Evaluation of two anti-seizure medication strategies in refractory epilepsy patients from a tertiary center with complementary insights from data visualization

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Evaluation of two anti-seizure medication strategies in refractory epilepsy patients from a tertiary center with complementary insights from data visualization

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ABSTRACT

Objective: To evaluate the healthcare resources in a tertiary center related to exclusive use of non-enzyme inducing anti-seizure medications relative to concomitant use of enzyme-inducing anti-seizure medications in patients with refractory epilepsy.

Methods: In this retrospective case-time-control study, we compared the effects of two anti-seizure medication strategies: exclusively non-inducing anti-seizure medications (NIND) or a combination of NIND and inducing anti-seizure medications (IND\textsuperscript{+}). The primary outcome parameter was the number of consultations with relevant healthcare professionals in our tertiary center, assessed with a negative binomial regression model, adjusting for several covariates like blood drug level and time interval (TI). Results from statistical models were visualized to explore the contribution of all covariates on the outcome in the total population and in subgroups.

Results: From the 21538 patients with refractory epilepsy referred to our center 1648 patients met the inclusion criteria. The regression model showed that the IND\textsuperscript{+} strategy was significantly associated with fewer consultations compared to the NIND strategy (p < 0.001), reflected in an incidence risk ratio (IRR) of 0.844 (0.799 – 0.890). Visualization of subgroups, defined by anti-seizure medications strategy, revealed patterns in contribution of blood drug level measurements on the outcome. Although sex was not included as a covariate in the regression model, as it was eliminated by the backward-elimination approach, visualization of this subgroup showed differences in effects of blood drug level and TI.

Conclusion: For patients with refractory epilepsy in our tertiary center, treatment following the IND\textsuperscript{+} strategy is associated with fewer consultations with healthcare professionals compared to the NIND strategy. Comprehensive visualization of the results facilitated the exploration of effects of covariates across subgroups.

1. Introduction

In the early 1990s the second generation of anti-seizure medications (ASMs) was introduced, most of them without enzyme-inducing effects. Currently, about twenty-five ASMs are available for clinical use that are classified as enzyme-inducing ASMs (IND) or non-inducing ASMs (NIND). There is no significant difference in effectiveness between most ASMs, but treatment strategies might be influenced by comorbidities or adverse effects. These adverse effects could result from drug-drug interaction or medication overdose. These combined factors may lead to decreased or non-compliance (Kwan and Brodie, 2000; Perucca et al., 2009; Uijl et al., 2009) and consequently have a negative impact on the...
quality of life (Luoni et al., 2011; Uijl et al., 2009).

Common adverse effects of ASMs include memory problems, fatigue, tremors, gastrointestinal symptoms, depression, drowsiness, dizziness, weight change and nausea (Carpay et al., 2005). The use of INDs may also increase the risk of more serious long-term adverse effects, such as osteoporosis and cardiovascular risk, especially in elderly patients with a comorbid condition that requires polypharmacy (Brodie et al., 2013; Luoni et al., 2011). Therefore, it is often recommended to switch from IND to NIND.

Many of the adverse effects require specialist care or hospitalization. The accompanying healthcare costs, patient and family costs (i.e., informal care), and costs in other sectors (e.g., loss of employment) can be significant (De Kinderen et al., 2014).

In this study, we evaluated the general recommendation to switch from IND to NIND (Borghs et al., 2020, 2017; Brodie et al., 2013; Gaitatzis et al., 2004). Moreover, because the availability of different ASMs have varied over the years, we sought to investigate possible differences between the ASM strategies over a period of 30 years. The aim of this study is therefore to compare the number of consultations with healthcare professionals between two ASM treatment strategies in patients with refractory epilepsy in a tertiary epilepsy center over the past 30 years. The underlying factors are explored using multivariate regression analysis. Furthermore, the results are visualized using a novel method for conducting Exploratory Data Analysis (EDA) (Tukey, 1977). Additionally, the contribution of the available covariates are put into context using the same EDA method.

