Physicians’ attitudes toward generic substitutions of antiseizure drugs in epilepsy

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Objectives: The safety of generic substitution of antiseizure drugs (ASDs) has been questioned for many years. This study aimed to identify physicians’ attitudes to the generic substitution of ASDs in epilepsy and which factors were of significance when deciding on compound substitutions.

Material and Methods: A cross-sectional web-based survey was sent to neurologists and neurology residents in public health care and at private practices in two Swedish regions between February and March 2020. The 30-item survey covered drug- and patient-related factors, as well as considerations relating to practical, cost-related, and pharmacokinetic issues.

Results: The total response rate was 55.8%. Respondents were generally positive to cutting costs through generic ASD utilization (74%) and prescribing generic compounds when starting a new ASD treatment (84.9%). The most substantial concern was a deterioration in seizure control (17.1%). Physicians refrained from switching if the patient wished to remain on the original compound (76.1%), had a cognitive impairment (52.5%), was on a drug with a narrow therapeutic index (47%), or had shown prior susceptibility to adverse effects (45.6%). Opinions on substitution decisions differed significantly between the Stockholm and Skåne regions. Less than one-third of the respondents were aware of supporting guidelines.

Conclusions: Neurologists generally accept the use of generic antiseizure compounds. Patient preference to remain on brand-name drug treatment was the most important factor that led to avoiding a switch. Our results may constitute material for consensus discussions to decide on quality indicators of interest for future research on substitution outcomes.

Keywords: anticonvulsants, drugs, epilepsy, generic, physicians, surveys and questionnaires
1  |  INTRODUCTION

Generic drugs offer potential cost savings, but the therapeutic equivalence of generic antiseizure drugs (ASDs) compared to brand-name ASDs is questioned and widely debated. Concerns about adverse substitution outcomes are widespread among people with epilepsy (PWE) and physicians.\textsuperscript{1-7} Multiple retrospective studies have reported dubious efficacy of generic ASDs.\textsuperscript{8-10} However, more recent studies have compared serum concentrations and pharmacokinetics between generic ASDs and branded counterparts, and between different generic compounds, without identifying significant differences.\textsuperscript{11-15}

Furthermore, prospective studies of generic ASD substitution report that similar proportions of patients switch back to the brand-name drug compared to substitutions of other drug classes.\textsuperscript{14-18}

Even though the current best evidence supports that switches from brand-name to generic ASDs are safe at group level, it is still possible that a minor subset of PWE may be at risk of harmful and potentially severe adverse effects, including a deterioration in seizure control. As a safety precaution, no automatic switches of ASD compounds are allowed at pharmacies in Sweden. It is up to the treating physician to decide whether a generic switch should be prescribed. Since no evidence-based guidelines exist on which patient characteristics may contraindicate a substitution, practices are likely to diverge significantly between different physicians, clinics, and geographical regions. Pharmacy data strongly support this hypothesis when looking at volumes of levetiracetam, an ASD with no indication other than epilepsy. During the first 9 months of 2019, the proportion of generic levetiracetam defined daily doses ranged between 22\% and 86\% among the 21 Swedish geographical regions.

This study focused on two of the largest regions: Stockholm (RSthlm) and Skåne (RSkane). Despite structural similarities, the prescription proportions of generic levetiracetam differed widely between the two regions (RSthlm 22\% | RSkane 72\%). One probable reason for the large difference is that RSkane has had a regional goal of increasing generic prescribing of generic levetiracetam since 2014. No such governing requirement exists in RSthlm. Both regions recommend prescribing a generic compound when initiating ASD therapy.

Our primary aim was to examine physicians’ attitudes to the generic substitution of ASDs in epilepsy and which factors were of significance when deciding on compound substitutions in daily practice, including both brand-name to generic and generic to generic substitutions. The secondary aim was to compare opinions on substitution decisions between RSthlm and RSkane.

2  |  METHODS

2.1  |  Study design and sampling frame

We performed a cross-sectional online survey on perspectives on generic ASD substitution in epilepsy. The sampling frame consisted of specialists and residents in neurology employed at adult neurological units, in the capital RSthlm with 2.38 million inhabitants and the southern RSkane with 1.38 million inhabitants. The survey addressed physicians working in public health care at university or general hospital levels and physicians at private practices. The Swedish Ethical Review Authority provided a limited advisory statement without ethical objections. As the survey did not collect any sensitive personal data or meet any of the other criteria for application of the Swedish Ethical Review Act, there was no legal requirement to obtain approval for the study.

