Adherence to Antidepressant Medication

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**Abstract**


Non-adherence to medication is a major obstacle in the treatment of depression. The objectives of the present study were to explore the effect of two interventions aiming to increase antidepressant treatment adherence, and to examine long-term consequences and costs of depression in adherent and non-adherent primary care patients.

A randomised controlled design was used to assess the respective effects of a written educational adherence enhancing programme and therapeutic drug monitoring in patients with major depression treated with sertraline for 24 weeks. All patients were prospectively followed during two years.

Treatment adherence was found in 41% of the 1031 included patients. None of the interventions resulted in a significant increase in adherence rate. However, significantly more patients in the group receiving the written educational material had responded at week 24 as compared to patients in the control group.

The overall remission rate after two years was 68%. In total, 34% of the responders experienced at least one relapse. Response and remission rates at week 24, year 1 and year 2 were significantly higher in adherent as compared to non-adherent patients. No relationship between adherence and relapse rate was seen.

The mean total cost per patient during two years was KSEK 363 whereof indirect costs represented 87%. No significant differences in costs between intervention groups or between adherent and non-adherent patients could be demonstrated. However, the mean cost per patient was 39% lower for treatment responders as compared to non-responders.

Non-adherence was predicted by age below 35 or above 64 years, no concomitant medications, personality disorder, sensation seeking personality traits and substance abuse.

The results indicate a strong positive relationship between treatment adherence and clinical outcome. In addition, the study shows that depression is a costly disease and that certain patient characteristics predict non-adherence.

**Keywords:** adherence, depression, randomised controlled trial, intervention, therapeutic drug monitoring, personality, health status, health care utilisation

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“Drugs don’t work in patients who don’t take them”
C. Everett Koop
List of publications

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


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Abbreviations

CGI-I  Clinical Global Impression- Improvement scale
CGI-S  Clinical Global Impression- Severity scale
CI     Confidence Interval
CP     Compliance enhancement Programme
CRF    Case Report Form
DDD    Defined Daily Dose
DIP-Q  DSM-IV and ICD-10 Personality Questionnaire
DSM-IV Diagnostic and Statistical Manual of Mental Disorders IV
EQ-5D  EuroQol-5 dimensions
GEE    Generalised Estimating Equations
GP     General Practitioners
HIV    Human Immunodeficiency Virus
HRQL   Health Related Quality of Life
ICD-10 International Classification of Diseases - 10
ITT    Intention-To-Treat
SEK    Swedish kronor
LOCF   Last Observation Carried Forward
MADRS  Montgomery Asberg Depression Rating Scale
MD     Major Depression
MPA    Medical Product Agency
NRI    Nor-epinephrine Reuptake Inhibitor
NS     Non Significant (p≥0.05)
OC     Observed Cases
OR     Odds Ratio
PD     Personality Disorder
QALY   Quality Adjusted Life Years
SD     Standard Deviation
SLICE  Swedish Long-term Implications of Compliance Enhancing Interventions in depression
SNRI   Serotonin and Nor-epinephrine Reuptake Inhibitor
SSP    Swedish universities Scales of Personality
SSRI   Selective Serotonin Reuptake Inhibitor
TCA    Tri/tetra-Cyclic Antidepressants
TDM    Therapeutic Drug Monitoring
Introduction

The effect of the pharmacological treatment of disease can be simplified as follows “Right thing, Right place, Right time”. The medications we have access to today are generally effective and they have the characteristics of both “Right thing”, and “Right place”. The effectiveness of the treatment, however, also requires “Right time”. A key factor here is that the patient in question must receive, or take, the medication as intended. Thousand of years ago Hippocrates (460-377 B.C.) warned that patients might often lie about taking their medications. Over time it has become increasingly obvious that treatment failures related to an imperfect use of prescribed medication constitute a true clinical problem resulting in worsening of disease, death and increased health care costs (47, 190). The discipline of “Pharmionics”, i.e. the study of how ambulatory patients take a particular drug, has been suggested as a complement to pharmacodynamics and pharmacokinetics of medications (211).

Adherence

Terminology

Several terms are used to describe how the patient follows a treatment regimen. “Compliance” was previously the most common term but today “adherence” is used more frequently. Adherence is used in this work as it suggests a more participatory position on the part of the patient and requires the patient’s agreement with the suggested regimen (59). However, neither of the terms gives a clear picture of how the patient takes medication and according to Steiner & Earnest (200) the language used to describe medication-taking behaviour needs to be reassessed.

The term concordance is also used in adherence literature. It describes the accordence between the patient’s and the caregiver’s view regarding diagnosis and treatment. Concordance requires two-way communication between the patient and the clinician regarding the patient’s treatment, and if successful it will lead to treatment adherence (44, 117).

Adherence in the medical context is often referred to as “the extent to which a patient’s behaviour (in terms of taking medications, following diets,
or executing lifestyle changes) coincides with medical or health advice” (77). It can be total, partial, nil or erratic and both under-usage and over-usage of medications can occur (32). On an individual patient basis, the adherence rate is usually expressed as the percentage of prescribed medication doses actually taken during a specified time. It can accordingly vary from 0 to more than 100% and is best viewed continuously over time as total adherence or non-adherence is rare (209). On a group level the extent of adherence is most often expressed as the proportion of patients who use the medication as prescribed. Adherence is then defined as a dichotomous variable, adherence versus non-adherence. There is no uniform view of what is acceptable adherence, however. Some authors suggest that intake of 80% or more of the medication is acceptable while others consider higher rates to be mandatory, such as when treating patients with human immunodeficiency virus (HIV) (152). Moreover, the relationship between adherence and outcome varies between different diseases and treatments (47).

Measures of adherence
It is difficult to accurately measure treatment adherence. Several methods are available but each has limitations and there is no one method against which to calibrate others (46). A distinction between direct and indirect measures can be made (56, 201). Direct measures include proof that the medication has been taken, such as by direct observation of the patient, measuring the level of the drug in blood or urine, or detection of a biological marker. Therapeutic drug monitoring (TDM) is a well-established method for assessing adherence. Variations in serum concentrations of the drug can indicate erratic adherence (7, 126, 169). Another direct measure of treatment adherence is the patient’s ability to follow a pre-set schedule of visits (179, 199).

Indirect measures of adherence include patient reports (interviews, diaries or questionnaires), pill-counts, pharmacy reports of rates and time of refilling, electronic devices recording the time of opening the tablet container, and assessing clinical response (32, 56, 154, 201). Whenever possible, measures that are continuous instead of dichotomous should be used, given their probable greater reliability and power (47).

All methods have shortcomings of one kind or another, and a combination is therefore recommended as the most effective way of analysing adherence (46, 56, 130, 156, 199).

Extent of non-adherence
Adherence to self-administered medications varies between 0% to over 100%, with an estimated mean of 50% on a group level (179). Studies have shown poor adherence to treatment across health states, treatments, and ages,
and there are indications that low adherence is not disease specific except possibly for psychiatric disorders where a lower adherence rate is often seen (33, 77). Higher adherence rates are more often seen in acute than in chronic conditions, and during long-term treatment a progressive decline in adherence is seen (31, 93). In clinical trials the average rates are usually higher than in clinical practice due to increased attention and selection of patients (157, 199). In a recent meta-analysis of 596 studies of adherence to non-psychiatric medical treatments, an average rate of non-adherence of 24.8% was found (46). Highest adherence rates were seen in HIV, arthritis, gastrointestinal disorders and cancer, and lowest rates were seen in pulmonary disease, diabetes and sleep disorders. A limitation of comparisons of adherence rates between different studies is that diverse methods of measurement are used (46).

Detailed information about medication taking behaviour has been obtained through electronic devices in the lid of the drug container. These studies have shown that omissions or delays in taking doses are the most common non-adherent behaviour (154). Another pattern worth mentioning is that patients commonly improve their medication taking behaviour in the five days before and after the consultation with the caregiver as compared with 30 days afterwards, a phenomenon called "white-coat adherence" (34, 57).

Barriers to adherence

The ability of patients to follow prescribed treatment is often hindered by different factors including social and economic circumstances, the health care system, the provider, the disease and its treatment, and by patient-related factors (152, 224).

Adherence can be reflected on or unreflected on by the patient. When reflected on, the patient is well informed and makes a conscious choice to follow the treatment guideline. If it is unreflected on the patient follows the guideline without any specific considerations (203). Belief in the doctor, the wish to leave medical decisions to professionals, fear of complications, no undesirable effects of the medication, the wish to avoid symptoms of the disease and an acceptance of the disease are the most common reasons for adherence (206).

Non-adherence can be conscious or unconscious. Conscious non-adherence is the result of an active decision not to follow the guideline, e.g. not taking the medication, temporarily or completely, or taking a lower or higher dose than prescribed. There are several underlying causes; the patient might find the treatment complicated, inconvenient, embarrassing, expensive, or disagree with the need for it (18, 201). Non-adherence can also be rational, taking into account potential treatment imprecision, toxicity or medical errors (187). Unconscious non-adherence can be due to poor
instructions but is most often a result of forgetfulness. In several studies patients have cited this as the most common reason for non-adherence (17, 32, 180).

The effects of different patient characteristics, including demographics, economic status, and personality, on adherence have been explored in many studies but the findings are inconclusive. The results indicate, however, that psychological and emotional factors, including social support, are of greater importance than demographics (21, 45, 87, 96, 152, 165, 191, 218).

Interventions to improve adherence

Approaches to increase adherence can be grouped into four major strategies: education, dosing, clinic scheduling, and communication (32). A review of adherence enhancing interventions by Haynes and co-workers, for the Cochrane collaboration (79) concluded that short-term adherence can be improved with simple interventions. Four of nine interventions studied in randomised controlled trials showed an effect on both adherence and at least one clinical outcome. However, there is little evidence that medication adherence in chronic health problems can be improved consistently. Almost all of the interventions that were effective for long-term care were complex, including combinations of more convenient care, information, reminders, self-monitoring, reinforcement, counselling, family therapy, psychological therapy, crisis intervention, manual telephone follow-up, and supportive care (79).

Major depression

Characteristics, epidemiology, and pathophysiology

In the classification systems most commonly used today, the International Classification of Disease and Related Health Problems, Tenth Revision (ICD-10) (222), and the Diagnostic Manual of Mental Disorders, forth revision (DSM-IV) (3), major depression (MD) is classified among the mood disorders. Mood disorders are generally defined as illnesses characterised by different combinations of several co-occurring symptoms for a defined period of time, contributing to significant psychosocial impairment or marked distress. The core symptoms of major depression are depressed mood and/or markedly diminished interest lasting at least two weeks. In addition, these must be accompanied by at least three associated symptoms, making a total of five, such as significant weight change, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy,
feelings of worthlessness or extreme guilt, decreased ability to think or concentrate, and suicidal ideation or thoughts of death.

MD is one of the most important reasons for disability in the world today. The Global Burden of Disease study indicated that unipolar depression is the fourth leading cause of disease burden, accounting for 4.4% of total disability adjusted life years in 2000, and that it causes the largest amount of non-fatal burden, accounting for almost 12% of total years lived with disability worldwide (212).

