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ANTIEPILEPTIC DRUG UTILIZATION: NEED OF SEX-SPECIFIC INFORMATION AND DECISION SUPPORT

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ANTIEPILEPTIC DRUG UTILIZATION: NEED OF SEX-SPECIFIC INFORMATION AND DECISION SUPPORT
THESIS FOR DOCTORAL DEGREE (Ph.D.)

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ABSTRACT

Antiepileptic drugs are used for the treatment of epilepsy and for other neurological and psychiatric conditions, and therefore is prescribing of antiepileptic drugs a concern for physicians from many disciplines. The age and sex-specific prevalence, as well as the role of sex and gender aspects, vary between the conditions for which antiepileptic drugs are used. The overall aim of this thesis was to gain more understanding of the use of antiepileptic drugs on various diagnoses, focusing on sex/gender differences, and to explore physicians' perceptions of sex and gender in decision making on drug treatment.

The first two studies describe the antiepileptic drugs used in epilepsy and other conditions. Clear age and gender differences in the use of specific anti-epileptics were observed. The use of antiepileptic drugs in children and adolescents was mainly limited to epilepsy and the individual antiepileptic drugs prescribed appeared to be in accordance with approved indications and treatment guidelines. However, some antiepileptic drugs were used off-label in children and adolescents.

The third study evaluated the effect of a warning issued by the European Medicines Agency in November 2014 on restricted prescribing of valproic acid to girls and women of childbearing potential. The analyzes showed that the warning only affected the prescribing in girls and women with a psychiatric diagnosis. Prescribing to girls and women with epilepsy had decreased long before the warning was issued, which could indicate an increased awareness of the teratogenic risk of valproic acid among neurologists treating women with epilepsy.

The fourth study examined how primary care physicians perceive sex/gender and gender equality related to drug prescribing. The results showed that physicians experienced insufficient knowledge of sex/gender differences in drug treatment, although their expressed clinical experience indicated some awareness. The patient's sex was considered during diagnosing while drug prescribing decisions followed the regional recommendation lists because these were believed to be evidence-based and gender-neutral. Overall, physicians wanted more education and knowledge about sex and gender in drug treatment. However, finding reliable information about sex and gender aspects for individual drugs may be difficult. This can be facilitated by the web-based knowledge base *Janusmed Sex and Gender*, as described in the fifth study.

In summary, this thesis demonstrates sex differences in use of certain antiepileptic drugs, which probably reflect the different benefit and risk from these between men and women. Knowledge of how antiepileptic drugs are prescribed and used in women and men with different diagnoses may be useful in discussions on rational drug prescribing and to propose measures to improve prescribing behavior. As shown in this thesis, regulatory measures may be one approach to improve rational prescribing and to highlight the importance of the patient's sex. Another approach may be to get acquainted with sex and gender-related pharmacological information through the knowledge base *Janusmed Sex and Gender*.

LIST OF SCIENTIFIC PAPERS

I. **Karlsson L**, Wettermark B, Tomson T
Drug treatment in patients with newly diagnosed unprovoked seizures/epilepsy
Epilepsy Research 2014;108(5):902-908

II. **Karlsson Lind L**, Wide K, Wettermark B, von Euler M
Utilization of Antiepileptic Medicines in Swedish Children and Adolescents with Different Diagnoses
Basic & Clinical Pharmacology & Toxicology 2018;123(1):94-100

III. **Karlsson Lind L**, Komen J, Wettermark B, von Euler M, Tomson T
Valproic acid utilization among girls and women in Stockholm: Impact of regulatory restrictions
Epilepsia Open 2018;3(3):357-363

IV. Loikas D, **Karlsson L**, von Euler M, Schenck-Gustafsson K, Bastholm-Rahmner P
Does patient's sex influence treatment in primary care? Experiences and expressed knowledge among physicians – a qualitative study
BMC Family Practice 2015;16:137

V. **Karlsson Lind L**, von Euler M, Korkmaz S, Schenck-Gustafsson K
Sex differences in drugs: the development of a comprehensive knowledge base to improve gender awareness prescribing
Biology of Sex Differences 2017;8(1):32

CONTENTS

LIST OF ABBREVIATIONS

AED	Antiepileptic drug
ATC	Anatomical Therapeutic Classification
DTC	Drug and Therapeutic Committee
EEG	Electroencephalography
EHR	Electronic health record
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
FGD	Focus group discussion
GAD	Generalized anxiety disorder
GP	General practitioner
ICD	International Statistical Classification of Diseases and Related Health Problems
ILAE	International League Against Epilepsy
ITS	Interrupted time series
NIH	National Institutes of Health
NPR	National Patient Register
OTC	Over-the-counter
PIN	Personal identification number
SIRE	Stockholm Incidence Registry of Epilepsy
SPDR	Swedish Prescribed Drug Register
VAL	Vårdanalysdatabasen

1 INTRODUCTION

Pharmacological treatment is one of the most common forms of treatment in healthcare and is therefore a critical part of clinical practice. Prescribing medications is complex and depends on a mix of knowledge, skills and behaviors [1]. Decision on the optimal treatment choice can be challenging particularly in patients with extensive co-morbidity and co-medications. Furthermore, every prescribing decision should be preceded by an individual evaluation of the benefit versus risk from medications, accounting for patient preferences and disease factors. Therefore, the benefit and risk from medications may differ between individuals and may change during an individual's life.

Several medications have presented different efficacy, safety and tolerability depending on the patient's sex. Consideration of *sex* (referring to biological differences between men and women, such as chromosomal, genetic or hormonal differences) and *gender* (referring to social and cultural differences between men and women) aspects in disease and pharmacological treatment can be essential for informed decision making and achieving clinical benefit from treatment [2]. However, research studies and treatment guidelines do not always consider sex and gender aspects specifically [3].

Some pharmacological classes can be used for treatment of several conditions. Antiepileptic drugs are prescribed not only to prevent epileptic seizures, but for a variety of neurologic and psychiatric conditions [4]. Therefore, prescribing of antiepileptic drugs are a concern for physicians from many disciplines. The age- and sex-specific prevalence, as well as the role of sex and gender aspects, differ between the conditions for which antiepileptic drugs are used. Accordingly, we need to gain better knowledge on how antiepileptic drugs are used on different conditions and in different patient groups.

Studies on utilization patterns of medications reflect both patients' needs and preferences as well as physicians' prescribing decisions [5]. Knowledge on how medications are used in real life is essential for understanding their benefit-risk profile. This thesis deals with utilization of antiepileptic drugs on different diagnoses with special focus on sex and gender differences, as well as exploring physicians' perceptions of sex and gender in decision on drug prescribing.

2 BACKGROUND

2.1 ANTIEPILEPTIC DRUGS

2.1.1 Historical perspective

The first antiepileptic drug (AED) was discovered in 1857, when Charles Locock used potassium bromide on young women with "hysterical" epilepsy. Some decades later, the anticonvulsant properties of phenobarbital and phenytoin were discovered [6]. The next AEDs to be introduced were ethosuximide, carbamazepine and valproic acid in the 1950s and 1960s. These are regarded as the first-generation AEDs. Since then, many AEDs have entered the market. The introduction of modern AEDs started in the 1980s when thousands of chemical compounds were screened under the Anticonvulsant Drug Development Program in the U.S. Among the newer AEDs developed were vigabatrin, lamotrigine, oxcarbazepine, gabapentin, topiramate, levetiracetam and lacosamide [7]. In the last few years, an additional number of new AEDs have been approved for treatment of epilepsy, including perampanel and brivaracetam (Fig. 1).

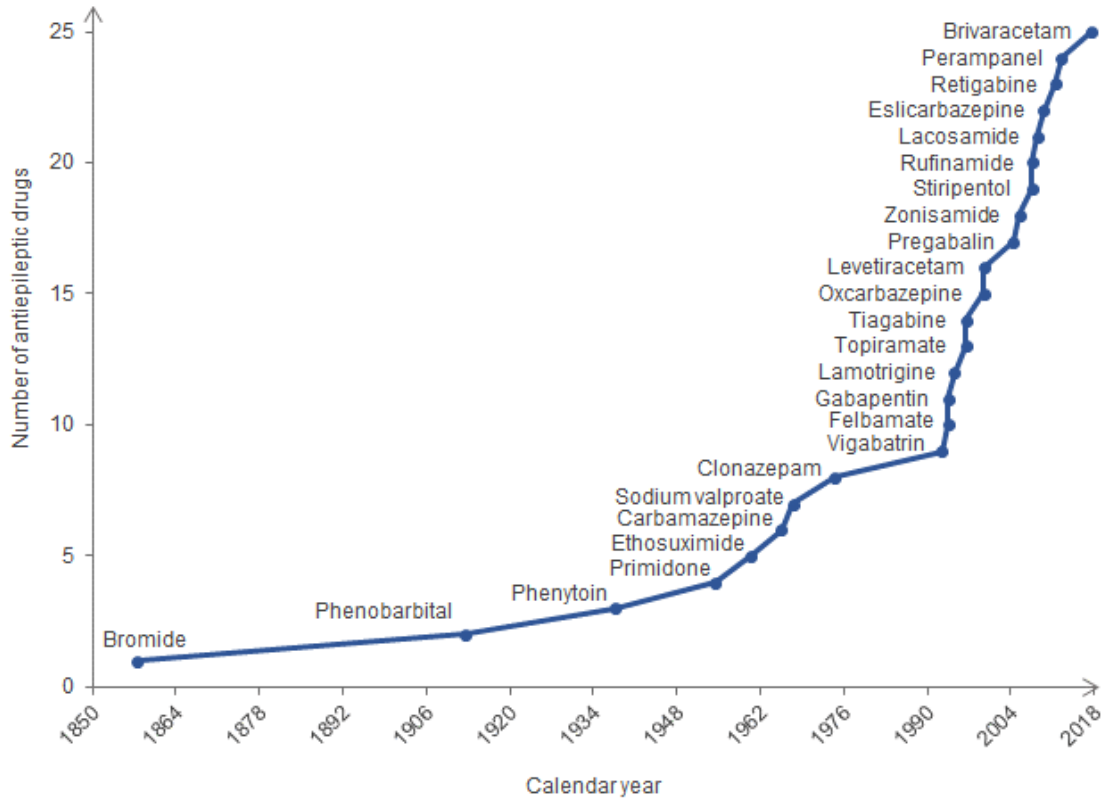

Figure 1. Timeline for antiepileptic drugs developed. Adapted with data from [6-8]. The specified year corresponds to the year of first mention of clinical use [6, 7] or year of approval in Sweden [8].

Table 1. Antiepileptic drugs approved in Sweden[1]

Drug	Approved indications	Age in which use is approved (monotherapy)	Age in which use is approved (adjunctive therapy)	First approval year
Brivaracetam	Epilepsy (partial seizures)		≥4 years	2016 (Briviact)
Carbamazepine	Epilepsy (partial and generalized seizures)	No age limit specified	No age limit specified	1965 (Tegretol)
	Alcohol abstinence	No age limit specified	No age limit specified	
	Trigeminal neuralgia	No age limit specified	No age limit specified	
Clonazepam	Epilepsy (partial and generalized seizures)	No age limit specified	No age limit specified	1974 (Iktorivil)
Eslicarbazepine	Epilepsy (partial seizures)	≥18 years	≥6 years	2009 (Zebinix)
Ethosuximide	Epilepsy (absence epilepsy)	No age limit specified	No age limit specified	1963 (Suxinutin)
Felbamate	Epilepsy (Lennox-Gaustat syndrome, resistant epilepsy)	≥14 years	≥4 years	1995 (Taloxa)
Fosphenytoin	Status epilepticus	≥5 years		1998 (Pro-Epanutin)
Gabapentin	Epilepsy (partial seizures)	≥12 years	≥6 years	1994 (Neurontin)
	Neuropathic pain (periphery)	≥18 years		
Lacosamide	Epilepsy (partial seizures)	≥4 years	≥4 years	2008 (Vimpat)
Lamotrigine	Epilepsy (partial and generalized seizures, Lennox-Gaustat syndrome)	≥13 years	≥2 years	1994 (Lamictal)
	Bipolar disorder (prevention of depressive episodes)	≥18 years		
Levetiracetam	Epilepsy (partial and generalized seizures)	≥16 years (partial)	≥1 month (partial), ≥12 years (generalized)	2000 (Keppra)
Oxcarbazepine	Epilepsy (partial seizures)	≥6 years	≥6 years	1999 (Trileptal)
Perampanel	Epilepsy (partial and generalized seizures)		≥12 years	2012 (Fycompa)
Phenobarbital	Epilepsy (partial and generalized seizures, neonatal convulsions)	No age limit specified	No age limit specified	1973 (Fenemal)
Phenytoin	Epilepsy (partial and generalized seizures)	No age limit specified	No age limit specified	1939 (Epanutin)
Pregabalin	Neuropathic pain (periphery and central)	≥18 years		2004 (Lyrica)
	Epilepsy (partial seizures)		≥18 years	
	Generalized anxiety disorder	≥18 years		
Rufinamide	Epilepsy (Lennox-Gaustat syndrome)		≥4 years	2007 (Inovelon)
Stiripentol	Epilepsy (Dravet syndrome)		No age limit specified	2007 (Diacomit)
Topiramate	Epilepsy (partial and generalized seizures, Lennox-Gaustat syndrome)	≥6 years	≥2 years	1996 (Topimax)
	Migraine prophylaxis	≥18 years		
Valproic acid	Epilepsy (partial and generalized seizures)	No age limit specified	No age limit specified	1980 (Absenor)
	Bipolar disorder (mania)	No age limit specified	No age limit specified	
Vigabatrin	Epilepsy (partial seizures, West syndrome)	No age limit specified	No age limit specified	1992 (Sabrilex)
Zonisamide	Epilepsy (partial seizures)	≥18 years	≥6 years	2005 (Zonegran)

[1] Information from the approved Summary of Product Characteristics (SmPC) for each medicinal product [8]. The terminology of seizure classification has changed over the years, the terminology used in this table is based on the approved SmPC.

2.1.2 Indications for antiepileptic drugs

AEDs were developed and originally used in controlling epileptic seizures, but some AEDs have demonstrated efficacy for treatment of other conditions, particularly within neurology and psychiatry [4]. Accordingly, some AEDs have been approved for treatment of neuropathic pain, bipolar disorder, and migraine (Table 1). Some of these conditions, if not severe, are managed in primary care. However, most of the AEDs used in non-epileptic conditions are only approved for use in adults and there is limited evidence supporting their use in children and adolescents [9]. Some of the conditions for which AEDs are used affect men and women equally, while other show large sex differences in prevalence.

2.1.2.1 Epilepsy

Epilepsy is a chronic neurological condition characterized by recurrent unprovoked seizures. The prevalence of epilepsy is around 0.6-0.7% globally with higher rates reported in low- and middle income countries. The prevalence is lower in children, around 0.4-0.5%. Geographic differences can be attributable to methodological factors such as data collection methods, sources of case ascertainment, and assessment criteria [10]. Higher incidence rates are found in childhood and in adults above the age of 65 [11]. In general, men have higher incidence of epilepsy than women [10], which might be explained by men's greater exposure to risk factors such as acute head injury, stroke, CNS infection, and alcohol [11], as well as cultural differences in seeking medical care [10]. Although epilepsy affects more men than women in general, there is evidence of sex differences in expression of many seizure syndromes [12, 13].

Most patients with epilepsy need pharmacological treatment with AEDs and treatment is often maintained for several years, sometimes for life. The treatment is prophylactic and aims at reducing the risk of seizures. Treatment with AEDs is generally initiated after two or more unprovoked seizures, since less than half of the patients with one unprovoked seizure will have a relapse [14]. Monotherapy is preferred, although some patients will need a multiple AED regimen. Around 50% patients with newly diagnosed epilepsy achieve seizure freedom with their initial AED, and additional 20-30% achieve seizure freedom with an alternative monotherapy [14]. There is therefore a need to improve the efficacy of therapy. During the last decades, several new AEDs have been approved for treating epilepsy, such as lamotrigine, levetiracetam, and gabapentin (Fig. 1). These new AEDs have demonstrated better tolerability and low drug-drug interaction potential, thereby providing better opportunities for more rational and individualized treatment [15]. Although monotherapy is preferred, most of the new AEDs have initially been approved as adjunctive therapy, and some of these have subsequently been approved also for monotherapy (Table 1). However, few of the new AEDs have been approved for use in children and even fewer for monotherapy in children.

