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*Digital Comprehensive Summaries of Uppsala Dissertations  
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# The influence of gender and depression on drug utilization

*Pharmacoepidemiological research in Sweden*

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ACTA  
UNIVERSITATIS  
UPSALIENSIS  
UPPSALA  
2017

ISSN 1651-6192  
ISBN 978-91-513-0088-7  
urn:nbn:se:uu:diva-330136

Dissertation presented at Uppsala University to be publicly examined in Sal IV, Universitetshuset, Biskopsgatan 3, Uppsala, Friday, 24 November 2017 at 09:15 for the degree of Doctor of Philosophy (Faculty of Pharmacy). The examination will be conducted in Swedish. Faculty examiner: Docent Susanna Wallerstedt (University of Gothenburg).

### **Abstract**

Thunander Sundbom, L. 2017. The influence of gender and depression on drug utilization. Pharmacoepidemiological research in Sweden. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Pharmacy* 238. 67 pp. Uppsala: Acta Universitatis Upsaliensis. ISBN 978-91-513-0088-7.

**Background** Drug use has increased over recent decades, and is especially great among women and among people with mental health problems. To take advantage of the full potential of drugs and to avoid drug-related problems, drug prescription needs to be correct and the drugs need to be taken according to the prescribed regimens. Research on drug utilization is thus important to the public health.

**Aim** To study the influence of gender and depression on drug utilization, prescription of drugs and self-reported use of drugs, i.e. adherence.

**Methods** The thesis included two population-based questionnaires and data from the Swedish Prescribed Drug Register (SPDR) covering Swedish citizens 18-84 years. The questionnaire in Study I and II included items on prescription drug use and adherence to treatment regimens; Study II also included the Hospital Anxiety and Depression Scale (HADS) for self-estimation of anxiety/depression. The questionnaire in Study III included the HADS and data from the SPDR on prescribed antidepressants. Study IV included data from the SPDR on all types of prescribed drugs.

**Results** Men and women differed in non-adherent behaviours and reasons for non-adherence, for example, men were more likely to report forgetting to take the drug, while women were more likely to report adverse drug reactions (ADRs) as a reason for non-adherence. Further, both anxiety and depression were associated with non-adherence and with ADRs as a reason for non-adherence. In addition, men reported depression to a greater extent than women did but used antidepressants to a lesser extent, while women used antidepressants without reporting depression more often than men did, which may be a sign of under-treatment among men and over-treatment among women. Moreover, the associations between antidepressants and other types of drugs differed by gender; they were often specific, or stronger, in women than in men, which may be a sign of a gender difference in comorbidity between depression and other conditions.

**Conclusions** Although the cross-sectional study design prevented confirmation of causality, the thesis found that gender and depression influence both prescription of drugs and adherence, and are thus important to pay attention to in clinical practice as well as research.

*Keywords:* adherence, anxiety, depression, drug utilization, gender, pharmacoepidemiology, prescription drugs, self-report

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ISSN 1651-6192

ISBN 978-91-513-0088-7

urn:nbn:se:uu:diva-330136 (<http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-330136>)

*Till Anton*

*Hjärtat blir aldrig fullt  
En livstid ska få plats där  
Allt det här och mer  
(J.Berg, Andromeda, 2016)*



# List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

- I Thunander Sundbom L, Bingefors K. (2012) Women and men report different behaviours in, and reasons for medication non-adherence: a nationwide Swedish survey. *Pharmacy Practice*, 10:207-221.
- II Thunander Sundbom L, Bingefors K. (2013) The influence of symptoms of anxiety and depression on medication nonadherence and its causes: a population based survey of prescription drug users in Sweden. *Patient Preference and Adherence*, 7:805-811.
- III Thunander Sundbom L, Bingefors K, Hedborg K, Isacson D. (2017) Are men under-treated and women over-treated with antidepressants? Findings from a cross-sectional survey in Sweden. *British Journal of Psychiatry Bulletin*, 12 Jan (1-6).
- IV Thunander Sundbom L, Hedborg K. (2017) Gender differences in the association between prescribed antidepressants and other prescribed drugs: a nationwide register-based study in Sweden. (Manuscript)

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# Abbreviations

ADR	Adverse drug reaction
ATC	Anatomical therapeutic chemical classification system
CI	95% confidence interval
HADS	Hospital anxiety and depression scale
HBM	Health belief model
MAO	Monoamine oxidase inhibitor
OR	Odds ratio
SAS	Statistical analysis system
SNRI	Selective noradrenaline reuptake inhibitor
SPDR	Swedish prescribed drug register
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant

## Notes

Anxiety and depression are sometimes used synonymously with self-reported mental health problems, i.e. symptoms of anxiety and depression.

Drugs are used synonymously with medication (Swedish: läkemedel and medicin).

Gender (Swedish: genus) refers to social, cultural as well as biological characteristics of men and women.<sup>1,2</sup>

Users refer to users of prescription drugs, including prescribed/dispensed drugs and self-reported use of drugs.



# Introduction

For many individuals, drugs are a part of everyday life, and in health care, drugs play a central role in the prevention, treatment, or diagnosis of disease.<sup>3</sup> Drugs are an amazing resource that, used correctly, can improve health and quality of life and, ultimately, save lives. While drugs offer great potential, there are also a variety of complex challenges that must be addressed. For example: that drug use is correct and safe, i.e. that the diagnosis and prescribing are appropriate; that the drugs are taken according to the regimen; and that the treatment is provided equitable, i.e. regarding different health problems and gender. To take advantage of drugs' beneficial effects, the risk of negative consequences must also be considered. Thus, research on drug utilization, including both drug prescription and intake, has important implications for public health. The studies in this thesis were conducted to contribute to new knowledge about drug utilization in the general population, with a focus on gender and depression.

## Pharmacoepidemiology

The use of prescription drugs has increased constantly during the past decades. In Sweden, approximately two-thirds of the population uses at least one prescribed drug annually.<sup>4</sup> In line with this increased drug use, an intensified awareness of the risks that come with drugs has led to the research discipline of pharmacoepidemiology. Pharmacoepidemiology investigates drug utilization in the general population and is defined as “the study of the use and effects of drugs in large populations”.<sup>5</sup> The discipline was first developed in the early 1960s when an increased consciousness of the risks associated with drug treatment began with the thalidomide tragedy (about 10,000 children, of whom 186 were in Sweden, are estimated to have been seriously injured when their pregnant mothers took thalidomide (Neurosedyn) to treat morning sickness).<sup>6</sup> Thus, pharmacoepidemiology is, compared to epidemiology, a relatively new field linking pharmacology (studies of pharmacodynamics and pharmacokinetics) and epidemiology (studies of the distribution and determinants of diseases in populations). Both epidemiology and pharmacoepidemiology deal with multiple causes, and it is almost a truism that there are no diseases where drugs are both necessary and may

cause harm. Thus, in the same way as epidemiology, pharmacoepidemiology is strongly connected with public health.

Pharmacoepidemiology covers: *patterns of use*, i.e. factors related to prescribing and dispensing (why drugs are prescribed, who the prescribers are, for whom they prescribe); *quality of use*, i.e. whether patients take their drugs correctly; and *outcomes of use*, i.e. the benefits (e.g., post-marketing effectiveness studies) vs. the risks (e.g., adverse drug reactions) associated with the drugs when used in the population.<sup>5</sup> Pharmacoepidemiological studies can be divided into two main types: descriptive (estimating rates, e.g., incidence and prevalence) and analytical (e.g. observational studies, experimental studies, and clinical trials). Studies looking at *patterns of* and *quality of* drug use (the focus of this thesis) are generally considered descriptive. For these studies, physician prescription records (prescribing), pharmacy-based prescription databases (dispensing), and interviews or questionnaires (intake, e.g., adherence) may be used (Figure 1). However, all three of these methods have limitations. A drug may be prescribed but not dispensed, and even if the drug is dispensed the drug may not be taken, and moreover, drug intake may be reported when actually not have happened.<sup>7</sup> As can be seen, the choice of method as well as an awareness of the limitations of the methods is crucial in pharmacoepidemiological research.

Figure 1. Pharmacoepidemiological studies; *patterns of*, and *quality of*, drug use



## Drug-related problems

Problems connected to drug utilization, often called drug-related problems, are defined as “events or circumstances involving drug therapy that actually or potentially interfere with desired health outcomes”.<sup>8</sup> Drug-related problems are common and important to consider in public health, because they can contribute to increased morbidity and mortality, decreased quality of life, and also increased health care costs for the individual as well as for society.<sup>9,10</sup> The problems caused by drugs involve effectiveness, necessity as well as safety problems. Drug-related problems vary from lack of therapeutic effect, over- or under-treatment, adverse drug reactions (ADRs), drug interactions (one drug affects the effect of another drug, which can result in either increasing or decreasing the drug’s effect),<sup>11</sup> and improper drug selection or improper doses, to drugs not being used by patients in the way they are prescribed (non-adherence).<sup>12</sup> That is, drugs may not be used when they are

needed and would be beneficial, or, vice versa, drugs may be used when they are actually not needed or when they may cause harm. It is not unusual for one drug-related problem to lead to another. For example, the risk of drug-related problems like ADRs, drug interactions, and non-adherence increases with the number of drugs used (polypharmacy).<sup>9,10,13</sup>

### **Non-adherence**

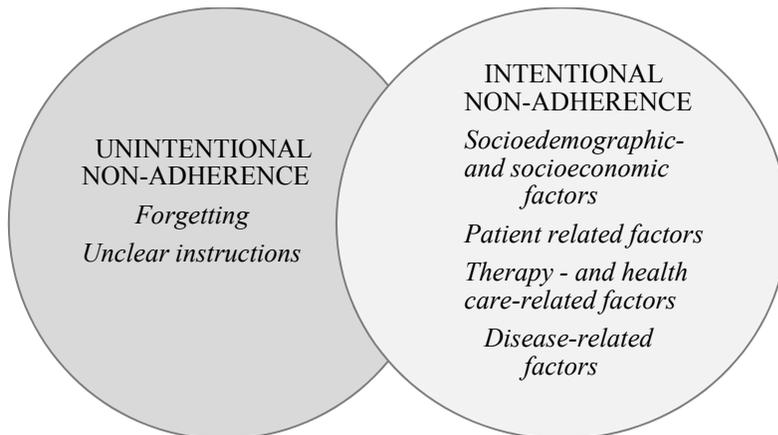
Non-adherence, i.e. a lack of ability or motivation on the part of the patient to follow treatment regimens, is a major problem worldwide. Irrespective of the condition or the study setting, correct adherence to drug regimens is on average only 50%.<sup>7,14,15</sup> In the 1970s, two influential articles caused researchers to take the problem more seriously.<sup>16,17</sup> Since then, awareness of non-adherence has increased and also shifted from a concept including the patient following the physician's order (compliance)<sup>18</sup> to a concept including an understanding between physician and patient (adherence). The expression adherence, used in the present thesis and currently the most widely used expression, is defined as "the extent to which a person's behaviour, taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider".<sup>15</sup> Non-adherence includes, for example, changing the dosage or dosage timing or not taking the drug at all, and can significantly affect the treatment outcome, even making the therapy ineffective.<sup>15</sup> It has been claimed that an improvement in adherence interventions might have a far greater impact on the public health than any improvement in specific medical treatments.<sup>19</sup> Consequently, development of new drugs with enhanced efficacy does not matter if they are not taken correctly. Thus, one way to improve treatment outcomes is to improve adherence to prescribed drugs.<sup>20</sup> However, improving adherence is a major challenge.<sup>21</sup>

*Drugs don't work in patients who don't take them*  
(C. Everett Koop)

Non-adherence is a health behaviour that can be either unintentional, i.e. forgetting to take the drug, or receiving unclear instructions, or intentional, i.e. actively deciding not to follow a drug regimen; see Figure 2.<sup>22</sup> However, non-adherence is often not based on rational decision-making; it is a health behaviour that is influenced by many factors, and the line between unintentional and intentional non-adherence is not completely clear.<sup>23,24</sup> Studies have found that many parameters can be involved, including *socioeconomic factors* such as educational level, income, and the level of social support;<sup>14,15,25</sup> *patient-related factors* such as the attitude to drugs, self-perceived needs for treatment, knowledge about the disease, and self-efficacy;<sup>14,25-29</sup> and *therapy- and health care-related factors* such as dosage regimen, polypharmacy, ADRs, and relationship with the prescriber.<sup>14,15,25,30</sup> *Socio-*

*demographic factors* (e.g., age and sex) also seem to influence adherence.<sup>14,15,26</sup> According to the literature, non-adherence appears to be associated more with women than with men, although differing results have been described.<sup>31</sup> However, publications with a gender perspective on non-adherence, especially including the reasons for non-adherence, are limited. Further, *disease-related factors* can be involved, like perceived symptoms of the condition. Also, in relation to mental health problems adherence is frequently poorer.<sup>32</sup> The reasons for non-adherence in anxiety and depression, however, like gender, have received only limited research attention. It would seem to be evident that more detailed knowledge about how gender as well as anxiety/depression affects non-adherent behaviours and the reasons for non-adherence would be useful in order to improve adherence. Therefore, it is important to investigate this multifaceted topic in some depth.

