up observation was limited to a median of only 18 months.

This study did not develop a novel specific modality of treatment but instead organized and implemented a multiplicity of therapeutic steps that had already been previously characterized. To the best of my knowledge, DRE studies similar to the present one, combining multiple measures, to elaborate a practically effective method have not yet been conducted. The limitations of this study are therefore due to its exploratory nature. Last, the methodology and the results shown in this study cannot be generalized. In fact, they reflect only the personal experience of the author with a limited number of patients. The results may not necessarily be reproduced by all epilepsy specialist providers and with larger groups of patients.

6. Summary and conclusions

Many patients with DRE do not benefit from surgery and must rely only on medical management. An accepted protocol for DRE medical management is not currently available, and this paper explored how to elaborate one. The clinical effectiveness of therapeutic steps combined in the optimization group has likely been underestimated among epilepsy specialists because each component may exert only a limited therapeutic effect. These components' clinical relevance may be better appreciated when combined; the small therapeutic impact of each would then accumulate to create a clinically relevant effect. This study's findings suggest that the improvement obtained through optimization is clinically relevant and can be easily achieved.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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