It is not uncommon for patients with epilepsy to suffer from concomitant psychiatric disorders, such as depression, and therefore the selection of AED may be tailored according to the patient's neurological and psychiatric comorbidities [9].

2.1.2.2 Bipolar affective disorder

Bipolar disorders are a spectrum of conditions involving episodes of depression, mania, hypomania and/or mixed episodes [16, 17]. The global prevalence of bipolar disorder has been estimated to be around 0.7% [18]. Previous studies are inconclusive whether the prevalence and incidence of bipolar disorder differs between the sexes: some studies report that women are more likely to have bipolar

disorder [18-20], while other studies report no sex differences [21, 22]. In children and adolescents, affective disorders appear to be more common in girls [23, 24].

Although lithium is the most widely used medication in bipolar disorder, valproic acid and carbamazepine are well-established therapeutic options. There is strong evidence that valproic acid is effective in the treatment of acute manic episodes and may even prevent recurrence of mania [25, 26]. For that reason, the European Medicines Agency (EMA) recommended all products containing valproic acid to be approved for treatment of bipolar disorder/mania in 2010 [27]. Long-term treatment with valproic acid has limited evidence [28]. Carbamazepine is approved in the U.S. for treatment of acute and mixed episodes, while it is not yet approved in Sweden. Lamotrigine is approved in the U.S. and in some European countries (including Sweden) for maintenance therapy to prevent of relapse in depressive episodes in adults [29].

2.1.2.3 Generalized anxiety disorder

Generalized anxiety disorder (GAD) is one of the most common anxiety disorders and are defined as ongoing levels of worry and/or anxiety to an overwhelming extent over a continuing period without a distinct cause [16, 17]. The 12-month prevalence of GAD in Europe ranges between 0.2-4.3% with lower rates among children and adolescents. Women are twice as likely as men to experience GAD [20, 24, 30]. Pregabalin is approved in Europe for treatment of GAD (Table 1). However, it is not recommended as a first-line therapy but offers a treatment option in patients suffering from intolerable adverse events or non-response from other agents [31].

2.1.2.4 Neuropathic pain

Neuropathic pain is defined as "pain caused by a lesion or disease of the somatosensory system" [32]. The prevalence varies between 0.9-17.9% globally [33], with higher rates reported in women than men [34]. Well-known neuropathic pain syndromes are diabetic neuropathy, post-herpetic neuralgia and trigeminal neuralgia. The prevalence rates for these specific conditions typically range between 0.07-0.09% [33].

Neuropathic pain is known to be difficult to treat effectively. Several possible effective agents are tried until an agent and dose provides satisfactory control of the pain. Therefore, many different medications have been used for treating various types of neuropathic pain, including AEDs [35]. Several different AEDs have been used but sufficient evidence of efficacy has only been found for gabapentin and pregabalin [35]. Gabapentin and pregabalin are recommended as first-line treatment in periphery neuropathic pain in adults in Sweden and pregabalin is recommended as first-line treatment in central neuropathic pain in adults (Table 1) [36]. Carbamazepine has shown efficacy in trigeminus neuralgia and is the recommended first-line treatment in Sweden [36], which probably explains why carbamazepine has been used off-label in other types of neuropathic pain syndromes [35]. Many of the neuropathic pain syndromes for which AEDs have been studied are uncommon in children and adolescents, although some forms of neuropathic pain do exist [9].

2.1.2.5 Migraine

Migraine is a chronic neurological condition characterized by recurrent headaches. Reported prevalence of migraine in western countries are varying and have ranged between 5-9% for men and between 12-25% for women in Europe and North America have. Globally, lower rates have been reported in Africa and Asia, while varying numbers have been reported in South America [37].

Among children and adolescents, higher rates have been reported in Northern Europe [38, 39] than in Southern Europe [37]. The reason for differing rates could be methodological problems in assessing right diagnosis but may also depend on the population studied (i.e. primary care, specialist care, hospital population) [37].

Overall, migraine predominately affects women, but the men/women ratio of migraine prevalence varies across lifetime. More boys develop migraine in younger ages, while girls are more affected after puberty [37, 38]. Some studies suggest that there are sex-specific pathways in migraine disease, explaining the differences in prevalence, incidence and presentation of migraine between men and women [40].

Topiramate and valproic acid have shown to be efficacious for preventing migraine attacks in adults [41, 42] and are recommended as preventive treatment of migraine [43]. In children, topiramate have limited evidence supporting efficacy, while there is no evidence of efficacy for valproic acid [44]. There is no available evidence to conclude efficacy for gabapentin, pregabalin or other AEDs [45, 46]. None of the pharmacological treatments have been evaluated based on sex-related differences [40]. In Sweden, topiramate is approved for migraine prevention in adults (Table 1). It was recently approved in the U.S. for use in adolescents 12-17 years [47].

2.1.3 Sex and gender aspects in antiepileptic drug treatment

Selection of AED in epilepsy is based primarily on its efficacy for specific seizure types and epileptic syndromes. However, pregnancy and pharmacokinetic drug-drug interactions with contraceptives or sex hormones can have a sex-specific impact on AED selection and dose adjustments [48]. Sex differences in certain adverse events from AEDs may also influence the AED selection. These aspects are described in more detail below.

2.1.3.1 Pregnancy

The risk of birth defects from use of AEDs during pregnancy have been known for decades. The first documentation of teratogenicity of AEDs were carried out in the 1960s [49, 50] and since then, large-scale pregnancy registers have been established to evaluate the teratogenic potential from different AEDs. A recent cohort study based on data from the European Registry of Antiepileptic drugs and Pregnancy (EURAP) compared the risk of major congenital malformations for eight commonly used AEDs in women with epilepsy. Valproic acid in monotherapy was associated with the highest risk of major congenital malformations and the risk seems to be dose-dependent [51]. The frequency of major congenital malformations associated with use of levetiracetam, oxcarbazepine and lamotrigine was similar with that of the general population [52].

Since AEDs are increasingly used for conditions other than epilepsy, the number of women of childbearing age exposed to AEDs with teratogenic potential is increasing. However, the teratogenic risk may differ by indication which have been observed for valproic acid [53]. Data from France shows that children to women treated with valproic acid in monotherapy for epilepsy had a higher risk of major congenital malformations than children to women treated with valproic acid in monotherapy for bipolar disorder (44.4/1000 vs 22.3/1000). The risk in the general population was 9.9/1000. However, to date, only a summary of data have been published [53]. The dosages of the AEDs used may differ between indications and therefore influence the teratogenicity [54]. Furthermore, it is possible that genetic and epigenetic factors may have different effects on the fetus depending on the

mother's disorder. New evidence suggests that children exposed to AEDs have a higher risk for major congenital malformations than children of untreated women with epilepsy [52]. Moreover, most women with active epilepsy need treatment with AEDs during pregnancy, while pregnant women with other disorders may have several safer treatment options. Thus, the benefit-risk assessment of continued treatment during pregnancy will probably differ between indications [55].

In 2014, the EMA strengthened the restrictions on the use of valproic in girls and women after emerging evidence concerning an association with impaired cognitive development of children exposed during pregnancy [56]. The warning stated that valproic acid should not be prescribed to girls or to women of childbearing potential "unless alternative treatments are ineffective or not tolerated". The new recommendations was sent as a 'Dear healthcare professional letter' to healthcare professionals in the EU [56] and were highlighted in academic press and reported in national media in Sweden [57, 58].

Pregnancy itself can affect the pharmacokinetics of some AEDs. For example, the serum concentration of lamotrigine decreases by an average of 50-60% during pregnancy. Other AEDs seems to be unaffected, such as carbamazepine. Declining serum concentration of AEDs during pregnancy have been associated with worsening seizure frequency. However, many pregnant women remain seizure free despite lower AED concentrations. Thus, decision on dose adjustments must be done on an individual level [59].

2.1.3.2 Sex hormones

Fluctuations in endogenous female hormones during the menstrual cycle might change serum concentrations of AEDs. However, there are limited available data supporting this [48]. Furthermore, some AEDs can alter the levels of different sex hormones in both men and women. The liver enzyme inducing AEDs, such as carbamazepine, increases serum sex hormone-binding globulin (SHBG) concentrations. Increased serum SHBG levels over a long time can lead to diminished bioactivity of testosterone and estradiol, and thus menstrual disturbances and reduced fertility [60]. Valproic acid can increase testosterone concentrations and are associated with menstrual disturbances and polycystic ovary syndrome [48, 60].

2.1.3.3 Sex-specific drug-drug interactions

Several AEDs exhibit a high drug-drug interaction potential and are involved in pharmacokinetic interactions with other medications and among themselves. Interactions between AEDs and medications used on sex-specific indications have been reported and are relevant both for men and women [48]. In women, estrogens used in contraceptives and hormonal replacement therapy can reduce the activity of lamotrigine and valproic acid. On the other hand, some AEDs may reduce the efficacy of contraceptives. In men, the serum levels of tadalafil, used for erectile dysfunction, can be reduced by CYP3A4 inducers such as phenobarbital, phenytoin and carbamazepine [48].

2.1.3.4 Sex-specific response to AEDs

Little is known about the anti-seizure efficacy of individual AEDs between men and women, because sex differences have not been explored in most clinical trials [48]. Even though sex differences in efficacy have been explored for some AEDs, the differences have been non-significant, as reported for topiramate, gabapentin, vigabatrin [61], lacosamide [62], and eslicarbazepine [63]. In bipolar disorder, men treated with lamotrigine have reported to have better response than women [64].

Sex differences in adverse events mostly relate to sexual function and reproductive organs. In women, valproic acid has been associated with increased risk of polycystic ovary syndrome and ovulatory dysfunction [48]. In men, carbamazepine and phenytoin have been associated with reduced serum testosterone levels and reduced fertility [48]. However, there are also reports of sex differences in other types of adverse events. For example, women seem to be more prone to weight gain from valproic acid [65], and weight loss from topiramate [66] as compared to men. Men are associated with an increased risk visual fields defects from use of vigabatrin [67].

2.1.4 Other sociodemographic aspects in antiepileptic drug treatment

Children/adolescents and older people are patient groups requiring careful management and special considerations. These patient groups have in general been underrepresented in AED trials [68]. Prescribing in children is often based on extrapolation from adult data due to the lack of pediatric data. However, off-label use of medications in children can be problematic because such use is not shown to be effective and safe. Further, extrapolation of AED efficacy data from adults to children is not always possible since some seizure types are specific to children, such as infantile spams. For certain seizure types, extrapolations seems possible [69], and the U.S. Food and Drug Administration (FDA) have concluded that extrapolation of adult data to children 4 years and older with partial-onset seizures is acceptable [70]. The newer generation of AEDs seems to have better tolerability in children, although few studies in children have been conducted [71].

Extrapolation of adult data also occurs to the elderly, which may lead to uncertain effectiveness or unexpected adverse events [68]. Further, the elderly often has other comorbidities multiple different medications and thus the risk for drug-drug interactions needs to be considered when selecting an AED. Moreover, pharmacokinetics and pharmacodynamics of AEDs may be altered in the elderly, contributing to a higher risk of adverse events. The newer generation of AEDs have better tolerability and a lower risk of drug-drug interactions [72].

Access to neurologists and individual AEDs among epilepsy patients depends on where the place of living and on their sociodemographic status. Adult patients in Sweden were more likely to be treated by a neurologist if they were women, young, had high education, living in large cities, or had high income [73]. Children were more likely to be treated by a neuro-pediatrician if the children were aged 1-5 years, were living in large cities, or had rehabilitation needs [74]. In addition, prescribing of specific AEDs for young children require appropriate drug formulations.

2.1.5 Utilization patterns of antiepileptic drugs

Several epidemiological studies exploring AED utilization have been conducted in many countries worldwide. The overall prevalence of AED utilization, regardless of indication, ranges between 11-26/1000 inhabitants in adults [75-80], and around 4/1000 in children [81]. An increased AED use over time have been reported in several countries [75-80, 82]. Statistics from Sweden shows that the proportion of individuals who claimed a prescription of an AED increased from 1.5% to 2.5% between 2006 and 2017 [83]. However, based on the epidemiology of epilepsy, it seems unlikely that the use of AEDs has increased due to increased use in epilepsy. A few studies have investigated indication of use, showing that many AEDs have been increasingly prescribed for indications other than epilepsy, while the AED prevalence in epilepsy has been stable or decreased [75-80, 82]. The introduction of many new AEDs approved for non-epilepsy disorders have contributed to the increased use [75-80, 82].

2.1.5.1 Age and sex differences

A few population-based studies worldwide have described AED utilization by age and sex. Use of AEDs in children is mainly restricted to epilepsy [81, 82, 84], while adults use AEDs on non-epilepsy disorders to a higher extent (Table 2). Variations in indication patterns between countries could depend on differences in methodology, study periods, and assessment of indications. Use of newer AEDs has increased primarily in adults and elderly [75-77, 79, 83], although some studies report a slight increase in adolescents [84, 85].

Analyses of sex differences have often been sub-analyses, reporting varying patterns [76-79, 82, 84, 86] or restricted to only epilepsy patients [87-93]. Girls/women are more likely to use newer AEDs [76, 77, 79, 82, 84], which could be due to treatment of disorders more prevalent in girls/women, as well as to better safety and tolerability than older AEDs [94]. A decreased use of valproic acid in women in epilepsy have been seen over time [82, 90, 93, 95].

Table 2. Distribution of diagnoses for AED treatment in different countries.

Country and year	Age group	Epilepsy	Psychiatry	Pain	Migraine	Others
Italy (2003-2005) **[76]**	≥15	30%	17%	48%	(included in Others)	6%
Italy (2005-2011) **[77]**	≥15	24%	21%	51%	-	4%
Denmark (2002) **[78]**	All ages	55%	23%	22%	-	-
Taiwan (2007) **[79]**	All ages	32%	22%	26%	3%	17%
Norway (2007) **[80]**	All ages	71%	15%	13%	<1%	-
Norway (2012) **[82]**	All ages	47%	20%	30%	<1%	-
Colombia (2014) **[96]**	All ages	48%	14%	27%	12%	-

2.2 SEX AND GENDER DIFFERENCES IN HEALTHCARE

Men and women have different epidemiology, manifestation and pathophysiology for many conditions [2]. These conditions can be classified in three categories; (1) conditions unique to one sex, such as conditions associated with reproduction, (2) conditions with higher prevalence in one sex, such as migraine, (3) conditions with sex-specific pathophysiology, symptomatology, or treatment response, such as myocardial infarction and stroke [3].

Epidemiological studies have shown women to consume more primary care [97, 98] and utilize more prescription medications [99] than men, except in the youngest and oldest age groups. Sex differences persist despite adjustments for medications related to reproduction and sex-specific conditions [97-99]. Although men have lower life expectancy in most countries [100], paradoxically, epidemiological studies on healthcare consumption and treatment patterns points to a greater morbidity in women.

Sex and gender differences in drug utilization patterns are a result of multiple factors. Some differences may be related to differences in morbidity, mortality and age between men and women and are thus motivated, while some differences cannot be explained by medical reasons or sex-specific needs. Such findings raise concerns because it may indicate that prescribing decisions are influenced by patient characteristics unrelated to the clinical condition. Medically unmotivated differences can lead to incorrect diagnoses or lack of treatment response [101-103]. It has been postulated that sex differences in treatment patterns could be due to differences in healthcare seeking behavior [97, 98, 104] and that women have more contact with primary care [104-106]. Men's high-risk behavior and lower utilization of preventive health care may contribute to their higher mortality rate [107] and thus increased need for more demanding specialist care [97]. Other potential explanations involve differences in physician's practice styles [108], communication skills [109], and interpretation of men's and women's symptoms [110]. A better understanding of the underlying reasons to observed differences in drug utilization is necessary to prevent unwarranted underuse or overuse of medications in both men and women [111].