2. Methods

In this retrospective case-time-control study we compared the number and costs of consultations with healthcare professionals, along with the prescription costs, of two ASM treatment strategies. Following this approach only relatively short term effects are assessed and not the usually defined long-term effects associated with ASM treatment. The first strategy is to prescribe NINDs exclusively while the second strategy is to prescribe INDs exclusively (Section 2.1). The study was conducted according to the Declaration of Helsinki 2013 and approved by the local medical ethical committee of Academic Center for Epileptology Kempenhaeghe, Heeze, The Netherlands.

2.1. Patient selection

Patients were selected from the electronic patient files of the Academic Center for Epileptology Kempenhaeghe, Heeze, The Netherlands - a center for tertiary epilepsy care. Patients visiting this center are known to have a refractory form of epilepsy. The time window for selection was from April 1988 until April 2018.

The following substances were classified as (strong) INDs: carbamazepine, phenytoin, phenobarbital, primidone. The following substances were classified as NINDs: acetazolamide, clobazam, clonazepam, ethosuximide, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, pregabalin, topiramate, valproate, vigabatrin, zonisamide.

Only patients who had both an IND prescription period as well as an NIND prescription period were included. Additionally, patients were excluded if the prescription period was less than 7 days. The accompanying flowchart is shown in Fig. 1. As mentioned before, concomitant prescription of NINDs was allowed during IND prescription periods. Because this study was a case-time study, the patients were matched with themselves based on the ASM treatment strategy.

2.2. IND and NIND prescription periods and group definition

A prescription period had a minimum duration of seven days, but IND prescription periods were extended with a four-week washout period resulting in a minimum period of five weeks. During this extended period, no NIND periods were possible. Note that the NIND periods and IND periods might alternate over time. The NIND periods and IND periods were grouped, respectively, into two distinct sets of periods per patient; both representing a ‘consecutive’ prescription period (Fig. 2). Based on these sets, the patients are matched with themselves (over time). All variables (e.g., the number of medical consultations) have been defined in line with this dichotomy. Each ‘consecutive’ prescription period spanned a time period of at most five years, starting from the initial prescription date.

Hence, two ASM treatment strategies were defined in this way; the NIND group had been prescribed exclusively non-enzyme inducing ASMs. The IND + group had been prescribed either enzyme-inducing ASMs or a combination of enzyme-inducing ASMs and non-enzyme inducing ASMs within a time period (hence the ‘+’-sign in the group name).

Fig. 1. Flowchart of the patient selection.
2.3. Outcome measure and costs

2.3.1. Primary outcome

The primary study outcome was the number of consultations with relevant healthcare professionals, defined as medical specialists who were primary treating physicians. In our case, these were neurologists and (neuro) psychologists. The outcome was predicted using a negative binomial regression model that included the covariates listed below.

2.3.1.1. Covariates. The covariates included in the regression model were:

- ASM treatment strategy (IND + or NIND as defined in Section 2.1.2).
- IQ class defined as a dichotomous covariate with two classes: 'mild impairment or intellectual disability' (IQ < 90) and 'no cognitive impairment' (IQ ≥ 90).
- The 5-year Time Interval (TI), as defined below.
- The initial age, which is the age at the first prescription for both IND + and NIND.
- The total length of the prescription period in number of weeks.

The remaining covariates were normalized using the length of the prescription periods. For interpretation purposes these are reported in numbers per year:

- The total number of seizures.
- The total number of medical examinations (neuropsychological examination and electroencephalography (EEG)).
- The total number of ASM dose switches.

2.3.1.2. Time intervals (TIs). Since prescription behavior may have varied over time (30 years), patients were also assigned to a specific time interval (TI) based on the initial prescription date (one for the IND + group and one for the NIND group). The TIs were divided into periods of 5 years as follows. TI1: 18-04-1988 until 17-04-1993, TI2: 18-04-1993 until 17-04-1998, TI3: 18-04-1998 until 17-04-2003, TI4: 18-04-2003 until 17-04-2008, TI5: 18-04-2008 until 17-04-2013, and TI6: 18-04-2013 until 17-04-2018.