2.2  |  Measures

A self-administered survey was developed specifically for this study after consensus discussions within the research group, comprising three senior clinical neurologists, one senior clinical pharmacologist, and two clinical residents. The survey consisted of multi-response questions and items answered on an arbitrary, six-point Likert Scale with an additional “No opinion” choice. A space for additional free-text comments was available for selected questions. The construction of each item was targeted at avoiding double negations and leading questions. Overall, short formulations were preferred.

The survey consisted of 30 items covering different aspects of generic substitution of ASDs. An English translation of the original Swedish version is shown in the supporting information. Nine domains stratified the items:

- Prescribers’ demographics: regional affiliation, age category, gender, medical affiliation, title, and the number of epilepsy outpatient encounters per year (seven items).
- General attitude to the generic substitution of ASDs (four items).
- Specific factors that may influence substitution decisions: patient-, disease-, drug-, and compound-related (four items).
- Practical aspects regarding time and type of healthcare contact (three items).
- Cost aspects (two items).
- Pharmacokinetic considerations (four items).
- Previous experience of generic substitution (two items).
- Guidelines and supporting material (two items).
- Other questions (two items).

A pilot study distributed among ten clinical neurologists tested the survey’s comprehensibility. The final survey design was approved by every researcher in the group after corrections based on input from the pilot study.

2.3  |  Data collection

We identified 276 registered e-mail addresses for neurologists and neurology residents in the digital healthcare catalogs available for health professionals (RSthlm: n = 165, RSkane: n = 111). The questionnaire distribution was managed by the Swedish University...
Computer Network (SUNET) Survey, Artologik Survey & Report, version 4.3.10.5 (Artisan Global Media, Växjö, Sweden). The digital tool showed when surveys were filled in and returned without linking to individual responders. To maintain anonymity, we also minimized the detail level of response alternatives to the demographic questionnaire items.

A link to the online survey, sent by e-mail, reached potential participants between February 17 and March 30, 2020. A preceding letter describing the study and its purpose reached potential respondents a couple of days in advance. In this letter, we emphasized that participation was voluntary and that consent to participate was given by answering the survey. Those who had not yet responded received a maximum of six reminders during the study period.

2.4 | Statistics

Answers to Likert items were, with a few exceptions, categorized as follows: 1–2 = disagree/speaks against substitution, 3–4 = indifferent/no strong impact, and 5–6 = agree/speaks in favor of substitution. Some items (Q12–15, 16–18, 21, 25–26, mainly from domains three, four, and seven) required prior experience of generic ASD substitution for answer creditability. Consequently, we deleted answers to these items from respondents who declared no previous experience (Q7). Indications of percentages in the results section refer to proportions of valid answers that expressed an opinion (Likert 1–2, 3–4, or 5–6), and n in the text refers to the number of respondents (excluding missing answers and the answer “No opinion”). Items without a clear direction of answers are shown in the appendices (Figure S1). Spearman’s rank correlation coefficients were calculated between the answers to see, whether the attitudes on substitution are influenced by the experiences or an association with the practice of therapeutic drug monitoring with level of significance set at \( p < .05 \). Free-text answers are presented for the item on compound-related factors that may influence substitution decisions (Q15). We used IBM SPSS® (version 25.0) for statistical analyses, and created figures and tables with Microsoft Excel® (version 1908).

3 | RESULTS

3.1 | Domain—Demographics

Table 1 shows the respondents’ demographics. A total of 154 physicians answered the survey, corresponding to a response rate of 55.8% (RSthlm 49.1%, \( n = 71 \) | RSkane 65.8%, \( n = 73 \)). Four respondents were neither residents nor specialists in neurology, and consequently were excluded from further analyses.

Most respondents were specialists in neurology, working at university hospital units (\( n = 88 \)). The majority estimated that they met fewer than 50 epilepsy outpatients per year (\( n = 99 \)). Table 1 shows that the overall gender distribution was almost equal (47.3% female, \( n = 71 \), with a female dominance in RSthlm and a male dominance in RSkane. Seventy-three percent of respondents had previous experience of generic substitution of ASDs in epilepsy.

3.2 | Domain—General attitude

Figure 1 shows the general perceptions toward generic drug substitution in epilepsy. A total of 65.1% (\( n = 93 \)) of respondents had a positive attitude toward generic substitution of ASDs, while 12.2% (\( n = 17 \)) had a negative attitude. Most respondents were neither worried about worsened seizure control nor worried about the emergence of other adverse effects after switching from a brand-name drug to a generic compound, or between different generic compounds. Among those who were worried, it was more common to worry about a deterioration in seizure control (17.1%, \( n = 25 \)) than the emergence of other adverse effects (8.9%, \( n = 13 \)).