The prevalence of depression has been studied in several large epidemiological investigations. One of the first, the Swedish Lundby study, which was a pioneer work initiated by Erik Essen-Möller, started back in 1947 and was repeated in 1957 and 1972 (174). In the Lundby study, the cumulative probability of suffering a first episode of depression was 27% in men and 45% in women. The more recent US National Comorbidity Replication Survey, which used DSM-IV criteria, reported a lifetime and twelve-month prevalence of 17% and 7%, respectively (114). Similar findings were obtained in a Norwegian psychiatric epidemiological study from Oslo using DSM-III-R criteria (119). However, in a later study from rural Norway, considerably lower figures were obtained (120). It was recently estimated that more than 21 million of the working population in Europe suffer from depression (196).

Depression may have its onset in early childhood. Before puberty the prevalence is low, and similar for boys and girls, but thereafter the prevalence largely increases and the gender difference seen in adults becomes evident. In a Swedish study, the one-year prevalence was found to be 6.7% for girls and 1.7% for boys at the age of 16 to 17 (150). Suggested reasons for the difference between genders include hormonal differences, early childhood trauma, negative life events and differences in social support (162).

No consensus regarding the aetiology of MD has yet been obtained. However there are many different theories, and the common belief is that depression is caused by a combination of inherited and external factors and that neurodegenerative factors are of importance in old age. It has been shown that depression is more prevalent in persons who have experienced stressful events in early childhood or later in life (15, 112, 113). Research has shown chronic stress to induce hyperactivity in the hypothalamus-pituitary axis (HPA-axis), involving the hormones CRH, ACTH and cortisol. It has also been found that approximately 60% of patients with severe depression have increased levels of cortisol and that chronic stress can cause depression (84, 147, 178). In 2003, Caspi et al (23) reported that the probability of depression is increased in relation to number of stressful events in subjects with a functional polymorphism in the promoter region of the serotonin transporter, which suggests that there is a gene-by-environment interaction.
In light of the therapeutic effects of antidepressant medications the neurotransmitters serotonin, norepinephrine, and possibly dopamine are thought to be involved in the pathophysiology of depression. Furthermore, recent reports have shown an association between major depression and selective and persistent loss of hippocampal volume, and it has been suggested that glucocorticoids may play a role in the hippocampal neuron loss (124).

Outcome and treatment of major depression

If untreated, the mean length of a major depressive episode is approximately six months, with very large variation (3, 166).

In the past decade, attempts have been made to standardise definitions of treatment outcomes in depression in order to enable useful and consistent comparisons of results from clinical treatment trials and facilitate communication among professionals. According to Frank and co-authors (60) the following definitions are suggested:

Response occurs when partial remission begins, i.e. when the criteria for MD are no longer fulfilled but the patient still has more than minimal symptoms of depression. Full Remission is achieved when the patient is symptom-free. If symptoms satisfying the criteria for the full syndrome return during remission, the patient has relapsed. However if the patient remains well for a longer time period he has recovered. A new MD episode after recovery is termed recurrence.

MD is recognised as a recurrent or chronic disease (98, 110). In a 15-year prospective follow-up study by Mueller et al (142), the cumulative proportion of recurrence after recovery from depression was 63% at five years, 80% at 10 years and 85% at 15 years. It has also been shown in cohort studies of inpatients that after five to 15 years a large proportion, ranging from 12%-40%, has not recovered (110, 116, 125).

The literature concerning the long-term outcome of depression treatment in primary care is limited (182). In a review by van Weel-Baumgarten et al (215) of the five-year outcome of depression, only two studies from primary care and six studies from community populations were identified. The recurrence rate in these studies varied between 30% and 40% as compared to rates between 40% and 86% in specialised psychiatry (5, 214). These results indicate that the long-term prognosis for depression in primary care is not as poor as in psychiatric care.

Suicidal thoughts are common in MD, and constitute an important risk factor for suicidal behaviour. Overall, MD leads to suicide in up to 15% of patients (5, 74, 210). The rates of suicide have decreased during the past 20 years. Probable reasons for this decrease are better recognition of depression and the increased use of antidepressant medications (66, 90, 92).
Treatment of major depression includes three major strategies, antidepressant medications, electroconvulsive treatment (ECT) and psychotherapy; only antidepressant treatment will be covered in this thesis. All antidepressant drugs affect the signal systems of the brain, but in different ways. They can be divided into the traditional tri/tetra-cyclic antidepressants (TCAs) with non-specific monoamine reuptake inhibition, the selective serotonin reuptake inhibitors (SSRIs), the selective nor-epinephrine re-uptake inhibitors (NRIs), the serotonin and nor-epinephrine reuptake inhibitors (SNRIs), drugs acting with pre-synaptic alpha-2 receptor blockade, and the monoamine oxidase inhibitors (MAOIs). In the treatment of mild to moderate depression, no differences in the antidepressant effect have been shown between the different groups of antidepressants (182). However, the SSRIs are recommended as the drugs of choice (136). In severe depression, the TCAs clompramine and amitriptyline have shown a better effect than the SSRIs (182). With all antidepressants, an individualisation of drug choice and dosage is necessary to obtain optimal efficacy in the individual (136).

Since introduction of the SSRIs in the early 1990s, the number of patients treated with antidepressants in Sweden has increased substantially with an increase from 25 million defined daily doses (DDD) in 1991 to 228 million DDDS in 2005 (204). One reason for this might be the less severe and more tolerable side-effects seen with the SSRIs and SNRIs as compared to the TCAs, resulting in deceased frequency of premature withdrawal (141).

The initial effect of the antidepressant is usually not seen until two to four weeks after initiation of treatment, sometimes longer, and in general it takes two to three months before full effect is reached. Research has demonstrated that achieved remission is associated with better long-term outcomes as compared to achieved response without remission (98, 99, 128, 158, 163, 164, 214). Sustained remission is accordingly suggested as the ideal treatment outcome for patients with MD (4, 65, 108).

In a multinational observational primary care study of major depression, the rate of complete remission after nine months ranged from 25% to 48% (37). These remission rates, however, are lower than those often found in controlled studies over a period of six months to one year (145, 175). In a recently published meta-analysis of remission rates in randomised controlled trials in primary care, the mean rate for antidepressant treatment was 62% in studies with a follow-up of more than six months. The remission rate for placebo was 32% and for usual care 35% (36). The high rates for placebo seen in most studies have been discussed (213). Plausible explanations include natural recovery, increased attention and selected patients in clinical trials.
Comorbidity
Patients with depression show a substantial co-morbidity with both psychiatric and somatic diseases (13, 114, 121). In a recent study in Finland, as many as 79% of the depressed patients also had a comorbid DSM-IV diagnosis. The most common were anxiety disorders, alcohol related disorders and personality disorders (137).

Somatic comorbidity is also common. Research has shown relationship between depression and e.g. cardiovascular disease, stroke, pain syndromes, rheumatoid arthritis, Parkinson diseases, epilepsy, cancer and diabetes mellitus (35, 58, 64, 97, 121, 134, 148). Furthermore, the presence of MD is suggested to be a significant risk factor for outcome of cardio- and cerebro-vascular diseases (9, 61, 62, 85, 127, 159), and in-hospital mortality overall (229). In addition, patients with depression have been shown to have an increased mortality due to both natural causes and unnatural causes (151).

Research has shown that depression is a risk factor for poor adherence to medical treatment in general (48), and to secondary prevention efforts after acute coronary syndrome (122, 170, 233), asthma therapy (192) and chronic obstructive pulmonary disease (230). Low adherence in patients with depression has been suggested to be one explanation for the increased mortality and morbidity in depressed as compared to non-depressed patients after acute coronary syndrome (232, 233).

Personality
Personality has been defined as “the ingrained pattern of thought, feeling, and behaviour characterising an individual’s unique lifestyle and mode of adaptation, and resulting from constitutional factors, development, and social experience” (223). Different dimensional models for classification and explanation of human behaviour have been outlined (139). Eysenck (55) proposed a factor model in which a large number of specific traits are organised into three higher-order factors, Extraversion, Neuroticism and Psychoticism. Five-factor models (29, 95) have also been suggested with the addition of Agreeableness and Openness-to-Experience. The various models have important differences, but they overlap to a considerable degree (22).

Several different inventories to assess personality traits have been developed (29, 71, 183). Studies using such inventories have shown that in adulthood basic personality traits are reasonable stable over time (30, 72, 171, 207). Personality traits have been found to be of importance for mental health. Both longitudinal and genetic analyses support the hypothesis that neuroticism strongly reflects the liability to MD (111, 115).

Personality disorders (PD) are characterised by a permanent pattern of thinking, experience or behaviour that causes suffering and/or significant functional impairment. Structured diagnostic interviews are used to diagnose
PDs. For purposes of research, self-rating questionnaires have been developed (86, 153).

PDs have been shown to be present in 41%-81% of patients with depression (82). A decreased response rate in depressed patients with concurrent PD has been reported (184). More recent studies have, however, not been able to replicate this finding (1, 54, 143), although it was concluded in a review by Reich (168), that dysfunctional personality has a negative impact of the outcome of MD. In addition, it was found in a Danish long-term follow-up study that comorbid personality disorder predicts suicide after MD (75).

Adherence to antidepressants

Adherence to antidepressant medication has been recognised as an important factor for optimal treatment outcome (59, 68, 101, 103, 109, 138, 186). Despite treatment recommendations, it is probable that less than half of primary care patients take antidepressants for six to nine months or longer (21, 41, 52, 91, 149, 189). In a large retrospective study of 22,947 patients starting treatment with SSRIs, the six-month non-adherence rate was approximately 57% measured by the length of treatment and medication possession ratio (21). In another recent study of outpatients prescribed antidepressants the result are even more disappointing: 42% of the patients had stopped their antidepressant medication during the first 30 days and 72% had stopped within 90 days (149). When the patients’ partial or erratic adherence to treatment is taken into account, the proportion of patients with adequate treatment probably decreases further. In studies measuring clearly defined non-adherence, the median prevalence is estimated at 53% (129). Overall, non-adherence to antidepressant drug treatment has been found to vary from 10% to 60% (129).

Research regarding predictors to poor adherence of antidepressant drug treatment is limited and inconclusive (39, 129, 155). The reasons for premature discontinuation of antidepressant medication seems to vary during the course of therapy, with adverse events being the most frequent reason in the beginning, followed by “feeling better” later in the treatment (41).

Contradictory results have been obtained concerning age and gender as predictors for adherence to antidepressants (16, 39, 59, 128, 191). Research concerning the impact of personality pathology on antidepressant adherence is sparse and somewhat conflicting. Compton et al (27) found that a personality disorder diagnosis was associated with poor adherence. Analogously, Sirey and colleagues (191) reported that medication adherence was predicted by the absence of personality pathology. In line with these findings, Ekselius et al (53) reported that sensation seeking personality traits predicted non-adherence to SSRIs as measured by means of serum levels.
Perceived stigma associated with mental illness and the individual’s views about the illness and the medication may also play an important role in adherence (14, 191). In addition, the quality of the physician-patient relationship, patient participation in decision-making, and the attitudes of family members have been shown to be predictors of adherence to antidepressant medication (38, 131).