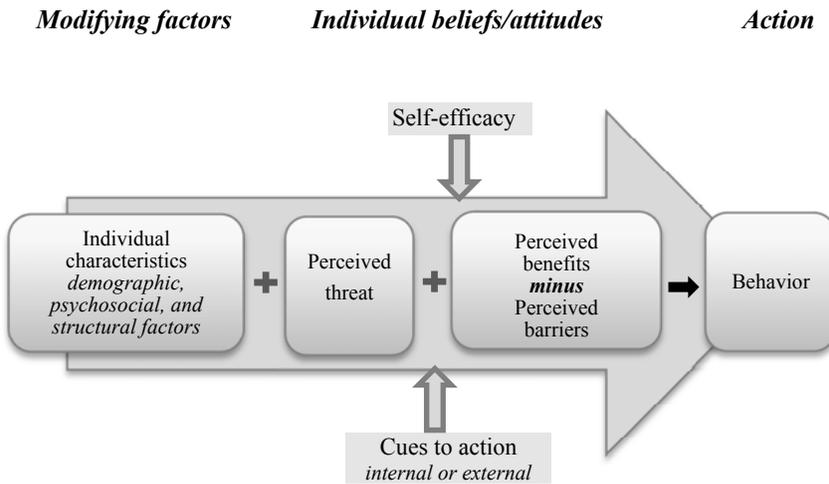
Figure 2. Intentional and unintentional non-adherence



Health behaviours derive from a complex interaction of biological, psychological, social and cultural factors. Many models have been developed during the years to try to predict as well as modify health behaviours. One such model is the Health Belief Model (HBM) that focuses on the importance of individual factors for behavioural changes.<sup>33</sup> The HBM was developed in the 1960s and is a widely used in, for example, adherence studies and intervention studies.<sup>34</sup> According to the HBM, an individual's beliefs and attitudes affect health behaviours. The model suggests that individuals will take action, e.g. seek health care or adhere to health regimens, if they: perceive themselves susceptible to the condition in question; perceive the condition as severe (perceived susceptibility + perceived severity = perceived threat); perceive the action to be beneficial (e.g., belief in effectiveness); and feel that the benefits outweigh the barriers (e.g., ADRs). Further, triggers in the

decision-making process, i.e. cues to action, like perceived physical symptoms (internal triggers), and advice from relatives or media (external triggers) are needed. Furthermore, self-efficacy, i.e., the conviction that one can successfully execute the behaviour, have been found important.<sup>35</sup> Moreover, individual characteristics are thought to modify health behaviours; these include: demographic factors (e.g., age, sex, income, and education); psychosocial factors (e.g., personality, social class, and peer pressure); and structural factors (e.g., knowledge about a condition and prior contact with the condition) (Figure 3).

Figure 3. The health belief model



Further, another model developed to predict health behaviours, the theory of planned behaviour, suggests that, above and beyond individual beliefs and attitudes, subjective norms affect behaviours.<sup>36</sup> That is, behaviours may be performed for non-health reasons such as social acceptability. Nevertheless, independent of their benefit or lack thereof for the individual, health behaviours are often difficult to change.<sup>37</sup>

### Polypharmacy

The use of multiple drugs, often called polypharmacy, is associated with many negative consequences, such as ADRs, drug interactions, prescribing cascades (drugs are prescribed for ADRs caused by other drugs), and non-adherence.<sup>13,38</sup> There is no standard cut-off point with regard to the number of drugs that are defined as polypharmacy. It has been defined as (i) the use of more drugs than are medically necessary, or (ii) the use of four-five, or more drugs.<sup>39</sup> Those two approaches differ, in that the first definition specifies prescriptions that are not needed. However, the problems connected to

polypharmacy may well happen even if the drug prescriptions are correct and the drugs are indeed necessary. That is, polypharmacy should always work as a warning signal, although the use of multiple drugs is not always a sign of poor treatment.<sup>40</sup> Whether or not the benefits of polypharmacy outweigh the disadvantages or risks depends upon the individual, the particular drug combinations and the diagnoses involved. At utmost risk for negative consequences connected to polypharmacy are the elderly, people with mental health problems, those with many physicians, and individuals with multiple medical problems.<sup>41,42</sup> Furthermore, polypharmacy is more common among women than among men.<sup>43</sup>

### **Adverse drug reactions**

Adverse drug reaction is defined by the World Health Organization as "any noxious, unintended, and undesired effect of a drug which occurs at a dose used in man for prophylaxis, diagnosis or therapy".<sup>44</sup> ADRs are a huge health problem; in previous studies about 10-20% of prescription drug users reported current ADRs.<sup>45,46</sup> It has been estimated that ADRs account for 5-20% of all hospital admissions and ADRs are also connected to an increased mortality.<sup>47-49</sup> Nevertheless, even though unpleasant as well as more serious ADRs may occur, the benefits of the treatment may outweigh the risks, especially in more severe conditions. Several potential risk factors have been identified for the development of ADRs, including a history of previous ADRs and polypharmacy.<sup>38</sup> Also, women have been found to have an increased risk of developing ADRs due to a higher vulnerability to ADRs caused by sex-differences in pharmacokinetics and pharmacodynamics. Moreover, studies have suggested that the preponderance of higher ADR prevalence among women may be a result of a higher overall drug use and/or a tendency to recall and report health problems more often than men do.<sup>50,51</sup>

## **Gender**

The definition of gender, compared to that of sex, is more complex and includes several aspects: biological as well as social and cultural.<sup>1,2</sup> Although there are indeed gender differences related to differences in men's and women's biology (such as reproductive organs and hormones), it is impossible to separate biology from the effects of social and cultural factors (such as life situation, social roles and gender norms).<sup>50,52</sup> It is, thus, important to be aware of gender bias in health, i.e. stereotypes related to gender that can lead to errors in diagnosis and treatment. Examples of such errors include giving men and women different treatments even when it is not medically justified or, conversely, disregarding differences and not taking gender-specific needs into account.<sup>53</sup> Further, differences within genders are often greater than between genders, and individuals may be seen as typical for their gender

even when they are not.<sup>54</sup> Other factors not connected to gender also influence treatment outcomes, for example individual genetic and epigenetic factors, which may be considered more fully in future personalized drug therapies.<sup>55</sup> As can be seen, it is difficult to definitively determine the causes of gender differences in health and drug utilization, and when grouping participants according to gender, one has to be vigilant about the risk of reinforcing gender stereotypes.<sup>54</sup> However, men and women are often categorized into two groups in order to simplify complex information. This is done, for example, in epidemiology and pharmacoepidemiology to generate knowledge about health and drug utilization in general.

## Drug utilization and gender

Studies have consistently shown greater use of prescription drugs among women than among men. In Sweden, 74% of all women were prescribed at least one drug in 2015, compared with 58% of men. Even when contraception and sex hormones are not included, drug prescription is substantially higher among women than among men.<sup>4,56,57</sup> Whether the higher overall drug use among women is due to higher overall morbidity is difficult to clarify. Sex-specific morbidity can probably explain some of the gender differences in drug utilization. However, the phenomenon of greater drug use among women raises the question of whether diagnoses and drug treatments always are correct or if gender bias occurs.<sup>56</sup> For example, women are more often diagnosed with conditions such as depression, anxiety, and chronic pain, and hence more often treated symptomatically with antidepressants, hypnotics, and analgesics. Men, on the other hand, are more often diagnosed with, and prescribed drugs for, heart disease and diabetes.<sup>58,59</sup> Nevertheless, the fact that women in most cultures have a greater life expectancy than men, but at the same time suffer from more health problems often called “the health paradox” might stem from these differences in conditions, i.e. that men have an excess of serious, life-threatening conditions, and women an excess of symptoms and less serious conditions.<sup>59</sup> However, one should note that if there is a perception that men do not seek care “at first”, then there is a risk that men’s problems will be unconsciously considered more serious.<sup>53</sup> Further, the fact that women and men differ at the population level in educational attainment, income and stressors related to work and household, factors that have been found to affect health, can probably explain some of the gender differences in health and drug utilization.<sup>52,58</sup>

To explain the gender disparities in health and drug utilization, attention must also be paid to health behaviours.<sup>37,50,60,61</sup> Studies have consistently indicated that women, compared with men, have a healthier lifestyle, seek health care earlier, and are more likely than men to engage in a variety of health-promoting and preventive behaviours. It is possible that health does

not have the same meaning for men and women.<sup>60</sup> Masculine attitudes towards health (such as a sense of immortality, reluctance to express emotions, pain or other discomforts) are associated with increased health risks. Men seem not to seek health care as often as women do and their detection of disease may therefore be delayed.<sup>58,60,62,63</sup> Moreover, men's lower health care utilization rates in Western countries have been found to be linked to their tendency to be fulltime workers, work long hours, and have less flexible schedules than women do.<sup>64-66</sup> In many conditions, women are diagnosed more frequently than men due to more frequent health care contacts, and women thus obtain more prescribed drugs.<sup>62</sup> Additionally, studies have shown that women are more likely to receive a prescription during their health care visits than men are.<sup>62,67</sup> The pronounced use of drugs in women is however not uncomplicated, because women, as mentioned above, have a higher risk of developing ADRs than men do.<sup>51</sup> Moreover, for women of childbearing age, the use of drugs poses additional concern, because some drugs have been linked to teratogenic effects and spontaneous abortions.<sup>68</sup>

## Depression

In 1948, "health" was defined by the WHO as; "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity".<sup>69</sup> Thus, this definition portrays health and ill-health as two dichotomous and as each other's opposites. However, this approach has come to be increasingly questioned. Most criticism concerns the word "complete" in relation to well-being, as the requirement for complete health is a utopia that increasingly see all states other than perfect health as required medical treatment. Concerning mental health, for example, the absence of mental well-being does not necessarily mean mental disease.<sup>70</sup> The concept of depression has been used in medical contexts since the 18<sup>th</sup> century; however, depression as a diagnostic category appeared first in the 1980s.<sup>71</sup> Today there are two generally accepted diagnostic guidelines used to diagnose depression, DSM-5 and ICD-10, both with criteria based on experienced symptoms.<sup>72,73</sup> Further, there are many self-report tools concerning depressive symptoms that are used in clinical practice as well as in research, mainly for screening purposes. However, diagnosis, as well as self-reported symptoms, in relation to mental health problems constitutes a kind of estimation of subjective experience. Everyday stresses and normal grief is often hard to distinguish from mental disease. Moreover, the symptoms are heterogeneous and vary across individuals. Also, the evaluation of symptoms, e.g. what is considered a disease, varies over time, across cultures, and between physicians.<sup>71,74</sup> Thus, health and diagnosis can in some ways be seen as fluctuating social constructs, i.e. we have looked at disease in different ways throughout history.<sup>71</sup>