3.3 | Domain—Specific factors

Figure 2 shows the main results from questions regarding factors that influenced the decision on substitution. Most physicians (76.1%, \( n = 83 \)) agreed with the statement that they refrained from generic prescription if the patient opposed a switch and wished to remain on the original drug compound. Other factors that led to avoiding a substitution were as follows: if the patient had cognitive impairment (52.5%, \( n = 53 \)), if the current ASD had a narrow therapeutic index (NTI) (47%, \( n = 47 \)), or if the patient had shown earlier susceptibility to adverse effects (45.6%, \( n = 47 \)).

Most physicians (55.1%, \( n = 54 \)) did not consider intractable seizures to have a strong impact on the substitution decision, while many (37.7%, \( n = 37 \)) considered intractable seizures to support a switch. The questionnaire responses did not indicate a clear opinion on generic substitution in patients with long-term seizure freedom.

In general, RSthlm respondents were more prone to refrain from generic substitution than those in RSkane. The most significant differences between the regions were when a patient: (1) was long-term seizure-free (RSthlm 46.9% | RSkane 26.9%), (2) was on an ASD with NTI (RSthlm 56.8% | RSkane 39.3%), (3) was cognitively impaired (RSthlm 61.2% | RSkane 44.2%), or (4) expressed reluctance to switch (RSthlm 84.6% | RSkane 68.4%).

Some free-text answers stated that compound-related factors affected the substitution decision at an individual level in particular situations. These were as follows: tablet size for patients with swallowing difficulties, type of packaging if motor difficulties affected finger skills, and tablet appearance changes, such as color or shape, if cognitive impairment was present. A few respondents stated that they were reluctant to prescribe generic substitutions since inconsistent deliveries are more common with generic products, enforcing switchbacks to the original compound or an alternative generic product.
3.4 | Domains—Practical and cost aspects

Figure 3 shows that most respondents considered the substitution risks to be the same when switching from one generic compound to another and when switching from the brand-name drug compound to a generic (65.8%, n = 79), although many respondents (19.5%) expressed no opinion on this issue. The majority did not prescribe a switch without first discussing their decision with the patient in person (57.0%, n = 61). Neither a lack of time nor forgetfulness seemed to be an essential factor behind most respondents’ decisions to refrain from generic substitution.

Most respondents agreed that generic prescribing was desirable to cut costs (74.7%, n = 106). In line with this statement, there was an overall agreement on choosing a generic compound upon initiating a new ASD treatment (84.9%, n = 118), with no apparent difference between RSthlm and RSkane.
Nearly half of the total respondents, and 57% (n = 27) of those based in RSthlm, agreed that NTI drugs hindered a generic switch. There was no consensus on which of the eight listed compounds were NTI drugs. The responses showed the highest uniformity for phenytoin (75.2%, n = 100), followed by carbamazepine (28.6%, n = 38) and then valproate (18.8%, n = 25). However, most physicians (51.0%, n = 53) did not routinely measure serum concentration of the ASD before and after the initiation of a generic switch to ensure the equivalence of the compounds. The practice to routinely measure serum concentrations was significantly correlated with having a negative attitude toward generic substitution of ASDs ($r = 0.26$, $p < .01$).

### FIGURE 2
Distribution of responses (%) to the items regarding specific factors that influence substitution decisions. The answer alternatives are categorized into 1–2 (red), 3–4 (orange), and 5–6 (blue). Only responses from physicians with prior experience of generic substitution of antiseizure drugs ($n = 109$) were counted.

### FIGURE 3
Distribution of responses (%) to the items regarding practical and economic aspects of generic substitutions. The answer alternatives are categorized into 1–2 (red), 3–4 (orange), and 5–6 (blue). † Only responses from physicians with prior experience of generic substitution of antiseizure drugs ($n = 109$) were counted.

### 3.5 Domain—Pharmacokinetics

In line with the pharmacy data presented in the introduction, the survey showed that it was much more common among the respondents in RSkane than among those in RSthlm to have experience of generic substitutions of ASDs (RSthlm 68.4%, $n = 52$ | RSkane 81.4%, $n = 57$).

Among those with such experience, only 16.7% ($n = 8$) in RSthlm declared that they often (Likert 5–6) prescribed generic AED compounds compared with 41.9% ($n = 23$) in RSkane.