Adherence enhancing interventions in MD

Different approaches to enhance adherence to antidepressant medication have been proposed. These include medication clinics, patient leaflets, drug counselling, cognitive behavioural strategies, psychotherapy, patient and family education, physician education, patient participation in decision-making concerning treatment, physician alerts, pharmacist intervention, measurement of plasma levels and changing the medication preparation (6, 8, 81, 131, 155, 172, 177, 220).

However, few randomised controlled studies of the proposed strategies have been performed. In a review by Pampallona et al (155), 14 randomised studies of adherence in the treatment of MD were identified. The studies included between 14 and 649 patients. The interventions most commonly tested were patient education and medication clinics, combined with a variety of other interventions. The authors concluded that there were no indications as to which interventions may be effective, although the studies indicated that adherence could be increased through interventions. One explanation for the inconsistent results in assessing effects of interventions to improve adherence may be the small number of patients and the lack of power to detect clinically important effects in most such studies (135).

In 2005 the Cochrane collaboration published an updated review of interventions to enhance medication adherence (79). Only two studies of interventions for patients with depression fulfilled the inclusion criteria. In the study by Katon et al (103), 386 primary care patients with recurrent MD or dysthymia who had largely recovered after antidepressant treatment were randomised to usual primary care or to a multifaceted relapse prevention programme comprising patient education, two visits with a depression specialist, three telephone visits and personalised mailings over a one-year period. Antidepressant medication adherence was assessed by telephone interview and by automated data from prescription refills. As compared to usual care controls, intervention patients showed significantly greater adherence over the 12-month follow-up and had fewer depressive symptoms, but not fewer episodes of relapse/recurrence.

The second study, by Peveler et al (160), investigated the effect of two different interventions, alone and in combination in 250 primary care patients over 12 weeks of antidepressant treatment. The interventions comprised a treatment information leaflet and drug counselling by a nurse at
weeks 2 and 8. Adherence was assessed by self-report and by
electromechanical monitoring. Counselling, but not leaflets, improved
adherence.

Health related quality of life

Health related quality of life (HRQL) can be defined as the impact an illness
has on quality of life, including the individual's perception of his or her
illness. An increasing variety of different measurements and variables are
accessible for this purpose, and some are disease or population specific,
while others are more general or generic measures (63). One of the most
commonly used is the standard generic questionnaire EuroQol 5-dimensions
(EQ-5D) (208). The HRQL in the general Swedish population has been
assessed using EQ-5D showing a mean of 0.86 in individuals aged 40-49
years (20).

The influence of depression on quality of life is substantial. In a Swedish
and in a French naturalistic observational study in a primary care setting, the
average health utilities for an untreated depression episode were shown to be
0.47 and 0.33, respectively, with higher depression severity resulting in a
lower utility (181, 194). In a recent randomised controlled trial of depressed
primary care patients, the average baseline health utility was slightly higher,
with a mean of 0.59 (161). Although treatment and length of follow-up
differed in these studies, HRQL improved by approximately 0.2 utilities
after 24 weeks to one year. Moreover, in a Swedish cross-sectional study
using the Medical Outcomes Study Short Form 36 (SF-36) (217) to assess
HRQL in the general population, it was shown that the health state utilities
were lower for individuals with depression as compared to those with
various other medical disorders (89).

Cost of depression

Depression constitutes a substantial economic burden for society both
because of its high prevalence and because of its consequences.
Furthermore, recent research has shown a large increase in the total societal
cost in recent decades. Using a top-down approach, i.e. the total costs for
illness in the society are dived among diseases according to main diagnosis
(83), Greenberg et al estimated the total cost for depression in the US in
1990 at $44 billion (70). The analysis was updated in 2000, when the cost
reached $83 billion (69). Sobocki et al estimated the total annual cost of
depression in Europe at €118 billion in 2004 (196). For Sweden alone, the
total societal cost of depression in 1997 was estimated at €1.7 billion, with
an increase to €3.5 billion in 2005 (197). The estimates included all direct
direct medical and non-medical costs) and indirect costs (productivity loss
due to the disease, including mortality) (51). In all the studies mentioned
above, the indirect costs were substantial, ranging from 65% to 86% of total costs (69, 70, 196, 197). In addition, the study by Sobocki et al (197) showed that the increase in total costs between 1997 and 2005 was mainly due to an increase in the indirect costs with a four-fold increase in costs for sick-leave and a two-fold increase in costs for early retirement. The cost associated with mortality increased only marginally. Drug costs made up 3% of total costs in 2005 in this study.

By means of a so-called bottom-up approach, data are collected directly from a sample of patients with the disease being studied (83). Studies using such an approach have most often only measured the direct costs (118, 161, 188). The results of these studies have varied substantially. In the multinational LIDO study by Chisholm et al (25) it was found that the costs differed more than 15-fold between the countries studied.

There has been limited research on the relation between treatment adherence and cost of depression. Katon et al evaluated the effect of adherence to antidepressants on comorbid medication adherence in dyslipidemia, coronary artery disease, diabetes mellitus and combinations of these diseases, and on medical costs for treating patients with these diseases (100). They found that patients adherent to antidepressants were also more likely to be adherent to comorbid therapy and that they had significantly lower disease-specific as well as total medical costs as compared to non-adherent patients. In a retrospective study of almost 23 000 patients beginning SSRI-treatment, adherent patients were found to have significantly lower yearly medical costs (21).
Background and aims

Background

There are large amount of unused medications in the bathroom cabinets of the western world population. This fact was already being emphasised back in the early 1980s when I was studying pharmaceutics. Since then, the problem of poor adherence, the underlying reasons for it, and how to overcome it, have been of concern to me.

This thesis is based on the clinical study “the Swedish Long-term Implications of Compliance Enhancing Interventions in depression (SLICE)”. The study was initiated because few large investigations had been performed in depressed primary care patients with the aim of exploring the overall effects of adherence enhancing interventions, the relation between adherence and outcome and the factors predicting non-adherence to antidepressants.

Aims

The specific aims of this thesis were:

1. To measure the effect of a patient educational compliance enhancing programme and the effect of therapeutic drug monitoring on treatment adherence and treatment response in depressed outpatients treated with sertraline and managed by general practitioners (Paper I).
2. To explore patients’ long-term outcome and, in particular, to examine the impact of patients’ treatment adherence on response, remission and relapse (Paper II).
3. To analyse the societal costs of depression and the distribution of costs into different cost components. The impacts of adherence and treatment response were also explored (Paper III).
4. To identify predictors of non-adherence to antidepressant treatment that can be ascertained by the physician before initiation of treatment (Paper IV).
Methodology

Study design
In the SLICE-study, male and female outpatients, 18 years or older, and with a diagnosis of major depression according to DSM-IV (3), were included in the study by general practitioners (GPs) in primary care. Before inclusion in the study, a clinical decision should have been made to start treatment with Zoloft® (sertraline hydrochloride). Written informed consent to participate was also obtained from the patient before inclusion in the study. The only exclusion criteria were contraindications to and/or interactions with sertraline, or participation in any other studies involving medication. Sertraline tablets were prescribed by the GPs at the baseline visit and collected and paid for by the patients at their local pharmacy.

The study was a controlled, open-labelled, multi-centre study with each centre randomised to one of three treatment arms: a patient Compliance Programme (CP-group), Therapeutic Drug Monitoring (TDM-group) or a control arm (Control group). GPs at primary care centres and at clinics specialised in company and occupational medicine in Sweden received a postal invitation to participate in the study, and a total of 114 practitioners in the selected areas agreed to do so. The practitioners were randomised to a treatment group after they had agreed to participate in the study and planned to participate in a start-up meeting. The randomisation was done in a consecutive way based on a computerised randomisation list with random permuted blocks of six and a treatment assignment relation of 1:1:1 (CP:TDM:Control). A total of 93 primary care physicians, 29 in the CP-group, 32 in the TDM-group and 32 in the Control-group, recruited patients to the study. This cluster design was chosen because it would have been difficult for a practitioner to avoid carrying over some of the features of the different adherence interventions between treatment groups.

The study consisted of two phases; (i) the initial 24-week active treatment phase, followed by (ii) a long-term naturalistic follow-up phase lasting up to two years from study enrolment. Irrespective of treatment group all patients were to be treated with sertraline during the initial 24 weeks. The second part of the study was intended to reflect clinical routine in a naturalistic way. During this period, the GPs made all decisions about treatment, including medication discontinuation, switches and re-initiations of antidepressants. All patients, including those discontinuing sertraline treatments prematurely,
were to be followed for two years. After the baseline visit (week 0), the
patients were seen by their practitioner at study-specific check-ups at weeks
4, 12 and 24, and after 1 and 2 years (Figure 1). All patient data were
registered by the practitioner in study-specific case report forms (CRFs).
Agreement between the medical records and the CRFs was monitored during
the performance of the study. In addition, in order to have information on
potentially eligible patients, the practitioners were also to record in a specific
log all patients not included in the trial, with information regarding age, sex,
drug name and reason for non-inclusion.

<table>
<thead>
<tr>
<th>Active treatment (weeks)</th>
<th>Follow-up (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (baseline)</td>
<td>4</td>
</tr>
<tr>
<td>Randomisation of centres CP TDM Control</td>
<td></td>
</tr>
<tr>
<td>Visits nr</td>
<td>1</td>
</tr>
</tbody>
</table>

CP = Compliance enhancement Programme
TDM = Therapeutic Drug Monitoring programme

Figure 1. Overview of study design

Interventions

Compliance enhancement Programme

Patients in the Compliance enhancement Programme (CP) group were
provided with the written educational material RHYTHMS (123, 144),
which covers typical issues and recovery patterns associated with successful
treatment of MD. The goal of the programme is to maximise therapeutic
outcome by encouraging adherence to treatment. A starter kit was given to
the patient when treatment began, and a total of five different letters were
mailed to the patient at weeks 2, 5, 8, 12 and 18. Each letter begins with a
particular topic, followed by patient case stories, a patient-doctor dialogue,
and a self-assessment questionnaire. The patients in this group were also
contacted twice by telephone at weeks 3-4 and 6-7.

Therapeutic Drug Monitoring

In the Therapeutic Drug Monitoring (TDM) group, blood samples from the
patients were collected for analysis of sertraline and desmethylsertraline at
weeks 4 and 12. The physician responsible for treatment and the TDM
laboratory communicated by means of standardised request forms. A clinical
pharmacologist evaluated the serum concentrations in relation to clinical information provided on the request form and gave the GP an immediate response as a basis for continued discussion with the patient. By means of TDM, dose optimisation for individual patients, including monitoring of adherence, side effects and drug-drug interactions, can be accomplished. TDM can also help the physician understand the clinically relevant pharmacokinetics of the drug and promote better grounds for making dose adjustments (11, 19, 132, 133, 167).

Control group
The two intervention groups were compared with a Control group in which patients were treated in accordance with the general practitioners’ clinical routine.

