# Generic Drug Switch in Epilepsy – Pharmacokinetic and Clinical Aspects

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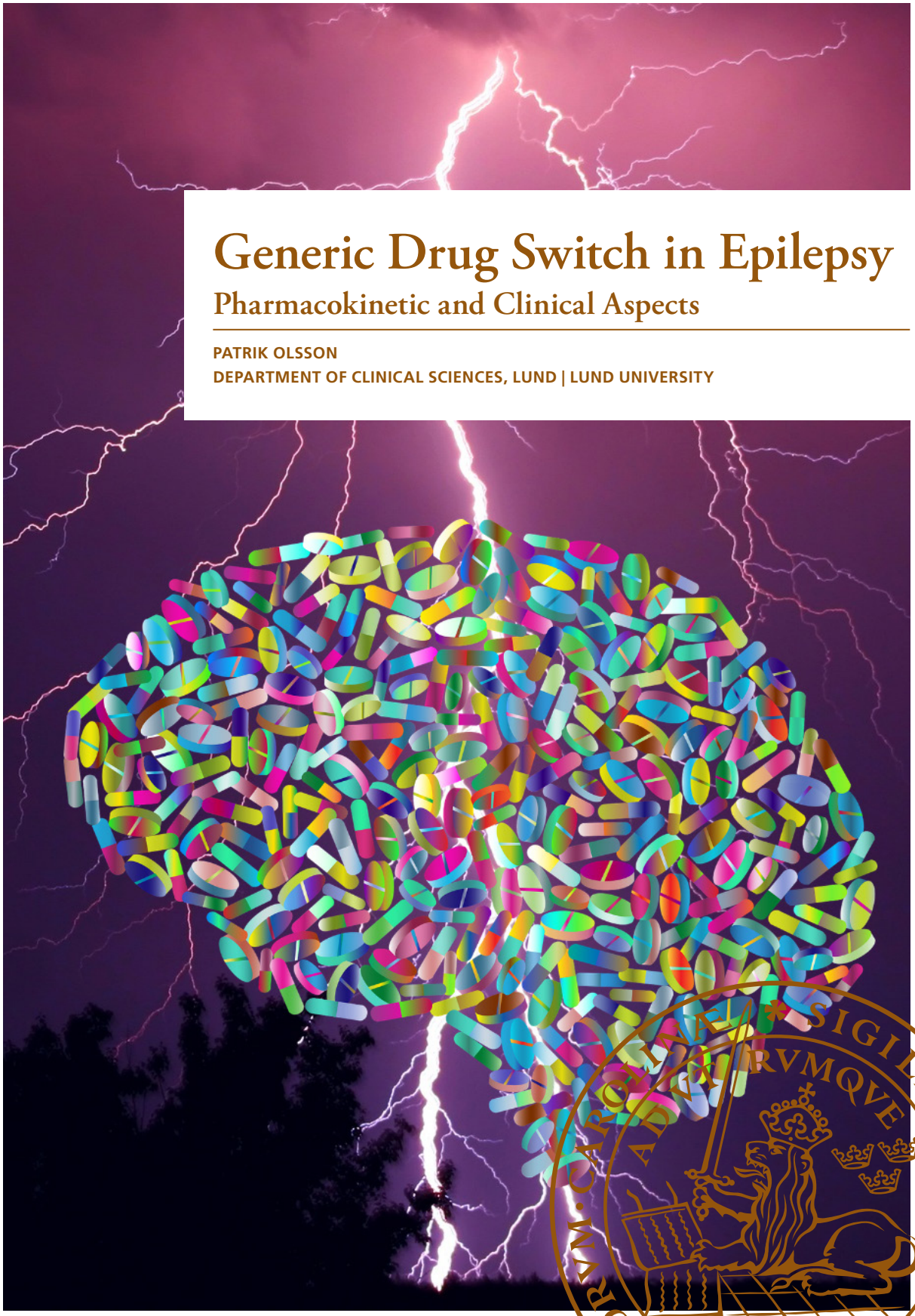

# Generic Drug Switch in Epilepsy

## Pharmacokinetic and Clinical Aspects

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# Generic Drug Switch in Epilepsy –
## Pharmacokinetic and Clinical Aspects

# Generic Drug Switch in Epilepsy – Pharmacokinetic and Clinical Aspects

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LUND UNIVERSITY

DOCTORAL DISSERTATION

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*Faculty opponent*
Leif Gjerstad, Professor Emeritus of Neurology, University of Oslo

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**Abstract**

**Background and aim: Generic drugs contain the same active ingredients as brand- name drugs, with the advantage of much lower costs. The aim of this thesis was to contribute new knowledge to the ongoing debate on the safety of generic antiseizure drug (ASD) substitutions. There was a particular emphasis on the pharmacokinetic and clinical outcomes.**

**Methods: In papers I and II, a prospective naturalistic study of generic drug switching of levetiracetam (LEV) was conducted with repeated LEV serum concentration measurements and assessment of quality of life before and after the switch. In paper III, a cross-sectional survey study was conducted to explore associations between the characteristics of people with epilepsy (PWE) and their attitudes toward the generic substitution of ASDs. In paper IV, an online survey study of physicians' perspectives on generic ASD substitution in epilepsy was conducted.**

**Results: Paper I: Fluctuation of LEV serum concentrations was equal with branded LEV and the generic LEV. Within-subject variability was much larger than the small, non-significant differences between the two LEV products. No switchbacks occurred. Paper II: Irrespective of brand or generic treatment, subjects were less worried about seizures at the end of the study compared to at inclusion. Paper III: High proportions of PWE express concerns about generic substitution of ASDs. Survey respondents with prior experience of generic ASD substitution were more likely to accept a future switch. Paper IV: Neurologists in two major Swedish healthcare regions generally have positive attitudes toward the generic substitution of ASDs in epilepsy.**

**Conclusions: Current evidence suggests that the pharmacokinetic consequences of generic substitutions of bioequivalent immediate release second-generation ASDs are negligible at group level. Data on clinical aspects of generic substitutions are not as robust, but real-world prospective data indicate that possible substitution risks are generally small to non-existent in treatment-adherent individuals. Future studies should elaborate on interventions to ensure treatment adherence and reduce worries in connection with a switch. A structured nurse-led follow-up could be a cost-effective example of such an intervention that could facilitate successful generic substitution and lead to substantial cost savings.**



**Key words Epilepsy, Generic, Antiepileptic drugs, Pharmacokinetics, Treatment outcome**

Classification system and/or index terms (if any)

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*Drowning in information,*
*starving for knowledge*

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2. Patrik Olsson, Arne Reimers, Kristina Källén. *Quality of life after switching to generic levetiracetam - A prospective comparative study*. Epilepsy & Behavior. 2019;96:169-174.
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# Populärvetenskaplig sammanfattning

Epilepsi är en av de vanligaste neurologiska sjukdomarna i världen och omkring 70 000 personer i Sverige har epilepsi. Gemensamt för alla med epilepsi är förekomst av oprovocerade epileptiska anfall. Behandlingen består av långvarig, ofta livslång, behandling med läkemedel som minskar risken för anfall, så kallade antiepileptika. Cirka två tredjedelar uppnår anfallsfrihet vid korrekt behandling med antiepileptika. Förutom anfall är det vanligt att personer med epilepsi lider av socialt stigma, sämre livskvalitet och samsjuklighet så som depression och ångest.

Generika är billigare kopior av originalläkemedel och innehåller samma verksamma substans. Bioekvivalens måste bevisas innan ett generiskt preparat får säljas, vilket innebär att samma mängd läkemedel ska absorberas oavsett om du äter en tablett av det generiska preparatet eller originalet (inom ett tillåtet intervall).

Generiskt utbyte innebär att byta behandling från ett originalpreparat till ett likvärdigt generiskt alternativ. Generiskt utbyte av antiepileptika har länge varit omdebatterat och kriterierna för bioekvivalens har ifrågasatts. Tidigare studier av lägre vetenskaplig kvalitet har visat en hög andel som byter tillbaka till originalpreparat och rapporterat om ökad anfallsfrekvens efter påtvingade byten till generika.

Till skillnad från de flesta andra läkemedel får epilepsiläkemedel inte bytas fritt till generika av apotekspersonal i samband med uthämtning av recept i Sverige. Läkemedelsverket har av försiktighetsprincip beslutat att förskrivande läkare alltid måste fatta beslutet om generiskt utbyte av antiepileptika. Det gör att många personer med epilepsi fortsatt behandlas med dyrare originalpreparat. Förutsatt att det inte är någon skillnad i behandlingseffekt mellan originalpreparat och generika, skulle samhället kunna spara mycket pengar genom ökad förskrivning av generika. De pengarna skulle kunna användas till andra angelägna ändamål, som exempelvis att anställa fler sjuksköterskor. Delarbetena i denna avhandling bidrar med ny kunskap som fördjupar förståelsen för effekter av generiskt utbyte av antiepileptika.

I delarbete ett jämfördes koncentrationen av epilepsiläkemedlet levetiracetam i blodet under behandling med originalpreparat och ett generiskt preparat av levetiracetam. En studiegrupp följdes under behandling med originalpreparat i tio veckor och därefter åtta veckors behandling med generika. En kontrollgrupp behandlades med originalpreparat under hela studien. Blodprover för att kontrollera läkemedelshalten av levetiracetam togs varannan vecka. De olika preparaten gav ingen skillnad i koncentration av levetiracetam och värdena varierade lika mycket mellan provtagningarna i båda grupperna. Ingen deltagare bytte tillbaka till originalpreparatet och de som var anfallsfria vid studiestart fortsatte att vara det under behandling med generika.