2.3.2. Indication of costs

A partial economic evaluation using a limited healthcare perspective was performed to obtain an indication of costs related to the used resources in our center. In our study, healthcare costs, related to IND + and NIND treatment strategy during the respective prescription periods, were defined as the sum of healthcare professionals’ costs and the costs of prescribed ASMs in our center. Unit prices of consultations with healthcare professionals are shown in Table 1. In order to calculate the costs per consultation, the number of consultations was multiplied using unit prices of the Dutch guidelines for costing studies in Healthcare (Hakkaart-van Roijen et al., 2016). In addition, the information required to calculate prescription costs of ASM treatments, such as drug name, dosage, and route of administration, were obtained from the electronic patient files. The costs of prescribed ASMs were calculated by multiplying the (standardized daily) doses with the cost of their Defined Daily Dose (DDD) over the prescription periods. All costs of prescribed ASMs...
were estimated based on the Dutch market prices (including 6% tax) (Zorginstituut Nederland, 2020). The costs were normalized using the total number of weeks in the prescription periods to adjust for their varying lengths and expressed as annual costs for interpretation purposes. The year 2018 was used as the reference year for cost calculations.

2.4. Statistical analyses

Since patients were self-matched differences between the IND and NIND groups could be directly assessed. A Wilcoxon signed-rank test was used to perform the related comparisons. Outcomes and costs are reported as medians and interquartile ranges [IQR].

2.4.1. Classical regression modeling (further referred to as standard regression analysis)

The primary outcome of the study was the number of consultations with relevant healthcare professionals per year. This dependent variable was predicted using a negative binomial regression model, with the covariates listed above in Section 2.2.1. Incidence risk ratios (comparable to the odds ratios) were reported with accompanying 95% confidence intervals. The covariates were studied and eliminated using the a backward-elimination method. The analyses were performed using SPSS 25 software (IBM SPSS Statistics Inc, Chicago, IL, USA).

2.4.2. Exploratory Data Analysis (EDA)

Standard regression analysis is sensitive to the selection and inclusion of the proper covariates, confounding, and interaction between covariates. These aspects have been investigated further using an Exploratory Data Analysis (EDA) approach. One aspect of EDA is the visualization of results in general. In this study, results from many statistical regression models were visualized with a novel software tool called RegressionExplorer (Dingen et al., 2019). With this tool, all possible combinations of covariates included in a regression model were visualized comprehensively. The resulting models (hundreds) were structurally compared, thereby putting the standard regression model into context. Hence, potential confounders can be noticed visually, which otherwise could have been missed with standard regression modeling. An example of the output of this visualization tool is shown in Fig. 3.

In addition to the main population, we conducted a structural analysis of subgroups defined by ASM strategy (IND+/NIND) and sex. Consequently, potential interactions can be detected visually. The interactions across the subgroups are visualized by the divided blocks, as depicted in Fig. 4. The results obtained using RegressionExplorer have been summarized qualitatively.

3. Results

3.1. Population characteristics

In total, 1648 self-matched patients were followed over a 30-year inclusion period. Of these patients, 914 (55.5%) were female. Around half of the population had an IQ over 90 (n = 868, 52.7%); 291 had an IQ < = 90 (17.7%); IQ data for the remaining patients were missing (n = 978, 29.7%). The median age in the NIND group was slightly lower than in the IND+ group (p < 0.001) (Table 2). The difference in the number of dose switches between the IND+ and NIND groups was not statistically different (p = 0.230), but the number of ASM was (p < 0.001). Hence, in the IND+ group the total drug load was higher.

![Fig. 3. Exploratory data analysis and validation.](image-url) Different models are depicted as rows, whereas the covariates are shown as columns. The first column indicates the quality of the model (based on the AIC score). In the remaining columns, the (black) blocks indicate the absence of a specific covariate in the model. The blocks are colored red or blue for statistically significant incidence rate ratios (IRR) > 1 or < 1, respectively. The brightness of the color corresponds to the level of significance. White blocks indicate a non-significant effect. Sixteen representative models out of 1024 are shown. The third row represents the model used in the standard regression analysis. The effect of the IND covariate is independent of the other covariates in the models as reflected by the uniform blue color in the IND-column.