Measures and assessments

Major depression: diagnosis, severity and change over time
Before a patient could be included in the study, major depression (MD) had to be diagnosed according to the DSM-IV diagnostic criteria for Major Depressive Disorder, single episode or recurrent disorder (3). Assessment of melancholic features consistent with DSM-IV was also performed.

At each study visit the severity and progression of the episode were assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS) (140). The MADRS is an established scale that is widely used in depression studies in order to evaluate the disease over time. The MADRS includes 10 items covering symptoms typical for MD, with a possible score for each item ranging between 0 and 6. The sum of the 10 items is a measure of the overall severity of the depression. Before the study started, co-rating meetings were arranged to assure uniform assessment of the patients. Prior to study start, an acceptable inter-rater reliability for MADRS ratings (deviation of ± 1 point from the steering committee rating was accepted) with a weighted Kappa of 0.7 was demonstrated.

In addition to the MADRS-rating, the one-item Clinical Global Impression – Severity (CGI-S) scale was used as an overall judgement of the severity of the depression (73). The CGI-S scale ranges between 1 and 7, from “normal, not ill” to “among the most extremely ill patients”.

To measure change in depression severity from baseline to week 24, the one-item Clinical Global Impression – Improvement (CGI-I) scale was used (73). The CGI-I scale is based on the CGI-S scale and ranges between 1 and
7 (“very much improved” to “very much worse”). In the present study, scores between 1-4 (“very much improved” to “no change” to) were used.

Demographics and sociodemographics
At baseline the following patient variables were recorded: gender, age, living status, number of children living at home, education level and employment/retirement status.

Comorbidity and psychiatric history
Overall medical history, including other psychiatric illnesses and substance abuse, were recorded at baseline. In addition, specific aspects of the patient’s depression history (number of previous episodes, age at first episode, hospitalisation, suicide attempts, antidepressant treatment and family history) were registered at the first study visit.

Personality
Personality traits were assessed by the Swedish universites Scales of Personality (SSP) (71). The SSP comprises 91 items divided into 13 scales with seven items in each. Each item is presented as a statement with a four-point response format, ranging from 1 = “does not apply at all”, to 4 = “applies completely”. The SSP mean scores are transformed into normative T-scores with means of 50 and standard deviations of 10 based on a Swedish gender-stratified non-patient sample. The internal consistency in terms of Cronbach’s alpha ranged between 0.59 and 0.84 (71).

Personality disorders were assessed at baseline, week 24, year 1 and year 2 using the DSM-IV and ICD-10 Personality Questionnaire (DIP-Q). This is a 135-item true/false self-report questionnaire designed to measure personality disorders according to DSM-IV and ICD-10 (3, 222). DIP-Q has been validated by comparing questionnaire-based results with those from a semi-structured interview in a clinical sample of 138 individuals (153). Agreement was acceptable on both a global level and a cluster level. Cohen's Kappa for any DSM-IV personality disorder was 0.61, and it was 0.56 for ICD-10.

Adverse events
At each study visit the practitioner recorded all observed or spontaneously reported adverse events in the CRF, regardless of treatment group or suspected causal relationship. The record included the severity (mild, moderate, or severe) of the event, the outcome, and the practitioner’s opinion concerning the relationship to the study drug.
Blood sampling and analytical methods

Venous blood samples were collected at weeks 4, 12 and 24 for analysis of trough concentrations of sertraline and desmethylsertraline. Time and date of the last dose and of sampling were recorded. Assays were performed using established validated high-performance liquid chromatography with ultraviolet-detection (HPLC-UV).

Patient satisfaction

Patient satisfaction regarding the information provided on depression and treatment, and the ease of understanding the information given was assessed using four questions with a five-point Likert-scale format after the initial 24-week treatment phase (123).

Health related quality of life

At baseline, week 24, year 1 and year 2, the patient’s Health Related Quality of Life (HRQL) was assessed using the EuroQol-5 dimensions self-report questionnaire (EQ-5D) (208). EQ-5D is a generic measure of health status. It includes two parts: (i) a visual analogue scale where the respondent is asked to indicate a self-rating of his or her current health state along a vertical line ranging from 0 (worst imaginable health) to 100 (best imaginable health), and (ii) five questions that defines health in terms of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Within each dimension there are three severity levels: no problems, moderate problems or severe problems. The respondent's health status can be expressed by combining the different levels from each dimension. EQ-5D defines a total of 243 unique theoretical health states (3^5) which have been given health state utilities ranging from −0.59 to 1 using the time-trade off method in the general UK population (49).

Quality Adjusted Life Years (QALYs), in which longevity and quality of life are combined in one single measure, were calculated as the area under the quality of life curve over the two-year study period (51, 94, 226). One QALY represents one year with full health.

Health care utilisation and costing

During the study, all utilisation of care, both outpatient care and inpatient care, was recorded for all psychiatric and somatic diseases. In addition, all use of pharmaceuticals, sick leave days and retirement were recorded, regardless of reason.

Cost was assessed by the basic costing principle of collecting information on resource consumption and multiplying each resource (quantity) by a unit
cost (price). Quantities were collected from the CRFs and unit costs were obtained from different public sources such as the National Insurance Board, the Statistical Yearbook of Sweden, the Swedish Pharmaceutical Reference Book, the Uppsala County Council price list, the Dept. of Laboratory Medicine, Huddinge University Hospital price list and Svensson et al (205). Unit costs and sources are presented in Paper III. All prices are given in KSEK, at the price level for 2002/2003.

Costs were divided into direct and indirect costs. Direct costs are usually referred to as the costs for detection, treatment, rehabilitation and long-term care of a disease (83). In this study, direct costs constitute the costs for outpatient visits, inpatient care, intervention, study drug and concomitant drugs. Costs for the GP-visits at year 1 and year 2 were not included, since they were considered to be study-specific.

Indirect costs are defined as costs from productivity losses due to illness (83). In this study, sickness absence from work and early retirement were included. The traditional human-capital approach was used to value loss of production (219). As a proxy for productivity, the average earnings for the Swedish population in all age groups, plus payroll taxes, were used. Total costs were calculated as the sum of all direct and indirect costs. For missing cost data, imputations were performed by means of linear regression analysis using the software SAS PROC MI.

Definitions

Adherence
The primary efficacy variable “Adherence” comprised a composite index. Patients were classified as non-adherent at week 24 if they discontinued sertraline treatment prematurely, withdrew from the study, or did not fulfil one or more of the following three adherence criteria:

- measurable serum levels of sertraline and/or desmethylsertraline at weeks 4, 12 and 24,
- self-reported assurance at weeks 4, 12, and 24 that the patient had taken sertraline as prescribed i.e. the GP asked the patient if he/she had taken the medication as prescribed. Based on the patient’s answer, the GP recorded a “Yes” or a “No” in the CRF,
- scheduled visits performed within the stipulated time-frames (i.e. 4±1, 12±4 and 24±2 weeks).
Response to treatment
Response was assessed by means of the MADRS (140), the CGI-S scale and the CGI-I scale (73). To be classified as a responder at weeks 4 and 12 and years 1 and 2, a reduction in total MADRS score of at least 50% from baseline and a CGI-S score between 1 to 3 (i.e. normal to slightly ill) were required. At week 24, the same definition was used with the addition of a CGI-I score of 2 at the most (i.e. much or very much improved).

Relapse/recurrence
Given the timing of the follow-up assessments, it was not possible to differentiate between relapse and recurrence. Thus, relapse is used to refer both to relapse and recurrence. Relapse was defined as any of the following:
1. an increase in total MADRS score of at least 50% compared with the lowest score obtained during the study, and a total MADRS score of at least 21, and a CGI-S score of at least 4,
2. a new episode of antidepressant treatment for the indication MD,
3. psychiatric hospitalisation due to MD, or
4. suicide attempt or suicide.
Response at week 24, at the latest, was a prerequisite for relapse. Since relapses were recorded during the entire study period, a patient could fulfil the criteria for a relapse more than once. Time to relapse was defined as the time from the visit where response was obtained to the time when the relapse occurred.

Sustained response
Sustained response required fulfilment of the response criteria at week 24 at the latest, and at year 1 and 2, and with no relapse.

Remission
Treatment remission was defined as a MADRS score of 9 or less as suggested by (236). Remission was assessed at week 24, year 1 and year 2.

Statistical analyses
The sample size was estimated based on an expected difference in adherence rates between the intervention groups and the control group of 11%, and an adherence rate of 52.5% in the control group. Given a 90% power, the number of patients needed in each group was estimated to 403.
Results presented in the papers are based on the Intention To Treat (ITT) population. For all data except costs, two approaches were used in analysing the data: (i) replacing missing data according to the last observation carried forward (LOCF) technique, and (ii) observed cases (OC). Missing cost data were imputed using linear regression analysis with intervention, age, gender, response and non-missing preceding cost as predictors. An exception was imputations of cost data for early retirement, where LOCF was used.

Statistical analyses were performed using SAS® software, version 8.0 or 8.2. In order to adjust for the cluster randomisation design, permutation tests (67) as well as Generalised Estimating Equations (GEE) (76) were used. All tests were two-tailed with a significance level of 0.05. Descriptive analyses were undertaken using demographic and baseline characteristics, as well as for overall outcome variables. Statistical analyses are summarised in Table 1.

Table 1. Statistical methods used in papers I-IV

<table>
<thead>
<tr>
<th>Statistical method</th>
<th>Paper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chi-square test</td>
<td>I, IV</td>
</tr>
<tr>
<td>Generalised estimating equations</td>
<td>II, III, IV</td>
</tr>
<tr>
<td>Factor analysis</td>
<td>IV</td>
</tr>
<tr>
<td>Linear regression</td>
<td>III</td>
</tr>
<tr>
<td>Permutation test</td>
<td>I, III</td>
</tr>
<tr>
<td>Stepwise logistic regression</td>
<td>IV</td>
</tr>
<tr>
<td>t-test</td>
<td>IV</td>
</tr>
<tr>
<td>Wald chi-square test</td>
<td>II, III</td>
</tr>
<tr>
<td>Wilcoxon matched pair rank sign test</td>
<td>III</td>
</tr>
<tr>
<td>Wilcoxon-Mann-Whitney test</td>
<td>I</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>II, IV</td>
</tr>
</tbody>
</table>

Ethics

The study was conducted in accordance with the Declaration of Helsinki (revised in South Africa in 1996) (228). The study protocol and informed consent documentation were reviewed and approved by the regional independent ethics committees at the universities in Göteborg, Linköping, Stockholm, Umeå, Uppsala and Örebro.
Results

Participants

Subject disposition and withdrawals
Between 8 June 1999 and 30 December 2000, patients were enrolled into the study. In total, 1651 patients were considered for inclusion in the study. Of these, 599 patients did not fulfil the inclusion criteria, with the most common reason being that the patient did not consent to participate. Overall, 1052 patients were included in the study, however, after completion it was found that 21 patients had been incorrectly included, and were therefore excluded from analysis. Accordingly, the ITT-population consisted of 1031 patients; 366 in the CP-group, 326 in the TDM-group and 339 in the Control group. Subject flow is shown in Figure 2. For a detailed description of reasons for withdrawal from the study see Papers I and II.