The first episode of depression often occurs after some psychosocial or medical burden. However, individuals have different genetic and psychosocial vulnerability to depression, and are affected by external factors to varying degrees.<sup>75</sup> The most common symptoms are different levels of depressed mood, apathy and impaired cognition. Other common symptoms include anhedonia, a feeling of worthlessness, social withdrawal, sleep disturbance and somatic symptoms such as loss of appetite, shortness of breath, and muscle aches. Suicidal thoughts are common, and the risk of suicide is increased. The most common depression is unipolar, i.e. without a period of mania exhibited in the bipolar depression.<sup>72,75</sup> The median age of onset is 25 years, and the majority of depressive periods occur once and persists 3-6 months.<sup>72,75</sup> In about 20% of cases, the depression relapses or becomes chronic.<sup>76</sup> Furthermore, depression often appears in combination with anxiety; studies show that more than 50% of those experiencing depression also suffer from anxiety.<sup>77,78</sup> Anxiety as a disorder is, however, heterogenic, ranging from panic disorders to general anxiety disorder. Common symptoms are feelings of uncertainty, concentration problems, restlessness, reduced stress resistance, and, as for depression, somatic symptoms.<sup>72,79</sup> When depression and anxiety appear in combination, the symptom burden is often more severe.<sup>80</sup>

## Prevalence in the population

Diagnosed depression was rather unusual 20-30 years ago, but its incidence increased remarkably in the 1980s with the introduction of new diagnostic guidelines and new drugs on the market.<sup>81</sup> Today, depression is one of the highest ranked diseases that decrease quality of life and is one of the most common causes of sick leave and disability.<sup>58,75</sup> The point prevalence of diagnosed depression in the general population is estimated as 5-8%, and the life-time prevalence is about 15-30%. The point prevalence of anxiety in the population is even higher than that of depression, at about 6-12%, and the life-time prevalence is on the order of 25%.<sup>77,78,82,83</sup> It has been suggested that prevalence values may be overestimated when everyday stresses are not distinguished from pathological conditions.<sup>84-86</sup> However, at the same time, it is likely that only a small percentage of those with depression are identified and obtains a diagnosis, probably partly because many depressed individuals do not have the strength to seek health care. Also, many of those with mental health problems do not fulfil the criteria for diagnosis or seek health care for somatic problems, which is why their depression, in many cases, will remain undetected.<sup>87-89</sup>

## Gender and depression

Women consistently show approximately double the prevalence of depression compared with men; about one in four women and one in ten men will develop depression severe enough to obtain a diagnosis at some time in their lives.<sup>78,83,90</sup> Also, women typically experience longer episodes and have a higher risk of recurrence compared with men.<sup>76</sup> The gender differences seem to appear in the early teens; before puberty boys are diagnosed slightly more often than girls. To date, however, there is no clear understanding of what causes these gender disparities in depression. It is considered likely to be a combination of several factors: biological, social, and cultural.<sup>91-93</sup> To begin with, the diagnostic criteria for depression were initially based on observations from psychiatric wards where most of the patients were women.<sup>71</sup> In this context, depression became a women's disease. This approach maintains the historically dominant view that female sex is closely associated with mental disease.<sup>94</sup> Even today there is a risk of gender bias due to the stereotypical male-female diagnostic criteria, i.e. that the criteria for diagnosis still derive from a female norm, which can lead to women's problems being over-diagnosed and men's going unnoticed.<sup>71,95</sup> Depression appears to present differently in women vs. men. Women's depression seems more often to be connected to a negative self-evaluation and feelings of guilt, and seem more often include diffuse somatic symptoms (called atypical symptoms) like increased appetite, reduced energy, and hypersomnia. Men's depression, on the other hand, seems more often to be connected to alcohol misuse and hostility, which at present is not classified as depression.<sup>90,96-98</sup> Men and women also seem to have different perceptions about the cause of their depression. Men are more likely to describe a dramatic debut involving external factors such as high workload, while women tend to describe depression as something that they themselves are responsible for and that is based on their shortcomings.<sup>64,99</sup>

Above that, burdens related to childbirth and caregiving have been connected to an increased risk of developing depression, such as postpartum depression, in women.<sup>100</sup> Socio-economic gender inequalities in society, stressors more likely encountered by women such as domestic and sexual abuse, economic problems, and double burdens (combining a career with household work) may also contribute to the greater prevalence of depression in women compared with men.<sup>52,101</sup> In addition, there are gender differences in health behaviours; for instance, it is more socially acceptable for women to seek care for mental health problems. While men more often seem to ignore their emotions in order to fit into the traditional male norm, including a belief that seeking care is unacceptable, women seek health care and hence receive a diagnosis.<sup>64,102,103</sup> Even though women are diagnosed with depression more often than men and attempt suicide more than three times as often, the death

rates for suicides among men are at least three times higher than those among women.<sup>58,104</sup> Thus, it is important not to presuppose a priori rigid gender difference in mental health problems to avoid gender bias in diagnosing depression. Clearly, further studies are needed to investigate the gender disparities in depression.

## Antidepressants

Treatment for depression usually lasts at least 6-12 months, and includes pharmacological therapy with antidepressants as well as psychological therapies.<sup>105,106</sup> In the 1950s, the tricyclic antidepressants (TCAs) were developed and used to treat depression, but it was when the selective serotonin reuptake inhibitors (SSRIs) became available on the market in the late 1980s that the prescription of antidepressants increased considerably.<sup>4,107</sup> The rise in prescribed antidepressants in Sweden from the 1980s until today has been huge and antidepressants are now one of the most commonly prescribed classes of drugs. In 2015, almost 10% of the Swedish population was prescribed antidepressants, and more than two-thirds of these antidepressants were prescribed for women; similar figures can be found in other countries.<sup>4,108</sup> A Swedish study points out that the prevalence of depression is essentially the same today as 50 years ago.<sup>109</sup> Thus, the reason for the rise in prescribed antidepressants during recent decades is unclear. Some have interpreted it as a sign of increased awareness and better recognition of depression, rather than as a result of increasing mental health problems. It may also be explained by an increasing number of indications for antidepressant use, e.g. neuropathic pain, various anxiety disorders, premenstrual syndrome (PMS), and eating disorders.<sup>107,110,111</sup> However, there has been considerable debate about the possibility of over-prescription. Increasingly, it seems that antidepressants are prescribed because of the lack of available psychological therapies, or as treatment for social problems. It also seems as though antidepressants are sometimes used as treatment for everyday stresses. Thus, a lower threshold for prescribing antidepressants may have raised the frequency of drug use.<sup>84,112-114</sup> This has been discussed in terms of medicalization, i.e. when a “new condition” is promoted as a major health problem in order to create a market for treatment. Critics have argued that this may create a dependency on the medical profession spurred by the pharmaceutical industry.<sup>115,116</sup> On the other hand, there seems to be a considerable variation in prescribing levels between physicians, and depression has repeatedly been shown to be inadequately treated in the general population.<sup>89,117,118</sup>

The antidepressants used are all based on the monoamine theory, which states that depression is caused by functional deficit of monoamine transmitters (for instance dopamine, serotonin and norepinephrine).<sup>11</sup> This theory was introduced in the mid-1960s and resulted in depression no longer being

seen solely as a natural response to stress, but as biological. Nevertheless, the theory of chemical imbalance in neurotransmitters has been questioned, and biological determinants of depression are far from being established.<sup>119,120</sup> The antidepressants prescribed today are primarily the SSRIs, although others, for example selective noradrenaline reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs) and TCAs are also used, depending on the symptoms and severity of the depression, the person's age and the antidepressants various ADRs.<sup>4,121</sup> Together with SNRIs, SSRIs are often judged to be equally effective in treating depression and, compared with the older TCAs, SSRIs and SNRIs have a milder ADR profile.<sup>122</sup> It has been claimed that SSRIs have benefits in severely depressed individuals and that the suicide rate has decreased in connection with the introduction of the SSRIs.<sup>123</sup> However, their effect is often limited in mild-to-moderate depression, where psychological therapies may be a better alternative.<sup>106,124</sup> Men and women differ not only in the number of antidepressants used, but also in type of antidepressants, where women are prescribed SSRIs more often than men and men are prescribed TCAs more often than women.<sup>4</sup> It has been suggested that gender affects the response to different types of antidepressants.<sup>125</sup> However, supporting data are limited and sometimes conflicting, and current treatment guidelines do not consider gender.

## Drug utilization and depression

People with depression are high health care utilizers and are prescribed drugs, for mental as well as for somatic health problems, much more often than those without depression.<sup>126,127</sup> This can partly be explained by the high degree of comorbidity between depression and other health problems. The prevalence of depression is significantly higher in people with chronic conditions, and depression is also connected to more severe symptoms of somatic conditions.<sup>128,129</sup> Further, medically unexplainable somatic symptoms like different pain conditions and irritable bowel disease are related to depression and often result in a high degree of utilization of health care as well as drugs.<sup>130</sup> Somatic health problems can cause depression due to the burden and disability that they bring. Conversely, depression can cause somatic health problems and premature death due to, for example, poor health behaviours such as an unhealthy lifestyle and non-adherence to medical recommendations.<sup>32,131</sup> Whether depression causes other conditions, or whether depression is a consequence of other conditions, is often hard to clarify however, as both causal pathways are likely.<sup>132</sup> Many patients consult health care for somatic problems and not primarily mental health problems, as mentioned before, and their depression could therefore go undetected.<sup>89</sup> It is important to recognize the comorbidity, as it complicates help-seeking, diagnosis, and treatment, and the likelihood of recovery is decreased.<sup>133</sup> The relationship between mental and somatic conditions is thus important to consider

in public health. Improving mental health in the population would also improve somatic health and vice versa.<sup>133</sup>

In some conditions, the relationship between the condition and depression has been found to differ between men and women. For example, for pain conditions, dermal conditions, and obesity, women seem to be more mentally affected than men are.<sup>134-136</sup> Yet few studies have focused on gender differences in the comorbidity between depression and other conditions, and hence the use of drugs for other conditions. Further, although it is well-known that people with mental health problems use more drugs than people in general, and that women use more drugs than men, studies on polypharmacy connected to depression focusing on gender are limited. High levels of drug use generate, as previous mentioned, several drug-related problems and are essential to consider.

## Overall and specific aims

The overall aim of the thesis was to investigate the influence of gender and depression on drug utilization by examining prescription of drugs and self-reported use of drugs in the general Swedish population.

The specific aims were to:

- Study I      Study the association between gender and self-reported non-adherent behaviours and reasons for non-adherence.
- Study II     Study the association between self-reported anxiety and depression and self-reported non-adherent behaviours and reasons for non-adherence.
- Study III    Study gender differences in the relationship between self-reported depression and prescribed antidepressants and in the type of antidepressants prescribed.
- Study IV    Study the association between prescribed antidepressants and other prescribed drugs, different types of drugs as well as polypharmacy, from a gender perspective.

# Methods

The studies in the present thesis originated from two population-based cross-sectional surveys using questionnaires (Study I, II and III), and from register data from the Swedish Prescribed Drug Register (SPDR) (Study III and IV); see Table 1. Thus, drug utilization was studied from the participant's own perspective by self-report as well as on the basis of prescription data from the SPDR.