Table 1

<table>
<thead>
<tr>
<th>Cost category healthcare professionals</th>
<th>Cost (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologist</td>
<td>91</td>
</tr>
<tr>
<td>(Neuro)psychologists</td>
<td>94</td>
</tr>
<tr>
<td>Occupational specialist</td>
<td>33</td>
</tr>
<tr>
<td>Dietician</td>
<td>31</td>
</tr>
<tr>
<td>Speech therapist</td>
<td>30</td>
</tr>
<tr>
<td>Psychiatrist</td>
<td>94</td>
</tr>
<tr>
<td>General practitioner</td>
<td>33</td>
</tr>
<tr>
<td>Social worker</td>
<td>65</td>
</tr>
<tr>
<td>Clinical geneticist</td>
<td>91</td>
</tr>
<tr>
<td>Pedagogic team (remedial educationalist and psychologist)</td>
<td>80*</td>
</tr>
<tr>
<td>Nurse/ Nursing specialist</td>
<td>66</td>
</tr>
<tr>
<td>Rehabilitation specialist</td>
<td>91</td>
</tr>
<tr>
<td>Pediatrician</td>
<td>101</td>
</tr>
<tr>
<td>Intensive care specialist</td>
<td>91</td>
</tr>
<tr>
<td>Psychomotor therapist</td>
<td>34</td>
</tr>
<tr>
<td>Physiotherapist</td>
<td>33</td>
</tr>
</tbody>
</table>

* mean costs for psychologists and nurses.
3.2. Consultations of relevant healthcare professionals and costs

The covariates sex and number of seizures were excluded from the final standard regression model. Since the current study design was retrospective in nature, it was impossible to retrieve data on seizure frequency automatically from free text fields of the electronic patient files. Also, quantitative data from seizure diaries had not yet been linked to the electronic patient files. Therefore, quantitative data on seizure frequency were only available for a negligible number of patients. The covariates that were included in the final model and their incidence rate ratios (IRR) are shown in Table 3.

In the standard regression analysis, the IND+ strategy showed an IRR of 0.844, which means ~15% fewer consultations with relevant healthcare professionals than the NIND group (Table 3). Furthermore, patients with mild impairment or intellectual disability (IQ < 90) were significantly less likely to have consultations with relevant healthcare professionals compared to patients without cognitive impairment.

In our study we took the costs for prescribed ASMs plus the costs of consultations with all healthcare professionals as an estimation for the annual median healthcare costs in our center. We found that these costs were significantly higher for NIND, €1,090 [€668–€1,603], compared to IND+, €1,011 [€665–€1,510] (7.2% difference, p = 0.004) (Table 2). In the IND+ group, the annual costs of the prescribed ASMs were 36.3% higher (p < 0.001) than those in the NIND group (see Table 2). Finally, prescription costs for IND ASMs are found to be lower than the prescription costs of NIND ASMs in our center. However, note that the total prescriptions costs in the IND+ group by definition includes prescription costs for both IND and NIND ASMs.

3.3. Exploratory Data Analysis (EDA)

Using RegressionExplorer for the EDA, we found that the initial model applied in the standard regression analysis (the third row in Fig. 3) was one of the best fitting models (based on AIC score / deep purple color). Note that the direction of the IRRs as indicated by the blue and red colors correspond to the values in Table 3. Moreover, the
professionals. Conversely, an incidence rate ratio with the total number of consultations with relevant healthcare professionals as medical procedures and costs for NIND and IND indicates an increase in the number of consultations with relevant healthcare professionals.

Results from negative binomial regression model (standard regression analysis)

Table 3
Demographics, anti-seizure medication prescription, number of consultations, medical procedures per year duration and presented as annual values for interpretation purposes. ASM - anti-seizure medications.

Table 2
Results from negative binomial regression model (standard regression analysis) with the total number of consultations with relevant healthcare professionals as the outcome.