All patients were to be treated with sertraline during the initial 24 weeks. However, during this period a total of 91 patients withdrew from the study with the most common reason being withdrawal of consent to participate. Another 158 patients discontinued study drug treatment but remained in the study. The main reason for discontinuation of study medication was adverse events, followed by the patient’s own decision to stop.

During the follow-up phase of the study an additional 105 patients were withdrawn. Overall, the most frequent reason for withdrawal was withdrawal of consent, and lost to follow-up.

In total, 835 patients completed the two-year study, 318 patients in the CP group, 266 patients in the TDM-group and 251 in the Control group. This corresponds to 86.9%, 81.6% and 74.0% of the ITT-population in the respective treatment arms.
Demographics and baseline characteristics
The majority of patients enrolled were females (71.9%), and the mean age was 48 years, ranging from 18 to 95 years. Most of the patients (61.4%) were married or co-habiting and the mean number of children living at home was 0.7. In total, 20.6% had a university degree, 67.3% were employed and 8.5% unemployed. Details on demographic and sociodemographic data for the ITT-population are presented in Tables 2 and 3. Overall, distribution of the demographic data was comparable in the different treatment groups.

Psychiatric history and baseline characteristics are presented in Table 3. The majority of patients had had previous episodes of depression (57.9%) with the first episode at a mean age of 34 years. A small proportion (6.9%)
had been hospitalised for depression. The mean severity of the present episode, assessed by MADRS, was 27 in all three treatment arms, and the mean length of the present episode was 26 weeks. Thirteen point one percent of the patients were judged to have an MD with melancholic features, 33.8% had a co-morbid personality disorder, and 7.8% had been or were currently abusing alcohol or drugs.
### Table 2. Demographic and sociodemographic data at baseline in the ITT-population

<table>
<thead>
<tr>
<th></th>
<th>CP N=366</th>
<th>TDM N=326</th>
<th>Control N=339</th>
<th>Total N=1031</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>107</td>
<td>29.2</td>
<td>96</td>
<td>290</td>
</tr>
<tr>
<td>Female</td>
<td>259</td>
<td>70.8</td>
<td>239</td>
<td>741</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>48±14</td>
<td>50±14</td>
<td>47±15</td>
<td>48±14</td>
</tr>
<tr>
<td>Min-Max</td>
<td>18-90</td>
<td>18-88</td>
<td>18-95</td>
<td>18-95</td>
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<tr>
<td><strong>Living status</strong></td>
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<td></td>
</tr>
<tr>
<td>Married/co-habiting</td>
<td>226</td>
<td>62.3</td>
<td>210</td>
<td>633</td>
</tr>
<tr>
<td>Single</td>
<td>138</td>
<td>37.7</td>
<td>116</td>
<td>398</td>
</tr>
<tr>
<td><strong>No. of children 0-18 years living at home</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>0.7±1.1</td>
<td>0.7±1.1</td>
<td>0.8±1.1</td>
<td>0.7±1.1</td>
</tr>
<tr>
<td>Min-Max</td>
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<td>0-4</td>
<td>0-6</td>
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<tr>
<td><strong>Highest education</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary school</td>
<td>110</td>
<td>30.1</td>
<td>102</td>
<td>310</td>
</tr>
<tr>
<td>High school</td>
<td>172</td>
<td>47.0</td>
<td>134</td>
<td>456</td>
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<td>University</td>
<td>62</td>
<td>16.9</td>
<td>84</td>
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<tr>
<td><strong>Employment status</strong></td>
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<tr>
<td>Employed</td>
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<td>73.5</td>
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<td>694</td>
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<td>Unemployed</td>
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<td>3.8</td>
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<td>Student</td>
<td>19</td>
<td>5.2</td>
<td>28</td>
<td>68</td>
</tr>
<tr>
<td>Retired</td>
<td>44</td>
<td>12.0</td>
<td>44</td>
<td>127</td>
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<tr>
<td>Early retirement</td>
<td>21</td>
<td>5.7</td>
<td>17</td>
<td>78</td>
</tr>
</tbody>
</table>

1 Missing information for 53 patients. 2 One patient with missing information in Paper I. 3 More than one option recorded by 24 patients.
<table>
<thead>
<tr>
<th></th>
<th>CP</th>
<th>TDM</th>
<th>Control</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=366</td>
<td>N=326</td>
<td>N=339</td>
<td>N=1031</td>
</tr>
<tr>
<td>First episode of MD</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td>155</td>
<td>42.3</td>
<td>133</td>
<td>40.1</td>
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<tr>
<td>Age at first episode of MD (years)</td>
<td>Mean ± SD</td>
<td>n %</td>
<td>n %</td>
<td>n %</td>
</tr>
<tr>
<td></td>
<td>33 ± 15</td>
<td>42.3</td>
<td>33 ± 15</td>
<td>40.1</td>
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<td></td>
<td>4-75</td>
<td>4-74</td>
<td>10-82</td>
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<tr>
<td>Previous treatment with antidepressants</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
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<tr>
<td></td>
<td>152</td>
<td>41.5</td>
<td>139</td>
<td>42.6</td>
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<tr>
<td>Previous hospitalisation</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>7.4</td>
<td>20</td>
<td>6.1</td>
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<td>Duration of present episode (weeks)</td>
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<td>28 ± 35</td>
<td>41.5</td>
<td>24 ± 31</td>
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<td>1-288</td>
<td>4-75</td>
<td>2-288</td>
<td>4-74</td>
</tr>
<tr>
<td>Melancholia</td>
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<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>13.7</td>
<td>24</td>
<td>7.4</td>
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<td>Presence of a PD at baseline</td>
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<td>n</td>
<td>107</td>
<td>31.6</td>
</tr>
<tr>
<td>Alcohol/drug abuse (past and/or present)</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td>31</td>
<td>8.5</td>
<td>20</td>
<td>6.1</td>
</tr>
<tr>
<td>MADRS score at baseline</td>
<td>Mean ± SD</td>
<td>n %</td>
<td>n %</td>
<td>n %</td>
</tr>
<tr>
<td></td>
<td>26.5 ± 5.9</td>
<td>41.5</td>
<td>27.1 ± 5.8</td>
<td>42.6</td>
</tr>
<tr>
<td></td>
<td>9-42</td>
<td>4-75</td>
<td>8-46</td>
<td>4-74</td>
</tr>
<tr>
<td>EQ-5D index score</td>
<td>Mean ± SD</td>
<td>n %</td>
<td>n %</td>
<td>n %</td>
</tr>
<tr>
<td></td>
<td>0.62</td>
<td>8.6</td>
<td>0.59</td>
<td>6.1</td>
</tr>
<tr>
<td></td>
<td>-0.18 - 1.00</td>
<td>8.6</td>
<td>-0.30 - 1.00</td>
<td>6.1</td>
</tr>
<tr>
<td></td>
<td>0.61</td>
<td>8.6</td>
<td>0.61</td>
<td>6.1</td>
</tr>
<tr>
<td></td>
<td>-0.48 - 1.00</td>
<td>8.6</td>
<td>-0.48 - 1.00</td>
<td>6.1</td>
</tr>
</tbody>
</table>

1 Percentage based on patients with personality assessment completed at baseline (n=961)
Effects of a written educational compliance enhancing programme and TDM on treatment adherence and outcome (Paper I)

The primary objective of Paper I was to evaluate the effect of two different interventions intended to improve adherence to antidepressant medications. The secondary objectives included evaluating the response to treatment, the relation between adherence and response, patient satisfaction, and tolerability.

Adherence to treatment

Overall, 40.5% of the patients were found to be completely adherent during the initial 24 weeks of treatment. When comparing the different methods of measuring adherence, the highest rate was seen using determination of serum levels, with 68.3% of the total patient population classified as adherent. There were no significant differences between any of the interventions as compared to the control group (Table 4).

Table 4. Treatment adherence in the ITT population

<table>
<thead>
<tr>
<th></th>
<th>CP N=366</th>
<th>TDM N=326</th>
<th>Control N=339</th>
<th>Total N=1031</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Questioning¹</td>
<td>235</td>
<td>206</td>
<td>200</td>
<td>641</td>
</tr>
<tr>
<td>%</td>
<td>64.2</td>
<td>63.2</td>
<td>59.0</td>
<td>62.2</td>
</tr>
<tr>
<td>Serum levels²</td>
<td>258</td>
<td>227</td>
<td>219</td>
<td>704</td>
</tr>
<tr>
<td>%</td>
<td>70.5</td>
<td>69.6</td>
<td>64.6</td>
<td>68.3</td>
</tr>
<tr>
<td>Visits kept³</td>
<td>216</td>
<td>171</td>
<td>176</td>
<td>563</td>
</tr>
<tr>
<td>%</td>
<td>59.0</td>
<td>52.5</td>
<td>51.9</td>
<td>54.6</td>
</tr>
<tr>
<td>Adherence⁴</td>
<td>155</td>
<td>139</td>
<td>124</td>
<td>418</td>
</tr>
<tr>
<td>%</td>
<td>42.3</td>
<td>42.6</td>
<td>36.6</td>
<td>40.5</td>
</tr>
</tbody>
</table>

¹ Questioning by the general practitioners
² Measurable serum levels at weeks 4, 12 and 24
³ Appointments kept at weeks 4, 12 and 24
⁴ Composite index including ¹, ² and ³

Response in relation to intervention and adherence

The response rates at weeks 4, 12 and 24 in the different treatment groups are presented in Table 5.

Significantly more patients in the CP-group (71.0%) had responded at week 24 as compared to patients in the Control group (60.5%). The difference between the TDM-group (68.1%) and the Control group did not reach statistical significance.
Table 5. Response rates (LOCF) in the ITT-population, at weeks 4, 12 and 24 in relation to intervention

<table>
<thead>
<tr>
<th></th>
<th>CP</th>
<th>TDM</th>
<th>Control</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>366</td>
<td>326</td>
<td>339</td>
<td>1031</td>
</tr>
<tr>
<td>Week 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>114</td>
<td>115</td>
<td>99</td>
<td>328</td>
</tr>
<tr>
<td>%</td>
<td>31.1</td>
<td>35.3</td>
<td>29.2</td>
<td>31.8</td>
</tr>
<tr>
<td>Week 12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>231</td>
<td>199</td>
<td>193</td>
<td>623</td>
</tr>
<tr>
<td>%</td>
<td>63.1</td>
<td>61.0</td>
<td>56.9</td>
<td>60.4</td>
</tr>
<tr>
<td>Week 24</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>260</td>
<td>222</td>
<td>205</td>
<td>687</td>
</tr>
<tr>
<td>%</td>
<td>71.0*</td>
<td>68.1</td>
<td>60.5</td>
<td>66.6</td>
</tr>
</tbody>
</table>

* CP versus Control, $\chi^2=8.7$, $p=0.014$

Table 6 shows the response rates at week 24 in relation to adherence measures. Regardless of adherence measure, a strong relation between response and adherence was seen. According to the composite index, 82.5% of adherent patients met response criteria as compared to 55.8% of the non-adherent patients.