Table 1. Overview Study I-IV

Study	Study Design	Study period	Response rate	Study population	
I & II	Population-based cross-sectional with postal questionnaire n=7,985 18-84 years	Oct 2004- Jan 2005	4,875 respondents (61.1% of total). 4,709 left after deleting missing values	<b>Study I:</b> 2,802 users <sup>a</sup> (59.5% of respondents)	<b>Men</b> 1,084 (50.2% of men)
					<b>Women</b> 1,718 (67.4% of women)
				<b>Study II:</b> 2,782 users <sup>a</sup> (59.1% of respondents) left after deleting missing HADS-values	<b>Men</b> 1,077 (49.9% of men)
					<b>Women</b> 1,705 (66.9% of women)
III	Population-based cross-sectional with postal questionnaire and register data n=16,000 18-84 years	Oct 2012- Jan 2013 and 6 months before	7,725 respondents (48.3% of total)	7,618 respondents left after deleting missing HADS-values including users <sup>b</sup> and non-users of prescribed antidepressants	<b>Men</b> 3,435 (44.8% of total) <b>Women</b> 4,183 (54.5% of total)
IV	Population-based with register data n=3,884,468 18-84 years	Oct-Dec 2016		3,884,468 users <sup>c</sup> of prescription drugs	<b>Men</b> 1,654,091 (42.6% of total) <b>Women</b> 2,230,377 (57.4% of total)

<sup>a</sup>users: participants who reported use of at least one prescription drug. <sup>b</sup>users: participants who were prescribed at least one antidepressant. <sup>c</sup>users: participants who were prescribed at least one drug. HADS= the Hospital Anxiety and Depression Scale.

**Prescription drugs:** drugs regulated by laws and dispensed at a pharmacy with a prescription from a licensed professional, e.g., physician.

# Study I

## Study population and data collection

Study I was based on a cross-sectional survey performed in the general Swedish population from October 2004 to January 2005. A postal questionnaire was sent to a random sample of the population (n=7,985) aged 18-84 years drawn from the national population register; see Table 1. Statistics Sweden (responsible for the population register in Sweden) administered the data collection and linked the returning questionnaires with sociodemographic information (age, sex, marital status, and education) from national registers, through the personal identification number (an unique lifetime personal identifier given to all Swedish citizens).<sup>137</sup> The response rate was 61.1%; higher among women (65.2%) than among men (56.8%). Of the respondents, 59.5% (50.2% men and 67.4% women) reported prescription drug use during the two weeks before receiving the questionnaire and analyses were based only on these participants, giving a study population of 2,802 participants.

## Questionnaire

The questionnaire covered questions on use of prescription drugs, non-adherent behaviours, and reasons for non-adherence. The questions on adherence were based on the Swedish survey of living conditions<sup>138</sup> and on general knowledge in the field.<sup>139</sup> The questionnaire also contained questions on personal economy, attitudes to drugs, somatic health problems and mental health problems; these questions were, together with information from national registers (age, marital status, and education), controlled for as potentially confounding variables; see Statistical analyses.

### **Use of prescription drugs**

The participants were asked about use of prescription drugs during the two weeks prior to receiving the questionnaire. Those who reported use of at least one prescription drug were classified as users of prescription drugs.

### **Non-adherent behaviours**

The questions on various non-adherent behaviours were phrased: “Have you ever...” followed by alternatives where several choices could be made: “forgotten to take your medication?”, “dispensed a prescription but not taken the medication?”, “changed the dosage on your own accord?”, “discontinued your medical treatment?”, “not had a prescription dispensed”? If at least one behaviour was reported, the participants were classified as non-adherent. Forgetting was classified as unintentional non-adherence, and the rest were classified as intentional non-adherence.

## **Reasons for non-adherence**

The questions on the reasons for non-adherence were phrased: “What was the reason for not following the drug regimen?” followed by alternatives where several choices could be made: “I did not need the medication”, “I recovered”, “I developed unpleasant adverse drug reactions”, “I had a fear of potential adverse drug reactions”, “the treatment was not effective”, “I wanted to save money”. The reason “I had practical problems” was excluded from the analyses because too few participants chose this response alternative.

## **Personal economy (i), attitude to drugs (ii), somatic health problems (iii), and mental health problems (iv)**

(i) The participants were asked if they had experienced any personal economic problems (e.g., in paying rent, bills, food) during the past 12 months.

(ii) The participants were asked if they judged drugs to be something positive or as something negative/dangerous.

(iii) The participants were asked about different current or chronic somatic health problems: in vision or hearing, hypertension, heart problems, obstructive lung problems, diabetes, cancer, gastrointestinal problems, rheumatism, musculoskeletal pain, and headache.

(iv) The participants were asked about different current or chronic mental health problems: anxiety, sleeping problems, and depression.

## **Statistical analyses**

The statistical analyses were performed using the Statistical analysis system (SAS®9.2, Cary, NC, USA). To examine gender differences in intentional and unintentional non-adherence, the chi-square test was performed ( $p=0.05$ ). The associations between gender and non-adherent behaviours and between gender and reasons for non-adherence (women vs. men; men as a reference group) were analysed using logistic regression analyses, and odds ratios (OR) with 95% confidence intervals (CI) were obtained. Information from the questionnaire and from national registers resulted in five sets of variables potentially confounding the differences between men and women: age, socioeconomic variables (marital status, education and personal economy), attitude to drugs, somatic health problems and mental health problems. The sets of variables in the multivariate analyses were added in consecutive order; step one controlled for age, step two for socioeconomic variables, step three for attitude to drugs, step four for somatic health problems and step five for mental health problems.

## Study II

### Study population and data collection

Study II was based on the same cross-sectional survey, performed during 2004-05 among the general Swedish population, used in Study I; see Table 1. Analyses in Study II were based only on users, just as in Study I. Participants with more than two missing values from the Hospital Anxiety and Depression Scale (HADS)<sup>140</sup> were excluded from the analyses, giving a study population of 2,782 participants, i.e. users (49.9% men and 66.9% women).

### Questionnaire

The same items covering the participant's use of prescription drugs, non-adherent behaviours, and the reasons for non-adherence used in Study I were used also in Study II. Moreover, Study II included the HADS as well.

### **The Hospital Anxiety and Depression Scale**

To measure self-rated mental health problems, a number of screening instruments have been developed. One such instrument is the HADS, a questionnaire for self-estimation of symptoms of anxiety and depression experienced the week prior to completing the questionnaire. At first, the HADS was developed for medical out-patient clinics for detecting clinically relevant problems. Later, it was found to also work well in the general population,<sup>141</sup> and has, during the years, been widely used in both clinical contexts and research.<sup>142</sup> The scale focuses on symptoms connected to anxiety or depression and does not involve somatic symptoms that might stem from a somatic condition; see appendices. It contains two subscales, one each for anxiety and depression, which can be used for estimating symptoms of anxiety and depression independently or summarized. The HADS scores (ranging from 0-21 for each subscale) can, for example, be interpreted by using cut-off scores that indicate different levels of anxiety and depression. The designers of the scale initially suggested different cut-off levels to identify subgroups according to symptom severity. A score of 8 and above indicates at least mild symptoms and was the cut-off used in this study. Thus, participants scoring  $\geq 8$  on the anxiety and depression scale were classified as having anxiety and depression. Participants were divided into groups according to the presence of symptoms of anxiety, depression, or both, or the absence of these symptoms.

## Statistical analyses

As in Study I, the SAS was used to perform the statistical analyses also in Study II. Logistic regression analyses (OR; 95% CI) were used to analyse the associations between anxiety/depression and non-adherent behaviours and between anxiety/depression and reasons for non-adherence (anxiety/depression vs. no anxiety/depression; no anxiety/depression as a reference group). Age and gender were controlled for as potential confounders.

## Study III

### Study population and data collection

Study III was based on a cross-sectional survey performed in the general Swedish population from October 2012 to January 2013 as well as on data on prescribed antidepressants from the SPDR<sup>4</sup>; see Table 1. A postal questionnaire was sent to a random sample of the population (n=16,000) aged 18-84 years drawn from the national population register. Data collection was administered by Statistics Sweden, who linked the returning questionnaires with sociodemographic information (age and sex). The response rate was 48.3%; higher among women (54.9%) than among men (45.1%). Respondents with more than two missing values from the HADS were excluded from the analyses, giving a study population of 7,618 participants (44.8% men and 54.5% women).

### Questionnaire and register data

The HADS used in Study II was used also in Study III, and the same cut-off level ( $\geq 8$ ) was used. However, in Study III, participants were divided into groups based only on depression, i.e. the presence of symptoms of depression, or the absence of these symptoms. Information on prescribed antidepressants was obtained from the SPDR 0-6 months prior to completing the HADS questionnaire. The participants who had at least one antidepressant prescribed during these 6 months were classified as users of antidepressants and the rest as non-users. Information from the HADS was linked (through the personal identification number) to prescription data from the SPDR. Antidepressants (N06A) were categorized according to the anatomical therapeutic chemical classification (ATC) system (4<sup>th</sup> level, see Table 2),<sup>143</sup> as TCAs (N06AA, e.g. amitriptyline, imipramine), SSRIs (N06AB, e.g. citalopram, fluoxetine), “others” (N06AX, including SNRIs [e.g. venlafaxine] and tetracyclic antidepressants [TeCAs, e.g. mirtazapine]), and MAOIs (N06AF, N06AG, e.g. moclobemide). The MAOIs were excluded because there were too few users.

## The Swedish Prescribed Drug Register

The SPDR is a Swedish national database established in 2005, regulated by the Swedish government (SFS 2005:363) and held by the National Board of Health and Welfare.<sup>4,144</sup> The SPDR contains data on all dispensed prescriptions for patients in ambulatory care from the entire Swedish population, and is widely used in research.<sup>145</sup> It contains information on age, sex, personal identification number, place of residence, the dispensed item (substance and amount, but not the indication for the treatment), the dates of prescribing and dispensing, and the prescribers' profession and practice, as well as reimbursement. Sweden has a public insurance system that includes most prescription drugs and that sets a limit on personal annual drug expenses (at present maximum 2200 SEK, around € 220, within 12 months). The register does not cover, for example, over-the-counter (i.e., non-prescription) drugs, herbal remedies, or drugs used in hospitals or nursing homes.

## The Anatomical Therapeutic Chemical classification system

All drugs in the SPDR are classified according to the ATC system.<sup>143</sup> The World Health Organization International Working Group for Drug Statistics Methodology determines the classification, and the system is now widely accepted as regards how to categorize drugs. In the ATC system, the active substances are divided into different groups according to the organ or system affected and their therapeutic, pharmacological and chemical properties. The drugs are divided into fourteen anatomical main groups (1<sup>st</sup> level), with therapeutic (2<sup>nd</sup> level), pharmacological (3<sup>rd</sup> level), and chemical (4<sup>th</sup> and 5<sup>th</sup> level) subgroups. As a clarifying example, the ATC code for citalopram is shown in Table 2. The first level, the N, specifies that the drug belongs to the class of drugs that act on the nervous system. The next level, 06, specifies it further as belonging to the group of psychotropic drugs, the next level A as an antidepressant, etc.

Table 2. The ATC code for citalopram

N	Nervous system (1 <sup>st</sup> level, anatomical main group)
N06	Psychotropic drugs (2 <sup>nd</sup> level, therapeutic subgroup)
N06A	Antidepressants (3 <sup>rd</sup> level, pharmacological subgroup)
N06AB	SSRIs (4 <sup>th</sup> level, chemical subgroup)
N06AB04	Citalopram (5 <sup>th</sup> level, chemical substance)

## Statistical analyses

Like in Study I and II, the SAS was used to perform statistical analyses in Study III. Chi-square tests ( $p=0.05$ ) were performed to examine gender differences in the prevalence of depression, and antidepressants, and to examine gender differences in the relationship between depression and antidepressants and type of antidepressants. Logistic regression analysis (OR; 95% CI) was used to analyse the association between gender and depression (men vs. women; women as a reference group), controlling for age as a potential confounder.