Delarbete två baserade sig på livskvalitetsdata från samma studie som delarbete ett. Studiedeltagarna gjorde en självskattning av livskvalitet och upplevda biverkningar vid studiestart, i mitten (innan ena gruppen bytte till generika) och när studien slutade. Utvecklingen var likartad i grupperna med generellt något högre självskattad livskvalitet vid studiens slut. Främst var deltagarna i båda grupperna mindre oroliga för anfall jämfört med när studien började. Ingen deltagare upplevde försämrade biverkningar under behandling med generika. Vår teori är att den strukturerade uppföljningen under studien hade en positiv inverkan på deltagarnas trygghet och att det, snarare än val av preparat, påverkade resultaten. Liknande uppföljning skulle kanske kunna förbättra utfallet vid generiska utbyten genom att öka patienters trygghet och minska negativa förväntanseffekter.

I delarbete tre genomfördes en enkätstudie. Studien riktade sig till personer med epilepsi som behandlades med ett originalpreparat, trots tillgängligt generiskt alternativ. Deltagarna fick fylla i en enkät om attityder till generiskt utbyte av antiepileptika, samt fyra enkäter om inställning till läkemedel, självförmåga, samt symtom på depression och ångest. Nästan hälften (46%) uppgav att de skulle neka till ett generiskt utbyte om deras läkare föreslog ett byte och hela 71% skulle oroa sig för försämrad anfallskontroll och/eller biverkningar vid ett byte. Personer över 50 år var mer skeptiska till generika. Tidigare erfarenhet av generiskt utbyte av antiepileptika minskade både oro och skepticism, medan högre utbildningsnivå och att vara anställd eller studera minskade oro. Således var en stor andel patienter negativt inställda till generika, men de som tidigare hade testat att byta hade god erfarenhet av det.

Delarbete fyra var en enkätstudie som riktade sig till neurologer och ST-läkare i neurologi i Stockholm och Skåne. Enkäten bestod av frågor kring olika aspekter av generiskt utbyte av epilepsiläkemedel och vilka faktorer som har stor påverkan på beslut om generiska utbyten. Majoriteten (65%) av läkarna var positivt inställda till generiskt utbyte och oroade sig varken för biverkningar eller försämrad anfallskontroll i samband med byte. De viktigaste faktorerna som ledde till att läkare avstod från att ordinera generiskt utbyte var patientönskemål (76%), kognitiv funktionsnedsättning (52%), om små förändringar av dos eller halt i blodet av aktuellt läkemedel kan leda till behandlingssvikt eller allvarliga biverkningar (47%), samt biverkningskänslighet (46%). Läkare från Stockholm var generellt sett mindre benägna att byta till generika.

# Abbreviations

| | |
|---|---|
| AED | Antiepileptic drug |
| AUC | Area under the concentration-time-curve |
| ASD | Antiseizure drug |
| BE | Bioequivalence |
| BMQ | Beliefs About Medicines Questionnaire |
| CI | Confidence interval |
| Cmax | Maximum concentration |
| EMA | European Medicines Agency |
| FDA | US Food and Drug administration |
| FI | Fluctuation index |
| GSES | General Self-Efficacy Scale |
| GTCS | Generalized Tonic-Clonic Seizure |
| HADS-A | HADS, anxiety subscale |
| HADS-D | HADS, depression subscale |
| HADS | Hospital Anxiety and Depression Self-Assessment Scale |
| ILAE | International League Against Epilepsy |
| LEV | Levetiracetam |
| LTG | Lamotrigine |
| MADRS-S | Montgomery-Åsberg Depression Rating Scale, self-assessment |
| MIC | Minimally important change |
| MPA | Medical Products Agency |
| NTI | Narrow therapeutic index |
| PNES | Psychogenic non-epileptic seizures |
| PWE | People with epilepsy |
| QoL | Quality of life |

# Introduction

## Epilepsy

Epilepsy is a neurological disease, characterized by an enduring predisposition to generate epileptic seizures [1]. The worldwide point prevalence of epilepsy has been estimated to 0.64% [2]. This makes it one of the most common neurological diseases, with substantial disability, mortality, and costs for society [3, 4].

Not all seizures are epileptic in nature. Examples of non-epileptic seizures include psychogenic non-epileptic seizures (PNES) and convulsive syncope [5]. Seizures can also be provoked by causes such as severe metabolic derangements, toxins, head trauma, and infections of the central nervous system (CNS) [5, 6]. The International League Against Epilepsy (ILAE) has issued diagnostic criteria for epilepsy. One of the following criteria is required for the diagnosis of epilepsy: (1) At least two unprovoked (or reflex) seizures occurring >24 h apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next ten years; (3) diagnosis of an epilepsy syndrome [7].

### Beyond seizures

People with epilepsy (PWE) often suffer from comorbidities and social stigma [8]. Depression, anxiety, dementia, migraine, heart disease, peptic ulcers, and arthritis are all much more common among PWE compared to the general population [9]. Epilepsy also has implications on career choices and the ability to obtain a driver's license. Altogether, in addition to the seizure burden, this results in lower quality of life (QoL) for PWE [10]. The main predictors of low QoL are the presence of psychiatric comorbidity, followed by seizure frequency and seizure severity [11]. Consequently, adequate epilepsy treatment and attention to psychological factors are key to improving QoL in PWE.

# Epilepsy treatment

Antiepileptic drugs (AEDs) are the cornerstone of epilepsy treatment. AEDs are symptomatic, meaning that they reduce seizure frequency without any effect on the disease itself or the long-term prognosis [12]. Antiseizure drugs (ASDs) or anticonvulsants are therefore better descriptive terms for the drug class.

Over 25 different ASDs are available for the treatment of epilepsy worldwide. The choice of which ASD is best for the individual patient depends on many factors, including – but not limited to – seizure type, comorbidities, age, sex, tolerability, and drug interactions [13]. The Swedish Medical Products Agency (MPA) published updated treatment recommendations for epilepsy in 2019 with five recommended first-line ASDs for monotherapy (carbamazepine, lamotrigine (LTG), or levetiracetam (LEV) for focal onset seizures, LTG, LEV, or valproate for generalized epilepsy, and ethosuximide for absence epilepsy without generalized tonic-clonic seizures (GTCSs)) [14]. Carbamazepine is not a first choice for the elderly due to its high potential for interactions and valproate is contraindicated in girls and women of childbearing age. Prescription volumes for the second-generation ASDs LTG and LEV have increased in recent years due to favorable tolerability aspects and lower propensity for drug interactions (figure 1) [15].

About two-thirds of PWE obtain seizure freedom on ASD treatment [13, 16]. Failure to obtain seizure freedom after trials of two appropriately chosen and used ASDs is defined as drug-resistant epilepsy [17]. Selected individuals with drug-resistant epilepsy may be candidates for epilepsy surgery, with around a 70% chance of postsurgical long-term seizure freedom [18, 19]. Neurostimulation is another non-pharmacological treatment with the potential to reduce seizure frequency for selected individuals with drug-resistant epilepsy [20].

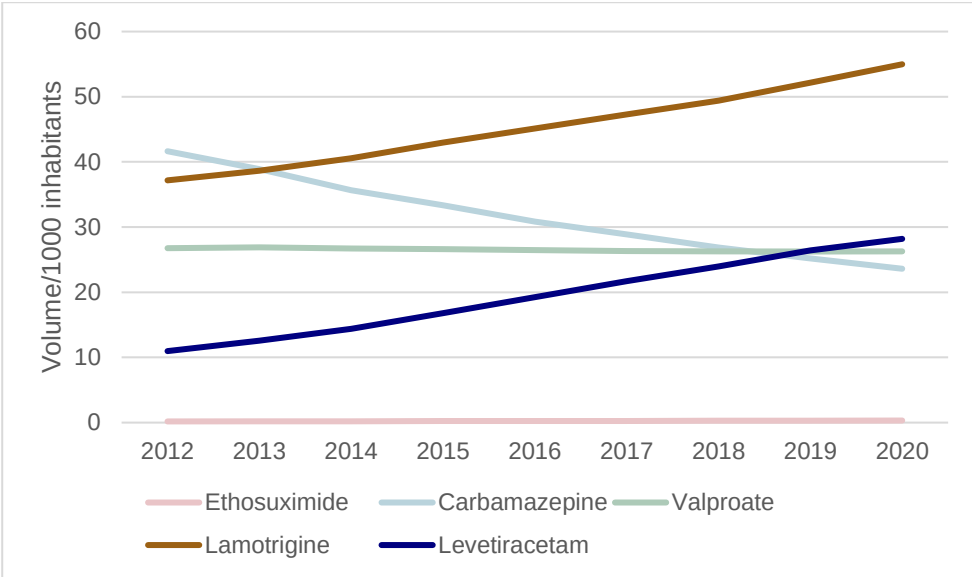


**Figure 1**
Prescription volumes of the five first-line ASDs in Sweden from 2012 to 2020. Prescriptions include all indications, not only epilepsy. Source: Socialstyrelsen, statistikdatabas för läkemedel.

