Major depressive disorder (MDD) and anxiety disorders are seriously disabling disorders with a 1-year prevalence of up to 10% and 19% respectively.\textsuperscript{1-6} Both diseases account for a substantial disability burden.\textsuperscript{7} In the World Health Organization (WHO) Global Burden of Disease Survey estimations MDD is expected to remain in the top three diseases with respect to the amount of disability experienced by sufferers in the years 2020 and 2030.\textsuperscript{8,9} Depression and anxiety disorders account for a significant loss of quality of life\textsuperscript{10,11} and also present substantial economic costs.\textsuperscript{12-14}

**PHARMACOTHERAPY IN DEPRESSION AND ANXIETY**

Effective pharmacological and psychological treatments have become available and have been included in the recommendations of all guidelines for the treatment of MDD and anxiety disorders in specialized care\textsuperscript{15-18} as well as primary care.\textsuperscript{19-21} Recurrence rates of MDD are high and range from 41% in five years to 67% in ten years follow-up.\textsuperscript{22,23} Recurrence as well as persistence of symptoms often result in long term pharmacotherapy.\textsuperscript{16,19-21} However, the efficacy of antidepressant is moderate.\textsuperscript{24} In clinical trials, response to placebo is high and only one out of five patients with a first episode of MDD actually improves as the result of antidepressant treatment.\textsuperscript{25} In chronic depression, only 56% of patients with MDD achieve remission after two consecutive treatments with antidepressants.\textsuperscript{26} Prolonged treatment for six months prevents recurrence in approximately one out of five patients and decreases the risk of recurrence from 30-50% to 10-30%.\textsuperscript{25} In anxiety disorders, antidepressants generally reduce symptoms effectively. Serotonergic antidepressants in particular have become the cornerstone of anxiety pharmacotherapy.\textsuperscript{19}

**TREATMENT ADEQUACY**

Although effective pharmacotherapy and psychotherapy are widely available, many patients suffering from depression and anxiety disorders do not receive adequate treatment. Studies on treatment rates in depression and anxiety disorders have reported inadequacy rates ranging from 6 to 87%.\textsuperscript{27-36} These varying results may have been caused by differences in data collection, such as telephone surveys, pharmacy records or insurance company data, and by differences in the populations investigated including the general population and primary or specialized care. In European countries treatment inadequacy respectively in general medical and specialized mental health care settings was 77% and 43% treatment inadequacy in depression and anxiety in, whereas in the USA this was 86% and 48%.\textsuperscript{32,34} It is known that both demographic factors like gender and age, and clinical factors like disorder severity, recurrence and co-morbidity, may influence treatment inadequacy.\textsuperscript{28-34}
With respect to treatment inadequacy, many studies have investigated whether or not patients are receiving any kind of therapy in depression and anxiety disorders. Largely because restriction in the way that data was collected, in these studies the quality of the treatments provided was not assessed. For instance, medication prescription and dispensing pharmacy data are easy to obtain, but these data are only a proxy of the medication actually taken by patients on a day to day basis. Thus, in the case that patient compliance is taken into account as well as adherence and adequacy of the prescribed pharmacological treatment, actual treatment inadequacy may be considerably higher.

**ANTIDEPRESSANT SIDE EFFECTS**

Antidepressant use is associated with a variety of side effects. Typical side effects of antidepressants are insomnia, sleepiness during the day, restlessness, muscle spasms/twitching, dry mouth, profuse sweating, sexual disorders, nausea, constipation, diarrhea, weight gain and dizziness. These type A side effects are commonly observed (more than 1% of users) and well known from clinical trials, which report prevalence rates of up to 27%. Type A side effect can be differentiated between patient-perceived side effects like dry mouth or sweating and physician perceived side effects like hypertension. Type B side effects are rare and become only apparent in daily practice after regular use in thousands of patients. Cohort studies and meta-analyses of large numbers of clinical trials, providing 10,000 or more cases, are necessary to quantitate these side effects. Examples of antidepressant type B side effects are suicidal behavior and ideation, lethal violence and hypoglycemia.

