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Mascha C. ten Doesschate

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1

General introduction

INTRODUCTION

This thesis focuses on several important clinical aspects of recurrent Major Depressive Disorder (MDD) or recurrent depression, which is one of the major health problems in current society. The presented findings are based on data obtained in the Depression Evaluation Longitudinal Therapy Assessment (DELTA) study, a project aimed at the prevention of recurrence of MDD. This introductory chapter starts with brief overviews of (recurrent) MDD and its prevalence, the design and methodology of the DELTA study and some of its major previous results. Next, the main topics of this thesis are introduced, which are respectively: health related quality of life (HRQOL) in recurrent depression, continuation and maintenance antidepressant use, adherence to antidepressants in recurrent depression, and predictors of a new episode in recurrent depression.

MAJOR DEPRESSION

Diagnostic criteria for Major Depressive Disorder

In our study we used the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) to classify patient's depression status, which is one of the most widely accepted classification systems for mental disorders. In the DSM-IV the key symptoms of MDD are depressed mood and loss of interest or pleasure.[1] For the diagnosis of MDD at least one of these key symptoms, together with 4 (or more) out of 9 additional symptoms must be present for a minimum of 2 weeks. In addition, the disorder must have caused clinically significant distress or impairment in functioning. The criteria needed for a DSM-IV diagnosis of MDD are presented in Appendix 1.

Epidemiology and burden of disease

MDD is a disease with severe individual and public health consequences.[2] For the Netherlands, the 12-month prevalence of MDD is reported to be 5.8% and the life-time prevalence 15.4%.[3] The prevalences are in line with reported prevalences in the United States (5.3% and 13.2%-16.2%, respectively).[4] In women, the prevalences are approximately two times higher than in men.[3;4]

MDD is typically associated with significant consequences for relatives, often referred to as family burden.[5;6] In addition, approximately 50% of mortalities due to suicide occur in association with MDD.[7-9] Moreover, in the Netherlands MDD accounts for 1.8 billion euros per year in medical care costs, loss of productivity and reduction of quality of life.[10]

Recurrent depression

Unfortunately MDD is often a recurrent affliction. The prevailing clinical opinion is that a single episode of MDD is unusual and especially rare in specialized care.[11] Recurrence rates increase with setting (general population, patients treated by general practitioners,

and psychiatric outpatients). Recurrence rates of 35% over a 23-year period are found in a population based sample,[12] and of 40% over a 10-year period in primary care.[13] Among psychiatric outpatients reported recurrence rates are even higher, ranging between 40% over a 5-years period,[14] 50-70% over a 1-year period among outpatients depending on the intensity of acute treatment a patient received and the number of previous episodes[15] and 80% over a 3-year period among recurrently depressed outpatients without prophylactic treatment.[16] Moreover, in 10% to 20% of patients suffering from MDD the illness has a chronic course.[12;17]

Definition of remission, relapse and recurrence

The terms 'response', 'remission', 'relapse', and 'recurrence' are not uniformly used in current literature. For this reason Frank et al.[18] proposed internally consistent definitions, which we adapted for our study:

- Response is defined as at least 50% reduction of depressive symptomatology
- Remission is defined as a(n) (almost) symptom-free period
- Relapse is defined as the early return of depressive symptoms following an apparent remission within 4 to 6 months
- Recurrence is defined as the appearance of a *new* depressive episode after 6 months of remission

In the DSM-IV, the diagnosis of recurrent MDD is based on the incidence of two or more Major Depressive Episodes (MDE). These episodes must be separated by an interval of at least 2 consecutive months in which criteria for a MDE (DSM-IV) are not met (see Appendix 1). In this thesis the terms relapse and recurrence are used interchangeably because the division seems largely arbitrary.

THE DELTA STUDY

Aims and methods of the DELTA study

The main aim of the DELTA study was to evaluate the effectiveness of a cognitive group therapy (CT) program in preventing relapse.[19] In brief, 172 patients participated in a randomized controlled clinical trial in which treatment as usual (TAU: i.e., specialty mental health care or care by a family doctor or no care at all), was compared with TAU augmented with an additional preventive CT.[19] The preventive CT consisted of eight weekly two-hour sessions and focused mainly on identification and change of presumed vulnerability factors of relapse and recurrence, i.e. rigid dysfunctional attitudes, according to the model of Beck.[20;21] The use of pharmacotherapy was not restricted during the study period. All patients reported use, dose and adherence to medication during the study period.

To be eligible subjects had to meet the following inclusion criteria:
a) At least two separate MDEs in the previous five years according to the DSM-IV;[1]

b) Current remission status according to DSM-IV criteria, for at least 10 weeks and less than two years;
c) A Hamilton Rating Scale for Depression[22] total score of 9 or less.[23]

Exclusion criteria were: current mania or hypomania or a history of bipolar illness, any psychotic disorder (current and previous), organic brain damage, alcohol or drug misuse, predominating anxiety disorder, recent electroconvulsive therapy, recent CT or getting CT at entry of the study, or current psychotherapy with a frequency of more than twice a month.

Participants were recruited between February 2000 and September 2000 at psychiatric centers and through advertisements. They completed telephonic screening (n > 1000), diagnostic interviews (n = 321) and each provided written informed consent to enter the protocol (n = 187). The protocol was approved by the institutional ethics review committees. Because the focus of this thesis is not the evaluation of the above-described preventive cognitive intervention, the analyses were performed, where possible, on the total sample, not including early drop-outs (CT plus TAU, n = 172; early drop-outs n = 15).

Previous results of the DELTA study

The three primary research questions of the DELTA study and their consecutive answers were:
1) Does augmentation of treatment as usual with a preventive CT module reduce and/or defer relapse/recurrence in remitted recurrently depressed patients?
Answer: Yes, it does. Augmenting treatment as usual with CT resulted in a significant protective effect, which became more pronounced with an increasing number of previous depressive episodes. For patients with 5 or more previous MDEs (41% of the sample), CT reduced the cumulative relapse rate over a 2-year period from 72% to 46%,[19] and over a 5.5-year period for those with four or more previous episodes (52% of the sample), CT significantly reduced cumulative relapse/recurrence from 95% to 75% (medium effect size).[24]
2) Is the studied preventive CT cost-effective?
Answer: For the total group the intervention was not cost-effective. However, it may be cost-effective in patients with a high-risk for recurrence, i.e. patients with at least 5 previous episodes. In this high-risk patient group preventive CT was more effective, although more expensive. The probability of preventive CT being cost-effective in the high risk group was over 50% up to over 95% at a societal willingness to pay respectively, €10000 and €35000 per relapse prevented.[25]
3) Who benefits from preventive CT?
Answer: Preventive CT was shown to be less effective in patients who experienced life events and in patients with a combination of more previous episodes and higher levels of avoidant coping. Over a 2-year follow-up period more depressive residual symptoms and higher levels of dysfunctional beliefs were predictors of an unfavorable outcome.[26]

THIS THESIS

So far the DELTA study answered a number of pertinent questions. However, other major research questions remained and in particular some related to the clinical aspects of the course of recurrent depression. In this thesis we will focus on patients' quality of life, on patients' use of antidepressants and adherence to antidepressive medication, and on developing a multivariate prediction model of recurrence in a remitted recurrently depressed group of patients. Each of these topics is introduced below.

Health Related Quality of Life

By the year 2000 MDD was already the fourth leading cause of disease burden worldwide in terms of Disability Adjusted Life Years.[27] This high burden of MDD is partly explained by its chronic nature and the risk of recurrence.[28] The World Health Organization (WHO) predicts that by the year 2020 MDD will cause the greatest burden of ill-health in developed countries.[29] Worldwide, it is expected to become the second leading cause of death and disability and estimated to affect nearly 340 million people.[29] According to recent projections for the years 2030, MDD will be among the three leading disabling conditions, together with HIV/AIDS and ischemic heart disease.[30;31]

Health is more than merely the absence of disease or infirmity (WHO, 1948).[32] Therefore, modern scholarship suggests that the improvement of patients' Health Related Quality of Life (HRQOL) in addition to the alleviation of symptoms is an important outcome measure in the management of chronic diseases. HRQOL is a broad concept that includes several dimensions of living in addition to health, e.g. physical health and mental health. Interestingly, HRQOL is not only decreased during the acute phase of a MDE but also in the period following such an episode.[33-37] Several authors reported an association between the severity of depression and the level of HRQOL.[38;39] Until now, there are no studies that have compared HRQOL in a sample of patients with remitted recurrent depression to a sample of the general population. There is also a lack of studies addressing the question whether changes over time in HRQOL are associated with similar changes in the level of (residual) depressive symptoms in patients suffering from recurrent depression. We hypothesize that HRQOL is more decreased in recurrent MDD compared to single episode MDD. For the development of further interventions it is important to know whether HRQOL is related to residual depressive symptoms in this more chronic disease. Both these issues will be addressed in Chapter 2.

Antidepressive medication

Continuation and maintenance use of antidepressive medication

In the period 1996 - 2006, over 6 million prescriptions for antidepressants were made in the Netherlands, mainly for mood and anxiety disorders.[40] The number of prescriptions per year has doubled in the past decade.[40] As a result, antidepressants have become the most commonly prescribed drugs.[40;41]

Although there is an abundance of trials that investigated the use of antidepressants in the acute phase (4-6 and up to 12 weeks) of MDD, the effectiveness and optimal length of continuation and maintenance antidepressant use to prevent relapse and recurrence has been studied only marginally. As a consequence international guidelines show little agreement with respect to the length of continuation and maintenance antidepressive therapy.[42;43] To prevent relapse in patients suffering from recurrent MDD who remitted during treatment with antidepressants, international guidelines recommend that these patients should be continued on this medication (referred to as continuation phase) for between 4-5 months (APA guideline)[43] and 6 months (Nice guideline).[44]

After the continuation phase, the guidelines recommend prolonged use of antidepressants (referred to as maintenance phase) ranging from one to three till five years to even longer (Dutch MDD guideline),[45] at least two years (Nice guideline)[44] to an indefinite period (APA-guideline).[43]

Adherence to antidepressive medication

Adherence to a medication regimen has been defined as the extent to which patients take medication as prescribed.[46] Non-adherence to medication treatment, especially in patients suffering from chronic diseases (somatic and psychiatric), is a global problem undermining the effectiveness of treatment.[46;47] Since suboptimal dosage and duration of antidepressive treatment potentially increases the risk of relapse and chronicity, non-adherent behavior might not only be of clinical, but also of economic and public health concern.[46] Generally, non-adherence undermines optimal treatment and in mental health care it is a risk factor for suicide.[48] Reported non-adherence rates to medication are alarmingly high. In the acute phase in MDD patients' antidepressant adherence rates decreases over a 3-month period to about 50%.[46;49-51]

In contrast to adherence in the acute phase, little is known about adherence to prophylactic (maintenance) antidepressive medication in remitted recurrently depressed patients. Previous, studies on maintenance antidepressant use, reported adherence rates of respectively 85% and 79%, but these studies suffered from methodological flaws.[52;53]

Risk factors for non-adherence to antidepressive medication

It is not known which patients are at risk for non-adherence to antidepressants. Yet, only 1% to 2% of all publications on treatment of affective disorders explore factors associated with medication adherence.[49] The reported findings concerning risk factors for antidepressant non-adherence are inconsistent.[54;55] There is, however, consensus that the adequate use of antidepressants is at least partly determined by complex doctor, patient and doctor/patient interaction characteristics.[46;49]

In conclusion, little is known about the length of use of antidepressive medication, the extent of non-adherence and about its risk factors in patients suffering from recurrent depression. This is remarkable since the continuation and maintenance phases together represent the longest treatment phase. Therefore, after determining every three months

the percentage of patients using antidepressants (chapter 3), antidepressants users were asked about the extent of their (non-) adherence to this medication. Chapter 4 focuses on prevalence of (non-) adherence to antidepressive medication and chapter 5 focuses on predictors of non-adherence.

Predictors of recurrence

Reported predictors for a first episode of MDD are: being female, having a low socio-economic status, comorbid psychiatric disorders, a family history of depression and negative life events.[56] Some previously reported predictors of recurrence of MDD are the same as for a first episode: having a family history of MDD and negative life events (see for a recent review Burcusa et al., 2007[57]). The number of previous episodes, residual symptoms, cognitions, coping, personality (neuroticism) and poor social support are other predictors for recurrent MDD.[57] Some of these predictors, such as residual symptoms and coping, are potentially modifiable by therapeutic interventions.

Still, predicting a recurrence is a complex matter. This could be due to the fact that depression in itself is heterogeneous, with a heterogeneous etiology and course. Recurrence of depression seems to involve a comprehensive and complex interaction of socio-demographic, psychological (coping) and biological (genetic) factors.[57-60] Researchers mostly studied predictors of recurrence using univariate models. However, given its complexity the development of multivariate prediction models for recurrence is warranted. Conradi et al. showed with a multivariate analysis, that among their set of predictors, having more than three previous episodes was the only variable predicting a shorter time to recurrence.[61] Unfortunately, the number of previous episodes is not a modifiable factor. In addition, among young adults with at least one previous MDE, Lewinsohn et al. presented a multivariate prediction model for recurrence with several predictors. These were: multiple previous episodes in adolescence; family history of recurrent MDD; borderline personality disorder symptoms; and for females only, increased conflict with parents.[62]

Besides the identification of predictors, quantification of the relative importance of the various predictors in terms of explained variation gives us more insight in the impact of these predictors. The combination of identification and quantification may lead to a better understanding of predictors of the course of this disease and enables us to enhance the efficacy of its (prophylactic) treatment. Thus far, no studies have reported multivariate prediction models of time to recurrence in combination with its explained variation. In chapter 6 we will explore and quantify both uni- and multivariately the effect of socio-demographics, illness and potentially modifiable coping related predictors on recurrence over a 5.5-year follow-up period in remitted patients with recurrent depression.

SUMMARY OF RESEARCH GOALS

On the basis of the literature described in the previous paragraphs, it can be concluded that MDD is prevalent, tends to recur and has a substantial negative impact on patients' quality of life. Surprisingly, the fact that MDD recurs is relatively neglected, in research as well as in daily clinical practice and in the public. So far, the most commonly used strategy to prevent relapse/recurrence is antidepressive medication. However, although considered effective, adherence with antidepressive medication is problematic for patients. Because clear predictors of non-adherence and recurrence are lacking, we will examine patients' management of recurrent depression and predictors of its course. This thesis specifically focuses on health related quality of life (chapter 2), prophylactic antidepressant use (chapter 3), adherence to this type of medication and its predictors (chapter 4 & 5) and potential modifiable predictors of recurrence (chapter 6). The chapters are followed by a general discussion in which the findings are critically appraised (chapter 7).

Appendix 1. Diagnostic Criteria Major Depressive Episode, Major Depressive Disorder and Recurrent Major Depressive Disorder (DSM IV-TR, APA 2000)

Diagnostic Criteria Major Depressive Episode

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either depressed mood (1) or loss of interest or pleasure (2).
   1. depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful)
   2. markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)
   3. significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day; note: in children, consider failure to make expected weight gains
   4. insomnia or hypersomnia nearly every day
   5. psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
   6. fatigue or loss of energy nearly every day
   7. feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
   8. diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
   9. recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B. The symptoms do not meet criteria for a Mixed Episode.

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).

E. The symptoms are not better accounted for by Bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

Diagnostic Criteria Major Depressive Disorder

A. Presence of a Major Depressive Episode.

B. The Major Depressive Disorder is not better accounted for by Schizoaffective Disorder and is not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.

C. There has never been a Manic Episode, a Mixed Episode, or a Hypomanic Episode.

Diagnostic criteria Recurrent Major Depressive Disorder

A. Presence of two or more Major Depressive Episodes.
Note: to be considered separate episodes, there must be an interval of at least 2 consecutive months in which criteria are not met for a Major Depressive Episode.

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2

Health Related Quality of Life in Recurrent Depression: a comparison with a general population sample

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ABSTRACT

Objective

In the acute phase major depressive disorder (MDD) is a disabling disease.
We compared HRQOL in patients with remitted MDD (rMDD) with a community sample and longitudinally assessed the relation between depressive symptoms and HRQOL in recurrently depressed patients.

Methods

We used 12-month data of patients from the Depression Evaluation Longitudinal Therapy Assessment (DELTA) study. HRQOL was assessed with the Medical Outcome Short Form (SF-36). Remission was determined with the Structured Clinical Interview for DSM-IV and depressive symptoms were assessed with the Beck Depression Inventory. Patients' mean SF-36 scores were compared with those of an age- and sex-matched Dutch reference population. The longitudinal relation between levels of SF-36 and levels of depressive symptomatology was assessed with a repeated measures linear regression analysis using the mixed models module.

Results

In patients with rMDD in the remitted phase, especially in women, both physical and mental HRQOL was lower than in a Dutch population sample. An increase in the level of depressive symptoms corresponded to a decrease in all scales of the SF-36.

Conclusion

Also in remitted rMDD patients, especially in women, HRQOL is lower than in the general population which emphasizes that also in this phase of recurrent depression HRQOL deserves attention. Furthermore, in patients with rMDD a higher depressive symptom severity level is associated with a lower HRQOL. These findings imply that residual symptoms should be treated aggressively and HRQOL enhancement therapies should be developed.

INTRODUCTION

Health related quality of life (HRQOL) and disability are two complementary aspects of health. Especially in chronic diseases, these measures can provide insight in the total impact of diseases on individuals. Besides reduction of depressive symptoms, HRQOL is increasingly recognized as an important outcome measure in studies on major depressive disorder (MDD).

At the beginning of this millennium MDD was rated the fourth leading disabling condition.[1] According to recent projections for the years 2030, the three leading disabling conditions will be HIV/AIDS, MDD and ischemic heart disease.[2] This high level of disability is not only related to the high prevalence of MDD, but also to an early age of onset, and the impact of recurrency, chronicity and mortalities, the latter mainly due to suicides at a relatively young age.

Previous studies on HRQOL in MDD primarily focused on the impact of the acute or depressive phase of MDD, and restricted their objectives to only some components of HRQOL like social functioning. These studies showed that the impact of these active phases of MDD on HRQOL was high.[3-7] Studies that included the remission phase reported that residual symptoms after a Major Depressive Episode (MDE) were also associated with an impaired HRQOL.[7-12]

So far, little attention has been paid to HRQOL in patients suffering from recurrent MDD (rMDD). This is remarkable considering that without prophylactic treatment the recurrence rate of MDD is approximately 80%[13] and therefore MDD is more and more considered a chronic condition. Consequently, we assumed that HRQOL is diminished in recurrently depressed patients even when remitted compared to the general population. Next, we wanted to know whether a significant longitudinal relation exists between HRQOL and depressive symptoms in patients with rMDD. Thus, a better understanding of HRQOL in rMDD could help to develop interventions to improve HRQOL in rMDD.

Therefore, we analysed data from the Depression Evaluation Longitudinal Therapy Assessment (DELTA) study,[14] which included patients with rMDD and followed them prospectively for two years, during which depressive symptoms and HRQOL were assessed.