# Generic drugs

Pharmaceutical companies that develop a new drug protect the property rights of their invention with a patent. Once the patent expires, typically after 20 years, anyone can produce a new version of the drug – a generic drug. Companies that produce generic drugs are not required to demonstrate the safety and efficacy of the drug [21]. These have already been demonstrated when the innovator drug was authorized. Instead, regulatory agencies – such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) – rely on pharmaceutical equivalence and bioequivalence (BE) to equal therapeutic equivalence[22, 23].

Pharmaceutical equivalence signifies that the generic drug contains the exact same active ingredient as the brand-name drug, and must have the same route of administration and dose strength. Pharmaceutical equivalence is a prerequisite for market approval. Pharmacologically inactive ingredients such as binding materials may differ, as may the appearance of the drug (color and form).

## Bioequivalence

BE means that the rate and extent of absorption of the active ingredient are similar between the products, within a predefined interval. Prior to market approval, generic drugs are required to demonstrate BE to the reference product. This is measured with two pharmacokinetic measures: area under the concentration-time curve (AUC) and maximum/peak concentration (Cmax). The FDA and EMA normally require that the 90% confidence interval (CI) of the average test/reference ratios for the Cmax and AUC fall within the 80% to 125% range to demonstrate BE [22, 24]. The acceptance interval is mathematically derived, based on the clinical judgment that a difference of less than 20% is not clinically significant.

*Narrow therapeutic index drugs*

Narrow therapeutic index (NTI) drugs are defined as "drugs where small differences in dose or blood concentration may lead to serious therapeutic failures and/or adverse drug reactions that are life-threatening or result in persistent or significant disability or incapacity" [25]. More stringent BE criteria apply to drugs that are considered to have an NTI. The accepted interval for AUC and Cmax test/reference ratios is tightened to 90–111%. Additionally, a four-way, fully replicated, crossover design is required with additional analysis of within-subject variability.

No international consensus exists on which ASDs should be considered NTI drugs [26]. The EMA and the Swedish Medical Products Agency (MPA) provide no list of drugs deemed to have NTIs, while the FDA applies the NTI BE criteria for phenytoin, carbamazepine, valproate (divalproex sodium and valproic acid), and everolimus [22, 27-31]. Others argue that almost all ASDs should be considered NTI drugs [32]. Phenytoin is a classic NTI drug with non-linear pharmacokinetics due to metabolism saturation, and small dose changes can therefore lead to disproportionate changes in phenytoin serum concentration [33].

## Cost of generic drugs

Generic drugs are usually considerably cheaper compared to brand name drugs, although the cost varies substantially between countries and different drug classes [34]. For example, generics accounted for 89.5% of all dispensed medications in the United States in 2016, but only 25.8% of the total pharmaceutical expenditure [35]. In Sweden, drugs with generic competition accounted for 60% of the sales volume of drugs in 2020, but only 19% of the total cost [36]. The lower cost is mainly an effect of competition once a patent expires, and the fact that pharmaceutical companies that produce generic drugs do not have to cover the costs of clinical trials required to demonstrate the safety and efficacy of the drug.

**Table 1**
Cost comparison of some of the commonly prescribed antiseizure drugs in Sweden with both brand and generic products available. Cost is reported as pharmacy purchase price per package in April 2021. Note that prices change frequently.

| Antiseizure drug | Brand (SEK) | Generic, low (SEK) | Generic, mean (SEK) |
|---|---|---|---|
| Carbamazepine slow, 200 mg, n=100 | 119 | 71 | 72 |
| Lamotrigine, 50 mg, n=56 | 136 | 22 | 91 |
| Levetiracetam, 500 mg, n=100 | 987 | 1 | 416 |
| Topiramate, 50 mg, n=60 | 199 | 120 | 148 |

Generic, low = lowest price among generic products. Generic, mean = mean price of generic products.
slow = slow-release. n = number of tablets per package.
Source: Tandvårds och läkemedelsförmånsverket, URL: https://www.tlv.se/beslut/sok-i-databasen.html. Accessed: April 21, 2021

# Generic substitution of ASDs

Generic substitution of ASDs has been a controversial topic for many years. Doubts about the safety of switching between different manufacturers of the same ASD started back in the late 1960s after reports of phenytoin toxicity following compound changes [37]. The debate continued into the 1990s, with several studies that found significant differences between phenytoin products and contrasting results of carbamazepine switches and subsequent clinical consequences [38-43].

Until then, the debate had focused on the first-generation ASDs (i.e., introduced before 1989): phenytoin, carbamazepine, and sodium valproate. No generic versions of second-generation ASDs were available at that time. Today, first-generation drugs are comparatively cheap, and the price difference between the products available on the market is generally small or nonexistent in Sweden (except for slow-release formulations of carbamazepine). Furthermore, many of the first-generation ASDs are considered NTI-drugs. Consequently, there are no strong incentives to advocate for compound substitutions of first-generation ASDs, and this thesis focuses on the generic substitution of second-generation ASDs in epilepsy.

Below is a brief summary of the main previous research on the topic up until the start of this Ph.D. project, and some of the concerns that have caused many neurologists and regulatory authorities to question the therapeutic equivalence of generic ASDs. When interpreting these study results, one must keep in mind that therapeutic failures of ASDs may have devastating or even fatal consequences [44]. Since the incentives for generic substitutions are merely financial and the individual patient usually has little benefit from substitutions in societies with subsidized drugs, any indications of deteriorated seizure control after substitutions are worrying. Then again, healthcare costs keep rising and it is important to investigate potential ways to reduce spending without worsened healthcare quality.

## Retrospective studies and survey studies

Beginning in the mid-2000s, several studies have investigated switchback rates (the proportions of patients who switch back to the brand name drug after a generic substitution) of various ASDs [45-47]. Switchback rates for ASDs were considerably higher (12.9–44.1%) compared to other commonly prescribed drug classes such as antihyperlipidemics, antidepressants, and cardiovascular drugs (1.5–9.1%). The reasons for switchbacks of LEV included increased seizure frequency (19.6%) and adverse effects (3.3%), while reasons for switchbacks were not described for the other studied ASDs [46]. Substitutions of LTG led to significant increases in daily LTG doses, physician visits, and hospitalizations [45, 47]. Altogether, these studies indicated very poor tolerance of originator-to-generic ASD switches.

Several studies have examined healthcare utilization after generic substitutions of ASDs, with mixed results. Some indicated significant increases in adverse clinical outcomes and that increased healthcare expenditure may outweigh the cost savings mediated by generic substitutions [47-52], while others found no differences [53-55]. One study found that increased seizure-related events were associated with refilling of ASD prescriptions per se, regardless of whether or not the refill involved a generic substitution [56].

Multiple survey studies have found that physicians and PWE share concerns about adverse substitution outcomes following brand-to-generic switches, and most physicians reported having cared for at least one patient with deteriorated seizure control that they attributed to a switch [57-64].

### Prospective studies

The alarming results from the studies mentioned in the previous section raised concerns that the regulations for authorizing generic drugs were not sufficiently strict [65-69]. BE studies are usually carried out on young and healthy volunteers [70]. Does average BE in such populations really imply that the generic compound is bioequivalent to the brand name drug in PWE with comorbidities and concurrent drug treatments with potential interactions?

These concerns were addressed in a rigorous FDA-sponsored randomized controlled trial of brand-to-generic LTG substitution [71]. The generic product was found to be bioequivalent to the innovator drug in PWE on steady-state treatment with LTG. In fact, the generic compound also met the more stringent criteria applied for NTI drugs. One subject experienced a significant increase in seizure frequency while on the generic product despite practically identical individual pharmacokinetic profiles.

Besides the study by Ting and colleagues, no prospective study of brand-to-generic substitution of second-generation ASDs of importance for the debate had been published when this Ph.D. project was started. Since then, several publications of interest have been published and these will be discussed in relation to the papers included in this thesis in the discussion chapter.

## Generic substitution of ASDs in Sweden

The MPA regulations prohibit automatic brand-to-generic and generic-to-generic substitutions of ASDs at pharmacy level [14, 72]. Instead, the treating physician must explicitly prescribe the desired compound. There are many possible reasons for compounds not to be considered interchangeable, and the MPA makes an individual evaluation for each active substance. The basis for the safety precaution of prohibiting automatic substitutions of ASDs includes the fact that some ASDs are NTI drugs, the potentially catastrophic consequences of therapeutic failure, and the fact that it is not possible to rule out that some individuals may be at risk of serious substitution outcomes, despite proof of BE at group level. A few exceptions exist when ASD compounds are considered interchangeable. This is true for products with a mutual origin, either through parallel import (compounds authorized in another country within the European Economic Area and deemed similar to a compound authorized in Sweden to a sufficient extent by the MPA) or duplicates of a compound authorized in Sweden under different names [73].

# Aims

The overall aim of this thesis was to study different aspects of generic substitution of ASDs and to contribute new knowledge to the ongoing debate on the safety and tolerability of generic ASD substitutions. Special emphasis was placed on the pharmacokinetic and clinical outcomes. The included papers study the impact on LEV serum concentration and quality of life after a generic substitution, attitudes toward generic antiseizure drugs among both PWE and neurologists, and factors of significance for clinical decision-making when deciding on compound substitutions of ASDs.

The specific aims of this thesis were:

*Paper 1*

To study the fluctuations of LEV steady-state serum concentrations in PWE before and after a switch from branded LEV to a generic LEV product.

*Paper II*

To study the short-term effects on QoL in PWE after a generic LEV substitution.

*Paper III*

To explore associations between the characteristics of PWE and their attitudes toward the generic substitution of ASDs in epilepsy.