Ideally all side effects should be known before an antidepressant is introduced in daily practice, but particularly lack of adequate side effect data is hindering the evaluation of antidepressant risk-benefit ratios. It is commonly accepted that type B side effects are not known before new drugs become available. However, type A side effect assessment in clinical trials concerning mental health is inadequate, notably with respect to long-term effects. To assess side effects adequately a structured and systematic side effect assessment based on pharmacological knowledge is needed. Examples of systemic assessments are the self-report Antidepressant Side Effect Checklist (ASEC-12) and the Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale, a semi structured interview by a health professional. A large scale meta-analysis of 143 clinical trials on antidepressants showed that proper strategies were used in only 21% of trials. Moreover, a systematic review on 115 studies revealed that adverse events were rarely pre-defined and that in only a few trials an objective side effect rating scale was used.

Most antidepressant side effect data originates from short term clinical trials providing information about the first two to three months of use. Clinical trials have revealed differences between side effects profiles of different types of antidepressants. However, it is unclear...
whether there is similarity between side effects reported in clinical trials and those observed in daily practice.\textsuperscript{50,51} Prescription Event Monitoring has provided naturalistic side effect data in a primary care setting of short-term (up to six months) antidepressant use\textsuperscript{52-54}, but antidepressant-induced side effects data in a long-term naturalistic setting is lacking. Side effects not only have a high impact on quality of life, but also interfere with optimal treatment dosages and may be the cause of medication non-adherence and discontinuation.\textsuperscript{55}

**MEDICATION ADHERENCE**

In 2003 the World Health Organization (WHO) published an evidence based guide to emphasize the importance and the magnitude of medication non-adherence.\textsuperscript{56} Medication non-adherence, defined as the extent to which a person's behavior on taking medication does not correspond with instructions from a health care provider, accounts for substantial worsening of disease and increased hospital admissions, healthcare costs and death.\textsuperscript{57-62} Of all medication-related general hospital admissions in the United States, 33 to 69\% are due to medication non-adherence.\textsuperscript{62} In developed countries medication non-adherence rates of chronic therapy are about 50\%.\textsuperscript{56} Despite advances made in the field of adherence research during the last decades, non-adherence rates have remained roughly unchanged.\textsuperscript{63}

In psychiatry, medication adherence is particularly troublesome, notably because several mental illnesses have interfering features. While depressed people lack motivation, patients with an anxiety disorder fear of side effects might increase medication non-adherence. Depression is a well-established risk-factor of medication non-adherence.\textsuperscript{56,62,64-66} Depressive disorders may compromise the ability of the patient to adhere to medication regimens, dietary instructions or lifestyle instructions that are important in successfully managing chronic disease conditions.\textsuperscript{65-67} About 50\% of the patients with depression also have an anxiety disorder.\textsuperscript{68}

However, as compared to depression, the impact of anxiety disorders on medication non-adherence is scarcely documented and the available evidence is inconclusive. A meta-analysis of a limited number of smaller studies reported small and inconsistent effect sizes.\textsuperscript{65} Bearing in mind that depression and anxiety disorders frequently occur in conjunction with other somatic conditions,\textsuperscript{69} the impact of depression and anxiety disorders on medication non-adherence also has consequences for the treatment of these somatic conditions. For instance, depression proved to be a risk factor of somatic medication non-adherence and recommended health behavior in cardiovascular patients.\textsuperscript{70,71}

It is very difficult to detect medication non-adherence in clinical practice. If non-adherence is assessed by the treating physician, patients are tempted to give subjective and socially desired answers and tend to overestimate correct medication intake.\textsuperscript{52} However, obtaining information by using objective measures, like biological markers or drug blood levels, is
expensive and not always feasible. Therefore, insight into risk factors of medication non-adherence in a naturalistic setting is important to focus clinical attention on patients at risk of medication non-adherence, optimize adherence and ultimately improve pharmacotherapy and outcome.