Men and women may react different to medications. Sex differences in efficacy and safety of medications have been described with examples from several pharmacological classes [112]. Differences in organ size, proportion body fat, hormone levels, enzyme activity etcetera can influence the pharmacokinetics and pharmacodynamics of medications and result in different effects in men and women [113]. Moreover, adverse drug events are more reported in women than men [114-116]. Reasons behind this can be pharmacokinetic sex differences leading women being overdosed, pharmacodynamic sex differences leading to women being more sensitive, or utilize more medications and thus having an increased risk of drug-drug interactions [113]. A review of withdrawn prescription drug products from the U.S. market between 1997 and 2000 concluded that eight out of ten withdrawn drugs posed greater health risks for women than for men. Four of these may had a higher use among women, and the other four had more adverse events in women even though they were widely prescribed to both men and women [117].

2.2.1 Sex and gender aspects in medical research

Women have historically been excluded from early Phase I and II trials for several reasons. After thalidomide was found to cause thousands of birth defects in the 1950s and 60s, FDA issued guidelines in 1977 that recommended excluding women of childbearing potential from participating in Phase I and early Phase II clinical trials until information on efficacy and safety had been assembled [118, 119]. However, this resulted in exclusion of women also in Phase III clinical trials which have caused knowledge gaps in the understanding of efficacy and safety of medications in women. In 1993, the National Institutes of Health (NIH) Revitalization Act issued guidelines requiring inclusion of women and minorities in government-funded clinical research [120] and FDA issued another guidance document specifying that participants in clinical trials should be representative of the patient population that is likely to be prescribed the medication after approval [121]. Both the FDA and EMA have issued regulation rules that states that new drug applications must present efficacy and safety data for demographic subgroups such as sex and age [122, 123].

Despite these regulatory policies, the impact of sex and gender on the efficacy of medications has in general been poorly investigated. Although sex is a fundamental aspect of human physiology and one of the most easy accessible biological variables, this essential variable is not systematically considered in preclinical research, and clinical research [3]. If patient's sex is not analyzed in early-phase clinical trials, there is a risk of missing important sex differences which can lead to withdrawal of medications.

Furthermore, despite participation of women in clinical studies, there have been a lack of analyses of efficacy to detect sex differences, as reflected by insufficient reporting of sex differences/similarities in published studies. This limits the ability to identify potentially important sex differences that may impact patient care. Some clinical disciplines address sex and gender differences in published studies to a higher extent, such as cardiology, endocrinology, and neurology [124].

Other sociodemographic variables, such as ethnicity and age, can interact with patient's sex and thereby confound studies. Sex and gender differences in pharmacokinetics may differ between ethnic groups [125, 126], and thus differences in ethnicity may mask potential sex-related effects from medications if ethnic background is not evaluated as a contributing factor. Further, access to healthcare is influenced by ethnicity [127] and economy level [128]. Response to medications in men and women can vary across the lifespan because pharmacokinetics and pharmacodynamics differ by age [126]. To complicate, there can be parts of both sex and gender in certain differences among men and women. Furthermore, unfortunately, researchers often use the term 'gender' incorrectly as a synonymous to 'sex' or vice versa [3].

2.2.2 Sex and gender aspects in treatment recommendations

Exploring how men and women react to medications is essential for optimizing treatment and increases the likelihood to identify medications that benefit both men and women [2]. This knowledge may help to create sex-specific treatment guidelines and dosing recommendations [103, 129, 130]. Despite the existence of sex and gender differences in efficacy and safety for some medications, there is a lack of incorporation of such information in drug labels and treatment guidelines. Most treatment guidelines do not consider sex and gender-related factors, not even well-investigated areas such as cardiology [2, 131].

Sex-specific dosing recommendations are rare. A FDA review of new drug applications between 1995 and 2000 found that even medications with significant pharmacokinetic differences between men and women had no sex-specific dosing recommendations included in the drug label [126]. Zolpidem, used to treat insomnia, is the only largely used medicinal product on the market for which FDA has suggested different doses based on sex. Early pharmacokinetic data showed higher zolpidem AUC (area under the curve) in women than in men, but did not warrant sex-specific dosing when approved by FDA in 1992 [130]. However, in 2013, after it was revealed that women have lower clearance and a higher risk of next-morning impairment, the FDA recommended a lower initial dose for women than men [132]. This example illustrate that it can take decades before noticing important differences in the outcomes among men and women and incorporate these in the drug label.

2.3 RATIONAL PRESCRIBING

Prescribing is one of the most important processes in modern healthcare and almost two thirds of all Swedish residents had been dispensed at least one prescribed medication in 2017 [133]. However, prescribing is complex and requires that physicians have skills, knowledge, and ability to formulate an appropriate treatment for their patients [1]. Further, prescribing can be particularly challenging in patients with extensive co-morbidity and many co-medications. This burden is exacerbated by a stream of information regarding treatment strategies from different sources that may or may not be helpful for prescribing decision. The large volume of information, sometimes of varying quality, can be overwhelming, and may cause physicians to rely on what they learned during training or from clinical experiences [134].

Rational use of medications requires that "patients receive medications appropriate to their clinical needs, in doses meeting their own individual requirements, for an adequate period of time and to the lowest costs to them and their community" [135]. That means prescribing of an appropriate medication on an appropriate indication in an appropriate dosage and duration. Many factors influence a rational prescribing, including prescriber factors, patient factors, medications factors [1]. Lack of knowledge and experience among prescribers are some of many underlying factors to irrational prescribing of medications [1]. Irrational prescribing of medications involves unmotivated polypharmacy, use of wrong or ineffective medications, and under- or overuse of effective medications. Consequently, this leads to ineffective and unsafe treatment [135].

To achieve rational prescribing, physicians are expected to back up their prescribing decisions with the best available evidence. One approach to promote rational prescribing of medications is by using evidence-based medicine, which aims at optimizing the decision-making process by integrating medical evidence, clinical experience, and patient factors [134]. However, it can be difficult for physicians to overview and incorporate all this information. The use of clinical decision support systems (CDSS) with underlying knowledge bases can facilitate the practice of evidence-based medicine [136]. A CDSS provide up-to-date pharmacological knowledge of recommended treatment for a specific patient at the time of prescribing, thus making it easier for physicians to make decisions about treatment. CDSS that are integrated into the electronic health record (EHR) will be readily adopted in the decision-making process. In Sweden, electronic CDSS have been available since 1990's to enable decisions on prescribing the right medication in the right dose for the individual patient. One such example is Janusmed Integrated (previously called Janus toolbar) [137, 138], a collection of knowledge bases of which some also are accessible via the web (www.janusmed.sll.se and www.janusinfo.se). Other strategies used to promote rational prescribing of medications are establishment of drug and therapeutic committees (DTCs), regulatory restrictions, educational interventions, and economic incentives [139].

3 AIMS

The overall aim of this thesis was to gain a better understanding on the use of antiepileptic drugs for different diagnoses in men and women and to explore physicians' perceptions of sex and gender in decision on drug prescribing.

Specific aims were:

I. To describe antiepileptic drug treatment in patients with newly diagnosed epilepsy or unprovoked seizures
II. To investigate the use of antiepileptic drugs on different diagnoses in boys and girls
III. To calculate trends of valproic acid utilization over time and examine the impact of a regulatory recommendations on restricting the prescription of valproic acid in girls and women of childbearing age
IV. To explore physicians' perceptions of sex and gender aspects in prescibing medications
V. To present concept, methods and use of a knowledge base providing sex-specific medical information to support drug prescribing

4 METHODS

This thesis includes five studies with various study designs, settings, and data sources. An overview of the methods used is presented in Table 3.

Table 3. Overview of the methods for Paper I-V.

Study	I	II	III	IV	V
Design	Cohort	Cross-sectional cohort	Cross-sectional cohort	Qualitative	Descriptive
Data sources	Stockholm Incidence Registry of Epilepsy, Swedish Prescribed Drug Register	Swedish Prescribed Drug Register, National Patient Register, Statistics Sweden	VAL database	Focus groups discussions	Published scientific literature
Setting	Northern Stockholm	Children and adolescents in Sweden	Stockholm County	Urban and non-urban areas in Sweden	n/a
Study period	2006-2008	2007-2014	2011-2017	2013-2014	2012-2016
Participants	367	18131	7402	29	n/a
Topic studied	Utilization of antiepileptic drugs in unprovoked seizures or epilepsy	Utilization of antiepileptic drugs on various indications	Effect of regulatory restrictions on the utilization of valproic acid		Information on sex and gender aspects for drugs
Analyses	Descriptive statistics	Descriptive statistics	Interrupted time series with a segmented logistic regression model	Thematic analyses	Descriptive statistics
Ethical approval	2008/507-31/2	2015/660-31	2015/660-31, 2016/517-32	2014/2161-31/5	n/a

4.1 PAPER I-III

4.1.1 Data sources

The data sources in Paper I-III comprised of Swedish national health registers and populations registers. Sweden has, as few countries in the world, the opportunity to study utilization of all medications prescribed to the Swedish population [140]. The registers use the unique personal identification number assigned to each Swedish resident which facilitate linking patient data between registers [141]. All data used in these studies were anonymized after record-linkage with no possibility of identifying individuals.

4.1.1.1 Swedish Prescribed Drug Register

The Swedish Prescribed Drug Register (SPDR) contains data for all dispensed prescriptions in Sweden since July 2005. Stored details include dispensed product and amounts, date of prescribing

and dispensing, the patient's sex and age, and the prescriber's profession and workplace. Included are medications prescribed in primary and specialized care, while over-the-counter (OTC) medications and medications used in inpatient care (hospitals) are not included. All medications are classified according to the Anatomical Therapeutic Chemical (ATC) classification system. The register is complete for the entire Swedish population (99.7%) [140]. Data from the SPDR was used in Paper I-III.

4.1.1.2 Stockholm Incidence Registry of Epilepsy

The Stockholm Incidence Registry of Epilepsy (SIRE) is a population based registry including all individuals with newly diagnosed unprovoked first seizures and epilepsy in Northern Stockholm [142]. The register is based on information from the medical records since 2001 and includes nearly 2000 individuals with a specific date of index seizure. The index seizure is the seizure that prompts the individuals to seek medical advice. Potential cases have been identified through multiple methods; medical record screening in specific hospital units (including outpatient clinics), network of health care professionals, emergency room services, and review of requests for electroencephalography (EEG). All potential cases have been classified based on all relevant information generated during the first six months after the index seizure. Each case has been classified as definite first unprovoked seizure or definite epilepsy. The SIRE is one of the largest population-based incident cohorts of newly diagnosed unprovoked seizures and epilepsy and is suitable for studies exploring comorbidities, risk factors and long-term follow-up of prognosis. Data from the SIRE was used in Paper I.

4.1.1.3 National Patient Register

The National Patient Register (NPR) contains data on diagnoses and surgical procedures recorded at hospitals in Sweden. Data on inpatient care is provided since 1987 and outpatient visits from both private and public caregivers since 2001. Diagnoses are coded according to the international classification of diseases (ICD) system. Diagnoses and procedures from primary care are not covered by the NPR. The NPR is well-validated and inpatient data have almost 100% coverage. The outpatient data, however, is estimated to have 80% coverage. All healthcare providers in Sweden, publicly and privately funded, are mandatory to deliver data to the NPR [143]. Data from the NPR was used in Paper II.

4.1.1.4 VAL

The administrative health register of the Stockholm region, Vårdanalysdatabasen (VAL) contains data for all residents in Stockholm. Diagnoses have been available for outpatient visits and hospitalization since 1993 and for primary care since 2003. Outpatient care in VAL are also covered in the NPR. Data on all prescription drugs dispensed by the Stockholm residents have been available since July 2010 and is also covered by the SPDR [144]. The data in VAL contains the same data as in SPDR and NPR. Data from VAL was used in Paper III.

4.1.1.5 Statistics Sweden

Statistics Sweden provide data on country of birth, educational level, and income of the residents in Sweden since 1985 [145]. Data on country of birth was used in Paper II.

4.1.2 Study designs and settings

4.1.2.1 Paper I

Patients with an index date between 1 January 2006 and 31 December 2008 were selected from the SIRE. The index date was considered as the date of inclusion in the study. Clinical data from the SIRE was linked to drug dispensing data in the SPDR. Patients who had been dispensed AED before index date were excluded from the analysis.

4.1.2.2 Paper II

Individuals aged 0-17 years with a first dispensed prescription of an AED (ATC code group N03) between 1 January 2007 and 31 December 2014 were selected from the SPDR. An incident case was defined as an individual with at least one AED prescription dispensed each year, without having the same ATC code dispensed during the preceding year. Thus, an incident case could be either an individual who was AED naïve or one who had switched from another AED between the study years. Data from the SPDR was linked to diagnosis data in NPR via the personal identification number to extract history of diagnoses prior to the first dispensing date of an AED.

Indications for prescription medications are not registered in the SPDR and therefore diagnoses associated with the approved indications for AEDs were identified for each individual in the NPR. A time window of 12 months prior to dispensing date was used to identify recorded diagnoses associated with the AED prescribing. This time window was considered sufficiently wide to include at least one healthcare consultation. Also, a prescription in Sweden is valid for 12 months after prescription date. Diagnoses were classified based on ICD-10 codes for the officially approved indications for AEDs in Sweden.

An indication hierarchy approach was used, inspired by an indication hierarchy exploring indications for statin prescribing [146]. Diagnoses in our indication hierarchy included in hierarchical order: 1) epilepsy; 2) unspecified convulsions; 3) psychiatric disorder; 4) pain disorder; 5) migraine; and 6) "others" excluding any of the indications 1-5 (Table 4). Individuals were assigned to the indication with the highest possible rank, for example if an individual had G40, F40, and M50 registered within 12 months prior dispensing date, the AED indication was classified as epilepsy, since this diagnosis had the highest rank in the hierarchy.

Table 4. Indication for antiepileptic drug utilization, according to a hierarchy of recorded diagnoses in register. *Reprinted from Paper II [147].*

Diagnoses in the indication hierarchy	ICD-10 codes	No recorded diagnosis of
1. Epilepsy	G40-41	
2. Unspecified convulsions	R25, R56, P90	1
3. Psychiatric disorder	F30-39, F40-48, F10, F55, F50, F60	1-2
4. Pain disorder	G50-59, G60-64, M79, G82, G95, G97.9, M50-54, M89, R20, R51-52, Z03.3	1-3
5. Migraine	G43-44	1-4
6. Other[1]		1-5

[1] Other diagnosis was assigned to individuals without any of the applied recorded diagnoses.

4.1.2.3 Paper III

Individuals with a first dispensed prescription of valproic acid (ATC code N03AG01) between 1 January 2011 and 30 June 2017 were selected from VAL. Incident use was defined as no dispensed prescription of valproic acid within the previous 365 days. Individuals were further stratified in two diagnostic groups: epilepsy (ICD-10 G40-41) and psychiatric conditions (ICD-10 F30-39, F40-48, F10, F55, F50, and F60).

4.1.3 Analyses

4.1.3.1 Paper I

We measured use of concomitant prescribed medications taken at the time of index seizure, defined as having a dispensed medication during 90 days' prior the day of inclusion (index date). Since the reimbursement regulations in Sweden allow a maximum quantity of prescribed medications to be dispensed each time that covers 90 days of consumption [148], this period prior to inclusion was applied to provide a good estimate of current use of prescribed medications, both for chronic and short-term treatment. The prevalence of dispensed medications in the study population at inclusion was compared with the prevalence of dispensing medications in the general population in Stockholm during 2008.