*Paper IV*

To examine physicians' attitudes toward 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.

# Methods

Below is a summary of the ethics, settings, main study methodologies, and statistics. For further details, please see the Material and Methods section of each paper.

## Ethics

The studies that led to papers 1–3 were approved by the Regional Ethical Review Board in Lund, Sweden. Paper 4 did not collect any sensitive personal data or meet any of the other criteria for application of the Swedish Ethical Review Act. Consequently, there was no legal requirement to obtain formal ethical approval for the study. An optional application was sent to the Swedish Ethical Review Authority, which provided a limited advisory statement without any ethical objections to the study design.

## Settings

The study participants in papers 1–3 were PWE with documented visits to the neurology outpatient clinics at Skåne University Hospital or Helsingborg General Hospital. Paper IV was directed at specialists and resident physicians in neurology in the Skåne and Stockholm regions. All studies were carried out between 2014 and 2020.

# Papers I and II

At the time when this study was planned, there were several retrospective studies and case reports of deteriorated seizure control and/or increased adverse effects after generic substitutions of ASDs. However, no prospective assessment of steady-state serum concentration or QoL after a switch from brand-to-generic LEV existed. Given the doubts about therapeutic equivalency, we considered randomization not to be defensible from an ethical standpoint. Instead, we performed a prospective, naturalistic cohort study on adult PWE on stable treatment with brand name LEV (Keppra®) for at least four weeks prior to inclusion.

Figure 2 shows an outline of the study design. A control group (KEP-KEP) and a study group (KEP-LEV) were monitored with bi-weekly drug-fasting serum concentration measurements of LEV during a ten-week baseline period on treatment with brand name LEV and during the subsequent eight-week study period when KEP-KEP continued with unchanged treatment and KEP-LEV switched to a generic LEV product (Levetiracetam 1A Pharma®). All study subjects knew whether or not they would switch to a generic product before signing to give their informed consent to participate in the study.

QoL and adverse events were assessed at scheduled epilepsy nurse visits at the following timepoints: study inclusion (T-10), after the baseline period (T0; before the drug switch for KEP-LEV), and at the end of the study (T8). For more details regarding the QoL assessments, please see the separate section on QoL measures. All participants made a retrospective estimation of their average seizure frequency during the 12 months before enrollment and then kept a seizure diary throughout the study.

Serum concentrations of LEV, fluctuations thereof, and QoL were compared both within groups and between groups. Adverse events data and seizure count were reported descriptively.

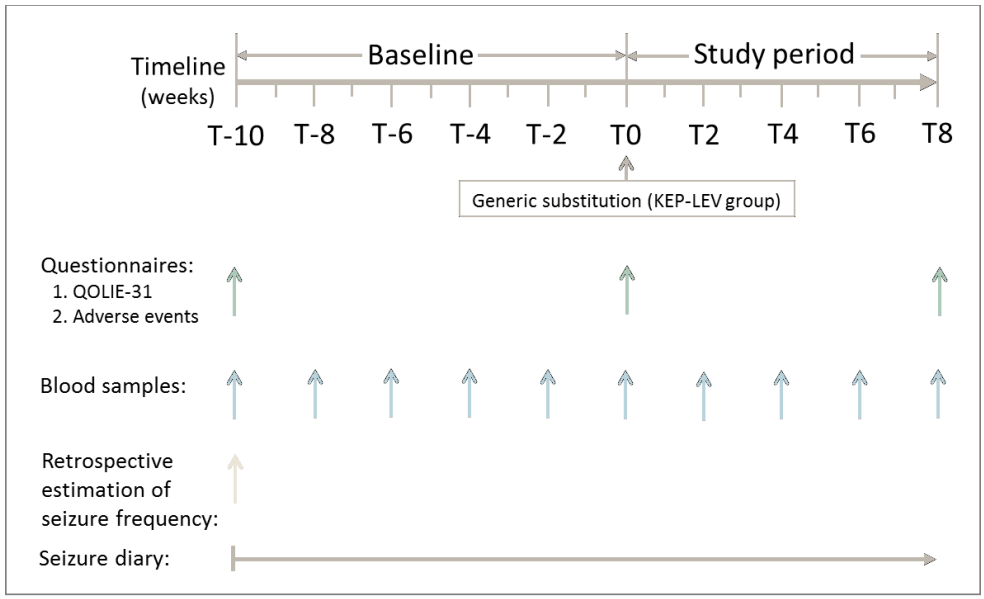


**Figure 2**
Outline of the study design. Source: Reimers et al. Epilepsy Research 134 (2017)

# Paper III

Patient preference seemed to have a strong impact on the decision on whether to remain on brand treatment or switch to a generic compound in the first study of this dissertation. We therefore wanted to study possible differences in characteristics between PWE who were willing to change their ASD treatment to a generic product and those who were reluctant to do so. We performed a cross-sectional survey study on adults with epilepsy on treatment with one of the following brand-name ASD treatments: Keppra® (levetiracetam), Lamictal® (lamotrigine), Lyrica® (pregabalin), or Topimax® (topiramate). Potential study participants were contacted by mail. A total of two reminders were sent out within a period of two months. Those who responded and signed an informed consent form were included in the study.

A questionnaire was developed specifically for this study. This contained questions regarding demographic data, attitudes toward generic substitution of ASDs, and epilepsy-specific questions. Additionally, responders were categorized into different groups based on their attitudes toward a putative generic switch. One question asked whether the study subject would accept (Gen-POS) or decline (Gen-NEG) a switch from their current brand ASD treatment to a generic product if suggested by their neurologist. Participants were further categorized as "with worry" if they would worry about adverse effects and/or deteriorated seizure control after a switch, or as "no worry" if they did not have any such concerns.

In addition to the general questionnaire, four different validated questionnaires were used to assess anxiety and depressive symptoms (the Hospital Anxiety and Depression Scale, HADS, and the Montgomery-Åsberg Depression Rating Scale, MADRS-S), self-efficacy (the General Self-Efficacy Scale, GSES), and beliefs about medicines (the Beliefs About Medicines Questionnaire, BMQ) [74-79].

Associations between the gathered variables and categorization as Gen-NEG and "with worry" were explored.

# Paper IV

Several precedent survey studies of physicians' attitudes toward the generic substitution of ASDs exist [57, 61-63, 80]. These were published over a decade ago and focused on concerns about generic ASDs in epilepsy. No such prior study was carried out in a Swedish setting or explored clinicians' reasoning behind substitution decisions.

We performed a cross-sectional online survey study of physicians' perspectives on generic ASD substitution in epilepsy. A self-administered survey was developed specifically for this study. A pilot study was carried out to test the survey's comprehensibility before the survey design was finalized. This consisted of 30 items with multi-response questions and items answered on a six-point Likert Scale. The items were stratified into nine different domains:

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

The survey was distributed via an online survey tool to neurologists and neurology residents in two of the major Swedish regions, Region Stockholm (RSthlm) and Region Skåne (RSkane).

## QoL measures

Instruments that measure QoL can be either disease-specific or generic (i.e. general, not focused on any specific condition). Specific instruments are generally more responsive and clinically useful, with the disadvantage that QoL results are not comparable between different diseases [81]. In paper II, we used the Swedish version of an epilepsy-specific instrument, the Quality of Life in Epilepsy Inventory-31 (QOLIE-31) version 1.1, to assess QoL [82]. QOLIE-31 is a validated tool to measure health-related QoL in PWE. It contains 31 items, grouped into seven subscales (seizure worry, overall QoL, emotional well-being, energy/fatigue, cognitive functioning, medication effects, and social functioning), plus an overall score, which is retrieved by calculating a weighted mean of the subscales. Scores can range from 0 to 100, with higher scores indicating better QoL.

## Statistics

All data were analyzed using Microsoft Excel (Microsoft Corp., Redmond, WA, USA) and SPSS versions 22, 23, and 25 (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test and assessments of histograms and skewness/kurtosis were used for normality testing. Between-group comparisons of continuous data were performed by two-sided unpaired Student's t-test in cases with normal distribution, and the Mann-Whitney U test for non-normal distribution. The corresponding statistical tests for within-group comparisons were paired Student's t-test and the Wilcoxon signed rank test. The significance level was set at $\alpha = 0.05$ for all hypothesis tests in the included papers.

*Paper I*

An *a priori* power calculation based on the standard deviation of 82 routine LEV serum concentration measurements resulted in a minimum sample size of 13 patients in each group, to reach 80% power to detect a ≥20% difference in mean serum concentrations. Drug fasting and time-standardized LEV-serum concentrations, fluctuations thereof, and concentration/dose ratio were compared both within groups and between groups. The main evaluation of fluctuations was based on a calculated fluctuation index (FI) for each individual, according to the formula $FI = (CmaxSS - CminSS) / CavSS$, where CmaxSS and CminSS = highest and lowest measured steady-state serum concentration in the respective period, and CavSS = average of all measured serum concentrations in the respective period.

Additionally, between-group comparisons of LEV serum concentrations before and after T0 were performed. For these comparisons, all serum concentrations were dose-normalized to 1500 mg and log-transformed. Four ratios (T2/T-6, T4/T-4, T6/T-2, and T8/T0) of the geometric group means and the 90% confidence intervals of the differences were then calculated.