Table 6. Treatment adherence in relation to response (LOCF) at week 24 in the ITT-population

<table>
<thead>
<tr>
<th>Responder week 24</th>
<th>No</th>
<th>Yes</th>
<th>$\chi^2$</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Questioning¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>117</td>
<td>524</td>
<td>174.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>227</td>
<td>163</td>
<td>41.8</td>
<td></td>
</tr>
<tr>
<td>Serum levels²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>135</td>
<td>569</td>
<td>201.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>209</td>
<td>118</td>
<td>36.1</td>
<td></td>
</tr>
<tr>
<td>Appointments kept³</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>116</td>
<td>447</td>
<td>90.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>228</td>
<td>240</td>
<td>51.3</td>
<td></td>
</tr>
<tr>
<td>Adherence⁴</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>73</td>
<td>345</td>
<td>80.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>271</td>
<td>342</td>
<td>55.8</td>
<td></td>
</tr>
</tbody>
</table>

¹ Questioning by the general practitioners
² Measurable serum levels at weeks 4, 12 and 24
³ Appointments kept at weeks 4, 12 and 24
⁴ Composite index including ¹, ² and ³
Antidepressant treatment and adverse events

The mean daily doses of sertraline during the first 24 weeks of drug treatment were similar in the three groups (CP-group - 59.6 mg, TDM-group - 58.4 mg, Control group - 56.9 mg).

During the first 24 weeks of treatment a total of 902 patients reported one or more adverse events, significantly more patients in the CP-group as compared to the control group (332 versus 284, $\chi^2= 8.9$, $p=0.02$). In the TDM-group 286 patients reported some adverse event (ns). Another finding was that significantly fewer patients in the TDM-group reduced or temporarily discontinued the study medication due to adverse events, including both adverse events considered related to the study drug (12 patients in the TDM-group and 42 in the control group, $\chi^2=17.1$, $p<0.001$), and all adverse events, regardless of relationship to sertraline (27 versus 56, $\chi^2=10.5$, $p=0.01$). No differences were seen for the CP-group as compared to the Control group.

Patient satisfaction

Assessment of patient satisfaction was added to the study protocol during the course of the study, and was therefore only done in 816 out of the 1031 patients. In general, there was a high degree of patient satisfaction with the information given about depression and treatment. However, significantly more patients in the CP-group found the information concerning depression easy to understand as compared to patients in the control group (88.2% versus 81.5%; $\chi^2=5.1$, $p=0.02$). No other differences were identified.

Response, remission and relapse over two years and the relation between adherence and outcome (Paper II)

Response, remission and relapse/recurrence over time

Response and remission rates for the whole population increased over time. For the ITT-population, with at least one post-baseline MADRS-rating and CGI-S-rating, the response rate, LOCF, at year 2 was 77.0% and the remission rate was 68.2%. Slightly higher rates were seen for observed cases (Table 7).
Table 7. Proportion of responders and remitters at week 24, year 1 and year 2 in ITT-population with LOCF and observed cases

<table>
<thead>
<tr>
<th></th>
<th>Week 24 (n=899)</th>
<th>Year 1 (n=863)</th>
<th>Year 2 (n=830)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td><strong>Response: ITT-LOCF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N=1031)</td>
<td>687 (66.6)</td>
<td>782 (75.8)</td>
<td>794 (77.0)</td>
</tr>
<tr>
<td><strong>Response: observed cases</strong></td>
<td>673 (74.9)</td>
<td>716 (83.0)</td>
<td>700 (84.7)</td>
</tr>
<tr>
<td><strong>Remission: ITT-LOCF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N=1031)</td>
<td>605 (58.7)</td>
<td>668 (64.8)</td>
<td>703 (68.2)</td>
</tr>
<tr>
<td><strong>Remission: observed case</strong></td>
<td>576 (64.1)</td>
<td>610 (70.7)</td>
<td>625 (75.3)</td>
</tr>
</tbody>
</table>

1 CGI-S missing for four subjects (n=826).

Sustained response during the two-year period was seen in 34.7% of the patients (358 of 1031). The corresponding figure for the completers was 42.9% (358 of 835 patients).

A total of 34.1% of responding patients experienced at least one relapse during the two years. The most common reason for being defined as having a relapse was a new treatment with an antidepressant drug (293 of the 357 registered events, 244 patients). Two thirds of the relapses (215 events) were seen during the second year. The mean time from response to first sign of relapse was 273 days (SD 185), median 218 days with a range of 4-760 days.

Relation between adherence and outcome

Significantly more patients responded to treatment among the treatment adherent patients over the two-year study period. Table 8 shows the relation between adherence and response over time.

Treatment adherence was an important factor regarding sustained response. Of the 418 adherent patients, 202 (48.3%) fulfilled the criteria for sustained response (OC) as compared to 156 of the 613 non-adherent patients (25.4%) \(\chi^2=9.00, p=0.0027, 95\% CI=17.0-28.8\). A similar observation was seen for the relation between adherence and remission (Figure 3).

No relationship between adherence and relapse rate was observed. However, the mean time from response to first sign of relapse was significantly longer in the adherent compared to the non-adherent patients (302 days versus 249 days, \(\chi^2=5.74, p=0.017; 95\% CI=9-97\)).
Table 8. Treatment adherence (week 0-24) in relation to response (LOCF) over time

<table>
<thead>
<tr>
<th></th>
<th>Adherent N=418</th>
<th>Non-adherent N=613</th>
<th>$\chi^2$</th>
<th>p</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 24</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responders</td>
<td>345 (82.5%)</td>
<td>342 (55.8%)</td>
<td>80.00</td>
<td>&lt;0.0001</td>
<td>21.4-32.1</td>
</tr>
<tr>
<td>Non-responders</td>
<td>73 (17.5%)</td>
<td>271 (44.2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Year 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responders</td>
<td>360 (86.1%)</td>
<td>422 (68.8%)</td>
<td>40.31</td>
<td>&lt;0.0001</td>
<td>12.3-22.2</td>
</tr>
<tr>
<td>Non-responders</td>
<td>58 (13.9%)</td>
<td>191 (31.2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Year 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responders</td>
<td>357 (85.4%)</td>
<td>437 (71.3%)</td>
<td>21.74</td>
<td>&lt;0.0001</td>
<td>9.2-19.0</td>
</tr>
<tr>
<td>Non-responders</td>
<td>61 (14.6%)</td>
<td>176 (28.7%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* $\chi^2=19.6$, p<0.0001, 95% CI= 9.6-21.5
** $\chi^2=34.2$, p<0.0001, 95% CI=10.0-21.5
† $\chi^2=31.8$, p<0.0001, 95% CI=11.0-22.0
‡ $\chi^2=4.40$, p=0.036, 95% CI=0.5-12.2

Figure 3. Proportion of remitters (MADRS-score ≤9) in adherent (n=418) and non-adherent patients (n=613) at week 24, year and year 2. Last observation carried forward (LOCF) and observed cases (OC) in the ITT-population.
Cost of depression: effect of adherence and treatment response (Paper III)

The objectives of Paper III were to analyse the societal cost of depression and the distribution of cost into different cost components. In addition, the relation between adherence and response with respect to costs and the impact of adherence and response on quality of life were examined.

Total cost of depression by intervention, adherence and response

The average total cost per patient during the two years of the study was KSEK 363. Figure 4 shows the distribution of costs into different components. Indirect costs dominated, comprising 86.8% of the total costs. Sick leave accounted for 80.9% of the indirect costs.

![Figure 4. Distribution of total cost per patient into different cost components](image-url)

No differences in total cost between the treatment arms were found. Nor was there any difference between total cost for adherent and non-adherent patients, although the cost of the study drug was higher, whereas the inpatient care costs were lower in adherent patients.

The average total cost per patient during two years was significantly lower for responders as compared to non-responders (KSEK 299 versus. KSEK 491; $\chi^2=50.72, p<0.0001$).

Health related quality of life

The mean quality of life score assessed by EQ-5D was 0.61 (SD 0.27) at baseline. During the study, the mean score improved by 0.16 (SD 0.28) from baseline to year 2 ($z =16.78, p<0.001$). There were no significant differences at any time between the three treatment arms. However, the improvement in quality of life was slightly more marked among adherent patients as compared to non-adherent patients (an increase of 0.19 versus 0.15 from
baseline to year 2, $\chi^2 = 3.59$, p=0.058). In addition, the self-rated health score, obtained using the visual analogue scale, also increased more in adherent patients than in non-adherent patients (0.25 versus 0.20; $\chi^2 = 10.79$, p=0.001).

The most pronounced difference in change in HRQL was seen when comparing responders to non-responders at week 24. The increase in mean quality of life score was 0.20 from baseline to year 2 in responders and 0.09 in non-responders ($\chi^2 = 33.57$, p<0.0001).

Predictors of non-adherence to antidepressant treatment in primary care (Paper IV)

The main objective of Paper IV was to identify predictors of non-adherence that can be ascertained by the physician before initiation of antidepressant treatment.

Prior to statistical predictor analysis, personality traits assessed by SSP were clustered using a maximum likelihood factor analysis with orthogonal rotation (varimax) in order to identify factors with an eigenvalue >1. Similar to the factor analysis of the normative data (71), the correlations of the 13 scales yielded a three-factor model. The factors are termed *Neuroticism*, *Aggressiveness* and *Sensation Seeking*. The corresponding scores from the three factors were subsequently used in the statistical analyses.

Predictor variables potentially associated with adherence were grouped into patient-related characteristics, illness-related characteristics and treatment-related characteristics. A bivariate comparison of association between patient- and illness- related characteristics and adherence showed a strong relation with non-adherence (p<0.05) for low age (18-34 years), living alone, unemployment, a high neuroticism-, aggressiveness- or sensation seeking- score, presence of a personality disorder, no concomitant medications, low age at first depression episode (0-29 years), and substance abuse. These characteristics, and additionally eight variables with a p-value of 0.25 or less, were included in a step-wise logistic regression analysis, controlled for intervention group. Only predictors remaining statistically significant (p<0.05) were retained in the model.

The first stepwise regression analysis of patient- and illness- related characteristics revealed that patients in the younger age group (18-34 years) and patients in the older age group (65 years and older), with the middle age group as reference, were more likely to be non-adherent, as well as patients with no concomitant medication, presence of a personality disorder, sensation seeking personality traits and substance abuse.
Strong bivariate associations between treatment-related characteristics and non-adherence at week 24 (p<0.05) were found for MADRS score, CGI-S score and (non-) response at week 12.

In a final stepwise logistic regression analysis, treatment-related as well as patient- and illness-related characteristics were included. The model resulted in the same explanatory variables as in the first model, with the addition of the CGI-severity score at week 12 (Table 9).