The number of days from inclusion to first dispensed prescription of an AED was calculated for each patient. Individuals with two or more AEDs prescription claims at the same date were handled separately. The cumulative proportion of individuals with a dispensed prescription of an AED within one year after inclusion was calculated. Dispensed AED prescriptions during the period 300-420 days after initial AED treatment were calculated for each individual to measure current use, switches and discontinuation.

Descriptive statistics, such as numbers and proportions, were used to describe the study cohort and utilization patterns, together with 95% confidence intervals (CI).

4.1.3.2 Paper II

Number and proportions of boys and girls newly initiated on specific AEDs was calculated for each study year and diagnostic group in the indication hierarchy. AED prevalence was calculated for each study year, defined as the number of individuals dispensed one or more AEDs in a particular year divided by the total number of individuals aged 0-17 years in the Swedish population in the same year. Sex-specific cumulative AED incidence was calculated for each study year, defined as the number of individuals initiated on AEDs in a particular year divided by the number of individuals aged 0-17 years in the Swedish population in the same year.

4.1.3.3 Paper III

Interrupted time series (ITS) analyses was used to measure change in number of valproic acid initiations after the EMA warning. The number of patients initiated on valproic acid was calculated for each month. For the analysis stratified by diagnosis, the number of patients were calculated each quarter due to insufficient number of initiations for an ITS analysis when calculating on a monthly interval. A segmented logistic regression model was used to calculate a trend (rate of change) in each segment in the time series. The model controls for baseline levels and trends, thereby estimating the

numbers of patients initiated on valproic acid if the EMA warning had not occurred [149]. The effect of the warning was determined after 1 month (level effect, "direct effect") and after 2 years.

4.2 PAPER IV

4.2.1 Study design, setting and data collection

In this qualitative study, focus groups discussions (FGDs) were conducted to explore perceptions and experiences of sex and gender in drug treatment. The informants were strategic recruited from five different health centers in different geographic areas in Sweden. Initially, three FGDs were conducted in an urban area of Sweden. The third FGD did not provide any new information, and thus two additional FGDs were carried out, in non-urban areas of Sweden, to conclude data collection. No additional information was obtained and thus saturation was assumed to be reached.

A semi-structured discussion guide with open-ended questions was used during the FGDs to provide insight about the GPs' perceptions and experiences of sex and gender differences in diagnosing and drug treatment. The discussion guide was pre-tested by one physician and two nurses, with the presence of a researcher member, to see if the questions had clear formulations and objectives and to secure that no question violating integrity was used. Based on this, the discussion guide was revised. Discussions were held between autumn 2012 and spring 2013 and lasted approximately 60 minutes. The FGDs were audio-recorded and transcribed word-by-word by the first author.

4.2.2 Analyses

Data were analyzed with thematic analysis with an inductive approach. Thematic analysis is a method for identifying, analyzing, and reporting patterns within data [150]. The analysis process was iterative, moving back and forth between different steps.

The analysis process was performed in six steps:

1) Transcripts and notes were listened to and read to get familiar with the material.
2) Parts of the transcripts relating to the research aim were extracted and grouped into two main categories; "Sex and gender aspects on patient visit" and "Patient's sex in relation to drug treatment". No predetermined categories were used.
3) The main categories were examined to identify patterns of meaning. Parts within each main category were grouped into preliminary subcategories.
4) Each preliminary subcategory were reviewed and redefined. Parts within each preliminary subcategory were grouped based on similarities and could be moved between old subcategories and new subcategories.
5) When a subcategory was established, it was given an informative label. Established subcategories were grouped into three categories.
6) Quotes were selected to illustrate the categories. Translation of qoutes to English was done by the research members. Cross-translation of quotes back to Swedish was done by a native English speaking person to ensure that the sense in the content wasn't changed in the translation.

4.3 PAPER V

4.3.1 Working procedure

In 2011, the development of a knowledge base for drug prescribing and dose recommendations considering sex-specific needs was initiated. The primary objective was to provide a national resource with sex-specific medical information and to provide prescribers with updated available knowledge at point of prescription. The main goal is to achieve a rational and safe drug treatment, thereby reducing the risk of inappropriate prescribing related to the patient's sex. The development of *Janusmed Sex and Gender* follow a concept developed for pharmacological knowledge bases [151]. The flow diagram (Fig. 2) shows the working procedure and is described in details below.

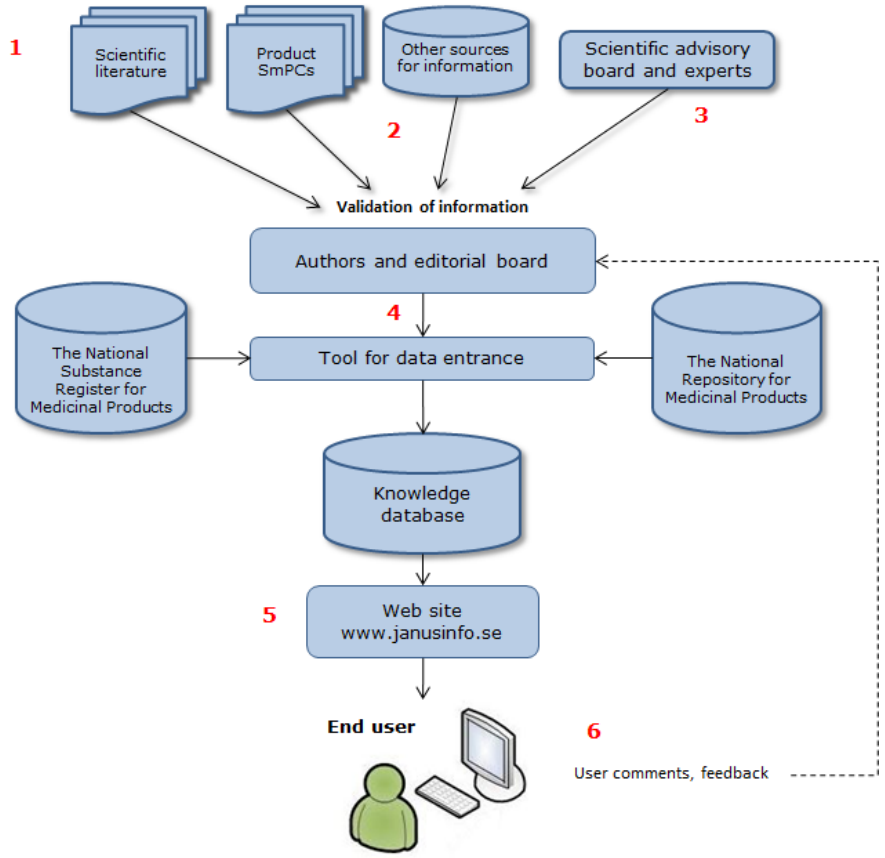

Figure 2. Workflow for producing and maintaining the knowledge base Janusmed Sex and Gender (modified from Nörby et al [152]). *Reprinted from Paper V [153].*

(1) Systematic structured literature searches are performed in PubMed using combinations of the following search terms: "gender", "sex", "sex factors", "sex differences", "gender differences", "female", "male", "women", "men" combined with individual substance names. Publications relevant to the topic are selected, based on analyses of titles and abstracts, and their full-text are read. Publications considered for inclusion are those reporting results regarding any of the following aspects: pharmacokinetics, dosing, effects, and adverse effects. We exclude reporting results from case reports, letters, non-full text articles, withdrawn studies, trials on animals, and studies including only one sex.

(2) In some cases, additional information is collected from reference textbooks, summary of product characteristics, and clinical review sections of new drug approval packages. For each substance, information on number of men and women with a dispensed prescription in the last year is extracted from the Statistical Database on Pharmaceuticals held by the Swedish National Board of Health and Welfare.

Relevant information generated by the literature searches are summarized for each substance into a text document. All documents are structured in the same way: (i) Summary with general recommendations; (ii) "Additional information" containing detailed information on pharmacokinetics and dosing, effects, and adverse effects. For some substances, information on potential for teratogenicity and drug-drug interactions with sex hormones are also presented; (iii) "Reference list" with all references to presented information and linkage to PubMed. Data on number of men and women with the dispensed prescription medication is available for users on the Swedish version.

(3) Each text document is reviewed by clinical experts in gender medicine, clinical pharmacology, neurology, cardiology and pharmacy. Other experts are consulted when needed, such as representatives from the regional DTC, the Swedish Medical Products Agency, FDA or the pharmaceutical drug company marketing the product. The substances are classified in the categories A, B, C and C! based on the amount of evidence found in the literature searches.

(4) The text documents are stored in an electronic database and linked to The National Substance Register and The National Repository for Medical Products covering all medications in Sweden. Linkage is enabled by using the unique substance identifiers number (NSL-id) and ATC codes. This makes it possible to exclude medications containing the same substances but with different formulations. The editorial tool also uses The National Repository for Medicinal Products to detect new products entering the Swedish market for linkage to the text documents and identifying changed or missing ATC codes.

(5) The knowledge base is distributed on a producer independent site of the DTC in Stockholm County Council (www.janusinfo.se).

4.3.2 Analyses

User frequency is evaluated regularly via a statistical function in the editorial tool. The total number of searches and opened documents can be identified. The geographical distribution of the users can be identified via Google Analytics.

User satisfaction of the knowledge base was evaluated in a pop-up-questionnaire on the Swedish start page for *Janusmed Sex and Gender*. The survey was carried between October 19 and December 20 in 2015.

4.4 ETHICAL CONSIDERATIONS

Paper I-III are based on register data. Register-based research can be conducted without informed consent from the patients. The ethical issues concerning register-based research relates to the balance between the patient integrity and the use of their personal data, as well as the benefits that can be achieved by effectively use the recorded data. The sensation of privacy intrusion should obviously be considered, but are minimized due to the anonymized register data. Personal integrity in this case is about a right to not be a subject for damage by data dissemination. Register-based research is also covered by large legal frameworks, such as The Law on Health Data Registers, The Swedish Personal Data Act and The Swedish Patient Data Act. All individuals in Sweden may receive an annual copy of all their recorded data. In order to use personal health data for research in Sweden, an ethical approval is required. Ethical approvals were applied for Paper I-III and granted by the Regional Ethical Review Board in Stockholm (Dnr 2008/507-31/2, 2015/660-31, 2016/517-32).

The registers used for Paper I-III includes individual data including data on patient's sex, age, place of residence, workplace codes, the prescriber's specialty etc. The SIRE also includes data of seizure type and date of index seizure. The information in the SIRE is retrieved from electronic medical records and not through individual questioning. Individual information is not provided to patients but the information is given orally in connection to the reporting and information is posted on the clinics where the patients are treated. The information given is the aims of a healthcare register and that all data records are handled confidential.

The data in the registers are managed and collected at group level. Personal identification numbers are decoded (anonymized) at the extraction by the National Board of Health and Welfare, and individuals can therefore not be identified. Thus, individuals in the registries can not suffer any direct harm from the use of anonymized data. In this project, already existing registers were cross-linked which means no direct patient contact. A direct patient contact to obtain individual informed consent to compile already existing information from various register would mean a risk of creating undue concerns for future health risks and contribute to stigmatization – which is particularly important to avoid for patients with epilepsy or an epileptic seizure. A direct contact with these patients could therefore pose a risk for damage. Another ethical aspect is the handling of the data. The records provided by the National Board of Health and Welfare are covered by confidentiality. Outpatient and inpatient care (not primary care) have statutory duty to provide data to the NPR. The quality of the data is checked regularly. The annual underreporting is estimated to be less than 1% according to the National Board of Health and Welfare, however this is nothing our research group can influence, and we can only assume that the reporting is accurate and that the National Board of Health and Welfare has adequate technical safety precautions for the data storage.

Paper IV did not meet the requirements for an formal ethical approval according to The Swedish Ethical Review Act [154]. Nevertheless, an ethical approval was applied for and granted by the Regional Ethical Review Board in Stockholm (Dnr 2014/2161-31/5). Furthermore, informed consent was given in multiple steps to all participants, both written and orally, about the study's purpose and what the results would be used for, about the focus group discussion, and that participation was voluntary and that they could withdraw their participation at any time.

Paper V is based on information from scientific papers collected in a knowledge database, without any individual data and therefore no ethical approval was required.

5 RESULTS

5.1 PAPER I-III

An overview of the characteristics of the study populations in Paper I-III are presented in Table 5.

Table 5. Overview of the study populations' characteristics in Paper I-III.

	Paper I	**Paper II**	**Paper III**
Study population	367	18 131	7402
Girls/women (%)	44.4	50.0	49.2
Mean age (years)	33.6	9.5	41.3
Diagnosis (%)	Epilepsy: 65.9 Single seizures: 34.1	Epilepsy: 46.1 Convulsions: 13.6 Psychiatric diagnosis: 10.7 Pain: 5.6 Migraine: 1.0 Other: 23	Epilepsy: 24.9 Epilepsy + psychiatric diagnosis: 4.5 Psychiatry: 43.9 Other: 26.7

5.1.1 Indications for antiepileptic drug treatment in children and adolescents

The total use of AEDs in epilepsy accounted for 68% of the total AED use in 2014 (Paper II). Among those initiated on AEDs had 49% of the boys and 44% of the girls an epilepsy diagnosis. Other common diagnosis were unspecified convulsions (14%) and psychiatric conditions (11%) (Table 5). Epilepsy and migraine were more common in boys, while psychiatric and pain disorders were more common in girls. However, diagnoses associated with the approved indications were only recorded for 77%.

5.1.2 First antiepileptic drug in epilepsy

During the first year after seizure onset, the majority of patients in Paper I (71%) had received their first AED. No major sex differences were seen. Half of the study population had dispensed an AED by day 75. Overall, the most commonly used AED was carbamazepine, both in men (40%) and women (40%). More men than women utilized valproic acid (27% vs. 17%), while more women than men utilized lamotrigine (17% vs. 9%). Use of oxcarbazepine, vigabatrin and phenobarbital were mainly restricted to children, while use of levetiracetam and phenytoin was restricted to adults and the elderly.

In children and adolescents with a recorded diagnosis of epilepsy (Paper II), the total utilization of AEDs increased slightly between 2007 and 2014. Overall, valproic acid was the main AED initiated in boys (31%). Girls received lamotrigine to a higher extent than valproic acid (27% and 23%, respectively) (Fig. 3).

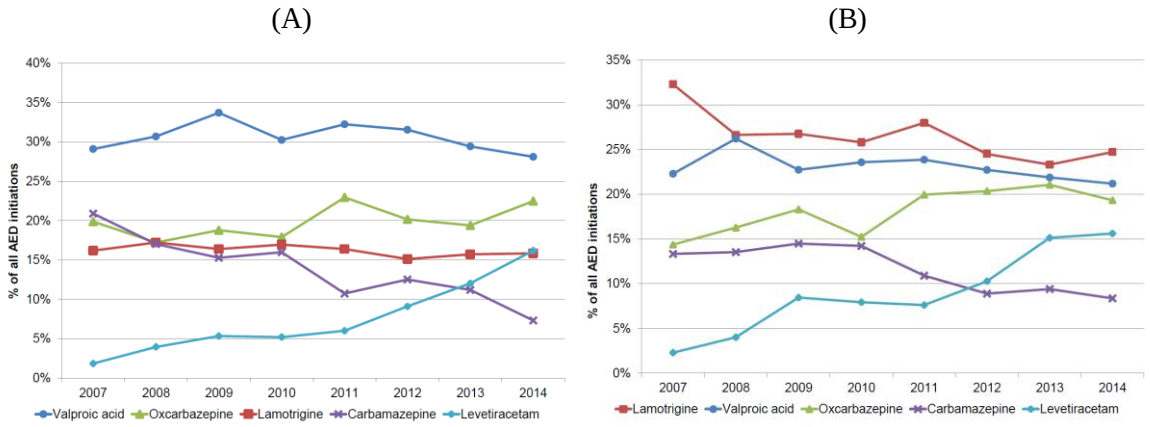

Figure 3. Initiations of the most common AEDs in boys (A) and girls (B) with epilepsy 2007-2014. *Reprinted from Paper II [147].*

5.1.2.1 Utilization of non-antiepileptic drugs at time of epileptic seizure onset

Nearly half of the patients in Paper I (51%) had claimed other prescription medications at the time of seizure onset, especially the elderly and particularly women. Women utilized more medications than men in all age groups above 16 years. The mean number of concomitant medications increased with age in both men and women (0-15 years: 2.2 for boys, 1.6 for girls; 16-49 years: 3.7 for men, 3.9 for women; 50-64 years: 4.7 for men, 5.3 for women; ≥65 years: 4.7 for men, 5.3 for women). Women were more likely than men to have a concurrent prescription for an antidepressant (N06A), antipsychotic (N05A), or analgesic (N02A, N02B).