Figure 4 shows the respondents' estimates of how many patients switch back to the original compound after a switch to a generic ASD. Most of the physicians reported that they had cared for at least one
patient (Likert 2–6) who switched back due to (1) breakthrough seizure (62.8%, $n = 49$), (2) increased seizure frequency (66.7%, $n = 52$), or (3) adverse effects (81.7%, $n = 67$). Correlations were seen between the experiences and having a general negative attitude toward generic substitution of ASDs among the physicians. The strongest correlation was observed for the experience of high proportions of switchbacks due to breakthrough seizures ($r = 0.46, p < .001$), followed by increased seizure frequency ($r = 0.37, p < .001$), and adverse effects ($r = 0.31, p < .01$). The reported proportions of switchbacks due to negative substitution outcomes were low (median 2–3). Many respondents (24%–28%) expressed no opinion on these issues.

3.7 | Domains—Guidelines, supporting material, and other questions

Less than one-third of respondents were aware of regional (31%, $n = 45$) or local (29.5%, $n = 43$) guidelines regarding generic substitution of ASDs. Many respondents (45.1%, $n = 60$) stated an increasingly positive attitude toward generic substitution during the past 5–10 years, while just as many (45.1%, $n = 60$) reported no change, and a few (9.8%, $n = 13$) referred to a more negative attitude.

4 | DISCUSSION

Respondents to this web-based survey widely accepted the use of generic ASD compounds in epilepsy treatment with low concerns regarding adverse effects. This implies an attitude change over the past decade toward increased confidence in generic substitution of ASDs. The primary aim was to examine physicians’ attitudes toward compound substitutions, and factors of significance for their decisions. The main reasons for refraining from switching to generics were if the individual patient wished to remain on the original compound (76.1%), had a cognitive impairment (52.5%), was on a drug with an NTI (47%), or had shown prior susceptibility to adverse effects (45.6%). Opinions on substitution decisions diverged significantly between regions on selected items, but the differences were not sufficient to explain the large difference in generic prescription rates between RSthlm and RSkane.

To the best of our knowledge, no precedent studies have examined the doctors’ reasoning behind substitution decisions regarding ASDs. Previous research was mainly published more than a decade ago and focused on concerns about using generic ASDs in epilepsy, particularly the risks of seizure breakthroughs and tolerance aspects. In this study—which had a response rate of 55.8%, the highest reported response rate to date among similar studies—we aimed to deepen the discussion by focusing on decision-making in professionals’ daily practices.

There is a growing body of evidence on generic substitution in epilepsy from prospective observational and pharmacokinetic studies. Although the prospective studies were not designed for identification of rare clinical events such as breakthrough seizures, these reports all together contradict the reported alarming frequency of switchbacks in previous retrospective studies. In line with other studies, most respondents (63%–67%) in the present study had cared for at least one patient with a deterioration in seizure control that they attributed to generic substitution of an ASD. However, the Likert scales provide more details compared to previous survey studies with dichotomized answer alternatives. Our study corroborates the observational data and the emerging knowledge from the clinical experience of generic substitutions that adverse substitution outcomes of clinical significance are infrequent. Nevertheless, despite strong indications that generic substitutions of second-generation ASDs are generally safe, we must not forget that every breakthrough seizure triggered by a switch may put the person in danger and be life-threatening in some circumstances. Gathering information on selection criteria, in order to determine when generic switches of ASDs should be avoided, would therefore add value. The importance is further underlined by the fact that not all switches can be avoided due to, for example, a supply shortage. Repackaged versions of the same drug (e.g., parallel imported drugs) are available in many cases, but otherwise generic substitutions (either between generic products or from a generic product to a brand-name counterpart) will be enforced to avoid a treatment gap. Inconsistent deliveries of originator products are rare, and some prescribers argue that this favors the use of brand-name ASDs in difficult-to-treat

FIGURE 4 Distribution of responses (%) to the items regarding previous experience of generic substitution. The answer alternatives are categorized into 1–2 (red), 3–4 (orange), and 5–6 (blue). Only responses from physicians with prior experience of generic substitution of antiseizure drugs ($n = 109$) were counted.

Among patients switched to a generic substitute, what proportion are switched back to the original drug due to:

- Seizure relapse?
- More frequent seizures?
- Appearance/worsening of adverse effects?

| None | 1 | 2 | 3 | 4 | 5 | 6 | All |
|------|---|---|---|---|---|---|-----|
| 0%  | 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% |
patients until we have a better understanding of substitution risks in subsets of patients and not only at group level.

Rare events require large cohorts and long follow-up times to study. Double-blinded randomized controlled trials with seizure control and adverse drug effects as outcome parameters are much anticipated, but would be challenging to carry out. An alternative way to collect evidence in the future would be the tools offered by digital medical records with the registration of disease-specific quality indicators, enabling prospective follow-up of large cohorts of patients who switch to generic ASDs. The introduction of systematic documentation of factors with potential impacts on substitution outcomes may detect at-risk subgroups and possible connections with drug compounds.