*Paper II*

Changes in QOLIE-31 subscales were evaluated considering both clinical relevance and statistical significance. Clinical relevance was based on minimally important change (MIC) values. MIC values are population-specific estimates of how much scores need to change to be of clinical relevance, and have been established for QOLIE-31 in several different epilepsy populations [83-85]. Changes in subscale scores (Δmedian = median T8 − median T-10) in this study were compared to the lowest of the previously reported MIC values. Some of the QOLIE-31 subscale scores were non-normally distributed in both groups. Consequently, we used non-parametric tests for group comparisons.

*Paper III*

Univariate logistic regression was used to explore associations between dichotomized independent variables from the questionnaires and the dependent variables Gen-NEG and "with worry". Independent variables with a p-value < 0.10 in the univariate analysis were analyzed in multivariable logistic regression models together with the predefined covariates of age and gender to determine predictors of Gen-NEG and "with worry" in separate analyses.

*Paper IV*

Survey answers were reported descriptively as proportions (%) of respondents who expressed an opinion (excluding the answer "No opinion" and missing answers). 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.

# Results

## Summary of paper I

A total of 33 PWE were enrolled in the study, allocated to either the study group KEP-LEV (n = 16) or the control group KEP-KEP (n = 17). None of the subjects who switched to the generic compound after T0 switched back to the brand-name product (switchback rate 0%).

Table 2 shows mean LEV serum concentrations, fluctuation index, and concentration/dose ratios per treatment group during the baseline and study periods. There was no statistically significant difference, either within-group or between-group. The 90% confidence intervals of within-group ratios (study period/baseline period) of mean dose-normalized serum concentrations were all within the boundaries for bioequivalence in both groups.

Equal fluctuations of serum concentrations were seen in the KEP-LEV group before (FI = 0.26 ± 0.1) and after (FI = 0.26 ± 0.13) the switch. A non-significant decrease in fluctuations was noted in the KEP-KEP group from baseline (FI = 0.29 ± 0.1) to the study period (FI = 0.24 ± 0.13). No significant difference in FI was found between groups in the baseline or study periods.

**Table 2**
Mean time standardized serum concentrations of levetiracetam, fluctuation index, and concentration/dose ratio (C/D ratio) per group during baseline (T-10–T0) and the study period (T2–T8).

| | KEP-LEV | | KEP-KEP | |
|---|---|---|---|---|
| | Baseline period | Study period | Baseline period | Study period |
| Concentration (µmol/L ±SD) | 97.1 ± 59.9 | 92.2 ± 55.6 | 85.7 ± 49.8 | 85.3 ± 51.2 |
| Fluctuation index (mean ±SD) | 0.26 ± 0.1 | 0.26 ± 0.13 | 0.29 ± 0.1 | 0.24 ± 0.13 |
| C/D-ratio (median (Q1–Q3)) | 0.05 (0.04–0.08) | 0.05 (0.04–0.07) | 0.05 (0.04–0.06) | 0.05 (0.04–0.07) |

SD = Standard deviation Q1 = First quartile Q3 = Third quartile

There were no significant differences in concentration/dose ratios at group level, either within-group or between-group. A total of 14 study participants (40% of the total study population) had at least one concentration/dose ratio deviating ≥25% from their own average ratios in the respective periods.

None of the patients who reported that they had been seizure-free during the 12 months prior to study enrollment experienced any seizures while on the generic LEV product.

In summary, within-subject variability was much larger compared to the non-significant differences between the two LEV products.

# Summary of paper II

A total of 32 study subjects, 16 in each group, finalized the study with completed QoL and adverse events questionnaires and were included in the analysis.

The Δmedian overall QOLIE-31 score increased from enrolment to the end of the study in both groups, indicating increased QoL. The score increased 6.5 points in KEP-LEV and 8 points in KEP-KEP. Both changes exceeded the MIC threshold but did not reach statistical significance.

Figure 3 shows subscales with Δmedian that were both statistically significant and above MIC. The most prominent difference was noted in the subscale seizure worry. Participants in both groups were less worried about seizures at the end of the study compared to at inclusion (KEP-LEV: $p = 0.01$ and KEP-KEP: $p = 0.02$). Additionally, social functioning increased in the KEP-LEV group ($p = 0.02$) and cognitive functioning increased in the KEP-KEP group ($p = 0.02$).

Nonsignificant decreases were noted in one subscale in each group. At group level, medication effects dropped 9 points in KEP-LEV and overall QoL dropped 7.5 points in KEP-KEP.

**Figures 3a and 3b**
QOLIE-31 scores per group for subscales with significant changes (seizure worry, cognitive functioning, and social functioning) from inclusion (T-10) to the end of the study (T8). Scoring ranges from 0 to 100. Higher scores indicate less worry about seizures and better cognitive/social functioning. Boxplots showing median (bold), first and third quartiles, and total range. The mean value is indicated with +. Source: Olsson et al., Epilepsy & Behavior 96 (2019).

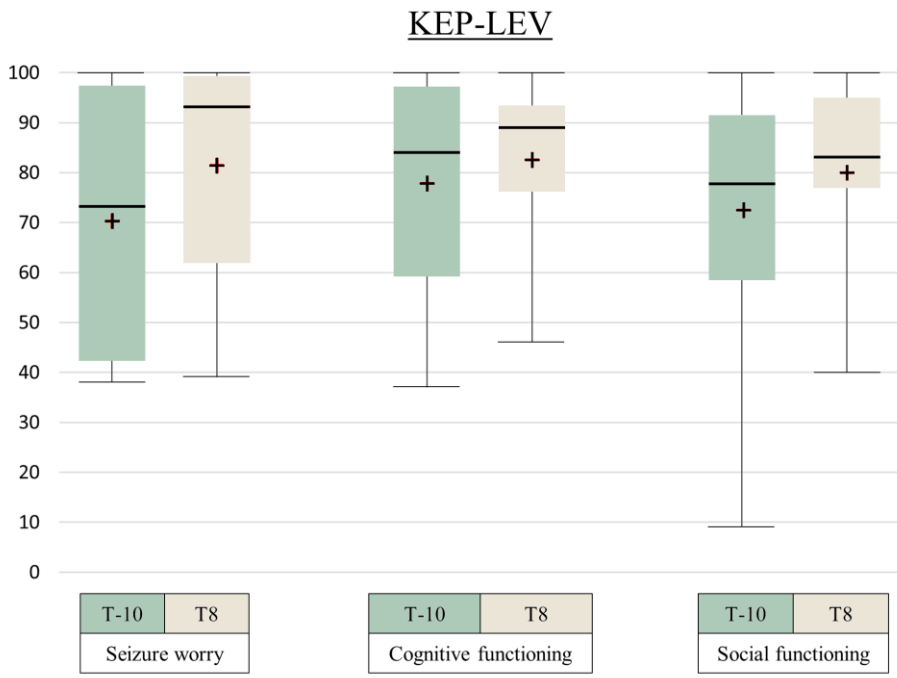


**Figure 3a.**
KEP-LEV = Changed to generic LEV at T0.

Various adverse symptoms were reported in similar proportions in both groups. None of the participants in the KEP-LEV group reported an increase in adverse events following generic substitution.

In summary, a similar increase in QoL was noted in both groups, regardless of treatment with a brand or generic product.

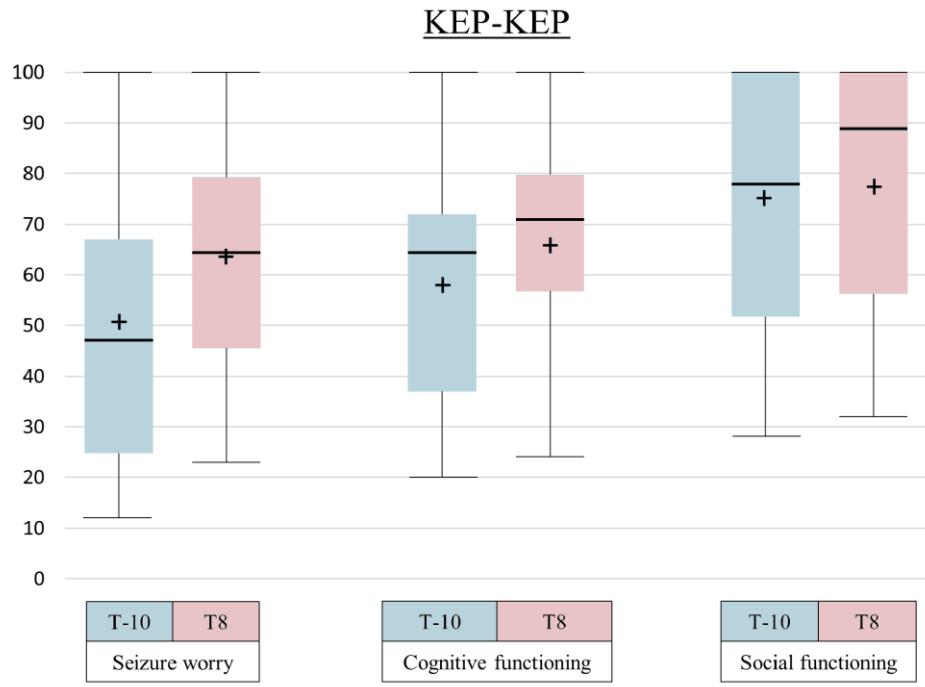


**Figure 3b**
KEP-KEP = On branded LEV throughout the study

# Summary of paper III

We were able to contact 429 PWE who matched the inclusion criteria, and received a response with informed consent to participate in the study from 178 individuals (41%). Twenty-two (12.4%) of the responders were represented by a caregiver who answered the study questionnaires on their behalf.