5.1.3 First antiepileptic drug in non-epilepsy disorders

The number of new AED prescriptions in psychiatry increased slightly during the study period. Lamotrigine was the mainly initiated AED in both girls and boys (77% and 55%, respectively). Valproic acid was used to a larger extent in boys (27%) as compared to girls (Fig. 4).

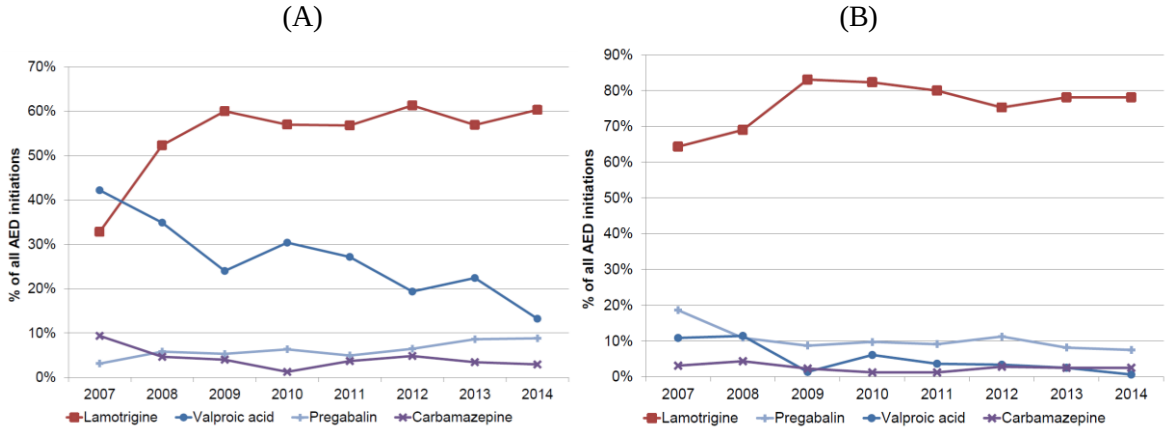

Figure 4. Initiations of the most common AEDs in boys (A) and girls (B) with psychiatric disorders 2007-2014. *Reprinted from Paper II [147].*

In pain disorders, the number of new prescriptions increased and to a larger extent in girls than in boys. The use of gabapentin increased during the study period. In 2007, gabapentin was the most initiated AED in girls (30%) and lamotrigine in boys (27%). In 2014, gabapentin was most common

in both girls and boys (47% and 23%, respectively). In migraine, topiramate was the main AED used in both boys and girls (52% and 58%, respectively).

5.1.4 Changes in AED treatment

In the cohort of epilepsy patients (Paper I), more than half remained on their initial AED by the end of the first year after their first AED utilization (57% of men and 56% of women). Almost 70% of the children remained on their initial AED. Men were more likely than women to switch to other AEDs (20% vs. 16%), while women were more likely than men to discontinue AED treatment (17% vs. 13%). Among women receiving valproic acid, a third (6/20, 30%) had switched to another AED or discontinued treatment.

5.1.5 Valproic acid utilization patterns

Valproic acid was the main AEDs initiated in boys with epilepsy (31%), and the second most initiated in girls with epilepsy (23%) (Paper II). Overall, 27% of the all valproic acid initiations in girls were issued to those without epilepsy or convulsions and 4% of these were for psychiatric diagnoses. No large change in the number of utilized valproic acid initiations was observed in boys and girls with epilepsy during the years 2007-2014. However, a decrease was observed in boys and girls with a psychiatric disorder.

Changes in valproic acid initiations were analyzed specifically in Paper III. Between 2011 and June 2017, a decrease in the total number of valproic acid prescriptions initiated in Stockholm was observed. Before the regulatory restrictions from EMA were issued in November 2014, slightly more females than males (2293 vs. 2198) were initiated on valproic acid, while the opposite occurred after the restrictions (1300 vs. 1516).

When restricting the analysis to epilepsy patients only, a decline in valproic acid initiations were seen before the regulatory warning in both men and women (Fig. 5). No significant changes were seen after the warning, neither in men nor women (Table 6). In patients with a psychiatric disorder only, an increase of valproic acid initiations was seen before the EMA restrictions (Fig. 6). However, after the warning, a significant decrease was observed in females 0-45 years of age. No significant changes were seen for males in the same age group (Table 6).

Table 6. Associations between the EMA warning and change in total number of valproic acid initiations. *Reprinted from Paper III [155].*

	Trend change (n)	Level effect (n)	Effect after 2 years (n)
All	0.03 (p = 0.91)	-6.06 (p = 0.29)	-5.39 (p = 0.45)
Women	-0.12 (p = 0.50)	-4.95 (p = 0.16)	-7.55 (p = 0.09)
Men	0.15 (p = 0.43)	-1.11 (p = 0.77)	2.16 (p = 0.65)
Females 0-45 years of age	-0.22 (p = 0.09)	-3.78 (p = 0.15)	-8.57 (p = 0.01) **
Males 0-45 years of age	0.00 (p = 1.00)	-1.29 (p = 0.66)	-1.29 (p = 0.72)
Females 0-45 of age with epilepsy only	0.54 (p = 0.42)	-1.45 (p = 0.75)	2.35 (p = 0.69)
Females 0-45 of age with psychiatric disorder only	-1.85 (p = 0.05) *	-9.01 (p = 0.15)	-21.96 (p = 0.01) **
Males 0-45 years of age with epilepsy only	0.90 (p = 0.27)	4.71 (p = 0.39)	11.00 (p = 0.12)
Males 0-45 years of age with psychiatric disorder only	0.60 (p = 0.49)	-10.17 (p =0.09)	-6.00 (p = 0.42)

*p < 0.05. **p < 0.01.

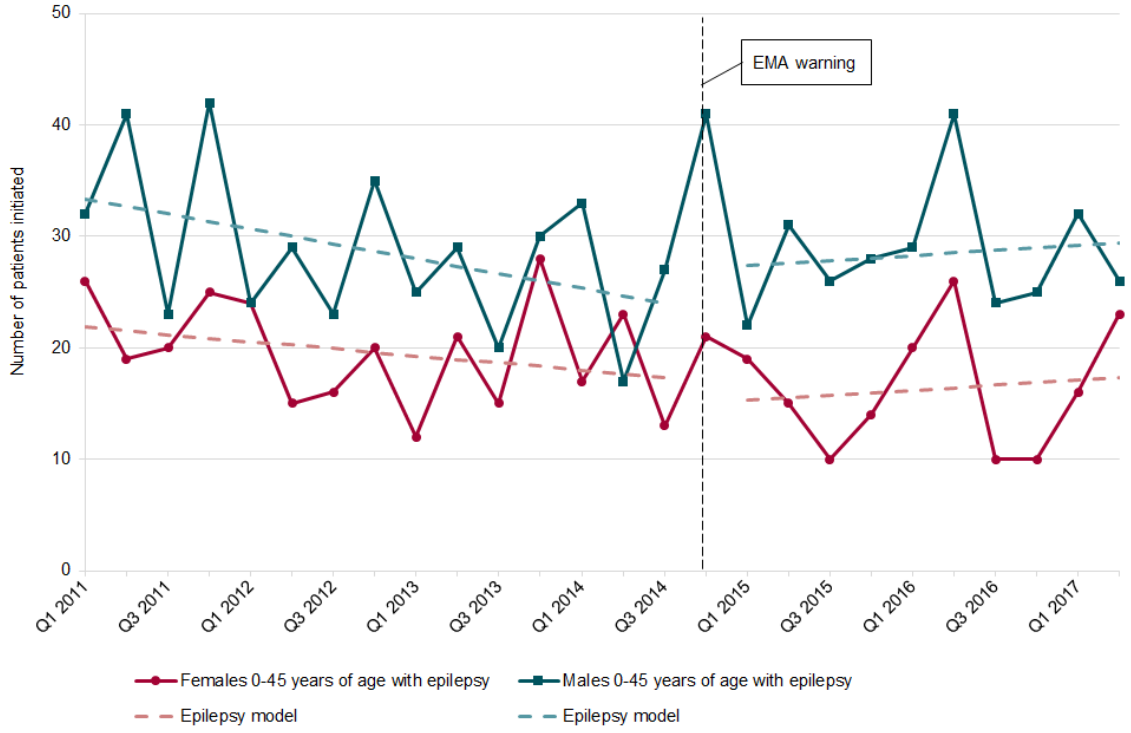

Figure 5. Patterns of valproic acid initiations in boys/men and girls/women 0-45 years of age diagnosed with epilepsy. *Reprinted from Paper III [155].*

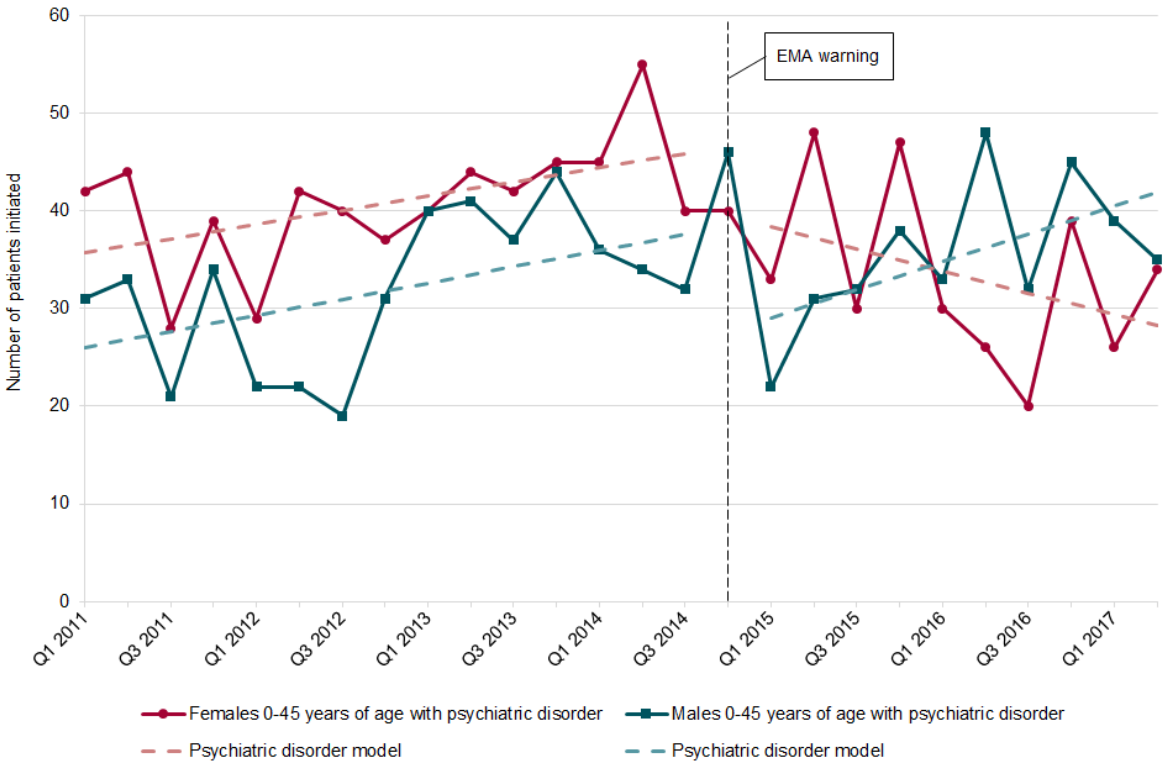

Figure 6. Patterns of valproic acid initiations in boys/men and girls/women 0-45 years of age diagnosed with psychiatric disorder. *Reprinted from Paper III [155].*

5.2 PAPER IV

In total 29 physicians participated in the five FGDs. Most participating physicians were specialists in family medicine, but there were also interns and resident physicians (Table 7). For simplicity reasons, all physicians who participated in the FGDs are referred to as GPs in this thesis.

Table 7. Characteristics of the physicians participating in the focus group discussions. *Reprinted from Paper IV [156].*

Characteristics	N	%
Sex		
Male	12	41
Female	17	59
Age		
20-29	1	3
30-39	6	21
40-49	7	24
50-59	8	28
60-69	5	17
70+	1	3
Unknown	1	3
Position		
Specialist in family medicine	19	66
Resident	4	14
Intern/Rotation	4	14
Specialist in internal medicine/cardiology	2	7

The thematic analysis resulted in three main categories (Table 8) presented in more details below.

Table 8. Overview of the results from the focus group discussions; main categories and subcategories. *Reprinted from Paper IV [156].*

Main categories	Subcategories
Experience of sex and gender differences in diagnosing and assessment of clinical findings	Sex differences in symptomatology, diseases and morbidity
	GPs' views on different health care seeking behavior in men and women
	Influence of sex on the interaction between GP and patient
Medical treatment in men and women	Making treatment decisions
	GPs' views on patients' attitudes to medications
	Adverse drug reactions in men and women
Knowledge of sex differences in drug therapy	GPs' expressed knowledge
	GPs' expressed ignorance

5.2.1 Experience of sex and gender differences in diagnosing and assessment of clinical findings

The first main category emphasized the physicians' experiences of sex differences in health care seeking behavior, management and morbidity. This category also included how the physician's and patient's sex influenced the physician-patient relation. The physicians stated that disease presentation and symptoms may differ between men and women, and therefore the patient's sex does affect how they examine, decide on diagnosis and consider treatment.

Further, women were believed do have a lower threshold for seeking healthcare. One suggested explanation was that women are more used to have contact with healthcare because they take a greater responsibility for the entire family's health. Another explanation was that there are more screening programs for women, which increases the contacts with healthcare (Example 1).

Example 1. Reprinted from Paper IV [156, p4].

> *Men are big and strong and have a higher threshold to seek health care. I can imagine that there are differences. But it is nothing that we possibly can affect that much.* (Female13 FGD3)

5.2.2 Medical treatment in men and women

The second main category emphasized the physicians' views on sex and gender aspects relating to the choice of medications to prescribe. Patient's sex was not taken into account when deciding on type of medical therapy (Example 2). Individual factors such as personality were believed to have a larger impact than the patient's sex. Examples where treatment decision was affected by the patient's sex were mentioned, such as treatment of depressive disorders and prescribing of painkillers.

Example 2. Reprinted from Paper IV [156, p5].

> *If I diagnose two patients, a man and a woman, they will get the same treatment regardless of sex. On condition that everything is consistent. But on the road to a diagnosis I might have missed that the woman is little different, or the man is little different, if you know what I mean. When I have come to the conclusion that I should treat someone for a specific disease then the sex is not relevant.* (Male1 FGD1)

In general, the choice of drug followed the recommendations from the regional Drug and Therapeutics Committee to a great extent as they were believed to be evidence-based and sex neutral. In general, they said they used the same drug doses in men and women, although some physicians said they prescribed lower doses of certain medications to women, especially older women, to reduce the risk of adverse events (Example 3).

Example 3. Reprinted from from Paper IV [156, p6].