## Study IV

### Study population and data collection

Study IV was based on data from the SPDR, including the entire section of the Swedish population, aged 18-84 years, who had at least one drug prescribed from October to December 2016, giving a study population of 3,884,468 participants (42.6% men and 57.4% women); see Table 1. Those who had at least one antidepressant (N06A) prescribed during the 3 months studied were classified as users of antidepressants. The same classification of users was also applied to all the other ATC groups. Analyses regarding polypharmacy (defined as  $\geq 4$  types of drugs other than antidepressants, i.e. at least 5 drugs including antidepressants)<sup>39</sup> also concerned ATC groups. The ATC groups were counted once, even if drugs from the group were dispensed more than once during the study period.

### Register data

Drugs were primarily divided into the anatomical main groups (1<sup>st</sup> level) in the ATC system. However, in main group A, diabetes (A10, 2<sup>nd</sup> level), and in main group N, analgesics (N01-N02, 2<sup>nd</sup> level) and antidepressants (N06A, 3<sup>rd</sup> level), subgroups were analysed separately due to the diverse indications compared to the other drugs in those ATC groups. The ATC groups P (Antiparasitic products, foremost preventive and over-the-counter drugs), and V (Various, foremost diagnostic aids and antidotes) were excluded from the analyses.

## Statistical analyses

The IBM SPSS Statistics for Windows (version 22.0, Armonk, NY: IBM Corp.) was used to perform the statistical analyses in Study IV. Chi-square tests ( $p=0.05$ ) were performed to examine gender differences in the prevalence of antidepressants in the study population. Logistic regression analyses

(OR; 95% CI) were used to analyse the associations between antidepressants and other types of prescribed drugs (different ATC groups as well as polypharmacy) among men and women (antidepressants vs. not antidepressants; not antidepressants as a reference group), controlling for age as a potential confounder.

## Ethical considerations

The present thesis complies with ethical research requirements. Study I and II were approved by Statistics Sweden Ethics committee in concordance with Swedish legislation before 2008.<sup>146</sup> Study III (Reg.no. 2012/073) and IV (Reg.no. 2016/235) were approved by the Regional Ethical Review Board in Uppsala, Sweden. Participation in Study I, II, and III was voluntary and information about the study objectives was sent with the questionnaires. Filling in and returning the questionnaire was regarded as the respondents giving their consent to participate in the study. The data were anonymous and unidentifiable for the researchers.

# Results

## Study I

The total numbers of respondents and participants, i.e. users, can be found in Table 1. In total, 66.4% of the users (65.4% men and 67.0% women) reported non-adherence. No overall statistically significant gender difference was found. However, women reported on average more intentional non-adherent behaviours than men did: 1.34 vs. 1.19 ( $p < 0.01$ ).

Regarding the different non-adherent behaviours, some gender differences were found in the logistic regression analyses; see Table 3. Forgetting to take the drug, i.e. unintentional non-adherence, was the most commonly reported behaviour for both men and women; and the logistic regression analysis showed men to be more likely to forget than women. Also, men were found to be more likely to changing the dosage on one's own accord. Women, on the other hand, were found to be more likely to report dispensing but not using the drug. When the five sets (age, socioeconomic variables, attitude to drugs, somatic health problems and mental health problems) of potential confounders were controlled for, the gender differences remained.

Table 3. Logistic regression analysis associating non-adherent behaviours with gender (women vs. men), controlling for potential confounders

<b>Non-adherent behaviours</b>	<b>OR<sup>a</sup> (CI)</b>	<b>OR<sup>b</sup> (CI)</b>
Forgot to take medication	0.79 (0.67-0.92)	0.81 (0.67-0.97)
Dispensed but not used the medication	1.35 (1.12-1.64)	1.25 (1.01-1.55)
Changed the dosage	0.67 (0.55-0.82)	0.62 (0.50-0.78)
Discontinued treatment	1.12 (0.93-1.36)	1.03 (0.83-1.28)
Did not dispense a prescription	1.14 (0.94-1.40)	1.05 (0.84-1.31)

<sup>a</sup>adjusted for age. <sup>b</sup>adjusted for age + socioeconomic variables + attitude to drugs + somatic problems + mental problems. OR = odds ratio; CI = 95% confidence interval.

Also concerning the reason for non-adherence, some gender differences were found. In Table 4, the results of the logistic regression analyses can be found. Men were found to be more likely to report recovery, while women were found to be more likely to report development of ADRs as reason for

non-adherence. The ORs for the reasons for non-adherence were not affected to any great extent when controlling for the potential confounders, with one exception. The gender difference concerning the fear of potential ADRs was statistically significant in the logistics regression analyses when controlling for age only, but not after controlling for the other potential confounders.

Table 4. Logistic regression analysis associating reasons for non-adherence with gender (women vs. men), controlling for potential confounders

<b>Reasons for non-adherence</b>	<b>OR<sup>a</sup> (CI)</b>	<b>OR<sup>b</sup> (CI)</b>
No need of medication	1.10 (0.87-1.38)	1.12 (0.87-1.44)
Recovered	0.76 (0.60-0.95)	0.72 (0.56-0.93)
Developed ADRs	1.98 (1.46-2.69)	2.14 (1.51-3.04)
Fear of ADRs	1.59 (1.17-2.17)	1.40 (1.00-1.98)
Treatment was not effective	0.97 (0.74-1.34)	0.89 (0.64-1.24)
Wanted to save money <sup>c</sup>	0.77 (0.50-1.21)	0.70 (0.43-1.13)

<sup>a</sup>adjusted for age. <sup>b</sup>adjusted for age + socioeconomic variables + attitude to drugs + somatic problems + mental problems. <sup>c</sup>age was not controlled for because of the small number of observations. ADR = adverse drug reaction; OR = odds ratio; CI = 95% confidence interval.

## Study II

The total numbers of respondents and participants, i.e. users, can be found in Table 1. In total, 11.0% of the users reported only anxiety, 3.9% reported only depression and 8.4% reported both anxiety and depression.

The results from the logistic regression analysis concerning non-adherent behaviours can be found in Table 5. Anxiety and depression, both independently and in combination, were associated with unintentional non-adherence, as well as, to a greater extent, with intentional non-adherence. Overall, depression was, compared with anxiety, more strongly associated with the different non-adherent behaviours, especially concerning intentional non-adherence.

Table 5. Logistic regression analysis associating non-adherent behaviours with anxiety/depression (anxiety/depression vs. no anxiety/depression), controlling for age and gender as potential confounders

	Forgot to take medication	Any intentional non-adherence	Dispensed but not used the medication	Changed the dosage	Discontinued treatment	Did not dispense a prescription
	OR (CI)	OR (CI)	OR (CI)	OR(CI)	OR (CI)	OR (CI)
<b>Anxiety</b>	1.33(1.06-1.69)	1.62(1.27-2.05)	1.33(1.03-1.73)	1.94(1.48-2.55)	1.92(1.49-2.48)	1.43(1.09-1.88)
<b>Depression</b>	1.45(1.02-2.06)	2.60(1.80-3.74)	1.92(1.32-2.82)	2.36(1.59-3.50)	2.41(1.64-3.53)	2.55(1.72-3.80)
<b>Both</b>	1.67(1.31-2.14)	2.06(1.60-2.64)	1.39(1.06-1.81)	2.32(1.76-3.04)	1.58(1.20-2.07)	2.10(1.60-2.74)

OR = odds ratio; CI = 95% confidence interval.

The associations between anxiety and depression and the reasons for non-adherence differed somewhat in the logistic regression analysis; see Table 6. For example, depression, independently and in combination with anxiety, was associated with the development of ADRs, while anxiety, independently and in combination with depression, was associated with a fear of developing ADRs. Further, depression was associated with the reason ‘recovered’ and, independently and in combination with anxiety, the reason that ‘treatment was not effective’. Anxiety, on the other hand, was, independently and in combination with depression, associated with ‘wanted to save money’.

Table 6. Logistic regression analysis associating reasons for non-adherence with anxiety/depression (anxiety/depression vs. no anxiety/depression), controlling for age and gender as potential confounders

	No need of medication	Recovered	Developed ADRs	Fear of ADRs	Treatment was not effective	Wanted to save money
	OR (CI)	OR (CI)	OR (CI)	OR(CI)	OR (CI)	OR (CI)
<b>Anxiety</b>	1.01(0.74-1.37)	1.18(0.87-1.61)	1.21(0.81-1.81)	2.60(1.81-3.72)	1.26(0.83-1.90)	2.04(1.14-3.64)
<b>Depression</b>	1.06(0.64-1.75)	1.87(1.19-2.93)	2.60(1.57-4.31)	1.55(0.81-2.98)	2.07(1.18-3.62)	2.41(0.99-5.86)
<b>Both</b>	0.81(0.57-1.14)	0.82(0.57-1.17)	2.32(1.63-3.29)	2.67(1.85-3.85)	2.60(1.83-3.70)	3.79(2.26-6.33)

ADR = adverse drug reaction; OR = odds ratio; CI = 95% confidence interval.

### Study III

The total numbers of respondents and participants, i.e. users and non-users of antidepressants, can be found in Table 1. In total, 11.7% (n=891) reported depression (12.3% men and 11.2% women). The chi-square test was statistically non-significant; however, in the logistic regression analysis the difference between men and women was statistically significant, i.e. men were more likely to report depression (OR 1.23; CI 1.06-1.41). Further, 7.6% (n=592) of the study population had been prescribed at least one antidepressant during the 6 months prior to the HADS evaluation, significantly more women (9.8%) than men (5.3%) ( $p<0.0001$ ). It was more common among men than among women to have more than one type of antidepressant prescribed during the study period ( $p<0.05$ ).

In Table 7, the relationship between depression and antidepressants can be found. Among men, 1.8% reported depression and used antidepressants, 10.5% reported depression but did not use antidepressants, and 3.6% used antidepressants without reporting depression. The corresponding figures for women were 2.6%, 8.6%, and 7.2%. The differences between men and women were statistically significant ( $p<0.001$ ).

Table 7. Relationship between self-reported depression and prescribed antidepressants, by gender

Men n=3,435				Women n=4,183				p-value <sup>a</sup>
Percentage proportions (%)				Percentage proportions (%)				
Depression		Not depression		Depression		Not depression		
AD-users	Non-users	AD-users	Non-users	AD-users	Non-users	AD-users	Non-users	
1.8	10.5	3.6	84.1	2.6	8.6	7.2	81.6	< 0.001

<sup>a</sup>Chi<sup>2</sup> analyses comparing men and women. AD = antidepressant.

The results with regard to the type of antidepressant prescribed can be found in Table 8. SSRIs were the most commonly prescribed antidepressants for men as well as women. However, women used SSRIs more often than men did ( $p<0.05$ ), while men used antidepressants from the ATC group ‘others’ (e.g., SNRIs and TeCAs) more often than women did ( $p<0.01$ ). No statistically significant gender difference was found for the TCAs.

Table 8. Types of antidepressant prescribed (ATC classification), by gender

ATC classification	Men n=182	Women n=410	<i>p</i> -value <sup>a</sup>
Percentage TCAs (N06AA)	14.8	10.2	N.S.
Percentage SSRIs (N06AB)	62.8	71.0	<0.05
Percentage “others” (N06AX), e.g., SNRIs and TeCAs	39.3	28.1	<0.01

<sup>a</sup>Chi<sup>2</sup> analyses comparing men and women. N.S. = not significant.