Figure 4 displays the categorization of the responders into Gen-NEG/POS and "with worry"/"no worry". Almost half (45.5%) stated that they would decline a generic substitution of their current ASD if suggested by their neurologist, and were consequently categorized as Gen-NEG. Most (71.3%) of the included subjects would worry about adverse effects and/or deteriorated seizure control after a putative switch, and were consequently categorized as "with worry".

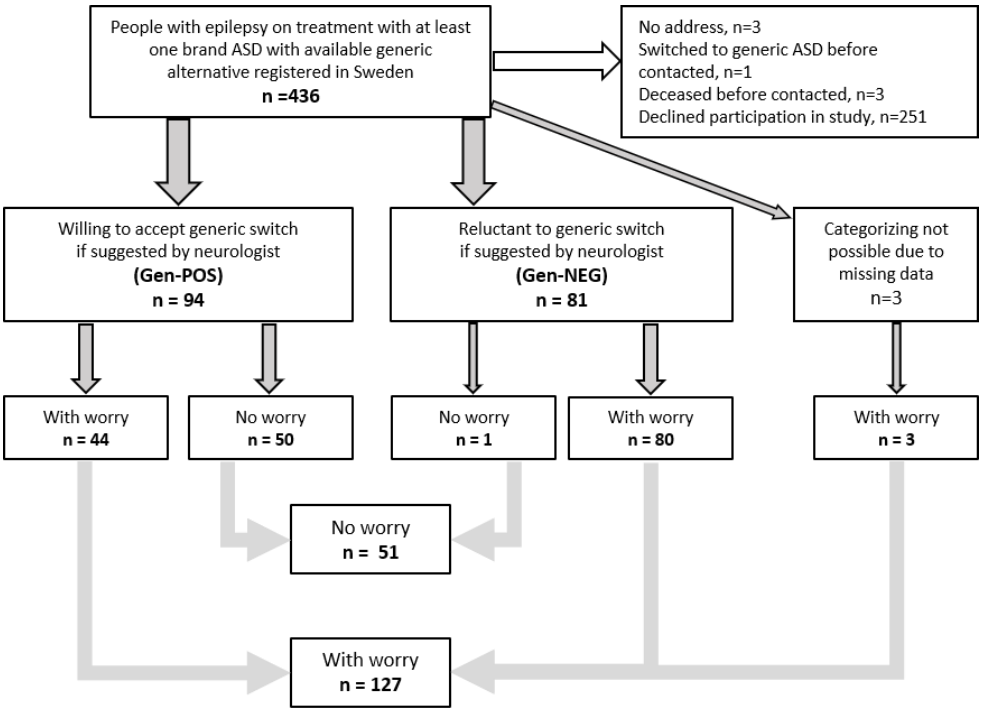


**Figure 4.**
Flowchart of identified people with epilepsy in the data search in medical records and categorization of study participants based on answers to the general questionnaire. With worry = Would worry about adverse effects and/or increased seizure frequency after a putative generic ASD switch. ASD = Antiseizure drug.
Source: Olsson et al. Epilepsy & Behavior 114 (2021).

Univariate logistic regression analysis identified four variables that were strongly associated ($p<0.10$) with Gen-NEG. Three variables decreased the odds of being Gen-NEG (education level of high school diploma or higher (OR: 0.50, 95% CI: 0.27–0.92), current occupational status of employed or studying (OR: 0.50, 95% CI: 0.27–0.95), and prior experience of generic substitution of ASDs (OR: 0.40, 95% CI: 0.21–0.74)). Age equal to or above 50 years increased the odds of being Gen-NEG (OR: 2.38, 95% CI: 1.29–4.37).

Figure 5 displays the results from the multivariable analyses with Gen-NEG as the dependent variable. Prior experience of a generic ASD switch remained negatively associated with Gen-NEG, and age ≥50 years remained a significant predictor of Gen-NEG when adjusting for gender and educational level.

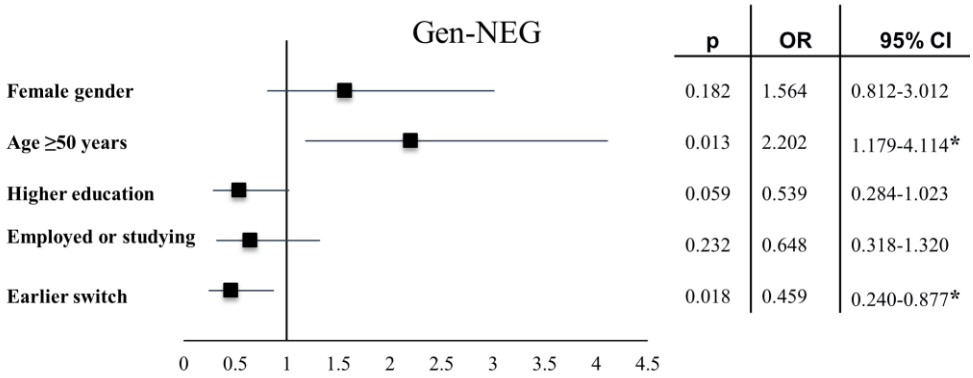


**Figure 5**
The forest plot shows the results of multivariable regression analyses with Gen-NEG as the dependent variable. The independent variables education level, occupational status and experience of earlier ASD generic switch were adjusted for gender and age in three separate analyses. The presented figures for gender and age were adjusted for education level. Source: Olsson et al. Epilepsy & Behavior 114 (2021).
* = $p < 0.05$ Gen-NEG = Would decline a generic switch if suggested by their neurologist
Higher education = Education level of high school diploma or higher
Earlier switch = Prior experience of generic ASD switch

All but one (21/22) of the subjects who were represented by a caregiver were categorized as "with worry". Having the questionnaires answered by a caregiver was strongly associated with "with worry" in univariate analysis (OR: 9.91, 95% CI: 1.30–75.73), but there were too few observations for this variable to progress to the multivariable model. The same three variables that decreased the odds of being Gen-NEG in the univariate analysis were also negatively associated with "with worry" (education level of high school diploma or higher (OR: 0.49, 95% CI: 0.24–0.99), current occupational status: employed or studying (OR: 0.48, 95% CI: 0.25–0.94), and prior experience of generic ASD substitution (OR: 0.50, 95% CI: 0.26–0.98)).

Figure 6 shows the results from the multivariable logistic regression analyses with "with worry" as the dependent variable. Higher education level, currently being employed or studying, and prior experience of a generic ASD switch all remained negatively associated with "with worry" in the adjusted models.

In summary, skeptic attitudes toward the generic substitution of ASDs were widespread within our sample of PWE.

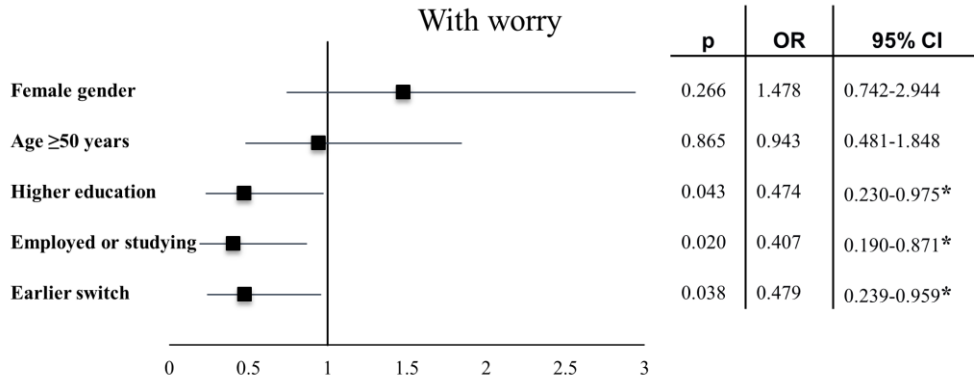


**Figure 6**
The forest plot displays the results of multivariable regression analyses with "with worry" as the dependent variable. The independent variables education level, occupational status and experience of earlier ASD generic switch were adjusted for gender and age in three separate analyses. The presented figures for gender and age were adjusted for education level. Source: Olsson et al. Epilepsy & Behavior 114 (2021).
* = $p < 0.05$
With worry = Would worry about adverse effects and/or increased seizure frequency after a putative generic switch
Higher education = Education level of high school diploma or higher
Earlier switch = Prior experience of generic ASD switch

# Summary of paper IV

The survey was distributed to 276 neurologists and neurology residents. The total response rate was 55.8% (RSthlm 49.1%, n=81 | RSkane 65.8%, n=73). Most respondents were specialists in neurology (68%), working at university hospital units (59%), and typically met fewer than 50 epilepsy outpatients per year (66%). The majority (73%) had previous experience of generic substitution of ASDs in epilepsy. It was much more common among respondents from RSkane to have such experience (RSthlm 68% | RSkane 81%).

Most respondents (65%) held a positive attitude toward generic substitution of ASDs in general, and did not worry about either deteriorated seizure control or other adverse effects after a switch. Among those who were worried (Likert 5–6), it was more common to worry about worsened seizure control (17%) than other adverse effects (9%). Equal proportions stated an increasingly positive (45%) or unchanged (45%) attitude toward generic substitution of ASDs during the past five to ten years.