<table>
<thead>
<tr>
<th>Description</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 18-35 years versus 35-64 years</td>
<td>1.83</td>
<td>1.30-2.57</td>
</tr>
<tr>
<td>65- years versus 35-64 years</td>
<td>1.65</td>
<td>1.05-2.58</td>
</tr>
<tr>
<td>Alcohol/drug abuse (past and/or present)</td>
<td>1.81</td>
<td>1.07-3.07</td>
</tr>
<tr>
<td>Absence of concomitant medication</td>
<td>1.80</td>
<td>1.32-2.46</td>
</tr>
<tr>
<td>Presence of personality disorder</td>
<td>1.32</td>
<td>1.01-1.73</td>
</tr>
<tr>
<td>Sensation seeking personality traits factor score (unit = 1 SD)</td>
<td>1.25</td>
<td>1.10-1.43</td>
</tr>
<tr>
<td>CGI-S week 12</td>
<td>1.31</td>
<td>1.16-1.48</td>
</tr>
</tbody>
</table>

1 Controlled for intervention group and adjusted for the cluster randomisation
Discussion

This thesis focuses on assessing the effect of two interventions aiming to increase antidepressant treatment adherence, and to examine long-term consequences of depression in adherent and non-adherent primary care patients.

Methodological considerations

Design

The present study utilised a randomised, controlled design during the initial 24-week intervention phase, followed by a long-term naturalistic evaluation phase lasting up to two years from study enrolment. Although randomised controlled trials have been suggested as the most reliable methods for determining the effects of treatment, there are a number of issues that could potentially affect external validity (176). One such issue is eligibility criteria. The present study had no specific exclusion criteria, with the exception of contraindications for, or interactions with the study drug, in contrast to most randomised, controlled studies (106). Moreover, only three visits were scheduled during the first 24 weeks. This was considered a minimum number of check-ups in the routine care of depression. However, it is important to keep in mind that the pre-defined visits included structured assessments, which are not usually a part of standard care. The study-specific visits may have increased adherence to medication in all treatment arms. In a recent study (42), adherence to an antidepressant treatment regimen increased on the days just before a clinic visit and decreased on the days afterwards. However, after five weeks this phenomenon was no longer apparent, suggesting that such effects fade away with time.

Another crucial issue is the randomisation procedure. In the present study a cluster randomisation was used, since it was considered difficult for the practitioners to avoid carrying over some of the characteristics of the different interventions to the other arms if treating patients in all three. This design has become more common in recent years (50). A key feature of cluster randomised trials is that responses from people in the same cluster tend to be correlated, or equivalently, the variation among observations from
different clusters exceeds the variation within clusters. Thus, a cluster randomisation design requires special considerations for both sample size estimation and data analysis, but researchers often fail to take into account the clustered nature of their data. This may result in underpowered studies. It also results in elevated risks for type I errors if proper statistical methodology is not used.

In this study, the estimation of sample size for the comparisons of adherence among treatment groups did not adjust for the fact that the observations within clusters would be correlated. In order to make such adjustments, information about the size of this correlation, would have been needed beforehand which, naturally, was not the case. After finalisation of the study, the intra-cluster correlation coefficient was estimated to 0.11 for the primary variable adherence. Moreover, no adjustment of the estimated sample size was performed in order to take into account that more than one comparison between treatment groups was performed.

However, in all the statistical analyses performed in this study, the cluster randomisation design was appropriately accounted for, either using permutation tests (67) or generalised estimating equations (76).

Another drawback of the present study is that it was not blinded; if had been the case, the possibility of bias would naturally have been less. In theory, the study could have been single-blinded if someone without knowledge of treatment had performed the adherence- and outcome-assessments. However, such a design would have required significantly more resources and was therefore not considered possible.

The naturalistic approach used during the follow-up phase implied that all treatment related decisions were based on the practitioner’s clinical judgement and not on a predefined protocol, with the exception of the two study-specific visits. A definite strength was that the study continued for two years making it possible to draw long-term conclusions. Previous primary care studies have often had a shorter duration (182).

Sample

Of the potentially eligible patients for inclusion, 64% were enrolled in the study. The participants had a wide age range from 18 to 95 years, with a mean of 48 years. Females constituted two thirds of the sample, and the severity of the depressive episode at baseline was a MADRS score of 27 points. The distribution of age and gender as well as depression severity thus seems to be consistent with naturalistic primary care studies (28, 52, 195).

The low dropout rate is a strength of this study. A total of 81% of the patients were followed for two years. The low dropout rate can be compared to rates of 20% to 37% in similar studies (102, 128, 188).
Methods

First of all, the measures and classification of adherence must be discussed. This is a tricky area that has been extensively disputed in the literature: however, no consensus regarding the optimal measure and definition of adherence has thus far been achieved (32, 47, 56, 201). All measures presently in use have shortcomings, and those used in studies are usually chosen more from a practical standpoint than based on a sound research approach.

In line with e.g. Liu et al (130), this study used a composite index of adherence based on three different measures, both direct and indirect. The direct measures included determination of sertraline and desmethylsertraline in serum at three occasions. This method usually has a high level of precision, but it is time-point-related. As the patients knew that serum samples were to be taken it is also possible that treatment adherence was improved before the visit in line with the “white-coat” effect described by Feinstein (57) and Cramer et al (34). A more longitudinal measure might be the metabolite/parent compound ratio suggested by Reis et al (169).

The second direct measure of adherence in this study was the patient’s ability to follow the pre-set visit schedule. This measure was included since clinic visits are considered to be an important part of the treatment of depression (24). It can be argued, however, that this measure has nothing to do with adherence to medication, and that failure to follow the schedule might be due to reasons involving the practitioner and/or the clinic, rather than the patient. Interestingly, and in line with this argumentation, this measure showed the smallest difference in response rates between adherent and non-adherent patients.

The third measure used in the present study was questioning of the patient, an indirect measure that has generally been thought to overestimate adherence (32). However, in the present study fewer patients were classified as adherent based on questioning as compared to measurement of serum levels. The reasons for this finding are probably the infrequent sampling, a generous serum level cut-off, and that the practitioners were probably more aware of issues regarding adherence than clinicians in general. In line with this finding, Stephenson et al (201) concluded that the method of questioning that is used probably affects the patient’s response, but that this method is still is the most widely applicable method of measuring adherence.

Furthermore, all patients who discontinued sertraline and those who withdrew from the study during the initial 24 weeks, regardless of reason, were classified as non-adherent. This approach might have resulted in an overestimation of non-adherence, as patients withdrawn from the study or the study drug for clinically justified reasons were classified as non-adherent. However, the composite index used to define patients as adherent
or non-adherent resulted in an overall adherence rate similar to the rate that has previously been reported in the treatment of depression (21, 129).

The definitions of response, remission and relapse also need to be considered. First, the definition of response used in this study was more conservative than in most studies (107, 182), i.e. in addition to a 50% reduction of the MADRS score from baseline, the patient had to be assessed by the practitioner as, at the most, “slightly ill” on the CGI-S scale. The remission criterion, on the other hand, was possibly less conservative (237). However, a MADRS score of 15 or less has frequently been used (107, 198).

A limitation of both definitions discussed above is the pre-defined assessment time-point, which has implications particularly regarding the relapse criterion. With assessments after only 4, 12 and 24 weeks and after 1 and 2 years it might be difficult to differentiate between relapse and recurrence. Furthermore, it cannot be ruled out that some patients might have responded to treatment at a time-point between two visits and already relapsed at the time of assessment. Finally the self-assessment of personality disorders must be mentioned as such assessments have been considered less accurate as compared to structured interviews (234).

Adherence enhancing interventions in the treatment of depression

In paper I the effects of two interventions with the aim of enhancing adherence were investigated. The rationale behind the written educational adherence programme used in this study was that evidence suggests that, irrespectively of disorder, patients who are engaged in treatment, satisfied with it, and better informed also tend to have better treatment adherence (157). Proactive patient/family programmes with education and active participation by the patient have been associated with low discontinuation rates and high rates of objectively measured adherence (105). However, leaflets or written information alone have not been shown to increase adherence significantly (160, 173).

Neither the written educational material nor TDM resulted in a significantly increased adherence rate, although both interventions resulted in numerically greater adherence rates compared to controls. This was also the case for an English version of the same compliance enhancing programme (123, 144). As previously pointed out, a major challenge in all adherence research is that the methods available for measuring adherence to self-administered medications regimens show a rather low specificity, and sensitivity (130). Given this, it follows that it can be difficult to show differences between groups. However, although not statistically significant, the numerical differences between the intervention groups and the control
group followed the same pattern in the present study, independent of measure used.

Previous studies focusing on extensive patient education have resulted in significantly increased adherence (101, 103-105, 160, 231). Thus, time-consuming, labour intensive interventions seem necessary in order to increase adherence. However, only two of these studies had a follow-up period of at least six months (103, 231). Furthermore, in all of the studies education was given by a professional, and in some cases written information or video material was provided in addition to the professional education. A limitation of these studies is the lack of control of the attention factor. The effect observed could be due either to the intervention proper, or simply to the non-specific effects of increased attention paid to the intervention group (135).

An interesting finding in the present study was the significantly increased response rate found in the group of patients who were allocated to receive the written educational material, as compared to controls. Only a limited number of previous studies have reported a positive effect of intervention on depression outcome (79, 135, 155). In two studies reporting results for six months or more, Katon et al (103) found significantly fewer depressive symptoms, but not fewer episodes of relapse/recurrence over a 12-month follow-up period. In the Kutcher et al study (123), no effect on response to treatment was shown over a 29-week period.

Adverse events have been suggested to be linked to non-adherence and to efficacy of treatment (42, 141). In our study, and in line with Bull et al (16), the number of patients reporting adverse events, regardless of relation to the antidepressant medication, was significantly larger in the CP group as compared to controls, but did not result in a larger proportion of non-adherence.

Information regarding patient satisfaction with treatment is limited. In the present study, overall patient satisfaction with information regarding depression and treatment was very high. Thus, more than 80% of the patients viewed the information as sufficient and easy to understand. In only one of the four items included in the patient satisfaction questionnaire did patients allocated to the compliance enhancement programme score higher than the control patients. In the study by Kutcher et al (123), however, all four items were scored higher in the CP group. The results are somewhat surprising, since a relation between satisfaction and adherence could have been expected (157).

**Short and long-term outcome of depression**

The overall treatment outcome in the present study, irrespective of adherence, was higher than in naturalistic studies in primary care. In our
study the remission rates after one and two years were 65% and 68%, respectively. These figures can be compared to remission rates between 23% and 48% after nine months that were reported in two naturalistic studies (28, 37). Our results are more in line with Mynor-Wallis et al (145), who showed remission rates between 54% and 66% after one year in a controlled study comparing four different treatments modalities.

The overall relapse rate in the present study was 34%. This is in line with previous studies in primary care (103, 128, 216) and can be compared with data from a review article with pooled data from 31 randomised studies in psychiatry (65). The authors reported a relapse rate of 62% after two years in patients who had discontinued treatment after four to six months, as compared to 24% in patients with continuous treatment.

Costs and health-related quality of life

This study used a bottom-up approach to investigate the costs and quality of life in patients with major depression. This approach is most often more accurate than the top-down approach, since the latter is based on national registers where important cost items frequently are missing and the diagnosis may be underreported or misreported.