## Study IV

The total number of participants, i.e. users, can be found in Table 1. In total, 15.3% of the study population had at least one antidepressant prescribed during the 3 month period, significantly more women (17.4%) than men (12.4%) ( $p < 0.001$ ).

In Table 9, the results from the logistic regression analyses are presented. Men and women showed somewhat different patterns. For both men and women, there were associations between antidepressants and drugs for alimentary tract problems, drugs for blood, analgesics, drugs for the nervous system, drugs for respiratory problems, and polypharmacy. The association was stronger for women compared to men concerning drugs for alimentary tract problems, drugs for blood, analgesics, and drugs for respiratory problems. However, for drugs for the nervous system and polypharmacy, the association was the reversed, stronger in men than in women. Further, for women, but not men, there were associations between antidepressants and drugs for diabetes, drugs for dermatological problems, systemic hormones, and drugs for musculoskeletal problems.

Table 9. Logistic regression associating different types of prescribed drugs with antidepressants (antidepressants vs. no antidepressants) by gender, controlling for age as potential confounder

ATC classification	Men	Women
	OR (CI)	OR (CI)
A01-A09, A11-A16 Alimentary tract & metabolism	1.67 (1.65-1.69)	1.69 (1.67-1.70)
A10 Diabetes	0.88 (0.87-0.89)	1.10 (1.08-1.11)
B01-B06 Blood & blood forming organs	1.26 (1.24-1.28)	1.42 (1.40-1.43)
C01-C10 Cardiovascular system	0.77 (0.76-0.78)	0.99 (0.98-1.00)
D01-D10 Dermatologicals	0.87 (0.86-0.88)	1.03 (1.02-1.04)
G01-G04 Genitourinary systems & sex hormones	0.95 (0.94-0.97)	0.60 (0.59-0.60)
H01-H05 Systemic hormonal preparations	1.00 (0.98-1.02)	1.03 (1.02-1.04)
J01-J07 Antiinfectives for systemic use	0.60 (0.59-0.61)	0.80 (0.79-0.80)
L01-L04 Antineoplastic & immunomodulating agents	0.75 (0.73-0.77)	0.83 (0.81-0.85)
M01-M09 Musculoskeletal system	0.80 (0.79-0.82)	1.16 (1.15-1.17)
N01-N02 Analgesics	1.55 (1.53-1.56)	1.74 (1.72-1.75)
N03-N05 + N07 Nervous system	5.06 (5.01-5.11)	4.47 (4.44-4.51)
R01-R07 Respiratory system	1.02 (1.01-1.03)	1.25 (1.24-1.26)
S01-S03 Sensory organs	0.77 (0.76-0.79)	0.90 (0.88-0.91)
Polypharmacy <sup>a</sup>	2.44 (2.42-2.47)	2.34 (2.32-2.36)

<sup>a</sup>Defined as  $\geq 4$  types of drugs other than antidepressants.

OR= odds ratio; CI= 95 % confidence interval.

# Discussion

Drugs are often essential in the treatment of disease. However, diagnosis and prescribing need to be correct, and the drugs need to be taken according to the regimen, otherwise they may cause more harm than good. The present thesis evaluates drug utilization in the general population, including prescription of drugs and self-reported use of drugs, with a focus on gender and depression. Both gender and depression have been found to be important factors affecting drug utilization; nevertheless, the number of studies with this focus and performed in the general population is limited.

## Gender and non-adherence

Gender has been found to be one of the most important factors influencing health behaviours.<sup>50,60,147</sup> The findings in Study I indicate that men and women have different behaviour patterns concerning following drug regimens. Women seemed to be more aware than men when choosing not to take a drug, in that women reported overall more intentional non-adherent behaviours. One possible explanation is the general greater awareness about health among women than among men.<sup>60,63</sup> The fact that women were found more likely to dispensing but not using a drug further indicates awareness. Perhaps women more often read the package leaflet before starting a drug therapy and are thereby deterred by possible ADRs. However, men were found more likely to intentionally changing the dosage. Changing the dosage on one's own accord could be seen as risky health behaviour. Men appear to be more likely than women to engage in risky health behaviours,<sup>147</sup> and it is more common for men to die due to drug intoxications than for women to do so.<sup>148</sup>

Further, men were found more likely to forgetting to take a drug, i.e. unintentional non-adherence. The fact that men seem to forget to take a drug more often than women do has also been found in other studies.<sup>149</sup> However, forgetfulness is not always a totally passive process, i.e. unintentional non-adherence may be more intentional than it seems.<sup>28,149</sup> Forgetting to take a drug could be a sign of disease denial, which may be connected to masculine attitudes towards health, like not expressing symptoms of discomfort and obscuring problems.<sup>64</sup> Although an understanding of disease severity seems to be associated with better adherence,<sup>33</sup> having perceived symptoms seems to influence adherence more than the actual threat.<sup>25</sup> That is, if symptoms

that trigger behaviour, like taking a drug, are not expressed and the disease is denied, non-adherence may occur. Further, men were more likely to report 'recovery' as a reason for non-adherence, which may be connected to the fact that men more often deny disease symptoms. One previous study found that men, compared with women, were more prone to stop taking their antidepressants prematurely as soon as they felt less functionally impaired by their depressive symptoms.<sup>150</sup> However, in many conditions, the absence of symptoms is not equivalent to recovery, and discontinuing may be connected with a risk of relapse.

Concerning the reason for non-adherence, in Study I, development of ADRs was found to be an important reason for not taking a prescribed drug among women, findings that correspond with other studies.<sup>23</sup> Any aspect of treatment involving safety, like a belief that the drug is harmful and development of ADRs, has been found to decrease adherence.<sup>23,25</sup> Women experience more ADRs than men do, and women tend to assess ADRs, including the teratogenic risks, as more serious than men do.<sup>51,151</sup> Men and women seem also differ in attitudes to drugs. Women have been found to have more negative attitudes to drugs than men do and to be more likely to think of drugs as something dangerous,<sup>23,152</sup> possibly due to their greater experience of ADRs. Moreover, the overall greater drug use among women compared with men probably entails experience of ADRs, which can trigger a negative attitude. The attitudes towards drugs have been found to greatly affect adherence negatively.<sup>26,29,153</sup> In our study, ADRs, i.e. perceived barriers, appeared to be a much more important reason for non-adherence among women than among men.

## Depression and non-adherence

In Study II, the findings imply that both depression and anxiety are associated with non-adherence, intentional as well as unintentional. The connection between depression and non-adherence is well-established.<sup>32</sup> Regarding anxiety, however, previous results have been somewhat conflicting.<sup>154</sup> The explanation for this is unclear, but may be related to the heterogeneity of anxiety, including different disorders. Anxiety can range from panic disorders, which seem not to affect adherence, to generalized anxiety disorder, which can lead to either increased or decreased adherence.<sup>32,154</sup> In our study, depression was more strongly associated with non-adherence, especially intentional non-adherence, than anxiety was. Various reasons for the strong relationship between depression and non-adherence have been suggested. For example, reduced energy could make the drug intake too heavy a burden, and feelings of hopelessness could create more negative expectations of treatment outcomes,<sup>32</sup> i.e. the perceived benefits might not outweigh the barriers. Moreover, decreased levels of cognitive function and lack of trig-

gers (such as absence of social support, common in depression due to social isolation) decrease adherence.<sup>32,155</sup> Depression also leads to low self-efficacy, thus negatively affecting the ability to perform health behaviour, like adherence.<sup>156</sup> In addition, depressed people use more drugs than people in general,<sup>126</sup> resulting in more opportunities to be non-adherent. It is important to detect depression, for example to identify possible future non-adherence. A negative spiral could plausibly be initiated if the depression is not discovered: poor mental health can result in non-adherence, which can result in poor somatic health, which can result in even poorer mental health and non-adherence, and so on.<sup>32</sup>

Further, in relation to both anxiety and depression, we found ADRs important reasons for not taking a drug, however, the associations differed somewhat. The fear of ADRs as a reason for non-adherence was associated more with anxiety, while the development of ADRs was associated more with depression. The association between the fear of ADRs and anxiety can possibly be related to anxieties and concerns about drugs that lead to non-adherence. The association between the development of ADRs and depression might be a result of that depression leading to increased sensitivity to drugs and thus development of ADRs that might cause non-adherence. Also, psychotropic drugs used to treat mental health problems are one of the drug classes most frequently reported to cause ADRs.<sup>51</sup> In addition, one has to consider the timing of the depression – the depression might be a result of the ADRs. ADRs as a reason for non-adherence in anxiety and depression may well be connected to the overall great drug use that probably leads to the fear as well as actual development of ADRs. Although there are some differences, ADRs seemed to be important barriers to taking the drug in both anxiety and depression.

## How to improve adherence

Given that it is very common, non-adherence should always be considered when evaluating a patient with poor treatment outcomes. Improving adherence has been found to enhance the effectiveness of drug treatments,<sup>20</sup> however, many interventions have failed in the long run.<sup>19</sup> Despite the considerable body of research on non-adherence, the question of how to improve adherence is far from solved and further studies are indeed needed. It is currently common to focus methods of improving adherence mainly focusing on forgetfulness, thus to use memory aids, for example.<sup>157</sup> While these methods are necessary, in that unintentional non-adherence have been repeatedly found to be common, particularly among men,<sup>149</sup> our findings indicate that intentional non-adherence requires more attention, particularly among women and among people with depression. It is moreover essential to identify the individual reasons for non-adherence. The findings in Study I

and II point toward ADRs as important reasons for not taking a drug among women and among people with mental health problems. It is thus crucial to discuss the benefits of the treatment with respect to the barriers, like ADRs. For instance, women seem to overestimate the risk of drug use during pregnancy and therefore information is essential.<sup>158</sup> Most people want more information about their medical treatment,<sup>24</sup> and education has been found to be an effective approach to overcoming barriers to treatment.<sup>19</sup> However, though efforts to improve adherence may improve the benefits of the drugs, they may also increase the ADRs. It is therefore essential that the prescribing be correct, i.e. that the treatment and dosage be suitable, so as to avoid unnecessary ADRs. Nevertheless, because ADRs as well as drug-related hospital admissions are common,<sup>45-47</sup> one can understand that prescribing is not always proper and that people sometimes hesitate to take their drugs. Consequently, adherence itself should not be the main target, but a tool for increasing health.<sup>159</sup>

## Gender and antidepressants

It is well-known that women are diagnosed with depression and treated with antidepressants more often than men are,<sup>90,108</sup> though it is difficult to determine whether this indicates that women are more depressed than men are. In Study III, we found that women used antidepressants without reporting depression twice as often as men did. This could be due to depression being in remission or due to antidepressant treatment for indications other than depression, such as pain disorders and eating disorders – disorders generally more common among women than men.<sup>160</sup> However, it may also be a sign that women are being over-treated with antidepressants. The great use of health care among women and the fact that women more often receive a prescription when visiting health care are probably one part of the explanation.<sup>62,67</sup> Women may be pathologized due to stereotyped gender standards in diagnosis, standards by which women historically were considered more likely to develop mental health problems and which still remain today.<sup>94</sup>

For as yet unclear reasons, the increased prescription of antidepressants in recent decades is especially notable among women.<sup>4,107</sup> It is unclear whether women actually have become more depressed, or if women in the past were under-diagnosed and under-treated. Perhaps the increased openness about, and decreased tolerance for, mental health problems is especially pronounced among women. Also, it seems that even mild symptoms are now considered indicative of disease and treated with drugs, although effectiveness is often limited in cases of mild-to-moderate depression.<sup>124</sup> The trend according to which it is abnormal to sometimes be unhappy – and normal to always be on top and achieve maximum results, shrinks the realm of “normal”.<sup>161</sup> Throughout history, women have been indoctrinated in the belief

that they are ill and need to be treated when they express their emotions beyond what is socially expected.<sup>94,162,163</sup> The possible medicalization of emotions<sup>115</sup> probably increases this belief further – if you cannot achieve at the highest level, then you require treatment. Perhaps women today are diagnosed as ill when they cannot live up to the high demands of today's society, often including double burdens. Getting a diagnosis can be both positive and negative for the individual. The diagnosis can be stigmatizing and can make you focus on the symptoms rather than the cause of the symptoms, but, can also provide a confirmation of an invisible suffering and access to treatment.<sup>163</sup> Today, we have great faith in the natural sciences and in biological solutions to all problems. However, as mentioned before, focusing on biomedical models has been called into question,<sup>120</sup> as it is claimed to lead to a disregard for and marginalization of the impact of the underlying social causes. The problems tend to be explained on an individual basis and not as a general social problem.