The aims of our study were:

1. to compare HRQOL in patients with rMDD with HRQOL in a general population sample.
2. to assess the relation between changes in depressive symptomatology and changes in HRQOL in patients with rMDD.

METHODS

Participants: the DELTA study sample

The background and methodology of the DELTA study have been described in detail elsewhere.[14] In brief, patients participated in a randomized controlled clinical trial in which Treatment As Usual (TAU: specialty mental health care or care by a family doctor or no care at all), was compared with TAU augmented with an 8 session preventive cognitive therapy (CT). To be eligible subjects had to meet the following criteria: (a) at least two Major Depressive Episodes in the last five years (DSM-IV);[15] (b) 'remission' according to DSM-IV criteria, for longer than 10 weeks and no longer than two years; and (c) Hamilton Rating Scale for Depression (HDRS)[16] score < 10. Participants were recruited at psychiatric centres and through media announcement. They completed telephonic screening (n>1000), provided written informed consent before diagnostic interviews (n = 321) and entered the study (n = 187). The protocol was approved by the institutional ethics review committees. There was no restriction on the use of pharmacotherapy during the two year study period.

Assessments

Health Related Quality of Life:

HRQOL was assessed with the Medical Outcomes Study 36-item Short-Form (SF-36)[17] at 12 months (t1), 18 months (t2) and 24 months (t3) after study entry. The SF-36 represents multi-dimensional health concepts and measurement of the full range of health states (during the previous 4 weeks), including levels of well-being and personal evaluations of health. The instrument has 8 dimensions formulated as statements or questions. A score from 0 to 100 is calculated for each scale, with higher scores indicating a better HRQOL.[18]

In the present study we used all eight scales:

- 'Physical Functioning' (PF; ten items): health related limitations on daily activities such as bathing, getting dressed and lifting shopping bags.
- 'Physical role functioning' (RP; four items): problems with work and other daily activities due to physical health problems.
- 'Vitality' (VT; four items): perception of energy and fatigue.
- 'Bodily Pain' (BP; two items): the amount of bodily pain and any limitations resulting from it.
- 'Mental health' (MH; five items): feelings of depression or nervousness. 'Emotional role functioning' (three items), which records problems with work and other daily activities as a consequence of emotional problems.
- 'Emotional role functioning' (RE; three items): problems with work and other daily activities as a consequence of emotional problems.
- 'Social Functioning' (SF; two items): limitations on social activities such as visiting friends and relatives.

- 'General Health' (GH; five items): the individual's subjective assessment of his or her general health.

The SF-36 has been widely utilized and tested in many groups of patients with chronic medical and psychiatric illness[17;19] including depressed patients.[18;20-22] We used the Dutch version of the SF-36 which is validated for the Dutch population.[23] Patients' SF-scores were compared with published age- and sex-matched Dutch reference population norms.[23]

Severity of depressive symptoms:
The 21-item self-report Beck Depression Inventory (BDI)[1;24] was used to assess severity of depression symptoms in the past week. The BDI was used at t1, t2 and t3. Scores may range from 0 to 63 (BDI). BDI scores of 0-9 indicate non-depressed, 10-18 mildly-moderately depressed, 19-29 moderately-severely depressed and above 30 severely depressed.[25] Furthermore, patients' baseline levels of depressive symptomatology were assessed with the 17-item Hamilton Rating Scale for Depression (HRSD).[16] The HRSD, administered by psychologists/research assistants who were blind to treatment condition, is a widely used semi-structured clinical interview that covers a range of affective, behavioral and biological symptoms and has acceptable psychometric properties.[26] Scores can range from 0 to 52. To assess the inter-rater agreement of the HDRS, a random sample of 17 interviews were rated a second time by a different interviewer. Inter-rater agreement was excellent (ICC = 0.94).

Recurrence of depression:
To determine 'remission' according to DSM-IV criteria we assessed current and past depressive episodes with the Structured Clinical Interview for DSM-IV (SCID-I)[27] at baseline and at t1 and t3 (12 and 24 months). In this study 'remitted' refers to a non-depressed status as measured with the SCID-I. At entering the DELTA-study all patients were remitted (not meeting DSM-IV criteria for MDD; HDRS <10).

All SCID-I interviews were audiotaped. Two independent experienced psychiatrists evaluated all interviews of participants meeting the DSM-IV criteria for major depression. In cases of disagreement, the ratings of the psychiatrists were used for further analyses. The kappa for inter-rater agreement between the interviewers and psychiatrist on categorization of a recurrence versus no recurrence was 0.96, indicating high agreement.

Statistics

The longitudinal relation between levels of HRQOL (SF-36) and levels of depressive symptomatology (BDI) was assessed with a repeated measures linear regression analysis using the mixed models module of SPSS 16.02. To be able to separate the cross-sectional and longitudinal effect of the BDI total score on the SF-36 scale scores we used a regression model recommended by Fitzmaurice et al.[28] For each of the SF-36 scales we build a regression model with the SF-36 scale scores at t1, t2 and t3 as the dependent variable,

the difference between BDI total scores at t_j and t_1 as independent variable (for j = 1 … 3) and the t1 BDI total score as covariate. The regression coefficient of the independent variable in this model can be interpreted as the longitudinal effect (i.e., the effect of changes in BDI over time on changes in SF-36 scale scores over time). The dependence of the longitudinal observations is modelled in this regression model by defining an unstructured covariance matrix. All analyses were adjusted for treatment condition, age, gender, baseline depression severity (HDRS) and number of previous depressive episodes at baseline. Because treatment condition did not modify the relationship between BDI and SF-36 subscales (the treatment condition by SF-36 subscales interaction was not statistically significant for any subscale) the analyses were performed on the pooled TAU and CT condition patients.

To compare the eight SF-36 scales patients with rMDD in the remitted phase with the general population norm scores we first assessed for each patients whether s/he was in remission at t1 and t3 with SCID-I. This sample included 144 patients. For patients who were in remission at t1 or at t1 and t3 we used their t1 SF-36 scale scores; for patients not in remission at t1 but in remission at t3 we used their t3 SF-36 scores; and patients not in remission at t1 and t3 were excluded for these analyses.

Then, we used a 3-step procedure, which takes the dependence of the SF-36 scale scores on age and gender into account. In the first step we defined 4 age categories: 20 through 35, 36 through 45, 46 through 55 and 56 through 65 and stratified the DELTA study sample by age category and gender. In each of these strata the raw SF-36 subscale scores were calculated according to the SF-36 user's manual.[18] In the second step the raw scores were converted to standard scores on the basis of a representative norm sample of the general population. This conversion was made for each age/sex stratum separately. In the third step we adjusted for differences in age and sex distribution in the norm sample and the DELTA study sample by direct standardization with the general population of the Netherlands in 2008 as the standard population. The resulting mean standard scores indicate how many standard deviations the observed scale scores in our remitted sample fall below or above the score of the Dutch general population. Because this is similar to the calculation of the effect size 'Cohen's d',[29] a mean standard score of 0.20 is considered a small deviation from the Dutch general population, and mean standard scores of 0.50 and 0.80 can be considered moderate to large deviations from the Dutch general population.[23;30] Standard scores are given for the remitted sample and separately for men and women.

RESULTS

Characteristics of the Sample

In the DELTA study we included 187 recurrently depressed patients in remission, of which 15 dropped out immediately after entering the study; 9 from the CT group and 6

Table 1 Demographic and clinical characteristics of the DELTA study sample[a] (n=172)

Characteristic	
Sex, female (%)	73
White (%)	98
Age (yr, mean ± SD)	44.7 ± 9.5
Years of education (8-18, mean ± SD)	14.2 ± 2.5
Marital status (%)	
Single	24
Married/cohabiting	58
Divorced/widowed	18
Type of current treatment (%)	
Family doctor	29
Psychiatric help	31
No treatment	40
Antidepressant medication (%)	51
HRSD score (mean ± SD)	3.8 ± 2.8
Previous episodes	
Median # of previous episodes ± IQR	4 ± 3.8
>2 previous episodes (%)	82
Age at first onset (yr, mean ± SD)	28.5 ± 12.5

[a]All data represent baseline values, HRSD = Hamilton Rating Scale for Depression, IQR = interquartile range

from the TAU group. These dropouts were slightly younger than study completers (t(170) = 2.25, p = 0.026; drop-outs: mean = 38.9, SD = 10.6, completers: mean = 44.8, SD = 9.5), but did not differ on other characteristics. Table 1 shows the characteristics of the DELTA study sample at study entry (n = 172). Over the two-year follow-up period 102 of 172 (59%) patients experienced a recurrence of MDD according to the SCID-I.

Longitudinal relationship of depressive symptoms and Health Related Quality of Life

First, table 2 shows the level of depressive symptoms (BDI) and HRQOL scores (SF-36) at t1, t2 and t3 in recurrently depressed patients. On average the SF-36 scale scores and the BDI score are relatively stable over time. However, averages don't imply stability at the patient level and the standard deviations show substantial heterogeneity.

The results in table 3 can be interpreted longitudinally and they show that changes in BDI total score were significantly related to changes in all SF-36 scale scores. An increase in the level of depressive symptoms corresponded to a decrease in all 8 scales of HRQOL. This relation was most pronounced for 'Emotional role functioning' and 'Social functioning', less pronounced for 'Mental health', 'Physical role functioning' and 'Vitality' and small (but still statistically significant) for 'Bodily pain', 'General health' and 'Physical functioning'.

Table 2 SF-36 scale score and Beck Depression Inventory (BDI) total score at 12 months (t1), 18 months (t2) and 24 months (t3) (mean (SD))

SF-36 scales	t1	t2	t3
Physical functioning (PF) (148, 155, 162)[a]	79.7 (24.0)	81.1 (22.0)	79.3 (22.7)
Physical role functioning (RP) (145, 152, 162)	63.4 (39.7)	58.3 (40.3)	56.9 (40.9)
Bodily pain (BP) (147, 155, 162)	69.3 (25.4)	66.5 (24.1)	68.1 (24.9)
Social functioning (SF) (148, 155, 162)	72.0 (25.7)	70.5 (27.9)	70.6 (27.1)
Mental health (MH) (147, 155, 162)	66.5 (19.1)	68.0 (19.0)	66.6 (19.1)
Emotional role functioning (RE) (144, 153, 162)	68.5 (39.6)	68.9 (39.5)	65.0 (42.8)
Vitality (VT) (147, 155, 162)	54.0 (22.5)	53.1 (22.9)	52.9 (21.7)
General health (GH) (147, 155, 162)	63.4 (21.5)	62.4 (21.8)	61.8 (23.2)
Beck Depression Inventory total score (151, 155, 161)	8.9 (8.0)	8.5 (8.2)	8.3 (7.7)

[a] Number of patients with a valid scale score at t1, t2 and t3

Table 3 Longitudinal relation between BDI total score and SF-36 scale scores[a] (n=148)

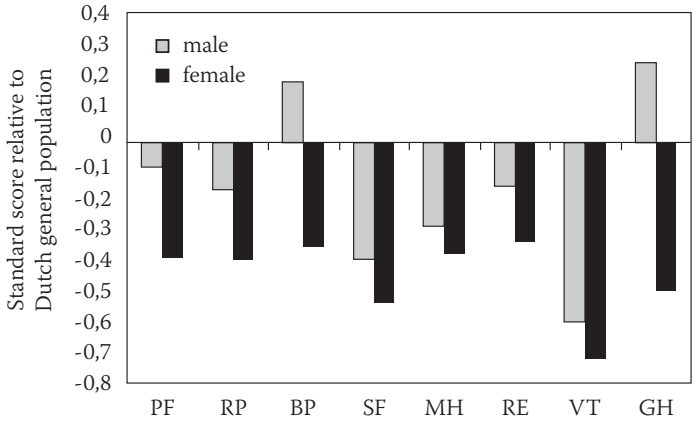
SF-36 scales	b	Se_b	p	95% C.I.
Physical functioning (PF)	-0.39	0.137	0.004	-0.67, -0.13
Physical role functioning (RP)	-1.50	0.295	<0.001	-2.08, -0.92
Bodily pain (BP)	-0.81	0.165	<0.001	-1.14, -0.49
Social functioning (SF)	-1.92	0.177	<0.001	-2.26, -1.57
Mental health (MH)	-1.60	0.108	<0.001	-1.81, -1.37
Emotional role functioning (RE)	-2.99	0.293	<0.001	-3.56, -2.41
Vitality (VT)	-1.30	0.136	<0.001	-1.57, -1.03
General health (GH)	-0.68	0.132	<0.001	-0.94, -0.42

[a] General linear mixed model analysis (SPSS proc mixed), with time as categorical variable, BDI total score as time dependent covariate, covariance structure = unstructured. The longitudinal effect of BDI total score is separated from cross sectional effect by incorporating both the BDI total score at t1 as a time stationary covariate and the BDI total score as time dependent covariate in the model (see statistical analysis section). All analyses adjusted for age, gender, baseline depression severity (Hamilton) and number of previous depressive episodes. The b coefficient can be interpreted as the change in mean SF-36 scale score as a result of a 1 point increase on the BDI total score. To interpret the negative sign one has to take into account that an increase in BDI score means more depressive symptomatology and an increase in SF-36 scale scores means a higher level of quality of life.

Comparison on Health Related Quality of Life of patients with rMDD in the remitted phase and a general population sample

Mean SF-36 scale scores of patients with rMDD in the remitted phase from the DELTA study sample (n = 144) were compared with the reference norm sample of the general Dutch population (see Table 4 of which the results are summarized in Figure 1). This comparison shows that women with rMDD in the remitted phase report a lower HRQOL on all 8 dimensions of the SF-36. In terms of effect size these differences were small to moderate on most scales but moderate to strong for 'General health' (-0.48), 'Vitality' (-0.70), and 'Social functioning' (-0.52).

Figure 1 Health-related quality of life (HRQOL) scores for patients with remitted recurrent depression (n=144) compared with a reference population



Standard scores of <0 indicate an HRQOL worse than that of the reference population, and scores >0 indicate better HRQOL. PF= Physical functioning, RP= Physical role functioning, BP=Bodily pain, SF=Social functioning, MH=Mental health, RE=Emotional role functioning, VT=Vitality and GH=General health.

With the exception of moderate differences on the scales 'Vitality' and 'Social functioning' the differences in HRQOL scores between remitted recurrent depressed men and men in the general population were small and did not reach statistical significance.

This gender effect underscores a stratified approach. The small difference (d = 0.11) on the 'General health' scale (lower level in remitted patients) in the total sample of remitted recurrently depressed patients and the general population for example obscures a moderate effect for women (lower level of 'General health' in remitted women as compared to the general population) and a small non-significant effect for men (higher level of general health in remitted men as compared to the general population).

Table 4 Age adjusted mean standardized SF-36 scale scores relative to the Dutch general population[a] (n=144)

SF-36 scales	total			male			female		
	$\bar{X}$	$Se_{\bar{x}}$	p	$\bar{X}$	$Se_{\bar{x}}$	p	$\bar{X}$	$Se_{\bar{x}}$	p
Physical functioning (PF)	-0.23	0.23	ns	-0.08	0.44	ns	-0.37	0.15	<0.05
Physical role functioning (RP)	-0.26	0.11	<0.05	-0.15	0.18	ns	-0.38	0.12	<0.01
Bodily pain (BP)	-0.07	0.09	ns	0.20	0.13	ns	-0.34	0.12	<0.01
Social functioning (SF)	-0.45	0.11	<0.01	-0.38	0.16	<0.05	-0.52	0.15	<0.01
Mental health (MH)	-0.31	0.10	<0.01	-0.27	0.18	ns	-0.36	0.10	<0.01
Emotional role functioning (RE)	-0.23	0.08	<0.01	-0.14	0.15	ns	-0.32	0.07	<0.01
Vitality (VT)	-0.64	0.13	<0.01	-0.58	0.22	<0.05	-0.70	0.12	<0.01
General health (GH)	-0.11	0.12	ns	0.26	0.21	ns	-0.48	0.13	<0.01

[a]Mean standardized scores are the amount of standard deviations the DELTA study sample differs from the general population. This can be interpreted as the effect size measure Cohen's d.

DISCUSSION

In this first comprehensive HRQOL-study in exclusively recurrently depressed patients we showed that even in remitted rMDD patients HRQOL is lower than in a reference sample of the general Dutch population on all scales measured with the SF-36. This difference was mainly apparent in women. However, the results for men have to be interpreted with some caution, since they were based on considerably fewer patients than for women.

Previously, in a study that also used the SF-36, HRQOL in depressed individuals with rMDD was not decreased compared to HRQOL in depressed individuals with a first depressive episode. Yet, as a group depressed individuals had an increased impairment of HRQOL compared to non-depressed individuals.[6] Kennedy et al.[31] described in their review a number of studies that showed that impaired social functioning persists even after remission from depression and that residual symptomatology, in line with our findings, may lead to enduring psychosocial impairment. Kennedy and Paykel[11] reported that patients with rMDD with residual symptoms had impairments in social adjustment.

Our finding can be explained in three ways. First, patients with rMDD might already have a lower pre-morbid HRQOL (trait effect). Indeed, Buist-Bouwman et al.[21] reported that HRQOL in their MDD patients returned to pre-morbid levels. After recovery HRQOL was still worse than in their control group. Second, this recurrently depressed sample might be scarred as a result of previous episodes (scar hypothesis). However, Kruijshaar et al.[6] found no difference in HRQOL between single and recurrent depression. Their finding does not fit well in the scar hypothesis unless scarring already emerges after the first episode, as proposed by dynamic vulnerability models. Ormel et al.[32] exclusively found a scar effect in severe rMDD as measured with the Groningen Disability Schedule. Our sample can be seen as more severe considering the number of previous episodes. Third, residual symptoms, as frequently reported by remitted patients, could contribute to a low HRQOL. Unfortunately, we could not test these hypotheses because we have no data on pre-morbid (i.e., before the first MDE) HRQOL.

Furthermore, we showed that in patients with rMDD changes in levels of depressive symptoms were significantly related to changes in HRQOL over a one-year period. An increase in the level of depressive symptoms corresponded to a decrease in all 8 scales of the SF-36. This relation was more pronounced for the mental health orientated scales, especially for 'Emotional role functioning', compared to the physical health oriented scales. One physical oriented subscale, i.e., 'Physical role functioning', showed a distinct correlation with depressive symptoms that was comparable with the SF-36 mental health oriented scales.
As MDD is a mental health problem, it is not surprising that the association between depressive symptoms and SF-36 scales was most pronounced for the mental health scales. This has already been reported for depressed patients in a primary care setting.[33] The

importance of impairment in 'Emotional role functioning' in MDD patients has also been reported by other authors.[21;22;34-37]

The limitations in physical HRQOL we found were mainly in the domains of physical role functioning and vitality. Presumably, patients label certain symptoms of MDD, for example lack of concentration, fatigue, pain, or tension as physical problems. Already in the seventies Paykel and Weissman[38] reported an association between depression and impaired physical functioning. More recently, Baune et al.[39] showed that the combination of MDD and medical co-morbidity has a negative impact on general functioning and HRQOL. In fact, the physical aspects of a depression have been recognized and described as early as the work of Hippocrates (460-357 BC), where a depression was associated with pathological excess of black bile that affected the brain. Until more recently the term 'endogenous or vital depression' was used for a more 'biological' MDE without a clear cause and with more physical symptoms in contrast to an 'exogenous depression'. Depressed patients frequently report physical problems and MDD commonly coexists with medical conditions.[40] About 50% to 65% of depressed patients seen in primary care are not recognized by their doctor because of the somatic expression of MDD.[40;41] Frequently reported physical symptoms in patients with MDD are fatigue, pain, psychomotor problems, weight changes, gastro-intestinal problems and other aspecific complaints.