In research, medication non-adherence can be assessed in several ways. Because monitoring all subjects for 24 hours a day and seven days a week is not feasible, one has to rely on measurements. In clinical trials pill counts are the simplest way of assessing medication non-adherence. Advanced medication containers, such as the Medication Event Monitoring System (MEMS), record both time and date when the container is opened providing extra information on top of pill count data. Pharmacy prescription filling data combined with prescribed daily dosages information provide a measure for the actual intake by the patient. Several self-report instruments are designed to assess medication non-adherence in large scale epidemiological studies. Assessment of medication non-adherence by a self-report questionnaire is a simple and inexpensive method to gather information and is generally considered to be reliable. The Medication Adherence Report Scale (MARS), is a self-report questionnaire measuring a range of non-adherent behavior. The MARS is well validated and has been used for a range of chronic diseases in various settings and different countries. Medication non-adherence, as measured by MARS, is defined by the tendency to forget, change the dose, stop for a while, skip one dose or take a smaller dosage than prescribed.

The MEMS System is considered the golden standard in medication adherence research. When compared with the MEMS System, self-report questionnaire data were moderately correlated in a meta-analysis which covered a number of different diseases. In depression, self-report questionnaire data showed acceptable reliability and were useful to identify noncompliant patients. Since adherence measured by self-report provides a current or short-term estimate of non-adherence, it has been purported that this method is more accurate in cross-sectional research. A major flaw of self-reporting usually is the tendency to underestimate non-adherence largely as the result of socially-desired answering. Therefore, it is important to use the self-report measurements in a non-judgemental setting independently of treating physicians, pharmacists and nursing staff.

**PHARMACOGENETICS**

Pharmacogenetic research aims at the identification of associations between genetic variability and differences in patient responses to drug exposure. Pharmacogenetic data offer great potential as a means to select the optimal treatment for individual patients. This specific approach is often referred to as personalized medicine. Given the limited efficacy and severe side effects burden of antidepressants, pharmacogenetic research and personalized
medicine approaches can be useful tools to optimize antidepressant pharmacotherapy. Pharmacogenetic information concerning CYP metabolizing enzymes has already been introduced in clinical practice in the Netherlands.87

The pharmacological effect of a drug is the result of its pharmacokinetic and pharmacodynamics attributes. As pharmacokinetics incorporate absorption, distribution, metabolism and elimination of drugs, it determines drug concentrations and effects in all body tissues. Apart from chemical and pharmaceutical properties of the drug, biological interactions with metabolizing, binding and transporting proteins determine pharmacokinetics. For the effects of antidepressant drugs, metabolizing enzymes and their penetration in brain tissue are important.

Pharmacodynamics concerns the interaction of a drug with biological systems, as the result of which the actions of these biological systems are altered. The interactions comprises binding to receptors, transporters, enzymes or ion-channels which creates a wide variety of pharmacological effects. With respect to antidepressants, reuptake inhibition of monoamines is believed to be highly important for the therapeutic effect,88 whereas their interaction with several types of receptors is considered to bring about antidepressant side effects.88;90

The human genome consists of about 3.3 billion base pairs. Common genetic variation originates from approximately 10 million base pairs, single nucleotide polymorphisms (SNPs), which differ between individuals.91 In general, there are two ways of investigating associations with SNPs: Genome Wide Association Study (GWAS) and candidate gene approach. GWAS has become available with the introduction of cheap high volume methods of analyzing SNPs. Associating disease traits with 500,000 to two million common SNPs has revealed many interesting genes which has sparked the development of many new hypotheses.92 The candidate gene approach starts with a biological or pharmacological pathway in which a relatively small number of SNPs (up to 100) are analyzed and associated with a disease state or a pharmacological effect. Associations from candidate gene studies may add to the knowledge from other fields of research and strengthen a hypothesis.