A large number of respondents believed that NTI drugs prevented a generic substitution. Unfortunately, there was disagreement about which drugs were considered to have NTIs, except for phenytoin. As previously mentioned, the Swedish Medical Products Agency (MPA) regulations prohibit generic substitutions of ASDs at pharmacy level. Instead, a doctor must explicitly prescribe generic compounds. According to the national recommendations for the treatment of epilepsy, the main reason for this is that some ASDs are NTI drugs and substitution of these can lead to severe consequences. However, the MPA does not specify which drugs it considers to have NTIs, and the directive applies to all ASDs. The FDA definitions of NTI drugs include phenytoin, carbamazepine, and valproate among the ASDs listed in this survey. Phenytoin is comparatively rarely prescribed for epilepsy in Sweden, while carbamazepine and valproate are two of the most common ASDs. Our results show that many clinicians disagree with the FDA’s standpoint on which ASDs should be considered NTI drugs. A clarification of the MPA recommendations on NTI definitions, possibly combined with increased knowledge of NTI drugs among physicians, could help to counteract the existing inconsistent routines at national level.

As mentioned in the introduction, RSkane has a regional directive to increase the proportion of prescribed generic levetiracetam compared to the originator drug Keppra®. No such directive exists in RSthlm, which has probably impacted the divergent regional generic drug volumes. However, awareness among respondents of the existing guidelines was low, and without any significant difference between the regions (RSthlm 27% | RSkane 35%). Furthermore, RSthlm respondents were generally more reluctant to prescribe generic substitutions, although the regional disparity about which factors contraindicated a substitution was generally small. The large difference between the regions in prescribed daily dosages of generic ASDs remains partly unexplained and needs further investigation. Possible explanations may include regional differences of patient-related factors and opinions that physicians are not in control of. Considering that patient reluctance was found to be the strongest reason for neurologists to refrain from substitution, this may be a plausible hypothesis. Unfortunately, we cannot adjust for such differences as our previous study on patient attitudes toward generic substitution in epilepsy only included PWE from RSkane. Another possible difference could be at what time the practice to routinely prescribe a generic compound upon initiating a new ASD treatment became the accepted standard in the respective regions. It seems less likely that differences in the proportion of PWE with cognitive impairment or treatment with NTI drugs should differ between the regions, the other two identified strong reasons to refrain from substitution.

In our previous study on attitudes among PWE toward generic ASDs, we found that patients and caregivers were much more reluctant to switch their current brand-name ASD treatment to a generic product than the neurologists in the current study. Our results in the present study contrast with the findings in a study by Berg et al published in 2008 that reported higher concerns regarding generic ASDs among neurologists compared to PWE. The contrasting results likely reflect an increased confidence among physicians over time to prescribe generic substitutions. Based on our comprehensive knowledge, to identify ways to diminish concerns and increase the support to patients with worries, alongside the continued search for reasons behind untoward substitution outcomes, are important directives for future research.

4.1 Limitations

The limitations of this study mainly pertain to the study design. The survey was designed specifically for this study, and despite our efforts to test comprehensibility by performing a pilot study, we cannot rule out that some items were misinterpreted. Furthermore, the original survey was written in Swedish. The English translation presented in the supporting information is a single translation with no cultural adaption or back-translation. Consequently, items in English may have a slightly different meanings compared to the original. Previous experience of generic substitutions was reported in retrospect and may suffer from recall bias. Additionally, untoward effects attributed to generic substitutions may have been caused by other factors and vice versa. The estimated frequency of negative substitution outcomes may therefore be overestimated or underestimated. Given the comparatively high response rate, survey responses are likely to mirror the current practice on substitution decisions among neurologists in RSthlm and RSkane. However, it was beyond the scope of this study to evaluate whether the consensus practice leads to better outcomes.

5 Conclusions

Neurologists in two major Swedish healthcare regions generally have positive attitudes toward the use of generic antiseizure compounds. Concerns about, and experienced frequency of, adverse substitution outcomes were low in our sample. Patient preference, cognitive impairment, whether the concerned ASD has an NTI, and patient history of susceptibility to adverse effects are important factors in current practice for substitution decisions. Opinions on substitution decisions diverged significantly between
regions on selected items, but the basis for this difference remains unknown. Our results may provide material for consensus discussions to decide on quality indicators of interest for future research on substitution outcomes.

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CONFLICT OF INTEREST
KK has received speaker's fees from UCB Nordic and Sandoz AB. The authors have no further conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT
The data supporting findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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