Implications

Improving HRQOL is important given the 60 – 80% prevalence of subjective impairment in partially remitted depression and its association with subsequent relapse.[42;43] Professionals should know that although remitted, patients with rMDD might still have impaired HRQOL even in case of mild and residual symptomatology during remission phases. Assessment of HRQOL might be a beneficial addition. The poor outcome of rMDD in terms of HRQOL emphasizes the need for applying specific treatments on residual symptoms after remission[44] and development of HRQOL enhancement therapies.
Furthermore, physical well-being is reduced in a large subgroup of patients suffering from rMDD and therefore deserves consideration for alternative treatments too. Our findings confirm that recurrent depression is a chronic condition with enduring effects.

Strengths and Limitations

Certain limitations must be considered. First, our findings may be influenced by selection bias. We applied a prospective cohort approach to the data of patients who originally participated in a randomized controlled preventive CT-trial. As stated by Hirschfeld et al.,[45] impairment in QOL (such as an inability to pursue normal social activities), rather than health status itself, is often the deciding factor for people to seek health care. This is in line with the fact that the recurrently depressed patients in this study although remitted were willing to participated in a preventive CT. This can be seen as a form of help seeking due to impaired HRQOL. A second limitation concerns the fact that we used self reported HRQOL; we did not collect data of other (independent) sources (for

example employers or family members). This might have resulted in an over- as well as an underestimation of HRQOL. On the other hand the SF-36 measures perceived HRQOL and as stated before is well validated and widely used.

Our study has some major strengths. First, we included patients with rMDD remitted on medication and/or psychological therapy or no treatment at all, without restrictions on medication status at entry to the study. As such, this study reflects a semi naturalistic cohort and was designed to maximize external validity, which suggests good generalizability of the findings. Second, we compared HRQOL in remitted recurrently depressed patients with an age- and sex-matched Dutch population sample and used an elegant mathematical calculation of differences in SF-36 scales. Third, we measured HRQOL and depressive symptomatology longitudinally over a 12-month period. Finally, we used the SF-36, which is a widely used, freely available, easy to administer and well validated questionnaire (that assesses patient's general health perception) and has also been shown to be sensitive to change.

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3

Continuation and maintenance use of antidepressants in recurrent depression

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ABSTRACT

Background

Maintenance antidepressant (AD) medication is the most commonly used preventive strategy in a highly recurrent disease, i.e., depression. Little is known about discontinuation of maintenance AD use and the association with recurrence in daily clinical practice.
The purpose was to examine the discontinuation rate of maintenance AD in daily clinical practice in recurrently depressed patients and the associated risk of recurrence.

Methods

Prospectively AD maintenance medication and recurrence were examined in 172 euthymic patients with recurrent depression. AD user profiles before recurrence (non-users, intermittent users, continuous users) were examined and related to recurrence over a 2-year follow-up period.

Results

Less than half of the patients (42%) used AD continuously. Taken into account the minimal required adequate used dosage (≥ 20 mg fluoxetine equivalent), only 26% of the patients used AD as recommended by international guidelines. Despite continuous use of AD, 60.4% relapsed in 2 years. This relapse rate was comparable to the rate of the intermittent users (63.6%). In patients who stopped taking AD after remission and who received additional preventive CT, the recurrence rates were significantly lower than in non-AD-using patients treated with usual care (8% versus 46%).

Conclusions

The majority of recurrently depressed patients treated with AD discontinue maintenance AD therapy in daily primary and secondary clinical practice. AD seems to offer poor protection against relapse in this patient group. Patients who stopped using AD experienced less relapse, especially if they were treated with preventive CT. Alternative maintenance treatments (including preventive cognitive therapy after discontinuation on AD) should be studied in recurrently depressed patients with intermittent good remission, not only in secondary but also in primary care.

INTRODUCTION

Major depressive disorder is a common, severe and chronic disease with a high recurrence rate, which in the absence of prophylactic treatment rises to about 80 percent.[1] Currently, maintenance antidepressant (AD) medication is the most commonly advised preventive strategy.[2] Guidelines (e.g.[3;4]) recommend that following remission on AD in the acute phase, patients should be maintained on this medication ranging from another 4-5 months (referred to as continuation phase[3]) to 2 years[4] to prevent relapse.

After the continuation phase, guidelines recommend prolonged use of AD (referred to as maintenance therapy) ranging between at least 2 years,[4] a not specified period[3] to even lifelong AD for preventing recurrence in recurrent depressive disorder. Geddes et al.[2] performed a systematic review on randomised trials on mostly continuation AD treatment in patients who remitted on AD treatment. This review included both patients with a first depression and patients with recurrent depression. The average relapse rate was 41% in placebo versus 18% in patients who continued AD. There are some limitations to this review as well as to the included studies. First, as pointed out by Fava,[5] they did not control for publication bias and therefore there is possibly an underestimation of negative trials,[6] which is described to affect AD trials in depression particularly.[7] Second, the optimal duration of the maintenance phase has not been studied well enough, since relatively few studies reported follow-up periods of longer than 1 year.[2] Third, the general applicability of the AD maintenance studies in this review might be limited, since these trials were mainly done in secondary care settings. Fourth, the definition of relapse/recurrence in AD trials is problematic. Some studies defined relapse/recurrence as requirement for change of drug treatment or a need for treatment rather than the use of a well-validated instrument to assess relapse/recurrence, as used in this study.[8-13] Other studies did not define relapse/recurrence at all.[14-16] Last, several studies are incorporated that included very small sample sizes, e.g., no more than 20 patients.[8;11;17-19] So, further long-term studies are needed in representative patient samples.

Recently high rates of early discontinuation of AD treatment during the acute phase have been reported in several clinical contexts (e.g.[20]). However, there is sparse information about discontinuation of maintenance AD use in daily clinical practice and the relation to recurrence in recurrent depressive samples. Rates range from 19% of the patients who proceeded to the maintenance phase (in secondary care[21]), to 59% of the patients receiving at least 5 years AD in a predominantly inpatient cohort.[22]

This study analyzes data from the DELTA study. A sample of 172 patients with recurrent depression, remitted on various types of treatments (including AD), was followed prospectively for 2 years after remission. Relapse/recurrence was assessed using a well-validated structured interview. In the DELTA study AD use was recorded but not controlled by the investigators and so developed according to preferences of individual clinicians and patients. This cohort is unique because of its representativeness; a remitted

recurrent cohort of patients with diverse type of care at entry of the study (no care, primary care and speciality care).

The paper has 3 aims: (1) to examine current AD use in a remitted recurrent depressive group; (2) to examine the course of maintenance AD use over the 2-year follow-up in patients who used AD for their last depression; and (3) to examine whether AD user profiles before recurrence predict relapse/recurrence in patients who used AD for their last depression.

METHODS

Sample selection

The background and methodology have been described in detail elsewhere.[23] In brief, patients participated in a randomized controlled clinical trial in which regular care, including no care at all, was compared with additional preventive cognitive therapy (CT). There was no restriction on the use of pharmacotherapy during the study. To be eligible subjects had to meet the following criteria: (a) at least 2 major depressive episodes in the past 5 years (DSM-IV); (b) current remission status according to DSM-IV criteria, for longer than 10 weeks and no longer than 2 years before; and (c) Hamilton Rating Scale for Depression (HRSD) score[24] <10.

Participants were recruited at psychiatric centers and through media announcement. They completed telephonic screening (n > 1000), diagnostic interviews (n = 321) and provided informed consent to enter the protocol (n = 187). The protocol was approved by the institutional ethics review committees.

Assessments

Medication. Patients were asked about their use of AD for the last depression before entry of the study and whether they continued using AD after remission. During the study, every 3 months, information on AD (type and dosage) over the previous month was monitored using the Trimbos/IMTA self report questionnaire for Costs associated with Psychiatric Illness[25] (TIC-P) which covers a maximum recall period of one month. Additionally information over continuous use over the whole 2 years period was also collected by the interviewer at the end of the follow-up period. For patients who used AD during the last depression preceding the study, 3 maintenance AD user profiles since remission were differentiated (either until the next recurrence in case of a recurrence or over the follow-up of at least 2 years): (1) continuous use; continued use of AD since remission; (2) intermittent use; stop of use of AD before recurrence or end of follow-up period (in case of no recurrence); stopping could be temporary or definite (did not start again after months of AD use); and (3) non-use; complete stop of AD after remission and not starting again. Adherence to medication was assessed using a 4-item self-reported adherence

measure: Medication Adherence Questionnaire[26] (Morisky). Selective serotonin reuptake inhibitors (SSRI's) were the most commonly prescribed ADs. The dosage in milligrams of fluoxetine daily dose equivalents was computed for all ADs.[27] Adequate dosage was defined as equivalent to at least 20 mg fluoxetine.

Relapse/recurrence. At baseline past depressive episodes were assessed with the Structured Clinical Interview for DSM-IV (SCID-I).[28] At baseline and at 3 follow-up assessments (3, 12 and 24 months), recurrences during follow-up were also assessed using the SCID-I. Besides recurrence as primary outcome measure, the mean severity of all relapses (as assessed by the SCID: light, <6 symptoms; moderate, 6-7 symptoms; severe, 8-9 symptoms), the number of relapses/recurrences and the duration of the depressive episodes during the follow-up period were used as secondary outcome measures.

Severity of depressive residual symptoms. The 17-item HRSD was used to assess participants' baseline levels of depressive symptomatology.[24]

Level of psychopathology. The 90-item Symptom Check List (SCL-90) was used to assess the total level of baseline psychopathology in the past week.[29]

Personality disorders. At baseline the 99-item self-report Personality Disorder Questionnaire (PDQ-4+) was used to assess personality disorders.[30]

Statistical analysis

To examine the use of ADs for the last depression and over the 2-year follow-up period (no use, intermittent, continuous use) descriptive statistics were used. For all comparisons of characteristics of patient groups[1], t tests (in case of 3 groups 1-way ANOVAs), χ^2 test and Mann-Whitney U tests were used, with an α-level of 0.05 (2-tailed). For these comparisons the following baseline variables were examined: demographic characteristics (sex, marital status, age, education level), historic illness-related characteristics (age of onset, severity last depression, duration of last episode, duration of remission since last episode, percentage of time illness-free since first episode), recent illness-related characteristics (level of psychopathology and level of residual depressive symptoms), type of care, personality pathology and familial psychiatric diseases.

The effect of user profiles of AD, in patients treated with AD in the acute phase, on time to recurrence was assessed with Cox regression; this takes into account differences in time at risk and censoring (no recurrence during the study period). Because the effect of the additional intervention on recurrence was modified by the number of previous depressive episodes,[23] the potential modifying effect of the number of previous episodes was taken into account. We used a 2-step procedure to assess effect modification by treatment condition: (a) by testing the 3-way treatment condition by AD user profile by number of previous episodes interaction and (b) by testing the 2-way treatment condition by user profile interaction term. In addition, confounding by treatment condition was

1 Compared groups were respectively: (a) those who used or did not use antidepressants for the last depression before entry of the study; (b) the three user profiles groups: no use, intermittent, continuous use; (c) the two user groups on secondary outcome (i.e., intermittent, continuous use); (d) the adequately dosage group versus the non-adequately dosage group; and (e) a Dutch community cohort versus the DELTA cohort

checked. When the interaction terms involving treatment were not significant and treatment condition did not confound the association between the user profiles and time to recurrence, analyses were performed on the total sample. Given the relatively lower power of tests for interaction compared to test for main effects, we used an α-level of 0.10 for all tests for interaction to control type II error.

RESULTS

Characteristics of the Sample

Of the total sample of 187 participants 15 (9 from CT; 6 from treatment as usual (TAU)) dropped out from the study immediately. They were slightly younger than completers ($t(170) = 2.25$, $p = 0.026$; drop-outs: mean = 38.9, SD = 10.6, completers: mean = 44.8, SD = 9.5) but did not differ on other characteristics. For the analyses 172 patients (84 TAU; 88 CT) patients were available. The CT and TAU groups did not differ on the variables assessed at baseline (all $p > 0.05$), except for experience of negative life events before the sixteenth year. No confounding effect of childhood life events was detected.

For analyses of AD profiles we excluded another 16 participants because of missing data on AD use over the follow-up period. These additional dropouts did not differ on the variables assessed at baseline (all $p > 0.05$), except for duration of the last depression before entry of the study (additional dropouts experienced a longer depression; mean = 13.7, SD = 18.6 versus mean = 7.2, SD = 6.7; $p = 0.008$).

Aim 1: Current AD use in a remitted recurrent depressive group

Of the 172 participants three quarters (76%; 131/172) were treated with AD for their last depression before entry, of whom 62% (81/131) still used AD at entry. Of former non-users 17% (7/41) started AD.

Patients who used ADs for their last depression were compared to those who did not on demographic, historic illness-related, and recent illness-related characteristics, type of care, personality pathology and familial psychiatric diseases (table 1). Both groups did not differ on these characteristics, except for marital status (56% singles in non-users and 37% in users, $\chi^2(1) = 4.483$, $p = 0.046$) and treatment at inclusion ($\chi^2(2) = 13.142$, $p = 0.001$): non-users more often received no aftercare (63% versus 33%) and less often aftercare by a family doctor (12% versus 34%).

Aim 2: Maintenance AD use since remission over alt least 2 years of follow-up

For patients who used AD during the last depression for entry of the study 3 maintenance AD user profiles since remission were defined either until the next recurrence or over the entire follow-up (of at least 2 years) in case of no recurrence. Of the 131 patients treated

Table 1 Demographic and clinical characteristics of the total sample, patient who were not treated with AD versus patients who were treated with AD for the acute phase before entry of the study (n=172)

Characteristic	Total sample (n=172)	No AD last depression before entry (n=41)	AD last depression before entry (n=131)	p value No AD versus AD for last depression
Female sex (%)	73.3	78.0	71.8	>0.05
White (%)	98.0	98	98	>0.05
Age (yr, mean ± SD)	44.7 ± 9.5	43.6 ± 9.8	45.0 ± 9.4	
Treatment condition (CT %)	51.2	53.7	50.4	>0.05
Years of education (8-18, mean ± SD)*	14.2 ± 2.5	14.8 ± 2.8	14.0 ± 2.4	>0.05
Single (%)	41.9 (n=72/172)	56.1 (n=23)	37.4 (n=49)	0.046
Unemployed (%)*	56.5 (n=96/170)	68.3 (n=28/41)	52.7 (n=68/129)	>0.05
Treatment at inclusion (%)				0.001
Family doctor	28.5 (n=49)	12.2 (n=5/41)	33.6 (n=44/131)	
Psychiatric help	32.0 (n=54)	24.4 (n=10/41)	33.6 (n=44/131)	
No treatment	40.1 (n=69)	63.4 (n=26/41)	32.8 (n=43/131)	
Antidepressant medication at entry (%)	51.2 (n=88/172)	17.1 (n=7)	62.8 (n=81)	0.001
SSRI**	68.1 (60/88)	57.1 (4/7)	69.1 (56/81)	>0.05
Mean AD equivalent (mean ± SD)***	22.8 ± 13.4 (n=88)	17.3 ± 12.3 (n=7)	23.3 ± 13.4 (n=81)	>0.05
Number of previous episodes	6.5 ± 8.4	8.3 ± 12.8	4.9 ± 6.3	>0.05
Age of first onset (yr, mean ± SD)	28.5 ± 12.5	25.7 ± 13.5	29.3 ± 12.2	>0.05
HRSD-17 score (mean ± SD)	3.8 ± 2.8	4.3 ± 2.9	3.6 ± 2.8	>0.05
Comorbidity axis I (%)	11.6 (20/172)	5.0 (2/41)	13.7 (18/131)	>0.05
Personality disorder (%) (PDQ-4+)	70.3 (121/172)	73.2	69.5	>0.05
Familial Psychiatric disease****	68.2 (107/157)	75 (30/40)	65.8 (77/117)	>0.05
Duration remission since last depression before entry in months	9.2 ± 6.7	8.2 ± 7.2	9.4 ± 6.5	>0.05
Duration last depression before entry in months	7.4 ± 8.5	5.8 ± 5.2	8.0 ± 9.3	>0.05
Severity last episode*****				>0.05
Mild	7.6 (13/172)	7.3 (3/41)	7.6 (10/131)	
Moderate	33.1 (57/172)	31.7 (13/41)	33.6 (44/131)	
Severe	59.3 (102/172)	61.0 (41/41)	58.8 (77/131)	

All percentages χ^2 test and all continuous variables T- tests. *2 missings **3 missings on type of medication *** Since selective serotonin reuptake inhibitors (SSRI's) were the most commonly prescribed fluoxetine daily dose equivalents was computed ****15 missings on familial psychiatric disease *****Due to low expected frequencies in cells Fisher exact test was used

with AD for their last depression, 20% did not use any maintenance AD-therapy (table 2), while 42% used AD continuously either until recurrence or over the 2-year follow-up period. About the same percentage of patients used AD intermittently either until recurrence or over the 2-year follow-up period (38%).
Table 2

Table 2 AD use and user profiles over 2 years or until recurrence in patients who used acute AD treatment (n=115)

Characteristic	(n=131)
No use of AD since remission last episode (%)*	20.0 (23/115)
Intermittent use (%)*	38.3 (44/115)
Continuous use of AD (%)*	41.7 (48/115)
Adequate dosage until first recurrence/end follow-up (%)**	62.5 (30/48)
Mean antidepressant equivalent over 2 years (mean mg, SD)***	22.1 ± 11.7
Adherent to medication over 2 years****(%)	25 (12/48)

*n=16 missing, no data on user AD-treatment during study **Adequacy:≥20mg fluoxetine equivalent ***n=9 missing, fluoxetine equivalent **** Completely adherent versus non adherent over 2 years

In the continuous AD users, mean AD-dosage use over 2 years in fluoxetine equivalent was 22.1 (SD = 11.7). Of the continuous AD users 38% did not receive a minimal adequate dosage (≥ 20 mg fluoxetine equivalent).