*"It needs a little chemical help to be a super mom"*

Susan, 44 year old, *Time Magazine*, 1993

In contrast, the finding in Study I that men used antidepressants to a lesser extent than women did, although they reported depression to a greater extent, could be a sign that men are being under-treated with antidepressants. This could be as a result of men denying the disease and not seeking health care due to male norms in society.<sup>63-66</sup> Thus, there is less chance that men's depression will be diagnosed and treated with antidepressants. Actually, it appears that seeking health care for emotional problems is more important predictor of the use of antidepressants than is a formal diagnosis.<sup>164</sup> Moreover, even if men seek health care for mental health problems, their depression might not be detected, because depression is not necessarily manifested identically in men and women. Diagnostic criteria for depression, as previously mentioned, originate from symptoms initially displayed by women.<sup>71</sup> There is also an unspoken hierarchy between somatic and psychiatric health care, and men's complaints may therefore more often be interpreted as somatic and women's as mental.<sup>53</sup> Further, even if depression in men is detected, men might be more reluctant to accept treatment with antidepressants, because having a mental health problem may be a greater stigma among men than among women. Health behaviours have been found to be affected by subjective norms and social acceptability.<sup>36</sup> It is also possible that men feel less of a health threat in relation to depression than women do and that men have strategies for coping with problems other than seeking professional care.<sup>165-167</sup> However, the suicide rates are much higher among men than among women, and it is thus important to detect and treat depression in men.

When assessing depression using the HADS, most previous studies have not found any gender differences, or like in study III, a greater prevalence in men.<sup>168,169</sup> The reversed gender difference in depression assessed with the HADS compared with clinically diagnosed depression could be due to the fact that HADS's focus is less on somatic (atypical) symptoms, experienced more by women than by men.<sup>96-98</sup> Further, perhaps men are less likely to report problems in real life than to admit them on a questionnaire. The HADS is a screening tool and not a diagnostic instrument, however, which is why a comparison in prevalence with depression assessed based on diagnostic criteria is difficult to make. Nevertheless, because it seems to be difficult to recognize and diagnose men with depression,<sup>95</sup> using rating scales such as the HADS could be a way to improve the basis for diagnosis in men.<sup>170,171</sup>

Concerning the types of antidepressants prescribed, some gender differences were found there as well. For example, women were prescribed SSRIs more often than men were. Some studies have indicated that women respond better than men to drugs that acting solely on the serotonergic system. One theory argues that the cause may be an interaction between oestrogen and serotonin activity.<sup>125</sup> However, supporting data are limited, and other studies have shown that women respond better than men do to antidepressants overall, regardless of type.<sup>172</sup> The fact that, in Study III, men were prescribed more than one type of antidepressant more often than women were may be the result of poorer outcomes for men. When effects are not seen, it is common to switch type or combine different types of antidepressants.<sup>106</sup> Further, men were prescribed antidepressants from the group "others" more often than women were, and some studies have found SNRIs to be more effective than SSRIs in depressed men, and the ADRs seem also to differ some between SSRIs and SNRIs.<sup>173</sup> Today, treatment guidelines do not take gender into account, and the clinical significance of this is unknown. However, in the cases of many other conditions, physicians consider gender when making a diagnosis or selecting therapy<sup>174</sup> and it is possible that this should also be the case with regard to mental health problems. That is, diagnostic and treatment guidelines should probably include gender. Nevertheless, increased knowledge among physicians on gender differences is needed,<sup>174</sup> as are further studies to confirm these differences

## Gender, depression and drug utilization

People with depression have been found to use more drugs overall than others do,<sup>126</sup> and this was found to be true in Study IV. For both men and women, a strong association between antidepressants and polypharmacy was found, with a somewhat stronger association in men. Polypharmacy is often used as an indicator of high morbidity and a valuable proxy for burden of disease.<sup>175</sup> However, it has been found that people with mental health prob-

lems seek health care more than people in general,<sup>127</sup> which itself can increase drug prescription for indications other than their underlying problems. Polypharmacy can thus also be an indicator of the many diffuse symptoms connected with depression. The somewhat stronger association in men in our study may well be interpreted as meaning that men with depression have a higher overall morbidity or overall more diffuse symptoms than women do. Perhaps men with depression increase their use of health care and thus are prescribed more drugs. It is possible that people with depression perceive a greater health threat compared to others, and therefore seek health care and, in turn, receive drugs. However, polypharmacy itself can be a health risk due to the increased risk of ADRs, prescribing cascades, drug-interactions, and non-adherence. Moreover, ADRs per se can cause depression.

Also regarding the association between antidepressants and different types of drugs, some gender differences were found in Study IV. For example, we found the use of antidepressants to be associated with diabetes in women but not men. These results correspond with findings from previous studies.<sup>176</sup> Women, more than men, seem to have many concerns related to diabetes self-management in daily life, i.e. barriers to treatment, which may cause depression. Also, self-efficacy, often decreased in depression, seems to be more important for women than for men as regards self-care in diabetes.<sup>176,177</sup> Concerning drugs for respiratory conditions and antidepressants, a stronger association was found in women compared with men in our study. Previous studies have found women in particular to report their asthma as a barrier to social life activities.<sup>178</sup> Because depression decreases adherence to treatment regimens, which is essential to both complication prevention and reduced mortality in diabetes and obstructive respiratory conditions,<sup>179-181</sup> it is important to pay attention to comorbidity – and as the findings in Study IV imply, especially in women.

The strong association found in our study between antidepressants and analgesics and drugs for musculoskeletal problems among women could be a sign that women are more mentally affected by pain conditions than men are. Female gender has been found to be connected to depression in relation to pain conditions in other studies as well.<sup>136,182</sup> Explanations for this could be that women, more often than men, are diagnosed with severe and chronic conditions related to pain, for example rheumatic conditions, and migraine.<sup>182,183</sup> These conditions generate great suffering and are a great health threat, and probably therefore related to depression. Also, because women seek health care more frequently than men,<sup>62</sup> it is possible that women have over-the-counter drugs prescribed, while men use the same drugs without a prescription. Further, concerning drugs used for dermatological problem and antidepressants, an association was found in women but not men. Other studies have also shown that women are more mentally affected

than men are by dermal conditions.<sup>135</sup> The gender difference seems to be related to appearance, as women report more often than do men that problems with visible body parts, like the face and hands, affect their mood, and constitute a barrier in their relationship with others.<sup>184</sup> Although often seen as insignificant in comparison to other conditions, the effect of dermatological problems on mental health is comparable to that of pain, diabetes, and asthma,<sup>185</sup> and therefore important to be cautious about.

The only ATC-group for which the association with antidepressants was found to be a bit stronger in men than in women was drugs for the nervous system. In other studies, comorbidity between depression and conditions treated with drugs in this group, like anxiolytics and hypnotics, has been found more common in women than in men.<sup>77,160</sup> Hypothetically, one could interpret this as meaning that the men in our study have comorbid mental health problems more often than the women do. Further studies investigating the other types of drugs included in this ATC group, like antipsychotics, antiepileptics, and drugs for Parkinson's disease, would be desirable and possibly reveal some gender differences not fully known today.

Overall, the associations between antidepressants and other types of drugs were often specific, or stronger, in women than in men, which indicate that comorbidity is more common among women than among men. However, whether the somatic problems have caused the depression or the reversed cannot be concluded – one has to consider the close association between somatic symptoms and depression. Nevertheless, the comorbidity between depression and other conditions impairs the possibility of recovery in cases of mental as well as somatic health problems and is thus important to consider.<sup>133,170,186</sup> For this reason, screening for depression could be valuable in some cases.<sup>187</sup>

## Methodological considerations

Although the cross-sectional study design prevented the confirmation of causal relationships, the present thesis contributes to new knowledge about how gender and depression influence drug utilization in the general Swedish population. A strength with the present thesis is the population-based design; in Study I, II, and III, a random sample was taken from the general population in Sweden, and in Study IV the entire population was included. However, participation in Study I, II, and III was voluntary and there may have been selection biases. For example, non-responders were more likely to be men than women. Men and women appear to have different reporting behaviours, in that women seem to be more prone to reporting medical complaints.<sup>50,60</sup> It is also possible that people with current mental health problems would be less likely to respond, further biasing participant selection in Study

II and III. Previous research suggests that survey respondents are more likely to be healthier than non-respondents.<sup>188</sup> Further, factors other than those controlled for in the statistical tests could have been potential confounders. For example, socioeconomic factors like education and personal economy, controlled for only in study I, are important factors affecting health and thus probably drug utilization.<sup>189,190</sup>

It is difficult to estimate non-adherence and anxiety/depression due to their complexity and the problems associated with measuring them accurately. Many studies are not comparable, as different definitions and different measurements have been used. The assessments of adherence (Study I and II) and anxiety/depression (Study II and III) in the present thesis were based on self-reporting. Subjective measures may be subject to information bias and have been suggested to overestimate the rate of satisfactory adherence, and underestimate the rate of anxiety/depression.<sup>188,191</sup> However, self-reporting tools perform well in screening procedures and have shown high reliability and high accordance with other measurements.<sup>192</sup> Questionnaires are also relatively simple and economical to use, and are also practical for larger population-based samples. Moreover, self-reporting enables possible discovery of subjectively perceived reasons for not being adherent, as well as subjectively perceived mental health problems. Nevertheless, it should be taken into consideration that responding to issues concerning mental health may be uncomfortable and that this can affect the responder's willingness to answer truthfully. However, the HADS, used in Study II and III, is a brief, widely accepted questionnaire. Also, the HADS screens for anxiety/depression symptoms rather than diagnosed disorders and, thus, HADS scores are not to be compared with diagnosed depression. Moreover, while the HADS cut-off level of  $\geq 8$  may have resulted in some false-positive cases, the reasoning was to include all participants with at least mild symptoms. Further, the cut-off of  $\geq 8$  has been found to be an optimal threshold in other studies, as it provides an optimal balance between sensitivity and specificity.<sup>193,194</sup>

The questionnaire items in Study I and II on adherence (“have you ever...”) were not directly linked with the items on prescription drug use (“two weeks prior to receiving the questionnaire”), medical complaints (“current” or “chronic” problems) or, in Study II, symptoms of anxiety/depression assessed using the HADS (“in the previous week”). Also, asking whether some event “had ever happened” may not truly measure long-term non-adherence in the participants; however, the main question was not the prevalence, but the gender differences in this respect. Moreover, in Study III, depression assessed using the HADS (“in the previous week”) was not directly linked to prescribed antidepressants via the SPDR (6 months prior to the HADS evaluation). However, depression is often a prolonged state, and problems in this

respect that were encountered in the previous week were probably not temporary.<sup>195</sup> Further, in Study III, antidepressants dispensed during a 6-month period, and in Study IV drugs dispensed during a 3-month period, were analysed without distinguishing whether the drugs had been used for a long or short time (Study III and IV) or simultaneously (Study IV).