Figure 7 shows the main results from the domain regarding factors that may influence substitution decisions. The main reasons for refraining from switching to generics were if the individual patient wished to remain on the original compound (76%), had cognitive impairment (53%), was on a drug with an NTI (47%), or had shown prior susceptibility to adverse effects (46%). Less than one-third of respondents were aware of any regional (31%) or local (30%) guidelines to support substitution decisions.

Respondents from RSthlm were generally more reluctant to prescribe a generic substitution compared to those from RSkane. The biggest differences regarding factors that led to avoidance of a substitution were when the patient had obtained long-term seizure freedom (RSthlm 47% | RSkane 27%), was on treatment with an ASD with NTI (RSthlm 57% | RSkane 39%), was cognitively impaired (RSthlm 61% | RSkane 44%), or expressed reluctance to switch (RSthlm 85% | RSkane 68%).

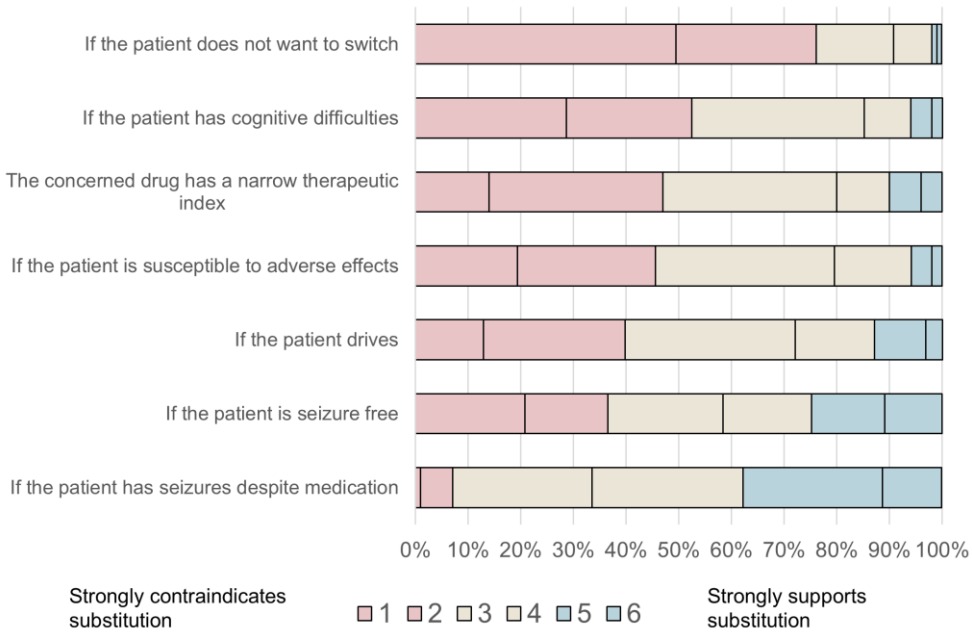


**Figure 7**
Distribution of responses (%) to the items regarding specific factors that influence substitution decisions. The answer alternatives are categorized into 1 – 2 (pink), 3 – 4 (beige), and 5 – 6 (blue). Only responses from physicians with prior experience of generic substitution of antiseizure drugs (n = 109) were counted.

Ongoing treatment with an ASD with NTI was one of the main reasons for avoiding a switch. However, there was no consensus among physicians on which ASDs should be considered NTI drugs. The highest uniformity was seen for phenytoin (75%), followed by carbamazepine (29%) and valproate (19%).

Among those with previous experience of generic substitutions, most had cared for at least one patient (Likert 2–6) who had experienced a breakthrough seizure (63%), increased seizure frequency (67%), or other adverse effects (82%) that they believed to be caused by a generic substitution and enforced a switchback to the original ASD product. However, the reported proportions of switchbacks due to such events were low, with a median Likert score of two for deteriorated seizure control and three for other adverse effects on a scale from 1 = None to 6 = All.

In summary, neurologists in Stockholm and Skåne generally accept the use of generic ASDs in epilepsy.

# Discussion

This thesis contributes novel knowledge to the ongoing debate on generic substitutions of ASDs in epilepsy. The included papers cover a wide span of different aspects of the debate, including the first prospective study of LEV serum concentration fluctuations and impact on QoL after brand-to-generic LEV switch, attitudes toward generic substitutions of ASDs among both PWE and physicians, and the first study to explore clinicians' reasoning behind substitution decisions regarding ASDs.

## Pharmacokinetic aspects of generic ASD substitutions

The criteria for demonstrating BE have been widely disputed and criticized for being too lax [65-69]. Current regulations allow the 90% CI of test-to-reference ratios of the pharmacokinetic measures AUC and Cmax to fall within 80–125%. Differences are usually much less than what is accepted, with mean differences in AUC and Cmax of 4%, and differences in AUC of less than 10%, for the vast majority of generic products overall (not just ASDs) [86].

In paper I, we demonstrated that the serum concentration of LEV was similar in treatment with brand-name LEV and a generic LEV product. This is in line with other prospective studies on the impact on serum concentrations of generic ASD substitutions, including high-quality evidence from a study on LTG and two less stringent studies on LEV [71, 87, 88].

In concordance with paper I, a retrospective study of plasma concentrations of LTG, LEV, and topiramate with brand and generic treatment showed that a considerable proportion of patients (33–41%) had potentially clinically important changes (±20%) in day-to-day plasma concentrations with stable brand-name treatment, with fluctuations of an equivalent magnitude in those switched to generic products [89]. Accordingly, available data (although limited in number of studies, participants, and adherence control) suggest that serum concentrations, and fluctuations thereof, are equal regardless of brand or generic ASD treatment.

Another concern regarding generic substitutions that has been widely debated is switching from one generic product to another [90]. Generic compounds are only obliged to demonstrate BE to the innovator drug, not to other generic compounds. In theory, a change from an authorized generic product with test/reference ratios of AUC and Cmax near the upper limit of the accepted interval (80–125%) to a different generic product with ratios at the lower end of the spectrum may cause larger changes in serum concentrations compared to brand-to-generic switches [91, 92]. This concern was addressed in two rigorously designed randomized controlled trials, one chronic dosing study of switches from the two most disparate on-market generic LTG products and one single-dose bioequivalence study of branded LTG and two generic LTG products [93, 94]. Treatment adherence was monitored meticulously in the chronic dosing trial. In summary, BE was demonstrated both between the generic products and between brand and generic LTG. The authors concluded that switches between bioequivalent products are unlikely to result in significant serum concentration changes, and that these findings demonstrate the soundness of current BE regulations with implications for other drug classes as well.

The safety of both brand-to-generic and generic-to-generic ASD switches from a pharmacokinetic viewpoint was further supported in a recent review of BE data for second-generation ASDs authorized in Europe [26]. Test-to-reference ratios of AUC and Cmax in BE studies for generic drug approval were reviewed, and showed that for 99% of the assessed products (excluding gabapentin), the 90% CIs of AUC ratios contained entirely within the more stringent acceptance interval applied to NTI drugs (90–111%). Within-subject variability for AUC was below 10% for 88% of products with available data. Thus, the very small non-clinically relevant changes observed in randomized controlled trials of LTG switches can be extrapolated to the vast majority of other second-generation generic ASDs. Gabapentin was identified as an ASD with larger differences in AUC, Cmax, and intra-subject variability. Generic substitution of gabapentin may therefore require further prospective evaluation.

# Clinical aspects of generic ASD substitutions

As mentioned in the introduction, the evidence regarding clinical outcomes after generic substitutions of ASDs was inconclusive at the time when this Ph.D. project started. Until then, the publications had been based on retrospective database analyses and survey studies without the documentation of important factors to draw any strong conclusions, such as drug serum concentrations, adherence, and seizure frequency [45-52, 57, 61, 62]. Two other more recent retrospective studies, with the same methodological flaws, found that manufacturer changes of ASDs were associated with seizures, but the association disappeared after adjusting for the process of refilling in one of them [95, 96].

In papers I and II, we reported seizure days and adverse events with no apparent differences in treatment with either brand or generic LEV. The switchback rate was 0%. This is in line with other prospective studies of generic substitutions of ASDs in PWE that have been published in the past few years, including the high-impact randomized controlled trials of LTG substitutions, one study on oxcarbazepine, and several other LEV studies [71, 87, 88, 94, 97-99]. Although limited in terms of sample sizes (n = 12–125), lack of randomization and blinding (except for the LTG studies), and short follow-up after substitutions in most studies (range: four weeks to four years), these studies consistently found no changes in seizure control or adverse events. Switchback rates were low (0–8%). These findings stand in stark contrast to the low tolerability and high switchback rates reported in retrospective studies, and do not indicate higher switchback rates compared to other drug classes [45-47, 100].

Paper III showed, in concordance with other similar studies, that PWE on brand-name ASD treatment are reluctant to change their treatment to a generic alternative and would worry about deteriorated seizure control and/or adverse effects after a switch [57, 59, 60, 62]. Those with prior experience of generic ASD substitutions were less skeptical and less worried, indicating overall good experience of prior switches and further emphasizing that generic substitutions seem safe and well tolerated at group level.

In paper IV, most physicians reported having cared for at least one patient with deteriorated seizure control and/or aggravated adverse effects that they attributed to a generic substitution. The reported proportions of substitutions that led to untoward effects were low, but the indication that problems are frequent enough for most physicians to encounter underlines the importance of the topic and motivates further research into the causes of such problems.