Characteristics of patients with different user profiles

The 3 groups (table 3) did not differ on baseline characteristics, except for duration of last episode before entry of the study ($F(1) = 4.203$, $p = 0.018$; 7 missing). The intermittent group reported the shortest duration of the last episode (mean = 5.8 months, SD = 4.6), while the no use group and the continued use group had a longer last episode (mean = 6.8 months, SD = 6.3; and mean = 10.7 months, SD = 9.6).

Aim 3: Predictive value of maintenance AD user profiles for recurrence in patients who used AD during the acute phase

To analyze whether the effect of user profiles on recurrence was modified by treatment condition (CT or TAU) we used Cox regression for testing the 3-way treatment condition by AD user profile by number of previous episodes interaction. Since coefficients did not converge, the possible modifying effect of treatment (3-way interaction) could not be determined for the group of patients who did not use maintenance AD (n = 23). Therefore the comparison will be restricted to the following 2 user profiles: intermittent and continuous users. Our main research question concerns the groups of patients who used maintenance AD (n = 92; intermittent and continuous users). We performed Cox regression analyses in this group and found no modifying and confounding effects of treatment and/or number of previous episodes on the relation between these AD user profiles and time to recurrence. So analyses could be performed in the total group (n = 92). Time to recurrence of the patients who took ADs continuously (n = 48) did not differ from patients who took ADs intermittently since remission (n = 44; Wald statistic (1, n = 92) = 0.038, p = 0.846, hazard ratio = 1.053, CI = 0.626-1.770) (fig. 1). The recurrence rate for the continuous group was 60.4% and 63.6% for the intermittent group (table 3).

To examine whether the effect of AD user profiles was confounded by number of previous episodes, duration of remission before entry of the study or residual symptoms we added these variables to the Cox model separately. No confounding effect on recurrence was

Table 3 Demographic and clinical characteristics of different user profiles (n=115)

Characteristic	No use of AD (n=23)	Intermittent use (n=44)	Continuous use of AD (n=48)	p value
Sex, female (%)	82.6 (19/23)	75.0 (33/44)	68.8 (33/48)	>0.05
Age (yr, mean ± SD)	42.9 ± 8.5	45.6 ± 9.3	45.9 ± 9.9	>0.05
Treatment condition (CT %)	52.2 (12/23)	56.8 (25/44)	54.2 (26/48)	>0.05
Years of education (8-18, mean ± SD)*	14.9 ± 2.2	13.8 ± 2.5	13.59 ± 2.5	>0.05
Single (%)	26.1 (6/23)	43.2 (19/44)	34.8 (15/48)	>0.05
Unemployed (%)	39.1 (9/23)	54.5 (24/44)	58.3 (28/48)	>0.05
Number of previous episodes	4.7± 3.9	6.1± 7.0	5.9± 6.1	>0.05
Age of first onset (yr, mean ± SD)	29.1 ± 12.1	28.6 ± 10.8	31.8 ± 13.2	>0.05
HRSD-17 score (mean ± SD)	3.0 ± 2.7	3.2 ± 2.8	3.8 ± 2.8	>0.05
Comorbidity axis I (%)	13.0 (3/23)	13.6 (6/44)	10.4 (5/48)	>0.05
Personality disorder (%) (PDQ-4+)	65.2 (15/23)	75.0 (33/44)	66.7 (32/48)	>0.05
Familial psychiatric disease**	65.2 (15/23)	72.1 (31/43)	62.5 (30/48)	>0.05
Duration remission last depression before entry in months	8.2 ± 7.2	9.4 ± 6.5	9.6 ± 6.6	>0.05
Duration last depression before entry in months***	10.7 ± 9.6	5.8 ± 4.6	6.8± 6.3	0.018
Severity last episode****				>0.05
Mild	0 (0/23)	13.6 (6/44)	8.3 (4/48)	
Moderate	34.8 (8/23)	34.1 (15/44)	22.9 (11/48)	
Severe	65.2 (15/23)	52.3 (23/44)	68.6 (33/48)	

All percentages χ^2 test and all continuous variables Oneway Anova tests. *1 missing on years of education in the continuous user group **1 missing on familial psychiatric diseases***7 missing on duration of last episodes (2 in no AD, 2 in intermittent and 3 in continuous) ****Due to low expected frequencies in cells Fisher exact test was used

Figure 1 Survival curve for continued (n=48) versus intermittent AD use (n=44) before recurrence

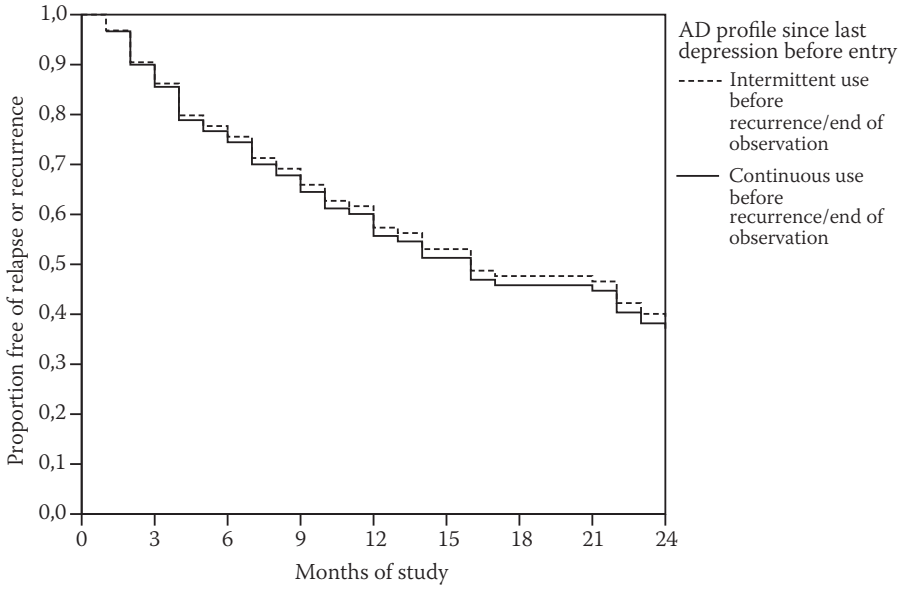

Table 4 Recurrence and severity of recurrences of different AD user profiles (n=92)

Outcome over 2 years	Intermittent use of AD (n=44)		
	CT (n=25)	TAU (n=19)	total (n=44)
Relapse/Recurrence	64.0 (16/25)	63.2 (12/19)	63.6 (28/44)
Number of recurrences			
1 recurrence	43.8 (7/16)	50 (6/12)	46.4 (13/28)
2 recurrences	56.3 (9/16)	41.7 (5/12)	50
3 or more recurrences	6.3 (1/16)	0 (0)	3.6
Mean severity of relapses/recurrences			
Mild	0 (0)	0 (0)	0 (0)
Moderate	81.3 (13/16)	66.7 (8/12)	75.0
Severe	18.8 (3/16)	33.3 (4/12)	25.0
Duration of relapses/recurrences*			
Short	37.5 (6/16)	33.3 (4/12)	35.7
Moderate	18.8 (3/16)	25.0 (3/12)	21.4
Long	43.8 (7/16)	41.7 (5/12)	42.9

All percentages χ^2 test, in case of low expected frequencies in cells Fisher exact test was used. *Duration in case of recurrences: mostly short: ≤ 4 weeks, mostly moderate: 5 to 12 weeks, mostly long: >12 weeks.

found (for number of previous episodes: Wald statistic (1, n = 92) = 0.041, p = 0.839, adjusted hazard ratio = 1.055, CI = 0.628-1.774; for duration of remission: Wald statistic (1, n = 92) = 0.058, p = 0.810, adjusted hazard ratio = 1.066, CI = 0.633-1.796; for residual symptoms: Wald statistic (1, n = 92) = 0.035, p = 0.851, adjusted hazard ratio = 1.051, CI = 0.625-1.768).

Adequacy of AD dosage (≥ 20 mg fluoxetine equivalent) in the continuous user group (n = 48) was not related to time to recurrence, Wald statistic (1, n = 48) = 0.059, p = 0.808, hazard ratio = 0.911, CI = 0.430-1.929. The absence of a relation between adequacy and recurrence could not be explained by baseline differences in prognostic illness-related variables, such as residual symptoms and number of previous episodes and demographic variables (all p > 0.05). Nonadherence (reflecting short period of discontinuation; e.g., forgot to take pills incidentally) in the continuous users was not related to time to recurrence (yes/no adherence over 2 years; 25 % (12/48) adherent over 2 years), Wald statistic (1, n = 48) = 1.960, p = 0.161, hazard ratio = 0.502, CI = 0.191-1.317.

Recurrence, severity and duration

Table 4 shows no significant differences between the intermittent user and continuous user groups and between CT versus TAU in the 2 user groups on the number of times a patient experienced a relapse, the duration and overall severity of relapses (for relapse in the 2 user groups: $\chi^2(1) = 0.101$, p = 0.751; for number of relapses/recurrences: Fisher exact = 5.465, p = 0.065; for severity of relapse: Fisher exact = 5.749, p = 0.094; for duration of relapse: $\chi^2(2) = 0.423$, p = 0.809; for relapse TAU versus CT: $\chi^2(1) = 0.173$-0.449, p = 0.599-

Continuous use of AD (n=48)			p value	
CT (n=26)	TAU (n=22)	total % (n=48)	CT vs TAU	total
53.9 (14/26)	54.6 (15/22)	60.4	>0.05	>0.05
			>0.05	>0.05
35.7 (5/14)	53.3 (8/15)	44.8		
28.6 (4/14)	30.0 (5/15)	31.0		
35.7 (5/14)	13.3 (2/15)	24.1		
			>0.05	>0.05
7.1 (1/14)	0 (0)	1.6		
50.0 (7/14)	40.0 (6/15)	44.8		
42.9 (6/14)	60 (9/15)	51.7		
			>0.05	>0.05
42.9 (6/14)	40.0 (6/15)	41.4		
14.3 (2/14)	30.0 (5/15)	24.1		
42.9 (6/14)	26.7 (4/15)	34.5		

0.739; for number of relapses/recurrences: Fisher exact, all $p > 0.05$; for severity of relapse: Fisher exact all $p > 0.05$; for duration of relapse: Fisher exact all $p > 0.05$).

Patients who no longer used AD since remission

Since the modifying effect of treatment could not be tested for the non-user group, recurrence rates will be reported stratified. The relapse rate in the group of patients who no longer used AD since remission of the last depression before entry (n=23) was significantly lower compared to the 2 user groups (26% for non-users versus 64% for intermittent users versus 60% for continuous users, $\chi^2(2, n = 115) = 9.653$, $p = 0.008$). In addition the relapse rate of the non-user group who received additional preventive CT was significant lower than in the TAU group (CT: 8% (1/12), TAU: 46% (5/11), $\chi^2(1) = 4.102$, $p = 0.043$). The mean time to recurrence was 24 months in CT (SD=1.9) and 16.2 in TAU (SD=3.0).

DISCUSSION

Less than half of the patients (42%) used AD continuously after remission on AD. Taken into account the minimal required adequate used dosage (≥20 mg fluoxetine equivalent), only 26% (30/115) of the patients used AD, according to the clinical guidelines for recurrent depressed patients (e.g.[3;4]). Unfortunately, this 26% might even be an underestimation of the actual percentage, since adequate dosage in the maintenance phase is determined by the individual dose during the acute phase (at least 20 mg fluoxetine equivalent). We did not have any information on dosage use in the acute phase before entry of the study.

High rates of early discontinuation of AD treatment during the acute phase have been documented[20] but our results indicate that high discontinuation rates are also applicable to maintenance AD use in daily clinical practice in a group with a high risk of recurrence. This rate is lower than a previously reported rate in a specific, i.e., predominantly inpatient, population,[22] but higher than the 19% of the patients who proceeded to the maintenance phase as reported with respect to a secondary cohort.[21] Studies suggest that both patients and prescribers contribute considerably to non-adherence to guidelines.[22;31;32]

Despite the continuous use of AD (before recurrence), 60.4% relapsed in 2 years. This recurrence rate was comparable to the rate of the intermittent users (63.6%). Also the number of times a patient experienced a recurrence as well as the overall severity of the recurrences and the duration of recurrences were comparable in the 2 groups. Additionally, time to recurrence was comparable in patients who used adequate versus inadequate dosages and adherent and non-adherent patients. The lack of difference in recurrence for both groups could not be explained by baseline differences in prognostic illness-related variables, such as residual symptoms and number of previous episodes and demographic variables. This finding is in line with a previous study.[33] They also reported a clinically non-significant difference between continuous AD use and intermittent AD use (20% versus 23% relapse).

Additionally, the recurrence rate in the group of patients who did no longer use AD since remission of the last depression before entry was significantly lower compared to the 2 user-groups (26% versus 64% versus 60%), which could not be explained by baseline differences in risk factors either (such as residual symptoms, number of previous episodes and demographic characteristics.[34] In this group participants who received an additional preventive CT relapsed less often than participants treated with usual care (8% versus 46%).

These results might reflect that sequential additional preventive CT, after remission and discontinuation on AD, could be an effective means of preventing recurrence. Some support for this alternative strategy was found by Blackburn and Moore.[35] In their study acute AD followed by maintenance AD treatment was compared to acute cognitive behavior therapy followed by maintenance cognitive behavior therapy versus acute AD followed by CT. No significant differences among treatments were found. Possibly the specific sequence in sequential treatment is crucial. As in cognitive behavior therapy for anxiety disorders,[36] CT utilizes cognitive interventions with specific attention to rehearsal of skills in multiple contexts to try to achieve long-lasting effects. One of these contexts in CT could be essential, e.g., an AD free period. After remission on AD, patients learn in an AD free context what they can do themselves to prevent recurrence while they are the least bothered by depressive symptoms. Discontinuation of ADs seems to be associated with patients' willingness to cope alone without medication.[21] The suggested sequential maintenance therapy could be an alternative for patients with this willingness.

These high recurrence rates in both user-groups and the relatively low one in the non-user group is not in line with the conclusion of a recent systematic review of studies (2) that maintenance AD can decrease the risk of recurrence. However, there are some limitations to this review as well as to the included studies, as pointed out in the introduction. In addition, the STAR*D study[37] demonstrated that relapse rates in medicated patients also depend on acute treatment steps. Patients who had or had not achieved remission at 1 year of follow-up experienced higher relapse rates among those who required more treatment steps (predominantly AD medication) to achieve 50% reduction in symptoms or re mission. Among those achieving remission, the relapse rates were (respectively with each treatment step) 33.5, 47.4, 42.9 and 50.0%. Moreover, there is some evidence in line with our findings that maintenance AD medication does not affect the course of outcome (for a review[38]). For instance 2 studies, a large double-blind placebo-controlled study[39] and an observational study[40] indicate that AD medication fails to protect after a period of 8-14 months (in the study of Dawson et al.[40] in patients with < 5 previous episodes). Hasler et al. in a study on usual care in patients, reported that long-term effects of AD (7 years) did not differ with untreated patients.[41] They question the transferability of results of outcome studies across clinical populations and in usual care. Further, Patten reported no influence of increasing AD use in the general population in episode incidence and duration.[42] This suggests that the impact of AD medications on population health may have been less than expected. Additionally, there is evidence that the patient's protection from recurrence ceases on discontinuation of the AD medication.[43] Fava pointed out that AD might worsen the course of depression for some high-risk patients (sensitization hypotheses).[44] According to the oppositional model of tolerance continued AD treatment may oppose the initial acute effects of AD or receptor alterations. Increased vulnerability to relapse, besides withdrawal symptoms, may be explained by oppositional processes after discontinuation of AD. Neurobiological mechanisms may be involved in increasing vulnerability.[44;45] Thus, further long-term maintenance studies are needed in representative patients using well-validated instruments for recurrence.

This study was designed to maximize external validity, which suggests good generalizability of the findings for this high risk group. We included a homogeneous subgroup of remitted recurrently depressed patients that are at high risk of recurrence despite of intermittent good remission. High recurrence rates were detected in spite of continuous AD use. We included patients who received various kinds of maintenance treatment (including no treatment), without restrictions to maintenance AD treatment status through the study. A further strength of the study is the fact that our cohort included a high risk group of recurrence for whom guidelines recommend maintenance AD treatment and that was followed prospectively for 2 years with structured interviews based on DSM-IV.

There are several limitations that need to be addressed. First, the study was not designed to examine the effect of maintenance AD on recurrence. A prospective randomized design comparing maintenance AD to intermittent use and no use (with and without an additional preventive psychological therapy) was not considered ethical. However, we did

not find differences between the user groups on risk factors for recurrence. Second, this sample might reflect a selected group with less confidence in the effect of maintenance pharmacotherapy because they were recruited for a maintenance psychotherapy trial. Third, information on AD use was collected by asking the patient (instead of the prescriber for example) every 3 months with a time frame of 1 month, which means that 2 months are unaccounted for. However, we also collected retrospective information over the entire follow-up period of 2 years. Fourth, the numbers were small, reducing the power to detect weaker associations. However, the difference in recurrence rate between the continuous and intermittent user groups was not only non-significant but also clinically insignificant. Consequently, it is unlikely that insufficient statistical power critically affected our results and conclusion.

In conclusion, we observed not only high rates of discontinuation of maintenance AD in daily clinical practice but also poor protection against relapse in case of continuation of AD. Patients who stopped using AD experienced less relapse, especially if they were treated with preventive CT. Up to now there are many unresolved questions about the impact of long term maintenance AD. Among several alternatives[46] the use of maintenance CT after AD-treatment has potential. Several studies found that the use of CT after AD treatment protects against recurrence.[23;35;46-51] These studies did not randomize over maintenance CT with discontinuation of AD versus prolonged maintenance AD, or even better additional AD placebo arms. There is a dearth of these randomized controlled trials in recurrently depressed patients. Results of such studies may help to prevent recurrence in this high-risk group by tailoring treatments to specific patient characteristics.[52]

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4

Adherence to continuation and maintenance antidepressant use in recurrent depression

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ABSTRACT

Background

In chronic diseases adherence is a problem. Little is known about adherence to antidepressants after the acute phase in recurrent depression. This study evaluates adherence to antidepressants in the continuation and maintenance phase in remitted recurrently depressed patients.

Methods

We prospectively assessed adherence to continuation and maintenance antidepressant use, the longest phase in antidepressant treatment, over 2 years and the association of adherence with future recurrence in 131 recurrently depressed patients remitted on antidepressants.

Limitations

Self reported non-adherence.

Results

Non-adherence ranged from 39.7% to 52.7%; 20.9% were always non-adherent, 48.4% were intermittently non-adherent and 30.8% were always adherent. Adherence rates did not significantly differ between intermittent and continuous antidepressant users (37.2% vs. 25%). Non-adherence predicted time to recurrence.

Conclusion

Non-adherence to continuation and maintenance antidepressant treatment in recurrent depression is frequent, like in other chronic diseases, and a potential risk of recurrence. Doctors continuously have to be aware of this problem and should keep on discussing it with their patients. Finally, as many patients don't seem to be able or willing to take AD as prescribed, alternatives to prevent relapse deserve more attention.