The SPDR, used in Study III and IV, has the advantage of offering complete data on all dispensed prescriptions and has contributed considerably to new knowledge on drug therapy.<sup>145,196</sup> Also, the data are free of information bias and it is a relatively low-cost method of identifying patient groups in the population. The most important limitations of prescription databases are that they might not be suitable for the study outcomes or adherence, since it is uncertain if the drugs are actually used by the individuals.<sup>197</sup> However, previous studies have shown that 95-97% of all prescriptions are at least dispensed by a pharmacy.<sup>198</sup> Moreover, prescribed drugs are often used as a proxy for disease,<sup>175</sup> but because the indications for drug treatment in SPDR are not fully known, the assumptions about conditions are somewhat uncertain. For example, antidepressants are sometimes prescribed for indications other than depression. Still, previous studies have reported that depression remains the main indication for antidepressant use.<sup>199</sup> Further, drug prescribing is influenced by several non-medical factors, such as physicians' prescribing patterns, type of practice, and patient load.<sup>121</sup> Therefore, the drug use measured by the SPDR, i.e. prescribed drugs, may not reflect actual morbidity.

## Conclusions

Drug therapy is important in the treatment and prevention of disease; however, it is crucial to be aware of the problems connected to drug prescription and drug use. Pharmacoepidemiological research can reduce the negative impact on public health by identifying drug-related problems and generate knowledge important for clinical practice as well as providing a basis for future studies. The findings in the present thesis – for example that men were more likely to report forgetting to take the drug and changing the dosage, while women were more likely to report ADRs as a reason for non-adherence, and that anxiety and depression, both independently and in combination, were associated with non-adherence and with ADRs as a reason for non-adherence – point toward that intentional and unintentional non-adherence as well as the reasons for non-adherence are important to take into consideration when aiming to improve adherence. Furthermore, the findings that men reported depression to a greater extent than women did but used antidepressants to a lesser extent, while women used antidepressants without reporting depression more often than men, could be sign of under-treatment among men and over-treatment among women. Moreover, the findings that the association between antidepressants and other types of drugs differed by gender indicate a gender difference in comorbidity between depression and other conditions, for example concerning diabetes, dermal conditions and pain conditions. Thus, diagnostic and treatment guidelines for depression should benefit from considering gender, and screening for depression could be valuable in some conditions. In summary, both gender and depression influence drug utilization – prescription of drugs as well as adherence – and are important to pay attention to if our aim is to improve and ensure more proper drug utilization.

*With my medication, I will be fine*  
*With my medication, I will be fine*  
*With my medication, I will be fine, I will be fine...*  
(L.Cole, Antidepressant, 2006)

# Acknowledgements

The work on the present thesis was carried out at the Department of Pharmacy, Uppsala University, and was funded by the National Corporation of Swedish Pharmacies Research Foundation, and the University of Gävle.

Many people have made this thesis possible, and I am deeply grateful to all of you. I especially want to thank:

☀ All of you who took your time to answer the questionnaires – without you, this thesis would not have been possible.

☀ My supervisors, Med Dr Kerstin (Chris) Bingefors, Prof Dag Isacson, Med Dr Kerstin Hedborg, and Prof Göran Frenning. Chris and Dag for giving me the opportunity to make this academic journey; Kerstin for dedication, support and for always spreading calm around you; and Göran for support with the final work.

☀ My colleagues at University of Gävle, particularly; the doctoral group led by Maria Engström; my PhD-colleague Ylva Pålsson for proofreading my thesis; my roommate Eva Dahlkvist for lively discussions; my friends in the medicine group for all their positive energy; Britt-Mari Wågström for always listening; my former boss Nader Ahmadi for believing in me and giving me this chance; and Hans Högberg for excellent assistance with the statistics – You were all a source of inspiration and support.

☀ My dear friend Gunilla Lindblad for all the long conversations – I really needed them.

☀ My wonderful parents, Ingrid and Sten, and my sister Annika, for their unending support over the years.

☀ My beloved family, Erik and Anton, for always being there and making me feel like everything is possible – my love for you knows no bounds.

# Läkemedelsanvändning i befolkningen (Swedish summary)

Användningen av läkemedel har ökat under de senaste decennierna; i Sverige använder cirka två tredjedelar av befolkningen minst ett receptbelagt läkemedel årligen. Av olika anledningar, mer eller mindre kända, så använder kvinnor generellt mer läkemedel än män, och speciellt vad gäller psyko-farmaka, såsom antidepressiva läkemedel, så finns det stora könsskillnader. Dessutom så använder personer med depression generellt mer läkemedel jämfört med resten av befolkningen, bland annat beroende på en stor sam-sjuklighet mellan psykiska och fysiska problem. I takt med den ökande läkemedelsanvändningen har medvetenheten om läkemedelsrelaterade problem, såsom läkemedelsbiverkningar, över- respektive underbehandling och bristande följsamhet till läkemedelsbehandlingar, ökat. För att kunna ta tillvara läkemedlens fulla potential och för att i möjligaste mån undvika problem så måste diagnosticering och läkemedelsförskrivning vara korrekt och det är dessutom av största vikt att läkemedlen tas enligt ordination. Forskning kring läkemedelsanvändning och läkemedelsrelaterade problem har därmed stor betydelse för folkhälsan. Sambandet mellan läkemedelsanvändning, kön och depression är dock bristfälligt studerat på befolkningsnivå.

Det övergripande syftet med avhandlingen var att studera hur kön respektive depression påverkar användningen av läkemedel; förskrivning av läkemedel likväl som självrapporterad användning. I avhandlingen ingick två populationsbaserade enkätundersökningar samt data från Läkemedelsregistret. Följaktligen – läkemedelsanvändning studerades utifrån individens eget perspektiv samt via registerdata.

I delstudie I studerades sambandet mellan kön och följsamhet till läkemedelsbehandling (självskattad genom enkät). Vi fann att män och kvinnor rapporterar olika typer av bristande följsamhet och olika orsaker till att läkemedlen inte tas enligt ordination. Till exempel så var det vanligare bland män än bland kvinnor att glömma att ta sina läkemedel och att ändra doserna. Läkemedelsbiverkningar som orsak till bristande följsamhet var däremot mycket vanligare bland kvinnor än bland män. Därmed, om följsamheten ska kunna förbättras, är det viktigt att beakta de könsskillnader som finns.

I delstudie II studerades sambandet mellan ångest/depression (självskattad genom formuläret HADS) och följsamhet till läkemedelsbehandling (självskattad genom enkät). Vi fann ett samband mellan såväl ångest som depression, dock främst depression, och bristande följsamhet. Vi fann även samband mellan depression och ångest och läkemedelsbiverkningar som orsak till bristande följsamhet. Resultaten tyder på att personer med ångest och depression har en ökad risk för bristande följsamhet och att läkemedelsbiverkningar är en viktig anledning till detta. Detta är viktigt att beakta om följsamheten ska kunna förbättras.

I delstudie III studerades könsskillnader i sambandet mellan depression (självskattad genom formuläret HADS) och antidepressiva läkemedel (data via Läkemedelsregistret). Vi fann att män använde antidepressiva läkemedel i mindre utsträckning än kvinnor, även om de rapporterade depression i större utsträckning, medan kvinnor använde antidepressiva läkemedel utan att rapportera depression i större utsträckning än män. Detta kan vara ett tecken på att män är underbehandlade och kvinnor är överbehandlade med antidepressiva läkemedel. Dessutom förskrevs män och kvinnor olika typer av antidepressiva läkemedel. Resultaten tyder på att kön bör beaktas i riktlinjer för diagnostik och behandling av depression.

I delstudie IV studerades könsskillnader vad gäller sambandet mellan antidepressiva läkemedel och andra typer av läkemedel samt polyfarmaci (definierat som användning av minst 5 olika typer av läkemedel) (data via Läkemedelsregistret). Vi fann att sambandet mellan antidepressiva läkemedel och andra typer av läkemedel skilde sig mellan män och kvinnor. I många fall fanns det ett samband endast bland kvinnor, till exempel vad gäller läkemedel för behandling av diabetes och hudsjukdomar. Detta kan tyda på att män och kvinnor skiljer sig åt i samsjuklighet mellan depression och andra tillstånd. Då samsjuklighet komplicerar diagnosticering och försämrar prognosen är det viktigt att uppmärksamma depression och beakta eventuella könsskillnader i samsjuklighet.

Sammanfattningsvis, även om studiedesignen i form av tvärsnittsstudier inte möjliggör fastställande av orsakssamband, så belyser denna avhandling hur kön och depression påverkar läkemedelsanvändning och bidrar därmed till ny kunskap viktig inom såväl klinisk praxis som en bas för framtida studier. Resultaten tyder på att kön och ångest/depression påverkar både följsamheten till läkemedelsbehandlingar liksom förskrivning av läkemedel. Detta är viktigt att uppmärksamma då man syftar till en förbättrad, säkrare och mer jämlik läkemedelsanvändning.

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# Appendices



Dessa frågor har ställt samman för att hjälpa oss att förstå hur du mår. Läs varje påstående och sätt ett tydligt kryss i rutan till vänster om det svar som kommer närmast hur du har känt dig under veckan som gått. Sitt inte och fundera för länge. Det första svar som dyker upp för dig på varje påstående är antagligen riktigare än ett svar du tänkt på länge.

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**1. Jag känner mig spänd eller "uppskruvad"**

- För det mesta
- Ofta
- Då och då
- Inte alls

**2. Jag uppskattar samma saker som förut**

- Precis lika mycket
- Inte lika mycket
- Bara lite
- Knappast alls

**3. Jag får en slags känsla av rädsla som om någonting förfärligt håller på att hända**

- Alldeles bestämt och rätt illa
- Ja, men inte så illa
- Lite, men det oroar mig inte
- Inte alls

**4. Jag kan skratta och se saker från den humoristiska sidan**

- Lika mycket som jag alltid kunnat
- Inte riktigt lika mycket nu
- Absolut inte så mycket nu
- Inte alls

**5. Oroande tankar kommer för mig**

- Mycket ofta
- Ofta
- Då och då men inte så ofta
- Bara någon enstaka gång

**6. Jag känner mig glad**

- Inte alls
- Inte ofta
- Ibland
- För det mesta

**7. Jag kan sitta i lugn och ro och känna mig avspänd**

- Absolut
- Oftast
- Inte ofta
- Inte alls

**8. Jag känner mig som om jag gick på "lågtryck"**

- Nästan jämt
- Mycket ofta
- Ibland
- Inte alls

**9. Jag får en slags känsla av rädsla som om jag hade "fjärilar i magen"**

- Inte alls
- Någon gång
- Rätt ofta
- Mycket ofta

**10. Jag har tappat intresset för mitt utseende**

- Absolut
- Jag bryr mig inte så mycket om det som jag borde
- Jag kanske inte bryr mig om det riktigt så mycket
- Jag bryr mig precis lika mycket om det som förut

**11. Jag känner mig rastlös som om jag måste vara på språng**

- Verkligen mycket
- En hel del
- Inte så mycket
- Inte alls

**12. Jag ser fram emot saker och ting med glädje**

- Lika mycket som förut
- Något mindre än jag brukade
- Klart mindre än jag brukade
- Nästan inte alls

**13. Jag får plötsliga panikkänslor**

- Verkligen ofta
- Rätt ofta
- Inte så ofta
- Inte alls

**14. Jag kan njuta av en bra bok, ett bra radio eller TV-program**

- Ofta
- Ibland
- Inte så ofta
- Mycket sällan

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