> *Doses, for example, you might not use as high doses to a woman as to a man, especially if they are elderly. I think women get more adverse effects, statistically speaking, and that is often a matter of dosage.* (Female17 FGD5)

5.2.3 Knowledge of sex differences in drug therapy

The third main category reflected the physicians' knowledge and ignorance about sex differences. The physicians assumed that medications will help equally in men and women. They reasoned; if there were important differences between men and women in adverse events, this would have been noted and treatment recommendations changed accordingly. Since they said they treated men and women in the same way, there could not be any major differences. Thus, if there were known large sex differences they would treat differently. The GPs expressed a need of more knowledge about sex differences in pharmacological treatment (Example 4).

Example 4. Reprinted from Paper IV [156, p7].

> *It is exactly at the moment of prescribing you decide on what kind of medication to choose, regardless if the patient is a man or a woman. I think we [GPs] in general have rather poor knowledge, it's not just me, I think everyone has. And many drugs are not studied in both men and women. In those cases where I know that there may be sex differences I try to take it into consideration.* (Female17 FGD5)

5.3 PAPER V

The knowledge base *Janusmed Sex and Gender* is available both in Swedish and English on the Swedish website Janusinfo (http://www.janusinfo.se), an independent site from the DTC in Stockholm County Council. Information for individual medicinal substances are presented in separate documents (Fig. 7). It is possible to search on substance name, ATC code or product name on the Swedish market. To date, *Janusmed Sex and Gender* contains information on around 300 medicinal substances within several therapeutic areas, covering almost 70% of the medications recommended by the regional DTC. Substances generating the most number of searches in 2016 were codeine, paracetamol, and ibuprofen. Other commonly searched substances were sertraline, methylphenidate and zolpidem.

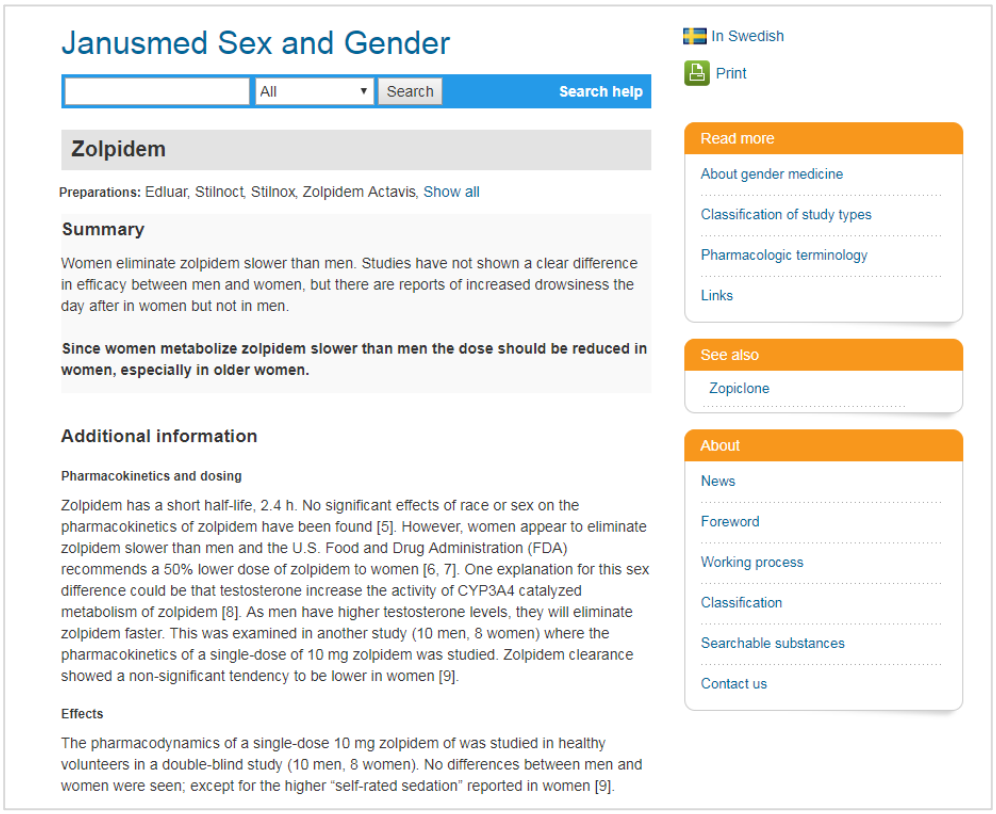

Figure 7. Example of a text document from the knowledge base Janusmed Sex and Gender. *Reprinted from Paper V [153].*

Nearly half of the substances evaluated belong to classification category A, '*No clinical relevant sex differences*' (Figure 8). Data on sex- and gender-related information are lacking for a third of the substances (class B). That is, available published studies are lacking sex-specific or gender-specific analyses, i.e. the influence of patient's sex and/or gender on the outcome have not been investigated, or have not stratified the results by patient's sex. Finally, clinically relevant sex differences needing consideration have been found for 15% of the substances (class C and C!). The distribution of AEDs among the classification categories shows that information on clinically relevant sex differences are published for 44% of the AEDs included in the knowledge base (Fig. 9).

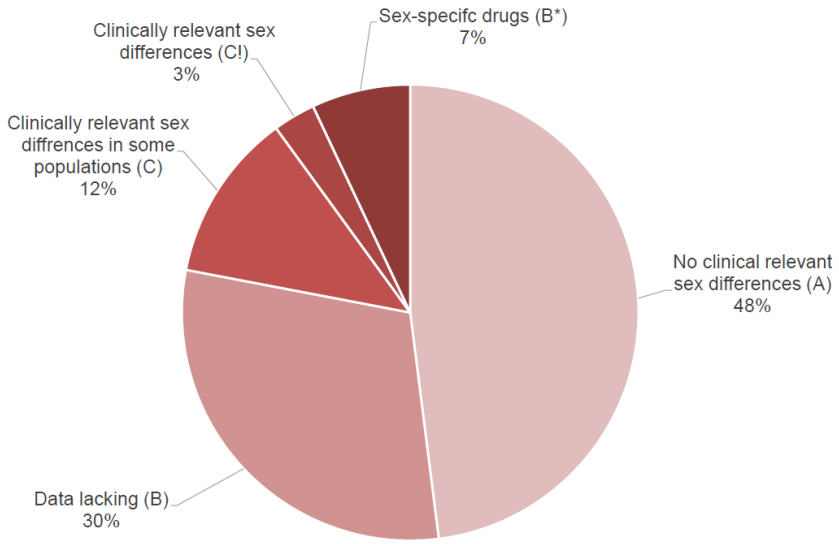

Figure 8. Distribution of classification categories among substances included in Janusmed Sex and Gender. *Reprinted from Paper V [153].*

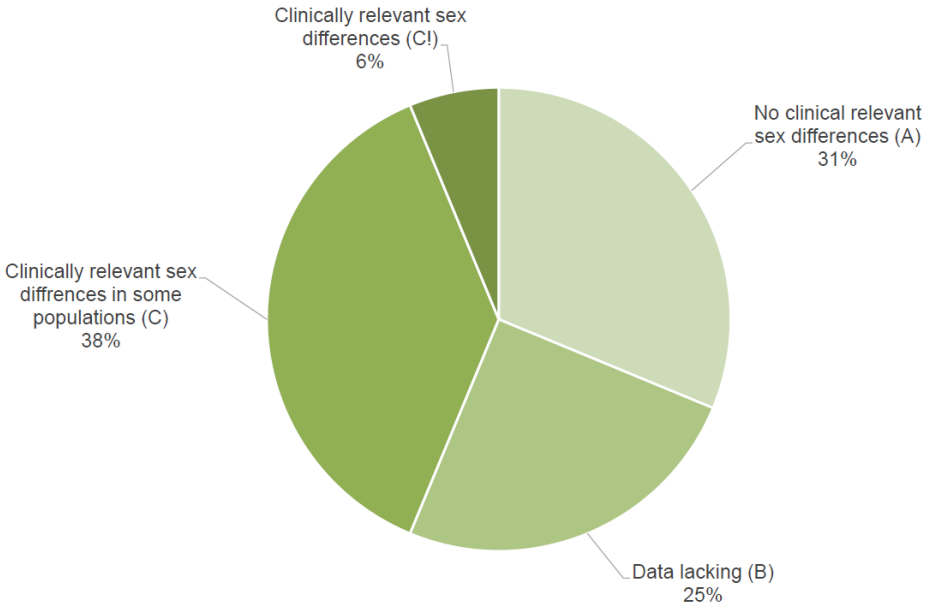

Figure 9. Distribution of classification categories among antiepileptic drugs included in Janusmed Sex and Gender.

Users of the knowledge base are located across Sweden, where the major part of the users is from outside Stockholm. Approximately 6% of the users are from outside Sweden. The main users in Sweden are pharmacists, resident physicians, and nurses. In a pop-up questionnaire including answers from 50 users (80% women), 65% replied that they were willing to recommend it to a friend or colleague. However, 38% did not know the existence of the knowledge base before answering the questionnaire. Overall, users stated that the knowledge base was easy to use (average score 6.07 on a scale 1-7) and contained trustworthy information (average score 5.33). Results from other parameters are shown in Table 9.

Table 9. Users' perception about Janusmed Sex and Gender.
Reprinted from Paper V [153].

Statement: **"The knowledge base *Janusmed Sex and Gender*…"**	**Average score (1–7)**	**Number of responders**
"...is supportive in practicing my profession."	4.71	14
"…provided me with knowledge."	5.06	17
"...will help increasing patient safety."	5.71	14
"…gave me insights and thoughts on gender-aware prescribing."	5.11	14

6 DISCUSSION

6.1 MAIN FINDINGS

This thesis provides information about AED treatment in patients with different diagnosis, with focus on sex and gender differences, as well as physician's perceptions on sex and gender in decision on drug prescribing.

First, I analyzed utilization of AEDs in epilepsy and in other conditions, asking the question **"How are AEDs used?"**. Paper I-III revealed clearly age and sex differences in the initiations of certain AEDs on different diagnoses. Boys/men were more often treated with valproic acid while girls/women were more often treated with lamotrigine regardless of diagnosis, although use of valproic acid in girls/women with epilepsy and psychiatric disorder was relatively high. Despite the large number of available AEDs approved for epilepsy treatment, most patients newly diagnosed with epilepsy remained on their first initiated AED after one year. One particular finding is that the effect of the EMA warning on the prescribing of valproic acid differed depending on the patient diagnosis. Our data show that valproic acid initiations decreased in women with a psychiatric disorder, while there were no significant changes in valproic acid initiations in women with epilepsy.

Next, I addressed the question **"Do prescribers consider patient's sex in drug treatment?"** by using a qualitative approach. A discrepancy between the GPs perceived knowledge of sex and gender aspects in drug treatment and their expressed knowledge and clinical experience was found. Another important finding was that they believed the lists of recommended essential medications already had considered patient's sex. Further, it seemed that some GPs based their drug decisions on stereotypical perceptions of men and women.

Finally, I attempted to answer the question **"How can prescribing be improved, taking the patient's sex into account?"** by describing the development of a knowledge base providing evidence of sex and gender aspects for individual drugs, which aims to support prescribing decisions in clinical practice. Results from previous research gave us reason to believe that physicians need more knowledge about this topic, and thus we decided to develop this knowledge base. Finding reliable information on relevant sex differences can be difficult and this comprehensive knowledge base offers a valuable source.

6.2 ANTIEPILEPTIC DRUG UTILIZATION ON DIFFERENT DIAGNOSES

Most children and adolescents utilizing AEDs had an epilepsy diagnosis, which corroborates findings from other countries [79, 81, 84]. This finding was expected since AEDs have few approved indications in this age group. Also, other conditions AEDs are used for, such as bipolar disorder and neuropathic pain are less prevalent in children [9, 19, 23, 34, 79]. Further, the evidence for use of AEDs in these conditions in children is low [9]. However, almost half of the AED-initiated children and adolescents did not have an epilepsy diagnosis, which also have been seen in a Swedish nationwide study including all ages [157].

AED users with epilepsy were more likely to be boys, while users with a psychiatric diagnosis or pain diagnosis were more likely to be girls. These sex differences reflect the differences in prevalence of the conditions between males and females as described earlier [20, 23, 24, 30, 34, 158]. The proportion with a psychiatric diagnosis in our study was a bit lower than seen in the Netherlands [81]. If this reflects other prescription patterns, other diagnoses recording or other epidemiology is not clear.

Almost one fifth of the children and adolescents had no diagnosis associated with the approved indications. We lack information if this was due to inadequate recording of these diagnoses, off-label prescribing, or diagnoses recorded in primary care and thus not available to us. In Sweden, treatment of children with epilepsy is normally managed by neuropediatricians or pediatricians. Children with psychiatric disorder are often initiated on treatment by specialists in psychiatry, but can thereafter be managed in primary care. Children with pain disorder are, if not severe, often only managed in primary care. Among adults, neurologists commonly initiate AED treatment for epilepsy and the subsequent prescribing may then sometimes be continued by GPs. Several nationwide studies have reported an increased prescribing of AEDs in primary care [75, 76, 89, 90, 92]. Our data showed that the overall initiations of AED treatment increased slightly in children and adolescents, regardless of diagnosis. Based on the epidemiology of epilepsy in children with decreased incidence in the 1990s [159], the increased AED use does not seem to be explained by an increased use in epilepsy.

6.2.1 Age and sex differences

Some age- and sex-related differences in utilization patterns were identified. Girls and women were more likely to receive treatment with lamotrigine, while boys and men were more likely to receive treatment with valproic acid. Similar findings have been reported in a Swedish nationwide study in children with epilepsy [74] and probably reflect the teratogenic effect and reproductive-related adverse events associated with valproic acid as compared to lamotrigine [160]. The age-related differences in use of individual AEDs might reflect age-dependent differences in prevalence of epileptic seizures.

Although valproic acid is not recommended for use in women of childbearing age, the use of valproic acid in girls and women with epilepsy were relatively high as compared to men with epilepsy. Valproic acid is the most effective treatment for some types of epilepsy and can be the only effective medication for some women [161]. This might to some extent explain the relatively high use of valproic acid in girls and women.

The AEDs utilization patterns in non-epilepsy disorders among children and adolescents revealed that certain AEDs are used off-label, such as lamotrigine in psychiatric disorder and gabapentin in pain disorder. Off-label use can be problematic because such use has not shown to be effective and safe.

6.3 PRESCRIBING DECISIONS

Given the large number of available AEDs, decision on prescribing an appropriate AED for epilepsy patients can be difficult. Available therapeutic guidelines from leading neurological associations do not cover complex patient profiles with comorbidities [162-164]. The physician must consider both patient factors and AED factors. Decision on AED treatment may also be complicated since patients use other medications (Paper I). Our data confirm that use of multiple prescription medications are common in patients with epilepsy, in particularly elderly women but also in younger men and women, and more frequently than the general population. Therefore, the risk for potential drug-drug interactions does not only concern the elderly.

Medications used for other conditions may complicate the management of comorbid disorders, particularly cardiovascular diseases and psychiatric disorders (Paper I). Some of these reflect known etiologies for epilepsy, such as stroke and dementia. Others are likely to be related to comorbidities such as depression, psychosis, and anxiety disorders [165]. The prevalence of many prescribed pharmacological classes was higher among the study population than in the general population. This probably reflect the higher prevalence of chronic conditions in people with epilepsy as compared to the general population [166]. However, utilization data from an age- and sex-matched control group would provide more precision on the prescription prevalence.

Potential pharmacokinetic and pharmacodynamic drug-drug interactions between AEDs and medications used for other conditions needs to be considered when finding the optimal AED for the patient, together with other patient-factors and AED-factors. Some of the observed switches and discontinuation of AEDs during the first year might to some extent be related to drug-drug interactions, although we lack information on reasons for switching. Nevertheless, the fairly frequent switchers and discontinuations, especially in women, highlight the importance of selecting an appropriate first AED for these patients. Previous research suggest that men are more likely to achieve seizure-freedom from the initial AED [167], but the underlying reason to this has not been investigated.