INTRODUCTION

Non-adherence undermines optimal treatment and is in mental health care a risk factor for suicide.[1] Without prophylactic treatment up to 80% of patients with Major Depressive Disorder (MDD) will have further episodes.[2] So, for patients with recurrent MDD, clinical guidelines recommend maintenance antidepressant (AD) use for at least two years to prevent relapses.[3] For them, like in other chronic diseases long-term adherence to medication might be a problem.[4] Hitherto, research on AD (non-) adherence in MDD was mainly done during the acute phase.[5] There is little known about adherence to maintenance AD use in patients with recurrent depression remitted on AD. This is notable, since the maintenance phase is the longest AD treatment phase in depression.
In this study we analysed adherence data prospectively for two years in a recurrently depressed patient group remitted on AD.

METHODS

We used data of the DELTA study which is described in detail elsewhere.[6] To be eligible subjects had to meet the following criteria: (a) at least two Major Depressive Episodes in the last five years (assessed with the Structured Clinical Interview for DSM-IV);[7] (b) current remission status according to DSM-IV criteria for longer than 10 weeks and no longer than two years; (c) Hamilton Rating Scale for Depression (HRSD) < 10.[8] There was no restriction in using pharmacotherapy. Patients participated in a trial in which regular care was compared with an additional 8-session group preventive cognitive therapy (CT).

From the DELTA-study (n = 172) we selected patients that were treated with AD for their last depression before they entered the study (n = 131). Next we excluded patients that did not use AD at all of the 7 adherence assessment points (3, 9, 12, 15, 18, 21 and 24 months). Adherence was assessed with the Medication Adherence Questionnaire (MAQ).[9] Non-adherence on this scale indicates that patients missed 20% or more of AD medication.[10] We determined non-adherence point prevalences at the 7 assessment points. Furthermore, based upon these 7 assessments, we classified patients as always non-adherent (all assessments non-adherent), intermittently adherent (not all assessments adherent) and always adherent (all assessment adherent).

In another recent report of the DELTA study[11] we defined two types of maintenance use of AD medication since remission: continuous AD use (n = 48) versus intermittent AD use (n = 43). The later was defined as a stop of AD use before a recurrence or a stop before the end of the follow-up period in case of no recurrence. We compared adherence between these two types of AD use. Finally, we did a survival analysis (Cox regression) with relapse/recurrence of depression over 2 years as the dependent variable and non-adherence (measured at 3 months = first assessment) as the independent variable.

RESULTS

Of the 131 patients we excluded 24 patients (28.2% male, mean HRSD score 3.6 ± 2.8), because they did not use AD at all of the 7 adherence assessment points. Non-adherence point prevalences ranged from 39.7% to 52.7% (mean: 47%) at the 7 assessment points (table 1).

Table 1 Non-adherence to antidepressants in patients with recurrent depression during 2-year follow up.

Time (months)	n	%
3	36/80	45.0
9	39/74	52.7
12	34/72	47.2
15	29/67	43.3
18	38/75	50.7
21	29/73	39.7
24	38/81	46.9

In the next analysis 16 patients could neither be defined as continuous nor as intermittent AD users because of missing data on AD use over the follow-up period.[11] These 16 excluded patients were comparable to the 91 remaining patients except for severity of last depression (excluded cases experienced less often a mild last depression; 0% vs. 10.1%; more often a moderate depression; 62.5% vs. 28.6%; and less often a severe last depression; 37.5% vs. 60.4%; $\chi^2(2) = 7.670$, $p = 0.022$). They also had a slightly higher baseline HRSD score ($t(105) = -1.73$, $p = 0.09$; excluded cases: mean = 4.8, SD = 2.7, completers: mean = 3.5, SD = 2.8). Of these 91 selected patients, 20.9% (n = 19) were always non-adherent, 48.4% (n = 44) were intermittently non-adherent, while 30.8% (n = 28) were always adherent.

Comparing the two types of maintenance use of AD medication, continuous AD use (n = 48) versus intermittent AD use (n = 43), we found no significant difference in the percentage of patients that was always adherent (25.0% vs 37.2%; p = 0.226). Furthermore, there was no confounding by treatment condition (regular care vs. regular care + CT).

Being non-adherent at 3 months predicted earlier time to first recurrence with an alpha set at 10% over a 2-year period (Wald statistic (1, n = 67) = 3.421, p = 0.064, adjusted hazard ratio = 1.803, CI = 0.965-3.366). The additional 8-session group preventive CT did not confound non-adherence at 3 months (for interaction with treatment: Wald statistic (1, n = 67) = 2.096, p = 0.148, adjusted hazard ratio = 0.391, CI = 0.110-1.394; for confounding non-adherence with treatment in the model: Wald statistic (1, n = 67) = 3.579, p = 0.526, adjusted hazard ratio = 1.831, CI = 0.978-3.427).

DISCUSSION

This is one of the first reports exploring (non-) adherence to continuation and maintenance AD use in recurrent depression. We found non-adherence rates ranging from 39.7% to 52.7% with a mean of 47% over two years. Only one in three patients was adherent over the whole follow-up period, while half of the patients was intermittently adherent. This is in line with studies on adherence in other chronic diseases,[4] but substantially lower than in two other studies on maintenance AD use, in which respectively 85% and 79% was adherent.[12;13] This difference can be explained by the fact that the first study predominantly consisted of in-patients (76%), being more severe cases (also chronic and not completely remitted patients) and in the last study patients were given an intervention to improve adherence.

While in the acute phase of MDD AD adherence decreases over time[5] to about 50%, our study found the same percentage (mean 47%) during the continuation and maintenance phase which was rather stable over time but fluctuated per patient. So, patients initially adherent will later not necessarily still be adherent. Furthermore non-adherence indeed seems to have clinical implications in terms of earlier recurrences.

One limitation of our study is the potentially biased group. Patients participating in a CT-trial reflect a group that is perhaps not completely generalizable to all patients who use continuation antidepressant medication. Secondly, we merely used self report adherence information instead of a multi-method approach like for example Brook et al. did in an adherence study to non-tricyclic ADs.[14] They found that only 3% of the 119 patients had taken their medication exactly as prescribed. However, the MAQ is often used and well validated.[9;10] Moreover, our results correspond to adherence studies in the acute phase of depression and to other chronic diseases.[4;5]

In conclusion, we found that non-adherence to AD in the continuation and maintenance phase in recurrent depressive disorder is frequent and there is a trend that it predicts recurrence. These results are applicable for patients at high risk for recurrence, i.e. patients with at least 2 previous episodes, treated in various settings. Like in other chronic (somatic) conditions, non-adherence can fluctuate per patient over time. So doctors continuously have to be aware of potential non-adherence and should keep on discussing this issue with their patients. Alternatively, given the increasing evidence for preventive effects of psychological interventions in recurrent depression, doctors should also discuss these alternative preventive strategies with their patients (Bockting et al.[6]; for a meta-analysis see[15]). Future studies should focus on improving adherence in recurrent depression to provide optimal recurrence protection. Finally, as many patients don't seem to be able or willing to take AD as prescribed, alternatives to prevent relapse deserve more attention.

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Predictors of non-adherence to continuation and maintenance antidepressant medication in patients with remitted recurrent depression

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ABSTRACT

Objective

To identify predictors of non-adherence to continuation and maintenance antidepressant medication among patients with remitted, recurrent depression.

Methods

We used data of 91 remitted, recurrently depressed patients (at least 2 major depressive episodes as assessed by the Structured Clinical Interview for DSM-IV Axis I Disorders) treated with continuation and maintenance antidepressant medication in a 2-year prospective study. Patients were recruited at psychiatric centers and through media announcement from February 2000 through September 2000. Adherence was assessed with the Medication Adherence Questionnaire. Non-adherence on this scale indicates that patients missed 20% or more of their antidepressant medication. We determined non-adherence point prevalences at the 7 assessment points. Based upon these 7 assessments, we found non-adherence percentages ranging from 39.7% to 52.7% with a mean of 46.5% over 2 years. We examined a set of potential risk factors (patient-related, disease-related and treatment-related) measured at baseline.

Results

In univariate analysis using a stringent significance level ($p \leq 0.005$), we found no independently related predictors of non-adherence over a 2-year period. In a multivariate analysis with backward elimination the baseline predictors for non-adherence over a 2-year period were a higher level of personality pathology and a higher level of education.

Conclusion

There are no clear predictors of non-adherence to antidepressants in the continuation and maintenance phases in remitted, recurrently depressed patients. Further research should focus on the process of becoming non-adherent to antidepressants in the longest phase of antidepressants use to maximize the potential protective effect of these medications.

INTRODUCTION

Major depressive disorder (MDD) is a common mental disorder with large economic and societal costs. Around 50% of patients with a first episode will have further episodes. The recurrence rate of MDD rises to 80% to 90% in patients with 3 or more episodes.[1;2]
International guidelines[3;4] recommend that recurrently depressed patients (at least two previous episodes) who remit while taking antidepressants (AD) should be maintained on this medication for another 4 to 5 months (referred to as the continuation phase, American Psychiatric Association guidelines[4]) to 2 years (National Institute for Clinical Excellence (NICE) guidelines[5]). Prolonged use of AD (referred to as maintenance therapy) ranges from at least two years (Nice guidelines[5]), to an unspecified period,[4] to even life-long AD use to prevent relapse of recurrent MDD.

However, poor adherence to treatment of chronic diseases (somatic and psychiatric) is a worldwide problem of striking magnitude.[6] We found non-adherence rates in recurrently depressed patients ranging from 39.7% to 52.7% with a mean of 47% over 2 years.[7] This finding is in line with studies of adherence in other chronic diseases.[8]

Since suboptimal dosage and duration of AD treatment increases the risk of relapse and chronicity, non-adherent behaviour is of clinical, economic, and public health concern. Unfortunately, clinicians are only 50% accurate in their identification of potentially non-adherent patients.[9] It would be helpful if doctors could more accurately assess the risk for non-adherence in patients to discuss non-adherence and/or adjust their treatment.

Just as for other (somatic and psychiatric) diseases, risk factors for AD non-adherence as presented in previous literature are inconsistent.[10;11] There is, however, consensus that adequate use of AD is at least partly determined by complex physician, patient and physician/patient interaction characteristics.[8;12]

In MDD, most predictive studies for AD non-adherence are predominantly assessed in the acute phase of treatment. These results may not generalize to the remitted phase in recurrent depressive disorder. First, the depression state itself is a risk factor for non-adherence. In the remitted phase, patients may assume that they are "no longer in need of AD" or may become less willing to continue tolerating previously acceptable AD side effects (for example sexual side effects) and may not feel the direct consequences of stopping AD.[13]
Second, in general adherence rates are typically higher in acute conditions as compared to chronic conditions.[8] In the continuation and maintenance phase patients are relatively more affected by fears of potent long-term cumulative or insidious adverse effects of AD, such as personality change, addiction or toxicity.[13]

Thus far, the only study of non-adherence in patients suffering from recurrent depression could not identify differences in demographic and clinical variables between adherent

and non-adherent patients.[14] However, that study was possibly biased because it derived from a medication trial with an intervention that aimed to create an alliance between treatment team, patient and family in order to improve adherence.[14]

The present study examines a set of potential risk factors for non-adherence in patients with remitted, recurrent depression taking continuation and maintenance AD. To our knowledge, this is the first study on risk factors for non-adherence in this kind of population. To improve external validity of our findings we used a semi natural cohort, which is a unique population for evaluating medication use because of the monitored non-controlled use of AD during the 2-year follow-up period of the study.

METHODS

Participants

Participants (n = 172) were remitted patients with a diagnosis of recurrent depression who took part in a clinical trial to assess the effect of cognitive behavioral therapy on relapse prevention.[15] They were recruited at psychiatric centres and through media announcement from February 2000 through September 2000. Participants all met the following criteria: (a) at least 2 major depressive episodes in the last 5 years defined according to DSM-IV[16] and assessed by the Structured Clinical Interview for DSM-IV Axis I Disorders[17] by trained evaluators; (b) current remission status according to DSM-IV > 10 weeks and ≤ 2 years ago; (c) a 17-item Hamilton Rating Scale for Depression[18] (HRSD) score <10; and (d) no current mania, hypomania, history of bipolar illness, psychotic disorder (current and previous), organic brain damage, alcohol or drug misuse, predominant anxiety disorder, recent electroconvulsive therapy, recent cognitive treatment or receipt of cognitive therapy at the start of the study, or current psychotherapy with a frequency of more than 2 times per month. There was no restriction on use of pharmacotherapy. Every 3 months and at 2 years' follow-up, we collected information on the use of AD. More details about participants, recruitment, and inclusion and exclusion criteria and medication use are available in Bockting et al.[15;19]

Of the original study sample (n = 172), we excluded 41 patients (22% male, mean ± SD HRSD score = 4.3 ± 2.9) who were not treated with AD at the moment they entered the study and 24 patients (28.2 % male, mean ± SD HRSD score = 3.6 ± 2.8) because they did not take AD at any of the 7 adherence assessment points. Sixteen patients were excluded because of missing data on AD use over the follow-up period. Therefore, the analyses were performed with 91 patients.

The 16 patients who were excluded because of missing data on AD use over the follow-up period were comparable to the 91 included patients except for severity of last depression (excluded cases experienced less often a mild last depression: 0% vs. 10.1%, more often a

moderate depression: 62.5% vs. 28.6%, and less often a severe last depression: 37.5% vs. 60.4%, $\chi^2 = 7.670$, df = 2, p = 0.022). They also had a slightly higher baseline HRSD score (t = -1.73, df = 105, p = 0.09; excluded cases: mean = 4.8, SD = 2.7; completers: mean = 3.5, SD = 2.8).

Study measures

Dependent variable

Non-adherence was assessed with the Medication Adherence Questionnaire (MAQ).[20] Non-adherence on this scale indicates that patients missed 20% or more of the doses of their AD medication.[21] We determined non-adherence point prevalences at the 7 assessment points. Based upon these 7 assessments, we classified 30.8% of the patients (28/91) as always adherent (adherent at all assessments), and 69.2% (63/91) as non-adherent (not adherent at all assessments) over 2 years.

Potential predictors

We examined a set of potential risk factors measured at baseline either by trained interviewers or self-rating scales. These potential predictors, categorized into 3 domains (patient-related, disease-related and treatment-related), are presented in Table 1.

Personality. Personality was assessed evaluated with the 99-item self-report Personality Disorder Questionnaire-4+ (PDQ-4+), which assesses DSM-IV personality disorders and has been widely used in personality disorder research. For this study, we used the PDQ-4+ total score.[22]

Axis I Comorbidity. Axis I comorbidity was assessed with the Structured Clinical Interview for DSM-IV Axis I Disorders.[17]

Number of previous episodes before baseline (first study assessment; T0). Number of previous episodes was assessed with the Structured Clinical Interview for DSM-IV Axis I Disorders.[17]

Severity of residual symptoms. The 17-item HRSD[18] was used to assess participants' baseline levels of depressive symptomatology. The HRSD, administered by psychologist/research assistants blind to treatment condition, is a widely used semi-structured clinical interview that covers a range of affective, behavioural, and biological symptoms and has acceptable psychometric properties.[23] Scores can range from 0 to 52. Our 4 interviewers (psychologist/research assistants) second rated 17 of the participants' interviews. The intraclass correlation was 0.94, indicating high agreement. Further the 21-item self-report Beck Depression Inventory[24] was used to assess baseline depression symptomatology in the past week. Scores may range from 0 to 63.[24]

Severity of last episode before T0 overall. Severity of last episode was assessed with the Structured Clinical Interview for DSM-IV Axis I Disorders.[17]

Duration of last episode before T0 overall. Duration of last episode was assessed with the Structured Clinical Interview for DSM-IV Axis I Disorders.[17]

Level of psychopathology. The 90-item Symptom Checklist[25] was used to assess the total baseline level of psychopathology in the past week.

Dysfunctional attitudes. Dysfunctional attitudes (baseline) were assessed with the Dutch adaptation of the Dysfunctional Attitude Scale (DAS).[26] The DAS is a 40-item scale that assesses excessive and rigid beliefs, hypothesized by Beck[27] to be vulnerability factors for depression. Participants rate their agreement with each belief on a 7-point Likert scale ranging from 'totally agree' to 'totally disagree'. Scores range from 40-280, with higher scores indicating greater levels of dysfunctional attitudes. Form A of the DAS which has been shown to have good psychometric properties, was used.[28]
Medication. Every 3 months, information on AD medication (type and dosage) over the previous months was monitored with the Trimbos/IMTA Self-Report Questionnaire for Costs Associated With Psychiatric Illness.[26;29]
Other patient-related and treatment-related potential predictors. Semistructured interviews were used to provide other (not mentioned above) potential predictors such as sociodemographic characteristics, psychiatric history and disease management.

Statistical analysis

For the analyses, we had to take into account the fact that half of our sample received an additional psychological intervention that prevented recurrence. The effect of this treatment depended on the number of previous depressive episodes.[15] One way to take this fact into account is to restrict all analyses to the control group, which of course would lower the power of these analyses considerably. An alternative approach is to assess whether the intervention had an effect on the relation between the predictor and non-adherence or not. In the first case, the analyses should be restricted to the control group; in the latter case, the analysis can be performed on the pooled experimental and control group data with a considerable gain in statistical power.

In a preliminary logistic regression analysis, we assessed for each potential predictor separately whether treatment condition in combination with number of previous episodes had a modifying and/or confounding effect on the relation between potential predictor and non-adherence. The modifying effect was assessed by the 3-way treatment by number of previous episodes by potential confounder interaction and the 2-way treatment by potential confounder interaction. In case of no effect modification, the confounding effect was assessed by examining the change of the regression coefficient for each potential confounder when treatment condition was added to the model. A 10% change in the regression coefficient was considered an indication for confounding.

Given the relatively lower power of the test for interaction compared to tests for main effects, we used an α-level of 0.10 for all tests for interaction to guard against type II error. Since the distribution of number of previous episodes was skewed, and the minimum number of previous episodes was 2, we used the following formula $P = \ln(p-1)$, with p the actual number of previous episodes and P the transformed variable used in the analysis.

For none of the potential predictors did treatment condition or the combination of treatment condition and number of previous episodes modify the relation between the

predictor and non-adherence, neither did treatment condition confound this relation. Consequently, all analyses were based on pooled data, and treatment condition was not entered into the analysis.

In order to assess the effect of predictors on non-adherence, we used a 2-step procedure proposed by Hosmer and Lemeshow.[30] In the first step, for each of the potential predictors, the effect on non-adherence was assessed in a univariate logistic regression analysis with non-adherence as the dependent variable and the potential predictor as the independent variable. Given the effect on type I error of the number of tests, we used a relatively stringent significance level of $p \leq 0.005$ for the interpretation of the univariate results. In the second step, all potential predictors related tot non-adherence (using a more lenient significance threshold of $p \leq 0.20$) were entered into a multivariate logistic regression model. A final prediction model was established using a stepwise procedure with backward elimination. Both odds ratios (ORs) and 95% confidence intervals (CIs) are presented. The Hosmer-Lemeshow goodness-of-fit statistic and Nagelkerke R^2 are used to assess the fit of the final model with the observed data. All analyses were performed using SPSS for Windows, version 12.0.1 (SPSS Inc., Chicago,Ill.).