## Possible explanations for the discrepancy between retrospective and prospective studies

Reasons for the reported high switchback rates and poor tolerance of generic ASD substitutions are most likely multifactorial, but have not been sufficiently studied to give any definitive answers. Some of the most frequently mentioned suspected reasons for the reported alarming substitution problems are discussed below [101].

*The nocebo effect*

Nocebo, the opposite of placebo, describes adverse events related to negative expectations of treatment and has gained interest in recent years due to its negative effect on treatment adherence, drop-outs in clinical trials, and falsely decreasing the reported safety of new drugs [102, 103]. Nocebo effects can only be measured adequately in blinded studies, and given the limited number of blinded trials of generic ASD substitutions, its magnitude in previous studies remains unclear [104, 105].

Paper III showed that most PWE on brand-name ASD treatment would be worried about deteriorated seizure control and other adverse effects after a generic substitution, which per se may elicit nocebo effects. One likely explanation for the large differences in switchback rates between retrospective findings and prospective studies is that the former studied mandatory overnight substitutions and/or substitutions in populations with distrust regarding generic drugs, while prospective studies have been carried out among subjects who switched voluntarily [45, 46, 100]. The retrospective studies were likely to include more people who held negative opinions toward generic ASDs and consequently were more prone to experience untoward substitution outcomes mediated by nocebo effects [106]. Additionally, as indicated by the results in paper II, seizure worries can be decreased by the additional monitoring and contact with healthcare personnel that comes with participating in a prospective study, which may decrease nocebo effects even further [107, 108].

*Nonadherence*

Failure to comply with treatment recommendations, nonadherence, is common in PWE [109-111]. As discussed in the previous section, nocebo effects can lead to nonadherence. Furthermore, generics frequently differ in shape and color compared to their brand-name counterparts, and it has been demonstrated that appearance changes in ASDs increase the odds of non-persistence [112]. To add to this confusion, switches to parallel imported drugs and duplicates of generic compounds may also result in different appearances of the drugs, packages, and label names. Such switches are not considered generic substitutions, since the drugs have a mutual origin and have been deemed interchangeable by the MPA, but likely result in the same confusion for patients with possible nonadherence as a result. Inconsistent supply of some generic compounds can lead to additional switches between interchangeable compounds [67]. For example, as at April 2021, several generic compounds of LTG are currently unavailable in Sweden.

Nonadherence was suspected in 40% of subjects in paper I, due to large within-subject variations of C/D ratios. The number of participants with suspected nonadherence was equal in both groups, and we did not see any tendency of the described effect of appearance changes on adherence in our study. This is not surprising, since the absolute difference observed in the study by Kesselheim and colleagues was only 0.23% and our study was not even close to having the power to detect such a small effect [112]. However, even this small effect size may be clinically relevant over time, since patients usually refill their medication several times a year and polytherapy of ASDs and other concomitant medications are common [113].

*Misattribution of adverse events*

Seizures in PWE are unpredictable and may present at any time. Spontaneous seizures that occur in close connection to a switch may be wrongly attributed to the treatment change. Participants in clinical trials probably have less likelihood of seizures and other adverse events due to decreased nocebo/increased placebo effects and resulting increased adherence as discussed above. Accordingly, in real-world data from settings including individuals with distrust regarding generics and routine follow up, there may be more reports of adverse events that subjectively were caused by generic substitution, but objectively have other explanations such as nonadherence.

# Future perspectives

The combined knowledge to date suggests that the reported substitution problems with generic ASDs are not caused by pharmacokinetic alterations, but rather by a combination of nonadherence, nocebo effects, misattribution of seizures and adverse effects that would have emerged regardless of whether or not a switch was performed, and most likely several other unknown factors. Prospective studies of generic substitutions of second-generation ASDs show that substitution risks are minimal in controlled settings. However, survey studies of both PWE and physicians show that that the frequency of negative substitution outcomes that are subjectively interpreted as being caused by generics is not negligible in daily practice. Regardless of whether or not the problem is due to the generic compound, the result will still be suboptimal if the patient strongly believes that the generic product causes harm.

Future studies could elaborate on pharmacokinetic outcomes of generic substitutions of ASDs with test-to-reference ratios of AUC and Cmax with larger discrepancy and higher within-subject variability compared to the rigorously studied LTG. Nevertheless, available data indicate that psychological factors and nonadherence are more important factors, and the focus should be on interventions that can ensure treatment adherence and decrease worries and nocebo effects among PWE.

Current evidence indicates that substitution risks are very low at group level. We live in a world with limited resources, and the savings from lower costs of generics could be used for other purposes within healthcare with known benefits for society. A small potential substitution risk might therefore be accepted, but the threshold of the accepted risk/benefit ratio is not only a medical question, but also a political and ethical one.

Future efforts should continue to search for potential subgroups of PWE or selected characteristics that may be associated with untoward substitution outcomes. Rare events require large cohorts and long follow-up times to study, which would make it very difficult and costly to study clinical aspects of generic substitutions in randomized controlled trials. A system to monitor switchback rates of drugs at population level has been developed, but lacks important information on motives for switchbacks [114]. Similarly, a lack of systematic documentation of important factors and underreporting of problems currently impede meaningful conclusions from retrospective studies [64]. The results from paper IV may provide material for consensus discussions to decide on quality indicators to ensure systematic documentation and to enable higher quality evidence based on data from medical records.

# Methodologic considerations

*Paper I*

The main limitations of paper I were that it was neither randomized nor blinded. This may have introduced a selection bias with possible effects on substitution outcomes. Ethical considerations due to the alarming reports of poor substitution outcomes in retrospective studies explain why the study was not randomized. Given the combined knowledge from prospective studies and clinical experience of generic LEV substitutions, I believe that both randomization and blinding would be rational if we were to redo the study.

Adherence to the prescribed drug regimen is one factor that may have been affected by the open-label design. We monitored adherence by means of therapeutic drug monitoring (TDM) of LEV serum concentrations, which indicated nonadherence in equal proportions in both groups. The addition of other measures of adherence, such as electronic medication monitoring, pill count, and/or patient self-report measures, may have been beneficial [115].

Additionally, it would have been interesting to know physicians' reasoning behind the decision on whether or not to prescribe a substitution, and perhaps some characteristics of the PWE who declined participation for a basic evaluation of selection bias.

*Paper II*

Assessment of QoL was a secondary aim of this study. The limited sample size and possible selection bias introduced by the open non-randomized design impede any definite conclusions. Accordingly, increased sample size, randomization, and blinding would lead to obvious study improvements.

Several previous studies have used parametric tests for group comparisons of QOLIE-31, which implies normal distribution of subscale scores in larger samples [116-118]. This was not the case within our sample and an additional benefit of an increased sample size could therefore be the use of parametric tests.

*Paper III*

In paper III, we explored associations between a total of 18 independent variables (characteristics of PWE) with the two dependent variables Gen-NEG and "with worry". Consequently, multiple statistical tests were performed and an adequate critique against this approach is that it leads to a high probability of incorrectly rejecting the null hypothesis (type I error). To account for this, it would be possible to correct for multiple testing, for example by using Bonferoni correction. However, this would drastically decrease power, and some argue that Bonferoni corrections are too conservative and result in too many type II errors (not declaring a result statistically significant when in fact it is) [119]. Given the exploratory nature of the study, we chose not to correct our α-level for multiple testing, but this should be taken into consideration when interpreting the results from the study.

*Paper IV*

In paper IV, we studied physicians' attitudes toward the generic substitution of ASDs in epilepsy and which factors were of significance when deciding on compound substitutions. We chose to carry out a quantitative survey study to answer our research questions. An alternative method, or a possible complement, would be to conduct in-depth interviews or use another qualitative research method.

# Conclusions

Altogether, current evidence suggests that the pharmacokinetic consequences of generic substitutions of bioequivalent immediate release second-generation ASDs are negligible at group level. Data on clinical aspects of generic substitutions are not as robust, but real-world prospective data indicate that possible substitution risks are generally small to nonexistent in treatment-adherent individuals. Further research is warranted to rule out the possibility that small subsets of PWE may be prone to experience significant drug serum concentration changes and/or negative clinical outcomes due to other reasons following a switch. Additionally, interventions to ensure treatment adherence in PWE in general, and particularly in connection with generic substitutions, require further emphasis.

The major conclusions from the individual papers were as follows:

*Paper I*

Fluctuations in LEV serum concentrations are similar for treatment with either a brand-name LEV or a generic LEV product. Within-subject variability is much larger compared to the small, non-significant differences between brands.

*Paper II*

We found increased QoL and less worry about seizures over time in PWE, regardless of brand or generic LEV treatment. The very similar change in both groups indicates that the observed effect was not caused by generic substitution, but rather by the structured follow-up during the study.

*Paper III*

High proportions of PWE express concerns about generic substitution of ASDs. Age equal to or above 50 is associated with skepticism toward generic substitution, while those with prior experience of generic ASD substitutions have more positive attitudes toward generics. Prior experience, as well as higher education level and currently being employed or studying, are associated with decreased worries about adverse events following a substitution. Caregivers who represent PWE with cognitive and communicative difficulties seem particularly concerned, and may require additional information and support in connection with generic substitutions.

*Paper IV*

Neurologists in the Stockholm and Skåne healthcare regions generally have positive attitudes toward the generic substitution of ASDs in epilepsy. Patient preference, cognitive impairment, whether the concerned ASD has an NTI, and patient history of susceptibility to adverse drug effects are important factors in current practice to consider when deciding on compound substitutions.

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