The study results are in line with previous research showing that depression is a costly disorder (25, 69, 197). The mean total cost per patient during the full two years was as high as KSEK 363 (€38 963). Indirect costs, primarily absence from work (sick leave), represented as much as 87% of costs, whereas drug costs accounted for a small share of total costs. The distribution of direct and indirect costs was largely in line with results of previous studies (69, 70, 197). In the Swedish naturalistic observational study, “Health Economics of Depression in Sweden” (HEADIS), of patients treated for depression in primary care, the total cost per patient over six months was estimated at €5 500 (195). Indirect costs constituted 65% of the total cost in that study. Thus, the higher total cost seen in the present study was primarily due to a higher cost for sick-leave.

Treatment of depression has been shown to reduce sick leave and increase work productivity (12, 26, 188). In line with these findings and with Sobocki et al (193), an important result of the present study is that treatment responders have considerably lower costs than non-responders. Cost savings are primarily derived from a reduction in sick leave for responding patients, thus substantially lowering the indirect costs. This is critical, since costs for sickness absence in Sweden are high, and psychiatric disorders were the most common reason for newly approved sick leave in 2005 (146).

In addition, a significantly greater increase in health related quality of life was seen in responders as compared to non-responders. Overall, the baseline HRQL of 0.61 utility weights is comparable to findings in previous research
and shows the significant burden depression imposes on the patient (161, 181, 194, 202). Over the duration of the study, well-being increased and average quality of life scores increased significantly during the two years, but were still lower than in the general population (20).

Interventions to increase response rates may increase direct costs in the short run, but given the small magnitude of drug costs and other intervention costs seen in this study, these are very likely to be compensated for by the reduction in lost productivity. The results therefore indicate that there are good health economic motives for supporting interventions to achieve high response rates, and that it is important to adhere to evidence based treatment guidelines for antidepressants.

Relation between adherence and outcome, cost and quality of life

A significant finding in this study is the relationship between treatment adherence and response to treatment at week 24, regardless of the intervention and adherence method used. This finding underscores the clinical importance of treatment adherence. Even when a simple method like questioning was used, 81% of the patients in the present study who said that they had taken their medication as prescribed were classified as responders, as compared to 40% of those patients who did not.

Since depression is often a chronic or recurrent disease, the significance of treatment adherence during the acute and the continuation phase with regard to long-term outcome is also relevant. Although no significant effect of the interventions on treatment adherence was observed in the present study, adherent patients as compared to non-adherent patients showed superior response and remission rates at all assessments over two years. In addition, there was a trend to a superior HRQL in the adherent patients. The better outcome in adherent patients may be explained, at least in part, by the fact that adherent patients were more likely to receive continuous antidepressant treatment over two years than non-adherent patients. In addition, a reasonable assumption is that the adherent patients also continued to be adherent to treatment during the follow-up phase. This finding is in line with recent research indicating a positive relation between treatment duration and outcome (65). Another possible explanation for the superior results in the adherent patients could be the high remission rate that was detected after six months. Such an interpretation is supported by research demonstrating that achieved remission is associated with better long-term outcomes as compared to achieved response without remission (98, 99, 128, 158, 163, 164, 214). On the other hand, the relapse rate did not differ between adherent and non-adherent patients in the present study, although the time to relapse
was significantly longer in the group of adherent patients. The lack of effect on relapse rate is consistent with the findings of Katon et al (103).

In contrast to the strong relation between adherence and clinical outcome, and in opposition to our hypothesis, no significant differences in costs could be detected between adherent and non-adherent patients in the present study. One explanation could be that in the case of cost data in particular large sample sizes are required in order to reach conclusions regarding differences in costs between patient groups. This is a general problem in health economic evaluations due to the skewed nature of costs and the usually considerable variations between patients. However, in contrast to our finding, other research groups have found significantly lower total costs among patients adherent to antidepressants as compared to non-adherent patients, also underscoring the importance of adherence in a societal cost perspective (21, 185, 209).

Predictors of non-adherence

Predictors of poor adherence to antidepressant medication can be a useful resource in identifying those patients who are most in need of interventions to improve adherence (152). However, previous research is limited and has most often involved small numbers of patients (39, 129, 155).

In the present study an attempt was made to identify risk factors for poor adherence that can be ascertained in connection with treatment start. It can be argued that a limitation of this approach is that different factors seem to be involved in prematurely discontinuation of medication and non-adherence to a treatment regimen (41, 43). As discussed above, no distinction was made between early discontinuation, regardless of reason, and non-adherence among patients on the medication during the complete treatment phase. However, it was considered most useful for the practitioner to be able to identify those patients who are at greatest risk of non-adherence, irrespectively of reason, already when initiating treatment.

A somewhat unexpected finding in the present study was that patients with no concomitant medication were more likely to be non-adherent (180, 225). Previous research on the impact of polypharmacy on adherence has mainly focused on the elderly. In a review by Vik et al (225), the authors concluded that, “an increased number of medications may adversely affect adherence, although findings have not been consistent”. A reasonable explanation for our finding may be that patients with no other prescriptions more easily forget to take their medication. Another tentative explanation is that depressed patients with no other diseases, and consequently no other medications, have less insight into their illness and less belief in the benefits of treatment (especially when they start feeling better), or they perceive it as a social stigma (191). In line with recent research in behavioural science, a
continuous and dynamic process is required in order to improve adherence (224). The patient population can be divided into segments according to level-of-readiness to follow health recommendations. A limitation of our study is that is was not designed to explore the impact of psychological factors such as the patients’ knowledge and beliefs about their illness, motivation to manage it, confidence in their ability to engage in illness-management behaviours, and expectations regarding the outcome of treatment (2, 40, 88, 224).

In the present study, presence of a personality disorder and substance abuse were shown to predict non-adherence, results that were not very surprising. Substance abuse is usually thought to be a risk factor for poor adherence, resulting in the exclusion of patients with these problems from most controlled clinical studies (235). Also, in a study of psychiatrist-reported treatment non-adherence among patients in routine psychiatric care, substance abuse was shown to predict problems with adherence (27). Personality pathology has previously been shown to predict non-adherence (27, 191). However, in a long-term study of prophylaxis in recurrent depression by Frank et al (59), no differences were observed between adherent and non-adherent patients with respect to the presence of personality disorders. Consistent with earlier findings, we found that non-adherence was predicted by sensation seeking personality traits (53). This finding is understandable, since individuals who are impulsive, non-planning, avoid routines and have a need for change may not find it easy or significant to adhere to daily medication regimens and follow-up visits. The finding is also in line with another study reporting a strong association between novelty seeking personality traits and early discontinuation from a clinical trial in patients with anxiety disorders (227).

In this study both younger age and older age were shown to predict poor adherence. The results of earlier studies of adherence to antidepressants, where age has been included as a potential predictor of adherence/non-adherence to antidepressants, are somewhat conflicting (16, 59, 128, 191). However, Demyttenaere et al (43) reported that young age was a predictor of premature dropout from antidepressant drug treatment.

Clinical implications

This thesis provides additional indications of an overall low adherence to antidepressant treatment (21, 129, 149, 155). Even though the patients were followed prospectively with structured assessments, and two thirds of them were included in intervention groups with the objective of improving adherence, only 41% of the included patients were completely adherent during the initial 24 weeks. The importance of adherence for a good clinical outcome of major depression was evident in this study and is in line with
previous research (59, 68, 101, 103, 109, 138, 186). Adherent patients obtained both a response and a sustained response, as well as remission, to a greater extent over the two-year study period as compared to non-adherent patients.

The results show that there must be greater focus on adherence in the everyday primary care practice. Improved adherence is a hidden resource. With improved adherence, the true effectiveness of antidepressant treatment can be obtained with less suffering, and at a lower overall cost (21, 185, 209). McDonald et al (135) concluded that, “Increasing the effectiveness of adherence interventions might have a far greater impact on the health of the population than any other improvement in specific medical treatments”.

However, attempts made to improve adherence to antidepressants have so far been rather disappointing (79, 155). In this study, neither of the two interventions resulted in an increased proportion of adherent patients. Previous research has shown that multifaceted interventions can be effective, but these interventions are not readily applicable in clinical routine with the limited resources that are available (155, 221). Until feasible interventions with proven effectiveness are available a more structured care with a pragmatic approach in everyday clinical practice is suggested (152).

Research suggests, however, that a group of individuals follow medical advice in general (10, 190). This group might not need specific attention. Focus should consequently be on those patients who are less likely to adhere to treatment or other regimens. With increased knowledge concerning which patients are at the highest risk of poor adherence, these individuals could be identified early in the treatment and appropriate efforts taken. It is most probable that different patients, e.g. the elderly and those with a personality disorder, need different kinds of interventions. A challenge for the future is to find and use tailor-made adherence enhancing interventions for patients at risk.

A major challenge both in research and clinical routine is the measurement of adherence regarding self-administered medications. More precise methods are needed. So far, the most accurate method seems to be electronic container caps (56). However, these are still most suitable for research. Asking patients, non-judgementally, about medication taking behaviour seems so far to be a useful approach for identifying non-adherence (78, 152, 201).

Finally, although this thesis focus on adherence to antidepressant medication, much of its contents may be generalised to other therapeutic areas, since problems with adherence constitutes a challenge within most medical fields.
Future research

In the book by Haynes and co-authors, “Compliance in Health Care”, published back in 1979 (77), it was recognised that “Although some battles have been won, the compliance war is far from over” and that “those who seek easy, universal solutions to problems in understanding, measuring, and improving compliance may be disappointed”. Almost 30 years later these insights are still highly relevant even though serious efforts to develop effective adherence enhancing interventions have been made since that (79, 155).

A major limitation in all adherence research, is as previously emphasised, that effective methods for measuring adherence are lacking. This is an important area for future research since valid measures are a prerequisite for the development of innovative interventions. Computerised devices incorporated in commercial packaging may be an option for measuring adherence, but this needs to be tested in future research. If this option turns out to be effective, the increased cost in the short term could very well be covered by savings in total costs. However, the patient integrity must be considered when using computerised supervision.

New technologies such as mobile phones and SMS may in theory be used to both measure (152) and increase adherence (80). However, research is needed in order to investigate the validity and effect of these strategies in depression.

Furthermore, individually tailored interventions probably have the greatest likelihood of improving adherence. Research focusing on those patients at most risk of non-adherence, and testing different interventions in different risk-populations, is suggested. In addition, the patient's attitude towards disease and treatment should be addressed when treatment is initiated, as these factors probably have a large impact on adherence.
The screening of this treatment is that you should take one tablet daily for six months.
Conclusion

Adherence to antidepressant medication is a challenging issue. In the present investigation less than every second patient was adherent to antidepressant treatment

The conclusions of the papers presented in this thesis are:

- The interventions, an educational compliance enhancing programme and therapeutic drug monitoring, did not increase antidepressant adherence. However, the response rate increased significantly in the educational compliance enhancing intervention group.

- Patients adherent to antidepressant treatment showed superior long-term outcome as compared to non-adherent patients.

- Major depression entails high costs for society, primarily due to indirect costs. Patients responding to antidepressant treatment generate considerably lower costs and have better health related quality of life than non-responders.

- Non-adherence can be predicted by age below 35 or above 64 years, absence of concomitant medications, the presence of personality disorder, sensation seeking personality traits and substance abuse.
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