RESULTS

Table 1 summarizes the results of the univariate logistic regression analyses. Using a conservative significance level of $p \leq 0.005$ to guard against an inflated type I error because of the relatively large number of significance tests, none of the potential predictors were significantly related to non-adherence.

However, in relatively small samples (as in our case), lack of statistical significance is not equivalent to no effect. It can also be an indication of insufficient power. For this reason we will also discuss the effect of potential confounders focussing on effect sizes (the ORs). In terms of effect sizes, male gender, higher education level, family history of psychiatric disease, Axis I disorder, more previous episodes, and low severity of psychiatric episode are relatively strong predictors for non-adherence.

Variables that were univariately associated with non-adherence at the $p = 0.20$ level were entered into a multiple logistic regression model (see multiple regression in Table 1). These variables were gender, education level, PDQ-4+ total score, number of previous episodes, severity of residual symptoms, severity of last depressive episode, number of dysfunctional episodes, and adequate dose of AD. The strength and direction of the relation of the potential predictors in this multiple regression model are comparable to the strength of the univariate relations with non-adherence.
Finally, we tried to find the most parsimonious prediction model using more stringent significance levels ($p \leq 0.05$) and a stepwise procedure with backward elimination. This

Table 1 Univariate predictors of non-adherence over 2 years among patients who continuously and intermittently took antidepressants (n = 91) [a,b]

Predictor	univariate			
	β	OR	95% CI	p
Patient factors				
Sex, female/**male**	-0.761	0.467	0.155-1.408	0.177*
Age	0.004	1.004	0.959-1.052	0.853
Personality (PDQ-4+ total score)	0.033	1.034	0.998-1.070	0.062*
Marital status, living alone/**not alone**	0.034	1.035	0.409-2.617	0.942
Education level (high/**other**)	1.099	3.000	0.921-9.773	0.068*
Familial psychiatric disease, yes/**no**	0.485	1.624	0.602-4.378	0.338
Smoking, yes/**no**	-0.370	0.691	0.242-1.969	0.489
Employed, yes/**no**	-0.419	0.658	0.268-1.612	0.360
Comorbidity Axis I, yes/**no**	0.637	1.891	0.375-9.538	0.440
Disease factors				
Number previous episodes before t0	0.558	1.747	0.978-3.119	0.059*
Severity residual symptoms t0	0.135	1.144	0.964-1.358	0.122*
Severity last episode before t0 overall	...	...	...	0.036*
Medium vs low	-2.197	0.111	0.012-1.007	0.051
Severe vs low	-1.123	0.325	0.038-2.803	0.307
Duration last episode before t0 overall	...	...	...	0.331
> 2 mo and < 8 mo vs ≤ 2 mo	-0.459	0.632	0.216-1.847	0.402
≥ 8 mo vs ≤ 2 mo	0.391	1.478	0.396-5.512	0.561
Onset before age 21 yes/**no**	0.460	1.583	0.554-4.529	0.391
Total DAS-A t0	0.011	1.011	0.996-1.026	0.161*
SCL-90 t0	0.302	1.353	0.271-6.54	0.713
BDI t0	0.357	1.429	0.826-2.473	0.202
Treatment factors				
Current treatment, specialty care, yes/**no**	-0.342	0.710	0.289-1.747	0.456
Adequate fluoxetine equivalent t0, yes/**no**	0.634	1.886	0.753-4.718	0.175*

[a] 30.8% (28/91) adherent over 2 years; 69.2% (63/91) non-adherent over 2 years. [b] Bold is reference category, * p ≤ 0.2. Symbol: ... = no data, Abbreviations: BDI = Beck Depression Inventory, DAS-A = Form A of the Dysfunctional Attitude Scale, OR = odds ratio, PDQ-4+ = Personality Disorder Questionnaire-4+, SCL-90 = Symptom Checklist.

Table 2 Multivariate logistic regression for non-adherence over 2 years [a,b]

Predictor	β	OR	p	95% CI
Personality (PDQ-4+ total score)	0.048	1.049	0.014	1.010-1.090
High education level yes/no	1.358	3.889	0.034	1.111-13.617

[a] 30.8% (28/91) adherent over 2 years; 69.2% (63/91) non-adherent over 2 years. [b] Nagelkerke R^2 of the model was 14.8%. Abbreviations: OR = odds ratio, PDQ-4+ = Personality Disorder Questionnaire-4+.

resulted in a model with only 2 risk factors (Table 2). The PDQ-4+ total score (increasing PDQ-4+ total score means increasing likelihood for non-adherence) and education level (higher education level means increasing likelihood for non-adherence). This final model explained approximately 15% of the variance in non-adherence (Nagelkerke R^2 = 14.8%).

multiple regression			
β	**OR**	**95% CI**	**p**
-0.836	0.434	0.113-1.656	0.222
...	...	...	...
0.037	1.308	0.978-1.101	0.221
…	…	…	…
1.558	4.747	1.052-21.428	0.043
...	...	...	...
...	...	...	...
...	...	...	...
...	...	...	...
0.598	1.818	0.887-3.727	0.103
0.136	1.146	0.922-1.425	0.219
...	...	...	0.120
-2.101	0.122	0.012-1.294	0.081
-1.154	0.315	0.032-3.136	0.325
...	...	...	...
...	...	...	...
...	...	...	...
...	...	...	...
-0.002	0.998	0.973-1.760	0.868
...	...	...	...
...	...	...	...
...	...	...	...
0.553	1.739	0.568-5.323	0.332

DISCUSSION

To our knowledge this is the first study that explores a set (patient-related, illness-related, and treatment-related) of potential predictors for non-adherence to continuation and maintenance AD use in remitted, recurrently depressed patients in a semi natural cohort. In a univariate analysis using a stringent significance level ($p \leq 0.005$), we found no independent predictors of non-adherence over a two years period. In a multivariate analysis the baseline predictors for non-adherence over a 2-year period were a higher level of personality pathology and a higher level of education.

Personality pathology and personality characteristics have been found to be predictors of non-adherence in other studies as well. For example, Cohen et al.[31] explored the relation of personality characteristics and non-adherence with AD in patients with acute MDD

and reported a significant relation between extraversion and non-adherence. Tedlow et al.[32] reported an association between lower rates of narcissistic-histrionic personality disorders and better adherence. In our sample, however, we found no relation between specific personality pathology and specific personality symptom clusters as assessed with the PDQ-4+ and adherence, which makes it delicate to set up a hypothesis on this subject. In general, personality pathology is thought of as behaviour patterns with limited adaptive capability.[16] Building further on this assumption, it may be that patients with more personality pathology are, because of less adaptive capability, less able to adapt to their doctor's advice.

Previous studies on adherence to AD use found either no association with education or even better adherence in higher-educated patients.[33-37] These different findings might be (partially) explained by the fact that most of these prediction studies did not specifically focus on remitted, recurrently depressed patients. In other chronic diseases, like asthma, an association between higher education levels and non-adherence has also been found.[38]

It is possible that higher-educated, remitted, recurrently depressed patients do not do what their doctor tells them to do when the disadvantages of AD do not outweigh the advantages in their opinion in this phase of treatment. Cooper et al.,[39] for example, found in a community study that non-adherence to psychotropic medication is most likely to be a deliberate decision by patients who just do not think they need it or do not want to take it. Hunot et al.,[40] reported concerns about AD (such as dependency and side effects) and preference for non-pharmacological treatments as predictors of non-adherence to AD for any psychiatric condition (e.g., not only for depression) in primary care. Perhaps higher-educated patients are more affected by these concerns. However, further research is necessary to replicate this finding and to provide an idea about specific factors that contribute to the relation of non-adherence in highly educated patients.

In summary, both predictors of non-adherence that we found suggest that less adaptive capability and education level can be barriers in following a doctor's advice. Our results suggest too that other factors than the studied patient-, illness- and treatment factors might play a key role in AD non-adherence in remitted, recurrent depression. We consider that adherence in this maintenance phase of treatment also could be affected by (patient and treatment) features like doctor-patient communication style, treatment preference and expectations and opinions about AD.[40]
Side effects are also mentioned as possible predictors of non-adherence. However, this argument seems less plausible considering the stable adherence percentages over the last decades despite the use of newer ADs with less side-effects.[39;41]

Limitations of the study

Certain limitations must be considered when interpreting the findings of our study. First, we applied a prospective cohort approach to the data of patients who originally

participated in a randomized, controlled cognitive therapy trial. Nevertheless, because the intervention neither modified nor confounded the relation between potential predictors and adherence, this should not have affected our findings.

Second, our data set did not include some other potential predictors of non-adherence like therapeutic alliance, patients' attitudes toward the illness, and the medication and side effects. These variables could be potential predictors of non-adherence in this phase of recurrent depression.

Third, given the relatively small sample size, the study may have lacked sufficient power to identify all relevant predictors. Another limitation of the study is the potentially biased patient group (patients participating in a cognitive therapy trial), and the use of merely patient self-report adherence information instead of a multi-method approach. However, the MAQ is often used and well validated,[20;21] and our results are in line with studies on adherence in other chronic diseases.[8]

Strengths of the study

We analyzed adherence data of a cohort of 172 patients with recurrent depression followed prospectively for 2 years after a remission. This cohort is unique because of its variety. It is a seminaturalistic cohort of recurrently depressed patients not participating in a medication trial (i.e., not controlling for AD use) who at study entry were in remission and were receiving maintenance AD therapy with diverse types of care (no care, primary care, and speciality care), suggesting that these findings are generalizable to remitted, recurrently depressed patients using maintenance AD.

Implications

We think that our findings are important for clinical management and further research. It is hard for doctors to recognize non-adherence in daily practice. Unfortunately, there is no specific patient profile that fully predicts non-adherence in remitted, recurrently depressed patients. Based upon our findings, it is too early to assess these predictors in daily clinical practice. For the moment, doctors have to be continuously aware of this silent problem and should keep on talking about it with their patients, not only in the acute phase, but also in the continuation and maintenance phases.

However, before we can conclude that there are no consistent predictors for non-adherence, qualitative research could be helpful (e.g., open patient interviews) to better understand non-adherent behaviour and its underlying mechanisms.

In conclusion, we did not find univariate (patient-related, illness-related, and treatment-related) predictors of non-adherence, but we were able to construct a risk profile for non-adherence over a 2-year period (higher personality pathology and higher education level). These predictors may suggest that a less adaptive capebility (viewed as an important

characteristic of personality pathology) and knowledge can be barriers in following a doctor's advice.

These results make clear that the process of becoming non-adherent is complex, and, thus, qualitative research must be done to understand non-adherence to AD in the continuation and maintenance phases in recurrent depression in order to maximize the potential protective effect.

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6

Prediction of recurrence in recurrent depression: a 5.5-year prospective study

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ABSTRACT

Objective

Depression is a disease with high recurrence rates. Identifying predictors of recurrence and their relative importance in patients with recurrent depression is important for a better understanding of the course of this disease. This type of knowledge can be used to optimize and tailor preventive strategies of recurrence. In this study we examined predictors of recurrence over a 5.5-year follow-up period and quantified to which extent these predictors explained observed variation in recurrence.

Methods

Data of 172 remitted recurrently depressed patients over a 5.5-year follow-up period were used. Recurrence was assessed with the Structured Clinical Interview for DSM-IV. Illness-, stress- and coping-related factors were examined as predictors of recurrence. Multiple Cox regression analysis was used and explained variation was assessed to quantify the relative importance of the predictors.

Results

Number of previous episodes and residual symptoms explained each 15% of the variation in recurrence, indicating a medium effect size. The final multivariate prediction model included: a higher number of previous episodes, more residual symptoms, and lower levels of positive refocusing (explained variation 29%, indicating a strong effect size).

Conclusion

In our multivariate prediction model the number of previous episodes, residual symptoms and a specific coping style were predictors of recurrence over a 5.5-year follow-up period in remitted recurrently depressed patients. Preventive therapies should focus on these factors. Although a substantial part of variation in recurrence (29%) was explained by these predictors, most of it remains unexplained. Consequently, recurrence remains a difficult to predict and only partially understood phenomenon.

INTRODUCTION

Major depressive disorder (MDD) is a disease with a high recurrence rate. Identifying predictors for recurrence in patients with recurrent depression is important for a better understanding of the course of this disease. This type of knowledge might contribute to optimizing and tailoring of specific prevention strategies for recurrence. To improve the clinical relevance of predictors of recurrence it is not only relevant to know which variables do predict recurrence but also to quantify their relative importance in terms of explained variation. We followed 172 recurrently depressed patients within a clinical trial comparing treatment as usual (TAU) with preventive cognitive therapy (CT).[1;2] Just like mindfulness-based cognitive therapy (MBCT) and wellbeing-therapy, this type of CT can prevent recurrence in recurrent depression, especially in patients with a high number of previous episodes.[1-11]

Previously, we reported predictors of time to recurrence over a 2-year follow-up period.[12] In this paper we will extend the follow-up period to 5.5 years. For the 2-year follow-up period, we found that a higher number of previous episodes, a higher level of residual depressive symptoms, and more daily hassles predicted recurrence.[12] We also found that factors related to coping style could predict recurrence; i.e. a higher level of dysfunctional attitudes, an avoidant way of dealing with problems, as well as a lower level of coping by refocusing on positive matters, such as thinking of other, pleasant matters instead of the actual event. Noteworthy, the effect of the latter two predictors was modified by the number of previous episodes, resulting in a diminishing influence as the number of previous episodes increased. Furthermore, we found little impact of socio-demographic variables on time to recurrence.[1]

As far as we know, there are no studies that reported predictors of recurrence and a multivariate prediction model in combination with a quantification of their relative importance in terms of explained variations for time to recurrence in remitted patients suffering from recurrent depression. In the current study we therefore examined 172 patients with recurrent depression, who were remitted at study entry, over a 5.5-year follow-up period, using structured interviews based on DSM-IV.[13] The study had four aims:

1. to determine predictors of time to recurrence over a 5.5-year follow-up period,
2. to quantify the explained variation of these predictors,
3. to find the most parsimonious set of predictors of time to recurrence (with a Cox regression model) during this 5.5-year follow-up period, and
4. to quantify the explained variation of the multivariate model.

METHODS

Participants

All respondents participated in a clinical trial of patients with recurrent depression, in remission at the start of the study, in which the effect of TAU on recurrence was compared to TAU with additional preventive CT.[1] To be eligible subjects had to meet the following criteria: (a) at least two separate Major Depressive Episodes (MDEs) in the last five years, as defined according to DSM-IV[14] and assessed by the Structured Clinical Interview for DSM-IV (SCID)[13] by trained evaluators; (b) current remission status according to DSM-IV criteria, for longer than 10 weeks and no longer than two years ago; and (c) Hamilton Rating Scale for Depression (HRSD)[15] of < 10. For this study the exclusion criteria were: current mania or hypomania or a history of bipolar illness, any psychotic disorder (current and previous), organic brain damage, alcohol or drug misuse, predominant anxiety disorder, recent electroconvulsive therapy, recent CT or receiving CT at the start of the study, and/or current psychotherapy with a frequency of more than two times a month. There was no restriction in using pharmacotherapy. Participants were recruited at psychiatric centers and through media announcement. They completed telephonic screening (n > 1000), diagnostic interviews (n = 321) and provided informed consent to enter the study (n = 187). The research protocol was approved by the institutional ethics review committees.

Procedure

Participants were screened on inclusion and exclusion criteria via the telephone version of the SCID-I. Kappa for interrater agreement between the interviewers (psychologist/research assistants), based on audiotaped interviews, for inclusion or exclusion was 0.77, which is indicative of good/excellent agreement.

Participants meeting the inclusion criteria were randomly allocated to:

(a) Treatment as usual (TAU), which involved 'naturalistic' care, i.e., standard care (including no treatment at all), as typically provided by the referring agencies. There was no restriction on the use of pharmacotherapy during the period from entry through follow-up.
(b) TAU + 8 weekly 2-hour sessions of group CT.

Randomization was performed using random permuted blocks and was stratified by study location and type of aftercare (family doctor/mental health centre/no aftercare). Consecutively numbered, sealed envelopes contained computer-generated cards with concealed assignment codes. This procedure was organized and administered by an independent research associate.

Study measures

Primary outcome measure. Recurrence was assessed with the Structured Clinical Interview for DSM-IV (SCID-I).[13] Using this instrument, current and past depressive

episodes were assessed at baseline and at five follow-up measurements at 3, 12, 24, 36 and 66 months after baseline. Cox regression analyses revealed no confounding effect of the duration of the last episode before remission on the relation between predictors and time to recurrence. Although, conceptually, one might distinguish between a recurrence (the appearance of a *new* episode of major depressive disorder which can, by definition, only occur in a period of recovery, i.e., a remission period > 6 months) or a relapse (defined as the early return of depressive symptoms following an apparent remission within 4 to 6 months), this distinction is still arbitrary. For that reason we do not make a distinction between relapse and recurrence and, to improve readability, refer to both as recurrence.

To maintain the blindness of assessors to treatment condition, we instructed participants not to reveal their treatment condition to the interviewers (psychologist/research assistants). All interviews were audiotaped. Two independent experienced psychiatrists who were blind to treatment condition evaluated the participants meeting the DSM-IV criteria for major depression. In case of disagreement, the ratings of the psychiatrists were used for further analyses. Kappa for interrater agreement between the interviewers and psychiatrist on categorization of a recurrence versus no recurrence over the follow-up period ranged from 0.94 to 0.96, indicating high agreement.

Predictor variables

The following potential predictor variables were assessed at baseline, i.e., at entry of the study: demographic characteristics (sex, marital status, age, education level), historic illness related characteristics (age of onset, severity of last depression, duration of last episode, duration of remission since last episode, percentage of time illness free since first episode, familial psychiatric disease), antidepressant use at study entry, recent illness related characteristics (level of residual depressive symptoms), coping and stress (daily hassles and life events).

Residual depressive symptoms. Participants' baseline level of depressive symptomatology was assessed with the 17-item HRSD.[15] The HRSD, administered by psychologist/research assistants who were blind to treatment condition, is a widely used semi-structured clinical interview that covers a range of affective, behavioral and biological symptoms and has acceptable psychometric properties.[16] Scores can range from 0 to 52. Our four interviewers (psychologist/research assistants) second rated 17 interviews. The intraclass correlation (ICC) was 0.94, indicating high agreement. The 21-item self-report Beck Depression Inventory (BDI) was used to assess baseline depression symptomatology in the past week. BDI scores can range from 0-63.[17] The 90-item Symptom Check List (SCL-90)[18] was used to assess the total baseline level of psychopathology in the past week. In this study, the total score (the sum-score of all 90 items) is reported.