3.3.1. Subgroup analysis

Potential interaction with covariates was investigated in subgroups based on treatment strategy and sex. A IND+/NIND subgroup interaction with the covariate number of blood samples was observed in multiple models (Fig. 4). For the NIND subgroup, the effect was comparable to that of the total population: the number of blood samples was associated with an increase in the outcome variable number of consultations with relevant healthcare professionals. This effect is reflected by the red color (IRR > 1) of the blocks across all subgroup-models. On the other hand, this effect was not statistically significant for the IND+ subgroup, which is indicated by the white blocks in many models.

In the standard regression model, sex was not included as a covariate as it was eliminated by the backward-elimination method. Nevertheless, it seemed an interesting and straightforward subgroup for EDA (see the Fig. 5). A distinct pattern appeared in different covariates for males and females. Especially initial age showed to be a non-significant predictor in the male subgroup. In contrast, the number of blood samples was a significant predictor in the male population, whereas many models showed a less significant effect for females. Finally, the TI seemed to be a more important predictor in the female subgroup than in the male subgroup.

4. Discussion

In this retrospective, case-time-control study, we predicted the number of relevant consultations with health care professionals and estimated the costs of two ASM treatment strategies related to care in our tertiary center. We used RegressionExplorer to obtain a selection of relevant covariates for a model with confidence. Moreover, RegressionExplorer was useful in the subsequent determination of the direction and the significance of the covariates that play a role in the different models. We confirmed that our standard regression model was of high quality (in terms of AIC score) and that subsequent models were in line with the standard regression analysis results.

One of the main study findings was the association of IND+ treatment strategy with significantly fewer consultations with relevant healthcare professionals, in comparison with the NIND treatment strategy. In the standard multivariate negative binomial regression model, the covariate IND+/NIND was independently associated with the consultations of relevant healthcare professionals. The IND+ strategy accounted for ~15 % fewer consultations with relevant healthcare professionals. One might expect the IND+ strategy to reflect a prescription period in which multiple strategies were needed (not only IND but also the combination of IND and NIND). Therefore, this period may reflect a less stable period in the patient’s epilepsy history. As the use of these complex treatment strategies can increase the risk of adverse events (Brodie et al., 2013; Gaitatzis et al., 2004), one might have
expected that the IND + strategy in our study would reflect less favorable results in terms of more consultations. However, an explanation of our results could be that only patients with refractory epilepsy are treated in our center. Possibly, for these patients, NIND therapy alone is inadequate to treat their epilepsy, resulting in more consultations. This hypothesis may be supported by the observation that in the IND + group the total drug load (number of ASMs) was significantly higher.

The reason that IQ was also positively associated with the number of relevant consultations (a higher number of consultations in the IQ > 90 patient group) could be that persons without cognitive impairment are more likely to communicate regarding their wellbeing. This seems to be in contrast with another study which suggested that patients with intellectual disability have increased medical expenditures (Pennington et al., 2012). This increased medical expenditure is assumed to be related to the fact that patients with epilepsy and intellectual disability tend to have a worse prognosis, polypharmacy, higher rates of comorbidities, and mortality. Our contradictory findings might in part be explained by the definition of the relatively ‘narrow’ outcome in our study. Nevertheless, since in our study patients served as their own controls, bias in comparison of the two ASM strategies is minimized.

With regard to the time intervals, it seems that there are more consultations with relevant healthcare professionals during the first time interval (1988–1993). This difference might be explained by the fact that, in contrast to the 80 s, a transition from the primary care center to tertiary expertise center took place. The timespan of 5 years was chosen arbitrarily for these Time Intervals and was not based on treatment options or different guidelines. Thus, the different Time Intervals only give a general impression of change over the years.

Furthermore, we found that annual costs for specialized care in our tertiary center (prescribed ASMs and consultations of all healthcare professionals) were lower, although the prescription costs of the IND + strategy were higher than the prescription costs for the NIND strategy. These results cannot be directly compared to two other retrospective cohort studies investigating healthcare consumption concerning ASM treatment strategies (Borghs et al., 2020, 2017), but provide an interesting indicative contrast. The similarities between these and our study include the relatively large number of patients included (n = 1902 (Borghs et al., 2017), n = 1648 for our study), the description of inducers IND (carbamazepine phenytoin, phenobarbital and primidone), and the extended time window for patient selection (over 12 years).