6.3.1 Sex and gender aspects

GPs in primary care considered patient's sex and gender during diagnosing and decision to treat or not. However, once the decision to treat was made, choice of medication followed the recommendations lists of essential medications issued by the regional Drug and Therapeutics Committee. The GPs assumed that these recommendation lists already had taken patient's sex into account and therefore they did not have to consider patient's sex when selecting medication to prescribe. These recommendations lists have high impact on prescribing patterns [168-170] and the GPs in our study believed these recommendations must be followed. Nevertheless, given the fact that the overall drug utilization patterns differ between men and women, although prescribed treatment are said to be equal – this discrepancy might indicate that GPs prescribing decisions are influenced by patient's sex and gender and stereotypes.

The belief among GPs that women consult more primary care is in line with both national and international studies [97, 98, 171]. The GPs in our study emphasized that this could possibly be due to women's more frequent contact with healthcare through family members and screening programs, which also was discussed in study from the U.S. [171].

6.3.2 Prescribing behavior

The GPs expressed a lack of theoretical knowledge of sex and gender differences in drug treatment although their expressed clinical experience indicated the opposite. It seemed that the GPs were unaware of their own knowledge and prescribing behavior.

The relation between action, knowledge, and learning can be interpreted as a modification of Maslow's hierarchy of needs (Fig. 10) [172, 173]. The four levels of action in the pyramid help to maintain different types of knowledge. The lower levels consist of routine-based and rule-based behaviors which use implicit and practical knowledge and is suitable for managing well-known and recurring tasks. The higher levels consist knowledge-based and reflective behavior and requires access of deeper knowledge to solve an arising problem [172]. This model may help explain the findings in Paper IV. The implicit knowledge of sex and gender differences among the GPs indicate a prescribing behavior without reflecting on the patient's sex. Given that the GPs' prescribing decision was expressed to be highly driven by the recommendation lists, it seems that they did not simultaneously reflected about their prescribing behavior taking the patient's sex into account (rule-based level). Deeper understanding about patient's sex and gender in drug treatment can only be reached with reflection of the own thinking and prescribing behavior (reflective behavior level). This might explain the gap between expressed theoretical knowledge and practical experience.

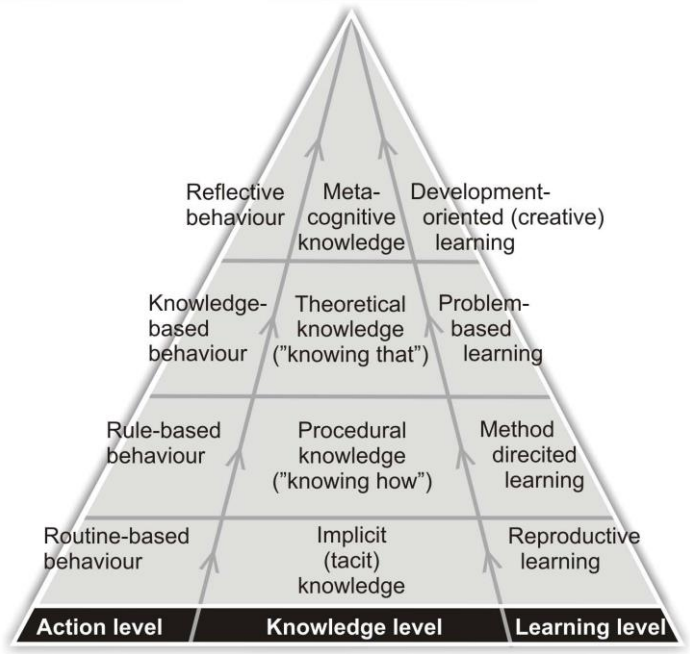

Figure 10. Relation between action, knowledge, and learning [172] in terms of Maslow's Hierarchy of Needs. *Reprinted from [173], used with permission. © 2012 Ingmarie Skoglund*

The non-reflecting prescribing behavior and level of knowledge could also depend on other circumstances, such as GPs' limited time for each patient consultation. Apart from patient visits, GPs have limited time for continuing learning [173]. Insufficient knowledge on this topic could also reflect the educational level in medical school. An U.S. study assessing knowledge of sex and gender medicine among post-graduates in medical school (response rate 17.2%) found a lack of consistent training about this topic in medical school and suggested more educational efforts to increase the knowledge and understanding the impact of sex and gender on the clinical practice [174].

6.4 IMPROVING PRESCRIBING DECISIONS

Prescribers and their medication choices and behaviors are major determinants of patterns of medication use. Hence, physicians' level of knowledge and physicians' behavior levels can impact on prescribing patterns [175]. Knowledge on how medications are prescribed and used can be valuable for discussions on rational drug use and to suggest measures to improve prescribing behavior [176]. In this thesis, utilization patterns of AEDs have been analyzed and two approaches of improving prescribing decisions related to the patient's sex have been addressed, regulatory warnings and knowledge bases/decision support system.

6.4.1 Regulatory warnings

6.4.1.1 Valproic acid utilization before the regulatory warning

The utilization data suggests a decline in prescribing of valproic acid to women with epilepsy between January 2011 and June 2017 (Paper III). Similar findings of a declined use among girls and women with epilepsy have been reported in nationwide Swedish study [157] and in other countries [90, 93, 177, 178]. It is likely that the largest decrease was among adult women, since the valproic acid utilization in girls was rarely unchanged during these years (Paper II). A corresponding increase in lamotrigine use could explain the high level of lamotrigine initiations in girls and women (Paper I-II), which also have been observed in other countries [93, 179].

In males and females with psychiatric disorders, a gradual increase of valproic acid was seen up to 2014 (Paper III). Since a decline was seen in children and adolescents (Paper II) the increase used probably reflects an increased use among adults. Similar patterns have been observed in pregnant women with psychiatric conditions [177]. A potential explanation could be an increased incidence of bipolar disorder. The incidence rate of diagnosed bipolar disorder in Sweden has increased the last 20 years and was around 4-6/10.000 individuals per year in 2010, with higher numbers in women [19]. At the same time, the incidence of epilepsy in the Northern countries has remained constant [180] or declined [181, 182] in most age groups. The incidence rate for epilepsy is 3-5/10.000 individuals per year in Sweden [142, 164].

Overall, boys were initiated on valproic acid to a higher extent than girls (Paper II). This is no surprise since valproic acid is recommended as second-line alternative to lithium in acute mania in boys while it is not recommended at all to girls [183]. The higher use of valproic acid in females with a psychiatric disorder compared to males (Paper III) could reflect a higher prevalence of bipolar disorder or other psychiatric conditions among girls and women, as reported in several studies [18-20, 23, 24, 30].

One possible explanation to these findings is that neurologists managing women with epilepsy have gradually adjusted their prescribing of valproic acid long before the EMA warning in 2014. The teratogenic risks from valproic acid have been known for several years. The DTC in Stockholm recommended other medications than valproic acid for girls and women of fertile age with epilepsy in the Wise List in 2005 [184]. A similar recommendation for patients with bipolar disorder was first introduced in 2012 [185]. The Wise List contains evidence-based treatment recommendations for prescribers and have high adherence and impact on prescribing [169]. Therefore, our findings could reflect a higher level of awareness about the teratogenic risks among neurologists.

In a Swedish register-based study of bipolar disorder, women were more likely to receive antidepressants, benzodiazepines, and lamotrigine, while men were more likely to receive lithium. Valproic acid was used to a similar extent in both men and women, even when restricting the analysis to women with childbearing potential [186].

6.4.1.2 Valproic acid utilization after the regulatory warning

Initiations of valproic acid decreased in women after the EMA warning (Paper III). However, when analyzed by indications, valproic acid initiations decreased significantly for psychiatric disorders but not for epilepsy. A possible explanation could be the difference in availability of treatments alternative for epilepsy and bipolar disorder. For some epilepsy types, valproic acid may be the most effective treatment and treatment alternatives are few [161]. In bipolar disorder, treatment alternatives include several different pharmacological and non-pharmacological treatment options [187]. Lithium is the gold standard in long-term treatment [28]. Valproic acid has shown efficacy in prevention of acute mania but also olanzapine [188] and aripiprazole [189] have shown efficacy. Therefore, it is possible that the women with psychiatric disorders may have switched to alternative treatments more easily and rapidly than the women with epilepsy.

Our findings are in contrast to that of a Finnish study, which reports a decline in prevalent use of valproic acid in women of childbearing age between 2014 and 2016 regardless of indication for use [95]. However, the Finnish study studied temporal trends of prevalent use while our study used an ITS design to analyze incident use.

6.4.1.3 Impact of regulatory warnings

Regulatory warnings on safety issues regarding prescription medications can have some impact on clinical practice. Previous studies examining regulatory restrictions on prescribing have reported mixed effects [190, 191]. Intensive media communication seems to be one crucial factor associated with successful impact of regulatory warnings [191]. Further, as discussed earlier, changing prescribing behavior is difficult without reflection and recognition that the own prescribing needs improvement [175].

Despite the regulatory warnings in 2014 and the developed communication materials on the risks of valproic acid, patient surveys indicated that women of childbearing potential remained unaware of the risks [192]. In March 2018, new measures was endorsed by the EMA to avoid valproic acid exposure during pregnancy [193, 194]. The new regulatory measures include a ban on the use of medications containing valproic acid for migraine or bipolar disorder during pregnancy, and a ban on treating epilepsy during pregnancy unless there is no other effective treatment available. Further, valproic acid is contraindicated in girls and women of childbearing potential unless a special pregnancy prevention program is followed [193]. The product information for medications containing valproic acid have been updated and now contains a visual warning concerning the risk of valproic acid use during pregnancy [8, 194].

6.4.2 Decision support with sex-specific medical information

Primary care physicians participating in the FGDs expressed a need of more knowledge about sex differences in pharmacological treatment. More education can bridge the gap between the GPs' theoretical knowledge and practical experience. Despite the growing body of scientific literature pointing out sex differences related to medication use, efficacy, and side effects, this information can be difficult to find for the prescribing physician. A web-based survey to physicians in the Stockholm region (72 responders, response rate 31%) showed that 52.8% of the responders expressed a need of support with sex-specific information related to the patient's medications. The therapeutic areas considered to be most interesting to have sex-specific information about were cardiology, endocrinology, psychiatry and neurology [195].

To meet this demand on more information and knowledge, *Janusmed Sex and Gender* was developed. Access to independent medical information is essential for promoting rational prescribing [139] and the increasing evidence of sex and gender differences in medication efficacy and safety thus justifies the need for appropriate approaches to support prescribers with such information. The major strength of *Janusmed Sex and Gender*, making it world unique, is the comprehensive amount of information collected in one place. It can be used as a decision support but does not replace clinical judgement. Additionally, it's freely available at no cost for the user, allowing prescribers to obtain information and knowledge without a login or cost barrier.

6.4.2.1 Data on sex and gender differences

Differences in efficacy and safety from medications may indicate differences in pharmacokinetics and pharmacodynamics between men and women [2]. Although there is well-described evidence of sex differences in pharmacokinetics for several medicinal substances included in *Janusmed Sex and Gender*, sex-specific dosing is rarely recommended by the manufacturer, not even for medications that have been on the market for several years, such as ondansetron. Pharmacokinetic sex differences could disappear when adjusting for body weight. However, most medication dosages are not adjusted for body weight, and thus increasing the risk for overdosing in women and potential adverse events. Further, pharmacokinetic differences appear often to be small and without any clear clinical relevance. Nevertheless, for medications with narrow therapeutic index these small differences can be of clinical importance, such as carbamazepine and phenytoin [196].

A systematic collection of data can be helpful for identification of clinical disciplines and pharmacological classes in need of more sex- and gender-based research. Overall, for most substances evaluated in *Janusmed Sex and Gender*, patient's sex or gender does not appear to affect the efficacy and safety. However, for some substances the available evidence suggests that men and women need different doses to achieve similar benefit. The complete lack of data for a third of the evaluated substances means that we don't fully understand if these medications are equally effective and safe in men and women. Further, it prevents the possibility of personalized medicine, which is the current trend. AEDs are one pharmacological class for which sex and gender aspects are well-documented, as illustrated in Figure 9.

The name of the knowledge base indicates consideration of both sex and gender differences. However, most of the differences described in the knowledge base depend on the biology (sex differences). Gender differences are, compared to sex differences, more difficult to measure. Nevertheless, 'sex differences' are sometimes named 'gender differences' in scientific literature, especially within

cardiology. One example of a gender difference is the higher utilization of topiramate among women in Sweden, which may reflect taking advantage of the potential of weight loss from topiramate which women tend to be more prone to [66].

6.4.2.2 Impact of decision support systems

The information presented in *Janusmed Sex and Gender* is currently only available via the web (www.janusinfo.se) and is based only on results from published scientific studies. Medication knowledge combined with patient-specific data within an EHR system can generate patient-specific treatment recommendations and thereby assist prescribers in the decision-making process [151]. If used from an EHR, physicians will receive automatically alerts/warnings when prescribing medications inappropriately to men and women. However, measuring the effectiveness of CDSS, in terms of actual improvement of patient safety and effects on patient outcome, is difficult and there is limited evidence that use of CDSS improve patient outcome [197-201]. Too many alerts within an EHR system might become overwhelming for prescribers and may cause alert ignorance and consequently, losing their effect. It is thus important to consider when, where and how alerts should be presented [151, 201].

6.5 METHODOLOGICAL CONSIDERATIONS

6.5.1 Register-based studies (Paper I-III)

Using administrative healthcare utilization databases offers many advantages for epidemiological research. These registers cover large-scale of data over a long period of time, enabling long-term follow-up. The completeness of data reduces the risk of selection bias. Another advantage is the representativeness of routine clinical practice, with data prospectively recorded for all individuals, which makes it possible to study medication efficacy and utilization of prescribed medications. Further, since the registers already exist, the time and cost for data collection is minimized [5]. In addition, they provide an opportunity of linking data between registers, such as linking drug dispensing data to clinical data. Data on dispensed medications are more closely related to the patient's actual intake of the medication, than data on prescribed medications.

Healthcare utilization databases can be useful for several approaches of which some relates to Paper I-III in this thesis. First, registers can be used for evaluating the appropriateness of medication therapy and to create a better understanding of physicians' prescribing decisions [5]. Further, information on incidence and prevalence of medication therapy is essential for assessing quality of prescribing and health system planning. These measurements can be compared between medications and thus, resulting in a comprehensive picture of a population's medication use [5]. Finally, registers can be used for evaluating the impact of regulatory decisions on drug utilization, by using ITS analyses [5]. ITS design is considered the best available study design for evaluating policy changes where it is almost impossible to employ a control group, and have been used in several studies examining interventions in drug utilization [149, 202].

6.5.1.1 Validity of diagnoses

In the Swedish healthcare utilization databases, hospital diagnoses are, in general, well-validated [143], while validation of primary care diagnoses are unknown [203]. In Paper II, a fifth of the study population lacked an approved diagnosis within one year prior to the first prescription. This could be a consequence of inadequate recording of diagnoses or off-label prescribing. From 2015, the reporting of data to the NPR was changed from yearly to monthly reporting [204]. Thus, it is possible that diagnoses recorded at the end of the 2014 were reported in 2015 and thus excluded. It is also possible that some of these patients had their diagnosis recorded in primary care, for which we had no data. We collected diagnoses within total 5 years prior to the first AED dispensation and it is possible that some patients had their diagnosis recorded earlier.

Diagnoses in the VAL database (Paper III) are retrieved from electronic medical records, which also include a high number of symptom diagnoses. However, the diagnostic accuracy varies between primary care health centers and over time [203]. This could be a possible explanation why 26.7% of the individuals in Paper III had no recorded diagnosis of epilepsy or a psychiatric condition within 5 year prior to the first dispensing of valproic acid. The SIRE database (used in Paper I) is also based entirely on data from medical records and the classified diagnoses may therefore not be identical with the diagnoses reported by the treating physician. Also, the 6 months follow up after index seizure could have affected the classification of cases. Those classified as single seizure could have had a relapse during the one year follow-up in our study.