Coping. We examined behavioral and cognitive coping. Information on *behavioral* coping with problems was obtained at baseline by using two subscales of the Utrecht Coping List (UCL);[19] i.e., Avoidant coping (8 items), characterized by an avoidant way of dealing with

problems and Active approach of problems (7 items). Participants were asked how they reacted in general to the mentioned items (e.g., avoid difficult situations). The UCL has good psychometric properties.[20]

Information on *cognitive* coping was obtained with the self-report Cognitive Emotional Regulation Questionnaire (CERQ), containing 36 items with 9 subscales such as Rumination, Self-blame and Refocus on other positive matters.[21] Participants were asked how they think in general when confronted with stressful events (e.g., I think about how I can change the situation). The subscale *Positive refocusing* refers to thinking of other, pleasant matters instead of the actual event (e.g., I think of nicer things than what I have experienced).

Dysfunctional attitudes These were assessed at baseline with the Dutch adaptation of the Dysfunctional Attitude Scale (DAS).[22] The DAS is a 40-item scale that assesses excessive and rigid beliefs, hypothesized by Beck[23] to be vulnerability factors for depression. Participants rate their agreement with each belief on a 7-point scale ranging from 'totally agree' to 'totally disagree'. Scores range from 40-280, with higher scores indicating greater levels of dysfunctional attitudes. Form A of the DAS (DAS-A) was used, which has been shown to have good psychometric properties.[24]

Stress. Daily hassles were assessed at baseline with the 114-item Everyday Problem Checklist (EPCL).[25] The items of the EPCL refer to stressors of daily living, particularly those in the domains of work, parenthood, relationship, and household activities. The EPCL assesses the frequency of daily hassles over the past two months, and has good psychometric properties.[25]

The experience of negative life events was measured at baseline with a 15-item checklist that covered adulthood (from the age of 16 to the start of the study). This checklist is based on the Negative Life Events Questionnaire (NLEQ).[26] Events can involve the participant or significant others. In previous studies,[26-28] the predictive validity of the NLEQ proved to be good as the number of negative life events predicted severity of depressive symptoms.

Statistical analysis

The effect on recurrence for all predictors mentioned was assessed with Cox regression. Here we took into account the fact that half of our sample received CT. The effect of this intervention depended upon the number of previous depressive episodes.[1;2] We did this by assessing for each predictor whether the intervention moderated the relation between the predictor and recurrence (i.e., whether the effect of the predictor on recurrence differed between patients that received CT and patients that did not receive CT).

To define the univariate effect of a specific predictor on recurrence we used a 2 step procedure. In the first step we tested, by a 3-way predictor by treatment by number of previous episodes interaction term, and a 2-way treatment by number of previous episodes

interaction term, for each predictor whether its effect on recurrence was modified by treatment condition, and whether the strength or direction of this modification depended upon the number of previous depressive episodes. In the second step we assessed by a predictor by number of previous episodes interaction term, whether the effect of a predictor was modified by this number of episodes. Depending upon the results of the first step these analyses were performed either in the total sample (n = 172), or (in case of a significant interaction with treatment condition), only in the TAU group (n = 84). In both cases the treatment factor will not be incorporated in the statistical model. In the first case since treatment had no effect on this relation, in the latter case since we restrict ourselves to one treatment condition (the control group).

To account for chance capitalisation because of multiple testing which affects type I error, we used a relative conservative α-level of 0.01 for all main effects tests. However, given the relatively lower power of tests for interaction compared to tests for main effects, we used an α-level of 0.05 for all tests for interaction to guard against type II error. Since the distribution of number of previous episodes was skewed and the minimum number of previous episodes was 2, we used the following transformation $P = \ln(p-1)$ with p the actual number of previous episodes and P the transformed variable used in the analysis.

Combined effect. To assess the combined effect of predictors on time to recurrence we used a method proposed by Hosmer and Lemeshow.[29] All variables univariately related to time to recurrence (using a lenient p value threshold of < 0.20) were entered in a multiple Cox regression, using a stepwise procedure with backward elimination with entry and removal criteria set at 0.01 for the main effects and 0.05 for the interaction effects. Both relative risks (RR), 95% confidence intervals and the amount of explained variation (Nagelkerke R^2) were calculated.

Explained variation. The relative importance of the predictor for recurrence is quantified in its explained variation. For logistic regression and Cox regression several explained variation measures are proposed. However, especially for Cox regression there is still not a single, simple, easy to interpret pseudo R^2 measure available.[29;30] A main problem is the sensitivity of existing measures to censoring. However, in our sample with only 20% censoring, this effect is expected to be small. Hosmer and Lemeshow propose the Cox-Snell R^2 as the easiest and best one to use. However, this measure has a maximum value that is smaller than 1. This problem is corrected by Nagelkerke. For this reason Nagelkerke R^2 will be used in this article as the measure of explained variation. All analyses were performed using SPSS for Windows version 16.

RESULTS

Sample characteristics

The baseline sample comprised 187 participants of which 15 participants (9 from CT; 6 from TAU) were excluded because they dropped out of the study immediately after randomization. Drop-outs (n = 15) were younger than completers (n = 172), t = -2.25, df = 170, p = 0.026 (mean = 38.9, SD = 10.6 vs. mean = 44.8, SD = 9.5), but comparable on all other characteristics. Demographic and clinical characteristics of TAU (n = 84) and CT (n = 88) patients are summarized in Table 1. Both groups were comparable on each of the characteristics except that, compared to TAU patients, a larger proportion of CT patients experienced negative life events before their sixteenth year of age (CT 84/88 experienced negative life events versus TAU 70/84; $\chi^2(1, n = 172) = 6.74$, p = 0.009). To examine whether this confounded the relation between the potential predictors and recurrence, the effect parameters in the model with and without negative childhood life events were compared. No confounding effect of childhood life events was found.

Table 1 Demographic and clinical characteristics[a]

Characteristic	**(n=172)**
Sex, female (%)	73
White (%)	98
Age (yr, mean ± SD)	44.7 ± 9.5
Years of education (8-18, mean ± SD)	14.2 ± 2.5
Marital status (%)	
Single	24
Married/cohabiting	58
Divorced/widowed	18
Type of current treatment (%)	
Family doctor	29
Psychiatric help	31
No treatment	40
Antidepressant medication (%)	51
HRSD score (mean ± SD)	3.8 ± 2.8
Previous episodes	
Median previous episodes ± IQR	4 ± 3.8
>2 previous episodes (%)	82
Age of first onset (yr, mean ± SD)	28.5 ± 12.5
Coping, mean ± SD	
Dysfunctional attitudes (DAS-A) (mean ± SD)	124.6 ± 33.5
Avoidant coping strategy (UCL) (mean ± SD)	17.1 ± 3.9
Refocus on positive matters (CERQ)	8.7 ± 3.3

[a]All data represent baseline values. Abbreviations: CERQ = Cognitive Emotion Regulation Questionnaire, DAS-A = form A of the Dutch adaptation of the Dysfunctional Attitude Scale, HRSD = Hamilton Rating Scale for Depression, IQR = interquartile range, UCL = Utrecht Coping List.

Recurrence

In the total sample (n = 172), 135 (79%) participants were diagnosed with at least one new depressive episode over a period of 5.5-year follow-up.

Predictors of time to recurrence

In table 2 we present the results of the Cox regression analyses for all potential predictors that were related to time to recurrence using a threshold of $p < 0.20$. As described in the statistical analysis section, effects that are modified by treatment condition are only presented for the control group. When the predictor by the number of previous episodes interaction is statistically significant, results for the main effect of the number of previous episodes and its interaction with the predictor in question are also presented.
Univariate predictors of recurrence are defined as those potential predictors with a univariate p value < 0.01 or in case of effect modification by number of previous depressive

Table 2 Predictors of time to recurrence over 5.5 years (n=172)[1]

Predictor[5]		Predictor	Number of episodes	Predictor* Episodes	Explained Variation[2]	Multiple regression model
Residual depressive symptomatology (HRSD)	β	0.096			0.06	
	SE(β)	0.029				
	p	0.001				
Residual depressive symptomatology (BDI)	β	0.507			0.08	
	SE(β)	0.141				
	p	0.000				
Residual symptoms (SCL-90) [4]	β	1.805			0.15	+
	SE(β)	0.322				
	p	0.000				
Duration last depression[4]	β	.526	0.513	-0.448	0.03	
	SE(β)	0.362	0.174	0.207		
	p	0.146	0.003	0.030		
Number of previous episodes [3,4]	β	0.525			0.15	+
	SE(β)	0.137				
	p	0.000				
Age of onset[3]	β	-0.022			0.06	
	SE(β)	0.010				
	p	0.031				
Avoidant coping (UCL) [3,4]	β	0.163	0.596	-0.070	0.10	
	SE(β)	0.055	0.153	0.030		
	p	0.003	0.000	0.021		
Positive refocusing (CERQ)[4]	β	-0.140	0.166	0.058	0.06	+
	SE(β)	0.046	0.094	0.030		
	p	0.003	0.078	0.055		
Acceptance (CERQ)	β	-0.034			0.01	
	SE(β)	0.024				
	p	0.153				

Table 2 Cont.

Predictor[5]		Predictor	Number of episodes	Predictor* Episodes	Explained Variation[2]	Multiple regression model
Self blame (CERQ) [3]	β	0.154	0.550	-0.084	0.07	
	SE(β)	0.064	0.149	0.041		
	p	0.016	<.001	0.039		
Rumination (CERQ)	β	0.062			0.03	
	SE(β)	0.026				
	p	0.016				
Catastrophizing (CERQ) [3]	β	0.080			0.05	
	SE(β)	0.042				
	p	0.056				
Other blame (CERQ)	β	0.044			0.01	
	SE(β)	0.030				
	p	0.139				
Dysfunctional attitudes (DAS-A) [4]	β	0.009			0.07	
	SE(β)	0.002				
	p	0.000				
Daily hassles (EPCL) [3]	β	0.514			0.09	
	SE(β)	0.185				
	p	0.005				
Marital status (single/ widowed/divorced vs married/cohabitating) [4]	β	1.103	0.365	-0.417	0.09	
	SE(β)	0.296	0.122	0.197		
	p	0.000	0.003	0.035		
Age	β	-0.017			0.02	
	SE(β)	-0.010				
	p	-0.081				
Education [3]	β	-0.455			0.04	
	SE(β)	0.249				
	p	0.068				

[1] Cox regression analysis. Reference values for predictors are: duration last episodes = 0 (0=<=2 months), number of previous episodes (transformed as P = ln(ndeps-1), where ndeps equals the raw number) = 0 (=2 previous episodes), ln(daily hassles-score) = 0 (APL score=1), marital status = 0 (married/ cohabitating), HRSD = 0 (Hamilton score 0), ln(BDI+1) = 0 (BDI=0) and ln(SCL90) = 0, (SCL90 = 1) education = 0 (low).

Other continuous variables were centered around their mean: avoidant coping (16), positive refocusing (8), DAS-A (119). Only predictors with a univariate p value < 0.20 are presented. Predictors that did not fulfill this criterion were: severity of last depression, duration of remission of last episode, percentage of time illness-free since first episode, other types of emotional coping, familial psychiatric disease, and life events between 16th year and the start of the study; [2] Nagelkerke R^2; [3] Only control group data (n = 84) used because of a significant modification by treatment interaction; [4] Significant predictor by number of previous episodes interaction; [5] *Univariate predictors* are presented in italics; Abbreviations: BDI = Beck Depression Inventory, CERQ = Cognitive Emotion Regulation Questionnaire, DAS-A = form A of the Dutch adaptation of the Dysfunctional Attitude Scale, EPCL = Everyday Problem Checklist, HRSD = Hamilton rating Scale for Depression, ln = natural logarithm, P = number of previous episodes, SCL-90 = Symptom Checklist-90, UCL = Utrecht Coping List.

episodes an univariate p value < 0.05 for the predictor by number of previous episodes interaction term. Univariate predictors are presented in italic. The explained variation by these predictors varies between 3% (duration last depression) and 15% (number of previous episodes and SCL-90 total score).

To assess whether the explained variation could be improved by a combination of predictors we entered all potential predictors with a univariate p value < 0.20 (i.e., all variables in Table 2) in a multiple Cox regression model. Backward elimination with p < 0.01 for main effects and p < 0.05 for interaction terms resulted in a model comprising the number of previous episodes, the SCL-90 total score and coping by refocusing on positive matters as predictors of recurrence. The latter was modified by number of previous episodes (Table 3). Patients with a higher SCL-90 total score at baseline had an increased risk of recurrence.

Table 3 Results multiple Cox regression analysis (n=84)[1]

	RR	p	95% CI for Exp(B)
Positive refocusing (CERQ) [2]	0.890	0.086	0.779 – 1.017
Number previous episodes [3]	1.528	0.006	1.130 – 2.065
Residual symptoms (SCL-90) [4]	3.609	0.008	1.402 – 9.293
Number previous episodes [3] * Positive refocusing [2]	1.117	0.021	1.017 – 1.226

[1] Cox regression analysis. Reference values for predictors are: number of previous episodes (transformed as P = ln(ndeps-1 i.e. number of previous episodes=1, ln(SCL90) = 0, i.e. SCL90 = 1; [2] Centred around mean (8); [3] ln(raw score -1); [4] ln(raw score).
Abbreviations: CERQ = Cognitive Emotion Regulation Questionnaire, CI = Confidence Interval, exp = exponent, ln = natural logarithm, P = number of previous episodes, RR = Relative Risk, SCL-90 = Symptom Checklist-90.

Table 4 presents the relative risks (RR) for all the univariate predictors and predictors comprising the multivariate prediction model. Predictors with RRs smaller than '1' indicate protective factors, i.e., relatively longer time to recurrence; those with RRs exceeding '1' indicate risk predictors, i.e., a relatively shorter time to recurrence. In case of effect modification by the number of previous episodes the RR depends on this number. To visualize this interaction effect the RRs for patients with respectively 2 and 8 previous episodes are presented.

The number of previous episodes, daily hassles, residual symptoms (as measured by the HRSD, BDI and SCL 90), and the score on the dysfunctional attitude scale (DAS) are all positively related to recurrence risk. The effect on recurrence of avoidant coping, duration of last depressive episode, refocusing on positive matters and marital status depends on the number of previous episodes. In general an increase in the number of previous episodes from 2 to 8 diminishes the effect of these predictors (the RR gets closer to 1). The effect of duration of the last depressive episode however changes its direction within this range of previous episodes. For patients with 2 previous episodes a longer duration of the last episode increases the probability for recurrence. In patients with 8 previous episodes a longer duration of the last episode decreases the probability for recurrence.

Table 4 Relative risks (RR), standard errors (SEs) of the natural logarithm of the relative risks and confidence intervals (CIs) for the relative risks[1]

Predictor	RR	SE	90% CI[8]	Previous episodes
Avoidant coping (UCL) [2,3,10]	1.177	0.0550	1.076-1.288	2
	1.027	0.0349	0.970-1.088	8
Duration last depressive episode [7,9]	1.692	0.3620	0.9346-3.064	2
	0,708	0.2198	0.4935-1.015	8
Positive refocusing (CERQ) [2,3,9]	0.869	0.0460	0.8062-0.9375	2
	0,973	0.0353	0.9184-1.031	8
Number of previous episodes [4,10]	1.690	0.1370	1.350-2.116	
Daily hassles (EPCL) [5,10]	1.672	0.1850	1.234-2.265	
Marital status [6,9]	3.013	0.2960	1.854-4.896	2
	1.339	0.2370	0.9168-1.954	8
Residual depressive symptomatology (HRSD) [2]	1.101	0.0290	1.022-1.186 (99% CI)	
Residual depressive symptomatology (BDI) [2,5]	1.660	0.1410	1.156-2.385 (99% CI)	
Residual symptoms (SCL-90) [2]	6.080	0.3220	2.658-13.91 (99% CI)	
Dysfunctional attitudes (DAS) [2,3]	1.009	0.0020	1.004-1.014 (99% CI)	

[1] Cox regression analysis; [2] continuous scores; [3] centered around mean: CERQ(8), DAS(119); ln(raw score); [4] ln(raw score -1); [5] ln(raw score+1); [6] dichotomized: single/widowed/divorced vs. married/cohabitation; [7] categorized: 2 months or less vs 3 (ref category) vs. 3 months or more; [8] 90% Confidence intervals are reported, unless otherwise specified (99%). Limits of the 90% confidence interval for RR are given by $RR/exp(Se)^{1.645}$ and $RR*exp(Se)^{1.645}$ Limits for the 99% confidence interval for RR are given by $RR/exp(Se)^{2.576}$ and $RR*exp(Se)^{2.576}$; [9] values are given for 2 and 8 episodes. Formulas used to assess CI for specific number of episodes (e.g P) are: Avoidant coping: $RR = 1.223848 * (0.923116)^P$ and $Se = \sqrt{(0.0036+0.001089*P^2-0.003259*P)}$ Duration last depression, $RR = 0.591555* (1.673639)^P$ and $Se = \sqrt{(0.161604+0.051076*P^2-0.148634*P)}$ Coping refocus on positive matters $RR = 0.862431*(1.07896)^P$ and $Se = \sqrt{(0.002916+0.001225*P^2-0.003092*P)}$; Single: $RR = 3.037394*(0.669650)^P$ and $Se = \sqrt{(0.115600+0.048400*P^2-0.119680*P)}$; Dysfunctional attitudes: $RR = 1.016129*(0.994018)^P$ and $Se = \sqrt{(0.000025+0.000009*P^2-0.000025*P)}$; [10] only control group data (n = 84) used because of a significant modification by treatment interaction.

Abbreviations: BDI = Beck Depression Inventory, CERQ = Cognitive Emotion Regulation Questionnaire, DAS-A = form A of the Dutch adaptation of the Dysfunctional Attitude Scale, EPCL=Everyday Problem Checklist, HRSD = Hamilton rating Scale for Depression, ln = natural logarithm, P= number of previous episodes, SCL-90 = Symptom Checklist-90, UCL = Utrecht Coping List.

DISCUSSION

This is the first prospective study that both univariately and multivariately examined predictors of time to recurrence over 5.5 years, as well as their explained variations for time to recurrence in a large and well defined cohort of remitted patients with recurrent depression. In summary, we found that earlier time to recurrence was univariately predicted by a higher number of previous episodes before start of the study, more residual depressive symptoms and a higher level of dysfunctional attitudes at the start of the study and more daily hassles. The percentage of explained variation by these predictors varied between 6% (baseline residual depressive symptoms: HRSD score) and 15% (baseline level of psychopathology: SCL-90 total score).

In addition, we identified several predictors with an effect on recurrence that was modified by the number op previous depressive episodes. A longer duration of the last depressive episode before start of the study mainly predicted a shorter time to recurrence in patients with a relatively low number of previous depressive episodes. This effect diminished with an increasing number of previous episodes. Furthermore, a higher level of dealing with problems in an avoidant way, a lower level of coping by refocusing on positive matters, and being single, widowed or divorced mainly predicted a shorter time to recurrence.