Fig. 5. Exploratory data analysis of alternative models with subgroups for sex. Twenty-five representative models are shown. The blocks are now subdivided into indicated subgroups; the top parts of the block represent the complete population (as in Fig. 3), whereas the bottom parts represent the male and female subpopulations, respectively.
Moreover, these studies were performed in different countries (the United Kingdom and The Netherlands). Also, treatment groups were defined in a different way. The IND + group in our study consisted of patients for whom exclusively IND or a mix of IND and NIND were prescribed. This choice was based on the assumption in the literature that a NIND strategy would perform better than an IND strategy in all respects (Borghs et al., 2020, 2017; Brodie et al., 2013; Gaitatzis et al., 2004). Our current study’s important finding is that this is not always the case, at least not in a specialized epilepsy center treating patients with refractory epilepsy.

4.1. Exploratory Data Analysis (EDA)

We showed that the standard statistical regression model can easily be validated with RegressionExplorer (Dingen et al., 2019). Also, additional insights into the effects of several covariates were obtained. First, we observed that during an IND + period, patients are less likely to consult relevant healthcare professionals (Fig. 4 and Table 3) and that this effect is independent of any combination of additional covariates. Second, when looking at the subgroups of IND + and NIND, the importance of number of blood samples to predict the number of consultations of relevant healthcare professionals was not pronounced in the IND + strategy but only in the NIND strategy. Whether this means that patients with an NIND have more blood samples taken and, therefore, more clinical contacts, should be further investigated.

Third, sex did not add significantly to the standard regression model, but in the subgroups, the covariate effects appeared to differ between male and female (Fig. 5). These effects are shown for multiple models consisting of different combinations of covariates and presented in such a way that the effects seem consistent. These findings are easily observed from the RegressionExplorer outputs, but need to be investigated and confirmed in future research.

With EDA, and especially with RegressionExplorer, a researcher is able to explore relations between covariates and their effects on the outcome in a comprehensive manner. Alternative models can also be constructed with classical software packages, but this entails tedious work. RegressionExplorer is not intended to pick the best model, but, to interactively explore the contents of the research data and obtain further insight. In RegressionExplorer, statistically significant values for the incidence risk ratios are represented by colored boxes. Moreover, when the user moves the mouse over the boxes, the values of the incidence risk ratios (as shown in Table 2) become visible. Hence, not only is the information about the direction and the significance of the effects available interactively, but also the magnitude of the effect.

4.2. Limitations

The first limitation of our observational study is its retrospective nature, which limits the investigation of causal relationships between covariates. However, the study included a rather large population of patients (n = 1648) where two ASM strategies were found within the same patients. This mitigates the chance of a potential selection bias, since patients were matched with themselves supporting the differences found between the two ASM strategies.

The second limitation is the lack of complete overview of comorbidities, (associated) relevant healthcare costs, and non-health care costs. The electronic patient files from our specialized epilepsy clinic were used as the only data source. Therefore, data regarding other diagnoses related to comorbidities and long adverse effects associated with ASMs were not readily available. Also, costs like (in)formal care and costs of productivity losses could not be included.

The third limitation of the study was the incomplete data on IQ and seizures, two covariates that were initially included in the standard regression models. However, the patients whose IQ data were missing could have been considered as an ‘average’ group. Seizure data were usually processed in free text format as mentioned. Quantitative data on seizure frequency was only available in a small number of patients.

The fourth limitation of the study was the lack of a group having exclusively IND prescribed. Even using this definition, we did find interesting differences inASM treatment strategies.

Fifth, the number of seizures, number of medical examinations, and number of ASM dose switches were used as covariates in the models but could have been considered as outcome variables as well. However, our study did not focus on causality and the study aimed to explore the data. The models that included these covariates should therefore be interpreted with prudence.

4.3. Conclusion

In our tertiary center an anti-seizure medication strategy with IND+ (prescription of either exclusively IND or a combination of NIND and IND) is associated with fewer consultations with healthcare professionals than the strategy to prescribe exclusively NINDS. Exploratory Data Analysis by means of comprehensive result visualization is of added value in the analysis and understanding of our data.

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