In contrast with monogenetic hereditary diseases, like cystic fibrosis, psychiatric disorders and their treatments are complex with many biological systems and many genes contributing to the clinical manifestation of the disease and the pharmacological actions of the drugs used for treatment. A complicating factor in molecular genetics research in psychiatry is that many environmental conditions, like childhood trauma, life events or social support, have the ability to considerably influence disease development and severity, making it harder to reveal true genetic associations. This exponentially increases the need for large numbers of subjects and SNPs. Moreover, it complicates replication of statistically significant findings, because in the replication cohort, all relevant confounders must be equally distributed or adjusted for.
NATURALISTIC COHORT STUDIES (NESDA AND LASA)

Study data presented in the present thesis were collected in two large longitudinal cohort studies in the Netherlands: the Longitudinal Aging Study Amsterdam (LASA) and The Netherlands Study of Depression and Anxiety (NESDA). While LASA is a cohort study on predictors and consequences of changes in autonomy and well-being in the ageing population (55-85 years of age), NESDA is designed to investigate the course and consequences of depressive and anxiety disorders in adults (18-65 years of age). Both studies cover a large numbers of subjects and many demographic, biological and psychosocial parameters. This is important in pharmaco-epidemiology as it provides solid associations, while adjusting for many or preferably all indicators that influence the independent variable. Although these cohort studies are an enormous undertaking in terms of money and personnel, they are most cost-efficient in terms of results. Variables can be associated with all kinds of outcomes, for instance cortisol data in depression and in osteoporosis. Both LASA and NESDA have carefully recruited subjects from different regions and settings in the Netherlands to provide a naturalistic cohort with excellent external validity to the Dutch population.

PSYCHIATRIC STATUS

Both depression and anxiety disorders are chronic mental disorders with high co-morbidity, low rates of full recovery and a high recurrence of episodes. Symptom severity fluctuates over the course of years. Comorbidity rates among depressive and anxiety disorders range from 30% through 60. The clinical histories of patients with depression and anxiety disorders differ, but often they arise sequentially within patients. The combination of a depression and anxiety disorders accounts for more severe symptoms, more disability, a longer duration of illness and are less likely to respond to treatment. After recovery symptoms often do not fully disappear. In depression this particular state are referred to as subthreshold depression or minor depression. Recurrence rates range from 30% to 95% and are often associated with more severe symptoms and less recovery. The above information underpins the need for clinical staging of depression and anxiety disorders.

In the epidemiology of depression and anxiety disorders, many cohorts use symptom severity as a measure for clinical disease. Although it does provide information on a subjects’ well-being at the time of data acquisition, it only serves as a proxy to identify patients with a psychiatric diagnosis. For instance, burn out and chronic fatigue can be easily mistaken for depression. In NESDA the WHO Composite Interview Diagnostic Instrument (CIDI, version 2.1) diagnostic interview is used for determining psychiatric diagnoses according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria. It is considered a
highly accurate and validated instrument for assessing depressive and anxiety disorders. The CIDI diagnostic tool establishes the presence and/or absence of a depressive disorder (major depressive disorder and dysthymia) or an anxiety disorder (panic disorder, social phobia, generalized anxiety disorder, and agoraphobia) both current as well as in the past and allows to categorize subjects based on their specific diagnosis or combination of diagnoses.

As compared to many frequently used symptom severity scales, the CIDI diagnostic tool is highly sensitive and specific. It can be used to extrapolate NESDA results to clinical practice and allows comparisons between subjects with various stages of depression and anxiety disorders as well as with subjects without a history of depression or anxiety disorders.

**AIM OF THE PRESENT THESIS**

The present thesis concerns a study of several aspects of the pharmaco-epidemiology of antidepressants in patients with depression and anxiety. In a naturalistic setting treatment inadequacy of depression and anxiety disorders is assessed as well as the occurrence of side effects and medication non-adherence in general. Associations of antidepressant side effects with specific genes are also explored.

**THESIS OUTLINE**

In chapters 2 we will describe our investigation on treatment inadequacy and predictors for treatment inadequacy in depression and anxiety disorders. The prevalence of antidepressant-induced long-term side effects and predictors of these side effects are addressed in chapter 3. Predictors for medication non-adherence in patients treated with antidepressants are examined in chapter 4. Chapter 5 explores possible relationships between antidepressant-induced side effects and the common genetic variation of two pharmacokinetic genes, ABCB1 and CYP2C19. Chapter 6 concerns a report of a genetic study on association of common variations in the glucocorticoid receptor gene and the modulation of the association between childhood adversity and depressive symptomatology. Finally, chapter 7 contains a summary and a concluding discussion of the results of the above-mentioned studies on the pharmaco-epidemiology of antidepressant treatment.
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