In Paper II-III, the underlying indication for which the AEDs were prescribed was unknown, and consequently, there is an uncertainty of the association between the recorded diagnoses and utilized prescriptions. However, Paper II-III provides a good estimate of possible indications related to the AED prescriptions. The indication could be validated by analyzing the free text field in each patient's prescriptions, but since the indication is not always specified and the studies included large sample sizes, this was considered as not feasible. In Paper II, a washout period of 1 year used to identify incident AED treatment is appropriate for in patients with chronic diseases, such as epilepsy. However, a longer washout period may had been more appropriate for identifying treatment in pain disorders.

6.5.1.2 Confounding and bias

Studies using healthcare utilization databases may have potential sources of bias. An electronic record for a diagnosis or a prescription claim is only generated when patients encounter with the healthcare system. Further, patient information can be incomplete or missing, and diagnoses can be miscoded, leading to misclassification bias [5].

The SPDR contains data on all purchased prescriptions issued in Sweden, however the true exposure is the patient's intake of the medication. Therefore, patients with a dispensed prescription medication may be classified as exposed when truly unexposed (low specificity). Further, patients using medications from internet pharmacies, medications dispensed abroad or OTC medications may be classified as unexposed when truly exposed (low sensitivity) [140]. Some biases are less likely to occur; recording of drug dispensing data in the SPDR occur independent of the patient, thus avoiding recall bias [5].

There may be a concern about selection bias in SIRE (Paper I) due to a likely underreporting of potential cases [142]. Further, patients may seek medical advice for their seizures outside Northern Stockholm, although this is less likely to happen. However, the distribution of case demographics in SIRE have been comparable to previous population-based studies, indicating no pronounced selection bias [142].

Potential time-varying confounding can affect the ITS analysis (Paper III) and it is possible that external factors, such as other interventions at the same time or changes in the study population, may have affected the results [202].

6.5.1.3 Generalizability

The generalizability from using healthcare utilization databases is limited by differences in patient characteristics, healthcare organizations, regional reimbursement systems, and recommendation guidelines. Access to neurologists among epilepsy patients depends on sociodemographic factors such as patient's sex, age, educational level, income level and place of residence [73]. This may affect the appropriateness in AED selection and thus, treatment outcome.

In Paper I and III, we used data for the Stockholm population and the results may not be generalizable to the whole Swedish population, or beyond. In fact, the Stockholm population is younger, has a higher educational level, and has a higher mean income [205]. In Paper III, the effect of the EMA warning could have a different impact on the utilization of valproic acid in other parts of Sweden, as well as in other countries in Europe. Further, there could be a lag period between the implementation of the EMA warning and the physicians' response to it. Since we only had data available for a limited

number of months after the EMA warning was issued, the timescale for detecting a change in prescribing was limited.

6.5.1.4 Measuring medication use in children and adolescents

Pharmacological treatment in children and adolescents has gained too little attention. In general, evidence guiding prescribing and pediatric drug formulations are lacking [206]. Thus, pharmacoepidemiological studies in this patient group are highly important and needed. Studying drug utilization in children and adolescents is particularly useful in assessing the quality of prescribing and identifying needs for long-term efficacy and safety studies. It can also be used for studying rational use of medications, as well as off-label use, in different pediatric populations and settings. However, the pediatric population is heterogenous and a large sample size is needed to obtain valid drug utilization data [206]. These methodological aspects were considered when designing Paper II, where we had a large dataset consisting of children and adolescents initiated on different AEDs.

6.5.1.5 Measuring sex and gender differences

Data from healthcare utilization databases can be used for conducting large population-based analyses of sex differences in healthcare and medication use, but the interpretation of such differences is limited by the data available in the databases. Patient behavior and physician prescribing can be influenced by factors not recorded in the databases used [5]. Therefore, observational studies can identify sex differences in drug use but an evaluation of the reasons behind such differences require more detailed information and targeted analysis.

6.5.2 Qualitative studies (Paper IV)

Focus group discussions (FGDs) was chosen as data collection method because it's particularly useful when determining the perceptions, feelings, and thinking of people about a specific topic [207]. The advantage of choosing FGDs was that the participants interacted and helped each other to explore and clarify an unreflected issue [207]. This group dynamics drives the participants to concretize thoughts and experiences, which could not be enabled in individual interviews [150]. We believe that the use of FGDs enriched the results and gave us more understanding of the GPs. Since the method is relatively quick to perform and involves several participants, we generated a lot of data in a short time [208]. A limitation with FGDs is the potential risk of modified or non-expressed answers among the participants or avoidance of conflict with other participants [207]. However, the participants in this study did not seem to have any hesitations about expressing conflicting opinions.

Healthcare centers were chosen since consultations in primary care often result in prescribing [173]. Also, AEDs are prescribed in primary care. Further, GPs maintain a holistic view of the patients and handle medications prescribed by physicians in other specialties. In addition, physicians in primary care are already a clear defined group and their shared experiences enable them to relate to each other at the same time as the group climate can be more open and friendly [208]. However, a mixed group or only a group of physicians not working at healthcare centers had been more suitable to include with regards to the AED studies in this thesis, since patients with epilepsy often are treated by neurologists and children and adolescents with psychiatric or pain disorders often are managed in specialty care. Moreover, the recommended medications by the regional DTC have a high adherence and impact on the prescribing in primary care as well as specialized care [168, 169]. In Stockholm, medication recommendations for specialized care are included in the 'Wise List' since 2007.

6.5.2.1 Trustworthiness

Qualitative research has been criticized for lacking appropriate rigor frameworks, lack of transparency in the analysis process, and risk of influence of subjective interpretation [209]. In qualitative research, reliability and validity are assessed by establishing the *trustworthiness* (credibility) in the interpretation of the findings. Following criteria can be used for evaluating the trustworthiness: *truth value*, *consistency/neutrality* and *applicability* [209]. In Paper IV, we used several approaches to ensure trustworthiness of the results, as described below.

- *True value*. Since the FGDs only provided us with data on what the GPs said they did and not what they actually do in clinical practice, we frequently used follow-up questions during the FGDs, asking for concrete examples of behavior. Follow-up questions were also used for clarification on areas on ambiguity. All FGDs were audiotaped and fully transcribed to ensure accuracy. Systematic text condensation of the transcripts and coding by categories were done by the moderators, followed by discussions with the research group to achieve consensus. In the research team, and present at the consensus discussions, were a team member with qualitative research expertise. Notes were taken during the discussions and decisions documented. The emerging categories and subcategories were re-analyzed and revised in an iterative process until saturation was achieved. If disagreements occurred, the transcripts were reread again to ensure that categories remained true to participants' expressions.

- *Consistency/neutrality*. Detailed descriptions of the process of data collection, data handling, data analysis, and interpretation of results maintained the consistency of the study. These descriptions provide insight and understanding for how categories and subcategories emerged from the data. Researcher neutrality was assessed by involving research team members with different backgrounds to ensure that the analysis and results reflected multiple perspectives.

- *Applicability*. The results of the study may be transferrable to similar contexts. The study provides a clear description of the methods, analysis process, and demographics of the participants which should be considered before applying our results into other contexts.

Taken all of this together, we believe that the clarity and transparency of the data collection and analysis process, backed up by quotations from participants, will ensure trustworthiness of the findings.

6.5.3 Knowledge bases (Paper V)

Janusmed Sex and Gender is a novel and unique knowledge base with evidence-based information on potential sex differences of drug treatment. The main advantage of knowledge bases is the standardization of information. Information sources such as the product information and Physicians' Desk Reference varies between medicinal products containing the same substance [151]. However, the lack of standardized terminology to describe sex differences in PubMed may have resulted in some studies not being detected in our literature searches. Further, the recommendations reflect the current available information, which may change over time and therefore, periodical updates are warranted to keep the knowledge base and recommendations up-to-date [151].

7 CONCLUSIONS

- Observed sex differences in utilization of valproic acid and lamotrigine could reflect the teratogenic effect and reproductive-related adverse events associated with valproic acid as compared to lamotrigine.

- Decisions on initial AED treatment in newly diagnosed epilepsy are challenged by a high use of other presciption medications, particularly in elderly women, which warrant that potential drug-drug interactions need to be taken into account.

- Treatment with AEDs in children and adolesents is mainly restricted to epilepsy and the individual AEDs used seems to be in accordance with the approved indications and treatment guidelines. However, certain AEDs are used off-label in children and adolescents, especially with pain disorders.

- The regulatory restrictions on the prescribing of valproic acid in 2014 had an effect in girls and women of childbearing age with a psychiatric disorder. The use of valproic acid in epilepsy had declined long before the restrictions was issued which could reflect an earlier higher level of awareness of the teratogenic risks among neurologists treating women with epilepsy.

- GPs perceive insufficient knowledge about sex and gender differences in pharmacological treatment although their expressed clinical experience indicated some awareness. Patient's sex and gender are considered in diagnosing while decision on medication to prescribe follows the regional recommendations lists on essentiel medications because GPs believe the recommendations to be evidence-based and sex neutral. However, this is not always the case. Overall, more education about sex and gender is desired. Increased knowledge about this major clinical topic could lead to better healthcare and drug decisions for men and women.

- Finding relevant sex-specific pharmacological information for individual medications can be difficult. To enable physicians to readily accessible information regarding sex and gender aspects for medications the knowledge base *Janusmed Sex and Gender* was developed. It is comprehensive and offering a breadth of information. The knowledge base is a unique and valuable resource that can support evidence-based prescribing decisions in clinical practice. Further, since the scientific community and prescribing physicians are in need of educational resources of sex- and gender-related pharmacological information, *Janusmed Sex and Gender* will provide an even greater resource.

- Anitepileptic drugs are one pharmacological class for which sex and gender aspects are well-documented. However, available scientific knowledge on sex differences are lacking for a third of the substances evaluated in *Janusmed Sex and Gender* which means we don't fully understand if these medications are equally effective and safe in men and women.

8 IMPLICATIONS AND FUTURE PERSPECTIVES

This thesis provides an overview of the use of antiepileptic drugs on different diagnoses in men and women, and understanding of physicians' perceptions of sex and gender aspects in decision on drug prescribing. By using comprehensive national and regional registries of dispensed medications, together with physicians' own reflections, we have generated valuable knowledge that may be useful in discussions on rational drug prescribing and when proposing relevant approaches to improve prescribing behavior relating to the patient's sex.

The findings in this thesis have several potential implications for clinical practice and future research. First, patient's sex is an important factor to consider when assessing benefit versus risk from antiepileptic drugs in clinical decision making on prescribing. Since antiepileptic drugs are used for treatment of different conditions, prescribing of antiepileptic drugs is a concern for physicians of many disciplines. However, this thesis has described the context of antiepileptic drugs but there are many other pharmacological classes for which patient's sex can be of great importance in decision-making and patient outcome.

Second, knowledge on how antiepileptic drugs are prescribed and used in men and women with different conditions can be useful in discussions on rational drug prescribing and to suggest measures to improve prescribing behavior. As illustrated in this thesis, regulatory actions can be an approach to improve rational prescribing. However, research from other countries suggests that the regulatory restrictions in 2014 on the prescribing of valproic acid to girls and women of childbearing age have been insufficient and more strengthened measures have been required. This highlights a continued need for analyzing antiepileptic drug prescribing patterns and evaluating whether the newest measures from EMA have had any impact on the prescribing of valproic acid. Also, the impact of the EMA warnings should be explored in larger materials. Nevertheless, the medical profession must recognize the teratogenic risks of valproic acid and implement the prescribing restrictions in order to reduce the number of girls and women with an unnecessary use of valproic acid.

Third, providing independent evidence-based sex-specific medication knowledge can be a valuable resource for supporting rational prescribing in the daily clinical practice. This can be facilitated by the freely and easily accessible *Janusmed Sex and Gender*.

Finally, without recognition of sex/gender differences and the underlying mechanisms, it is difficult to improve treatment and patient outcomes for both men and women. Consideration of patient's sex needs to be incorporated in all levels of clinical medicine and drug development to identify medications that benefit both men and women. Although the regulatory authorities pay attention to sex/gender differences in approval applications, there are still knowledge gaps, especially for medications that have been on the market for a long time. Further, there are still medical peer-reviewed journals that don´t have policies that require sex/gender-specific reporting, which is important to avoid drawing incorrect conclusions and to facilitate meta-analyses. Also, policy makers interested in optimizing pharmacological treatment in men and women should consider patient's sex in treatment guidelines and recommendations lists. Education on sex and gender aspects in disease and pharmacological treatment should be included in the curriculum in all medical schools. Increased recognition about this major topic among researches and prescribers may result in better driven prescribing decisions and potentially reduce irrational use of drugs related to the patient's sex.

9 SVENSK SAMMANFATTNING

Antiepileptika används för behandling av epilepsi men också för andra neurologiska och psykiatriska tillstånd och därför är förskrivning av antiepileptika en angelägenhet för läkare inom många specialiteter. Den ålders- och könsspecifika prevalensen, samt betydelsen av köns- och genusaspekter, varierar mellan de tillstånd som antiepileptika används vid. Det övergripande syftet med avhandlingen var att få en ökad förståelse för användningen av antiepileptika på olika diagnoser, med fokus på könsskillnader, samt att undersöka läkares uppfattningar om kön och genus vid beslut om läkemedelsbehandling.

Avhandlingens första två studier beskriver vilka antiepileptika som används vid epilepsi och andra tillstånd. Tydliga ålders- och könsskillnader i användning av specifika antiepileptika observerades. Användning av antiepileptika hos barn och ungdomar var huvudsakligen begränsad till epilepsi och de enskilda antiepileptika som förskrivits verkar vara i enlighet med godkända barnindikationer och behandlingsriktlinjer. Vissa antiepileptika användes dock på icke godkända indikationer hos barn och ungdomar.

Den tredje studien utvärderade effekten av en varning som den europeiska läkemedelsmyndigheten EMA utfärdade i november 2014 om begränsad förskrivning av valproinsyra till flickor och kvinnor i fertil ålder. Analyserna visade att varningen endast hade effekt på förskrivningen till flickor och kvinnor med psykiatrisk diagnos. Förskrivning till flickor och kvinnor med epilepsi hade minskat långt innan varningen utfärdades vilket skulle kunna visa på en tidigare högre medvetenhet om den fosterskadande risken från valproinsyra bland neurologer som behandlar kvinnor med epilepsi.

Den fjärde studien undersökte hur läkare inom primärvården uppfattar kön/genus och jämställdhet relaterat till läkemedelsförskrivning. Resultaten visade att läkarna ansåg sig ha otillräcklig kunskap om könsskillnader vid läkemedelsbehandling, trots att deras uttalade kliniska erfarenhet indikerade viss medvetenhet. Patientens kön beaktades vid diagnos medan beslut om läkemedel att förskriva följde de regionala rekommendationslistorna eftersom läkarna tror att rekommendationerna är evidensbaserade och könsneutrala. Dock återfinns inte alltid könsbaserade rekommendationer även om en ökad medvetenhet kan ses. Sammantaget önskade läkarna mer utbildning och kunskap om kön och genus inom läkemedelsbehandling. Det kan dock vara svårt att hitta pålitlig information om köns- och genusaspekter för enskilda läkemedel. Detta underlättas nu av det webbaserade kunskapsstödet Janusmed Kön och Genus, som beskrivs i den femte studien.

Sammanfattningsvis visar denna avhandling att det förekommer könsskillnader i användning av vissa antiepileptika vilket troligen reflekterar skillnad i nytta och risk för dessa mellan kvinnor och män. Kunskap om hur antiepileptika förskrivs och används hos kvinnor och män med olika tillstånd är användbart vid diskussioner om rationell läkemedelsförskrivning och för att föreslå åtgärder för att förbättra förskrivningsbeteendet. Som framgår av denna avhandling kan regulatoriska åtgärder kan vara ett sätt att förbättra rationell förskrivning och uppmärksamma betydelsen av patientens kön. Ett annat sätt kan vara att ta del av kön- och genusrelaterad farmakologisk information via kunskapsstödet Janusmed Kön och Genus.

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