The most parsimonious multivariate model (stepwise multiple Cox regression analyses with backward elimination) comprised the following predictors - a higher number of previous episodes, a higher level of residual symptoms, a lower level of coping by refocusing on positive matters and – and one interaction term (number of previous episodes * positive refocusing) accounting for 29% of the variation in time to recurrence.

The predictors we found in univariately analyses were the same as those identified over a 2-year follow-up period.[12] These variables continue to be predictors over 5.5 years in this recurrent depressive sample. As reported in our 2-year analyses, we again found little impact of other illness-related features, except for the number of previous episodes. The predictors in our multivariate model are in accordance with findings in several previous studies (see for a review Burcusa et al.[31]). Residual depressive symptoms and the number of previous episodes were predictors of recurrence in several former studies.[12;32-36]

Coping-related factors have also been associated with depressive symptoms and recurrence in several studies.[32;37-41] Other aspects of coping are the beliefs of patients or dysfunctional attitudes. Teasdale and colleagues studied the extremity of the attitudes by focusing on the frequency of extreme response categories on the DAS-approval subscale.[42] They found that the frequency of extreme response categories of this subscale was correlated positively with negative therapy outcome. In a more recent study, Petersen et al. examined whether the extent of change in extreme responses differed significantly between patients who received CBT in combination with antidepressants versus patients who solely received antidepressants during the continuation treatment phase.[43] They found that patients in the medication only group showed a significant increase in the number of extreme responses on the DAS-approval over the course of the continuation phase versus no significant increase in patients receiving CBT in addition to medication in this period. These findings indicate that not only focusing on this type of coping, i.e., dysfunctional attitudes is important, but attention should also be paid to the way people process depression related material.[42] Yet, the specific coping style 'refocusing on positive matters' has not been described as a predictor of recurrence before.

To understand our finding that a lower level of coping by refocusing on positive matters predicted recurrence, we might utilize a theory on the working mechanism of CT. In short, in this theory, as stated by Brewin,[44] CT does not directly modify negative information in the patient's memory, but assumingly targets on creating more positive competitor

representations to win the retrieval competition. Analogous to this, we hypothesize that the coping style 'refocusing on positive matters' creates more positive competitor representations, which can prevent recurrence of depression. Furthermore, effective preventive psychological interventions with cognitive elements, such as preventive CT, MBCT, and wellbeing-therapy, might all share the promotion of more helpful coping strategies.[1;3-9] The focus on coping strategies (e.g., endure refocusing on positive matters and diminish avoidant coping) might be an essential ingredient in psychological preventive strategies.

The strongest univariate predictors we found are the number of previous episodes and residual symptoms, which each explained 15% of variation in recurrence, indicating a 'medium' effect in terms of effect sizes.[45] Both are well-known predictors of recurrence, but in terms of clinical relevance they are not too impressive in predicting recurrence. Using a multiple Cox regression model the predictors explained a substantial part of the variation (29%). This is a 'strong' effect in terms of effect sizes[45] and considerably better than the best single predictor. However, from a clinical point of view this is still moderate, even though we examined the most promising predictors of recurrence.

Not included factors, like genetic, neurobiological and endophenotypic factors play a role in recurrence too. The heritability of MDD is likely to be in the range of 31% - 42% (see for a review Sulivan et al.[46]). Yet, these abovementioned factors were not part of our analyses. Additionally, sample sizes were too small to examine all potential interactions, like the interaction between avoidant coping with daily hassles and life events and dysfunctional attitudes, as stated by Holahan et al..[47]

Strengths and Limitations

Our study has some major strengths. It comprises a representative cohort, including exclusively patients with at least two previous episodes and was followed prospectively for 5.5 years with structured interviews based on DSM-IV. Furthermore, we included patients with recurrent depression remitted on medication and/or psychological therapy or no treatment at all, without restrictions on medication status at entry to the study. As such, this study was designed to maximize external validity, which suggests good generalizability of the findings. Finally, we calculated explained variations of the predictors of recurrence.

However, some limitations should also be noted. First, the relatively small sample size reduces power to detect weaker associations between recurrence and prediction factors and potential interactions between these factors. Although we used an α-level of 0.05 for interaction with treatment condition (n = 172) to account for a lower power we cannot completely rule out that CT did not influence the relation between the predictor and recurrence in case of non-significant interaction terms with treatment condition.

Furthermore, this study is restricted to patients with two or more previous depressive episodes, and comprises almost exclusively Caucasian patients. We do not know whether our results can be generalized to patients with less previous episodes and to other ethnic groups. Another limitation concerns the retrospective nature of the information on the number of previous episodes before the start of the study as collected with a structured interview, although major predictors seemed relatively little impaired based on retrospective recall.[48] One more limitation concerns the (well-validated) self-report measures which are subject to social desirability and therefore further research is needed with interview based stress and coping measures.

Finally, the Cox regression analyses in this article took right censoring into account. However, the inclusion criteria pertaining to the duration of the remission of the last depressive episode before study entry also introduced left truncation. This might have biased the predictor estimates. Yet, since the duration of the left truncation was not related to recurrence ($p = 0.992$) and the mean hazard scores were comparable for different categories of left truncation duration ($p = 0.510$), this bias is probably small or not existent. For this reason we refrained from more complicated statistical analyses and used the standard Cox regression analysis.

Conclusion

In our final prediction model we found that the number of previous episodes, coping style and residual depressive symptoms were predictive of recurrence in remitted recurrently depressed patients in a 5.5-year follow-up study and that these predictors were rather stable over time. Although the final prediction model explained a substantial part of the variation (29%) in recurrence, most of it remained unexplained. This suggests that prediction of recurrence is a complex and multivariate phenomenon yet not completely understood. In ending, focus on enhancement of coping-related factors and reduction of residual depressive symptoms by specific psychological interventions might be essential in preventing future recurrences of this highly recurrent disease.

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7

General discussion and conclusions

OVERVIEW

This thesis focused on some important topics related to the clinical course of recurrent depression: health related quality of life (HRQOL), continuation and maintenance use of antidepressants, adherence to antidepressants, predictors of non-adherence, and predictors of recurrence of depression. In this final chapter the main findings will be summarized and discussed. Furthermore, limitations, clinical implications and suggestions for further research will be presented. Studies in this thesis were based on data collected from the DELTA cohort, a unique, relatively large, well defined and homogeneous population as it included exclusively remitted patients with at least two previous depressive episodes. Some of the important previous results of this project have been described in the introduction of this thesis.

MAIN FINDINGS

Health Related Quality of Life

Health Related Quality of Life (HRQOL) reflects a broader concept of 'well-being' across several health domains (i.e. mental and physical) than the more narrow symptom-based measures of a disease, which may not accurately represent the overall state of an individual.[1] Increasingly, HRQOL is acknowledged as an important outcome measure in the treatment of many diseases in addition to symptom relieve. This holds in particular for chronic conditions that are increasingly prevalent due to improved health care, a higher standard of living and aging and in which HRQOL is often decreased for longer periods of time.[2;3]

In chapter 2 we assessed the level of HRQOL in the DELTA cohort, compared it with that of the Dutch general population and studied its longitudinal relation with depressive symptoms after the acute phase of treatment. This had not been done before in exclusively recurrently depressed patients. First, we found that these patients reported lower HRQOL scores than individuals recruited from the general Dutch population, both for the physical and mental health domains. This difference was most evident in women. In men, the difference was smaller and non-significant, which could be due to an under-representation of men in our patient group.

Second, we found that changes in the level of HRQOL were related to changes in the level of residual depressive symptoms in these patients. An increase in levels of depressive symptoms corresponded to a decrease in all 8 domains of the SF-36, the quality of life scale we used. These results are in accordance with earlier studies revealing that residual symptoms after a Major Depressive Episode (MDE) are associated with an impaired HRQOL.[4-9]

Prior to our study, as far as we know, there have been no studies that compared complete HRQOL profiles of remitted recurrently depressed patients with those of a general population sample, adjusting for age and gender differences. However, recurrently depressed patients have been compared to patients with a first depressive episode.[10] The authors of this study reported that patients with a recurrent depressive episode did not show more impairment of HRQOL than those with a first depressive episode. They also found that as a group (i.e. first episode plus recurrently depressed individuals), depressed individuals had increased impairment of HRQOL compared to non-depressed individuals.

This thesis provides further evidence that patients with recurrent depression may recover from a depressive episode, but, even when in remission, are not functioning at the same level as a general population sample. In other words: a positive clinical outcome is not necessarily accompanied by a complete functional recovery of their quality of life. This is an important finding as impairments in HRQOL, rather than health status itself, are often the crucial factor for people to seek mental health care.[11] The interpretation of differences in functioning between remitted patients and a general population sample, however, is not straightforward. Because we did not have HRQOL data of our sample in the period before the first onset of depression, we cannot exclude that the lower HRQOL already was a pre-existent phenomenon or the result of having had one or more depressive episodes, or a combination of both. Yet, our finding that the level of HRQOL was inversely related to the level of depressive symptoms supports the second assumption. Additionally, as depressed patients frequently report physical problems and MDD tends to concur with somatic conditions, this may have contributed to the impaired HRQOL in the physical domains.[12]

Clinical implications and suggestions for further research

For mental health care professionals, the assessment of HRQOL might be a beneficial addition to the evaluation of symptomatology. In remitted patients these impairments in social activities, housekeeping or working are easily overlooked, which may result in frictions in the patient- professional relationship. Furthermore, improving HRQOL itself may also be an important goal given its association with subsequent relapse[13-15] above-and-beyond current depressive symptoms.[16] Currently, disease management programs are available for patients with persistent depressive symptoms to help them focus on improving their social functioning and quality of life.[17] Our results indicate the need for the development of interventions to improve HRQOL also in remitted recurrently depressed patients.

Antidepressive medication

Continuation and maintenance use of antidepressive medication

The current Dutch MDD guideline advices clinicians to continue antidepressive medication for recurrently depressed patients after the recovery on antidepressants to

prevent relapse/recurrence for a period of at least one year up to three or even five years.[18] However, little is known about the actual antidepressant use in the continuation and maintenance phase in recurrently depressed patients following successful acute treatment and its effects on outcome.

In chapter 3, we assessed long-term patterns of antidepressive medication use from the last depressive episode before study entry until 2 years after study entry. This was done by means of a structured interview. All patients were in remission at study entry, as this was one of the inclusion criteria. For patients who used antidepressants during the last MDE preceding the study, we defined three patterns of antidepressant use after remission: 'continuous use', 'intermittent use' and 'non-use'.

We found that 76% (131/172) of the patients was treated with antidepressants for the last MDE before entering the study, of whom 62% (81/131) was still using antidepressants at study entry. Of the latter group 42% (48/115 (n = 16 missing, no data on use of antidepressants during study) continued maintenance antidepressant treatment either until the first recurrence or to the end of the 2-year follow-up period, over one third (38% (44/115)) used antidepressants intermittently, and the rest (20% (23/115)) did not use antidepressant treatment at all after remission. Of the 'continuous users' 63% (30/48) used antidepressants in an adequate dosage (≥ 20 mg fluoxetine equivalent). Consequently, the large majority of our sample (77% (101/131)) did not receive adequate antidepressant treatment in the continuation and maintenance phase. Unfortunately, we do not know whether the patients' doctors did not follow MDD guidelines or the patients did not follow the doctor's advice (or both of the two).

Furthermore, we found that despite continuous use of antidepressant medication, 60% (29/48) of the patients relapsed within two years. This relapse rate was comparable to the rate of the 'intermittent users' (64% (28/44)), even after controlling for the effect of minimal required dosage and non-adherence. The relapse rate in 'non-users' (26% (6/23)) was significantly lower compared to the two other user-groups, which could not be explained by baseline differences in risk factors. Since the three groups were not composed by randomization, an explanation for the relapse/recurrence differences between the three user-groups could still be some unknown baseline characteristic. Another possibility is an effect of the preventive cognitive therapy (CT), which was associated with a significantly lower relapse rate than treatment as usual (TAU) (CT; 8% (1/12), TAU: 46% (5/11), $\chi^2(1) = 4.102$, $p = 0.043$). Because of the small number of patients in the non-using group we could unfortunately not test the modifying effect of the CT intervention.

Our results contribute to a better understanding of antidepressant use after the acute phase in recurrent depression. Noteworthy, although recurrently depressed patients represent the most important group of patients in mood disorders programs, to date little is known about discontinuation rates of maintenance antidepressant medication in these patients in clinical practice. Only recently, Holma et al. described a 5-year follow-

up study on maintenance antidepressant medication for recurrent MDD in secondary mental health care in Finland.[19] In their study they examined the implementation of the recommended maintenance therapy for recurrently depressed patients. They found that a little over half (57%) of the patients with recurrent MDD received this maintenance antidepressant therapy. Although a clear definition of maintenance use was lacking in their study, maintenance antidepressant treatment seems more prevalent compared to our percentage of continuous use (42%). Nevertheless, this Finnish study reveals again that recommendations in guidelines and actual use in clinical practice differ.

Recently, the effectiveness of antidepressant medication in general is heavily debated, both in the scientific world as well as in the public domain. Critics state that antidepressants are not more effective than placebo for most depressive patients, are being prescribed too easily, for the wrong indications, and also have too many (partly unknown) side-effects.[1;20-26] This point of view is supported by the results of recent meta-analyses by Turner et al.[27] and Kirsch et al.[28] of trials studying the effectiveness of antidepressants in the treatment of MDD in the acute phase. The meta-analysis of Turner et al. demonstrated that over the past decennia the effect sizes of antidepressants have been overestimated by one third as a result of publication bias of positive studies.[27] Furthermore, Kirsch et al. showed in another meta-analysis that antidepressants, in comparison to placebo, were only effective in severely depressed patients.[28]

Recent Dutch research showed that the potential users themselves (among other reasons) might be skeptical about antidepressants as well. A quarter of the patients to whom antidepressants have been prescribed (for several indications, including MDD) refuses to use them from the start or discontinues them way too early.[29] In line with the findings of Turner et al. and Kirsch et al., the Dutch MDD guideline does not recommend antidepressants for mild depressions.[18] Additionally, Dehue, a professor of philosophy and history of science, criticizes the role of pharmaceutical companies by putting forward that they market depression along with their medicines and 'make money out of misery'.[20] Pharmaceutical companies indeed actively promote the prescription of medication both to patients and doctors. Yet, for several years psychiatrists, national and international, have taken notice of this issue and are increasingly aware of the negative effects of (over-) prescription.[30-32]

In line with our results, several studies showed that maintenance antidepressant medication does not influence the course of MDD after having been used for 8-14 months.[33-35] However, two partially overlapping meta-analyses that both included over 4000 patients in 30 randomized trials studying continued antidepressant treatment in patients with MDD who have responded to acute treatment concluded that continuing antidepressant treatment reduced the odds of relapse by 70% compared to antidepressant treatment discontinuation.[36;37] A possible explanation for the discrepancy between our results and both meta-analyses could be that the results of these meta-analyses were influenced by a selection bias that was not corrected for. The patients with MDD

included in the meta-analyses could represent a different subgroup than our sample. Indeed, the trials included in the meta-analyses mainly studied secondary care patients, possibly reflecting a more severe population, while our study included both patients in primary and secondary care as well as patients who were not treated in the post-acute phase. Nevertheless, our patient group mostly experienced moderate to severe depressive episodes too. Alternatively, as shown before in antidepressant research,[27] the meta-analyses were influenced by a publication bias. Finally, our follow-up period was 2 years, while most of the trials included in the meta-analyses had follow-up periods of 1 year or less. Interestingly, the most recent meta-analysis revealed that the preventive effect of antidepressants was smaller for patients with more previous episodes than for patients with less previous episodes.[37] This corresponds with the small effect of maintenance antidepressant medication on the prevention of recurrence in our sample, since these patients experienced a relatively high number of previous episodes (median = 4). In contrast, preventive CT seemed more effective with an increasing number of previous episodes.[38;39]

There are several hypotheses about the causes of relapse/recurrence during maintenance antidepressant treatment. First, for patients for whom antidepressants are effective, non-adherence to antidepressants undermines the optimal treatment effect.[40] Second, both recovery and relapse/recurrence occur independently from the use of antidepressants. Some patients improve irrespectively of their use of antidepressants and not because of a true drug effect. Consequently, the relapse/recurrence does not represent a loss of drug effect because the patient has not even experienced a true drug response at the start of pharmaceutical treatment.[41] Thus, in some cases the disease tends to follow its own rhythm.[42;43]

Third, a potential explanation for the failure of maintenance antidepressant treatment is the loss of the placebo response.[34;44;45] In the acute phase, the placebo response is believed to play an important role in the effectiveness of antidepressants.[34;44;46-48] The existence and size of a long-term placebo response, i.e. after the acute phase, is less clear.[49] In trials studying prevention of relapse during the maintenance phase placebo was found to be less effective.[38;50] 'Expectations' and 'hope' are considered as important ingredients of this placebo response. Possibly, while not depressed anymore, patients (and possibly doctors too) have diminishing expectations of the prophylactic effect of antidepressants (after the acute phase) resulting in the loss of the placebo response. Consequently, patients that benefit most from prophylactic antidepressant therapy are the true drug responders.[45]

Finally, Fava et al.[34;51] and Solomon et al.[52] have suggested tolerance and tachyphylaxis as a cause of recurrence of MDD. Tolerance and tachyphylaxis refer to the concept that a prior effective therapy eventually (partly) loses its effectiveness. Sometimes these terms are used interchangeably. However, usually tolerance is seen as a slow process, which is for example observed in psychoactive drugs such as sedative hypnotics and opiates, while tachyphylaxis is used for a rapidly decreasing response to a drug after administration

of a few doses, which is for example mentioned to play a role in broncho-active drugs. Alternatively, antidepressants might worsen the course of depression for some high risk groups (referred to as sensitization hypothesis). However, studies focusing on the underlying biochemical mechanism of these phenomena are necessary to corroborate these hypotheses.

Adherence to antidepressant medication

Especially in chronic diseases, treatment non-adherence is inevitable and has been an important, though surprisingly, largely ignored topic, until the WHO published a report on this issue in 2003.[53] Unfortunately, in daily clinical practice non-adherence still is a subject under taboo, both for doctors and for patients. This is a missed opportunity as non-adherence undermines treatment and possibly is in itself a predictor of general health outcome.[54]

Studies showed that non-adherence is hard to recognize in daily clinical practice: clinicians were able to accurately identify patients' non-adherence in only 50% of cases, which is no more than chance.[55] Unfortunately, the development of tools to assist clinicians in identifying non-adherence has been rather complicated, due to problems with the definition of non-adherence, and due to the lack of a golden standard to assess it. Methods of adherence measurement can be roughly divided into subjective and more objective ones. Subjective adherence measurements include clinical judgment, assessment of clinical response, case notes and patient self-reports, including self-rated instruments. More objective adherence measurements seem more reliable and include directly observed therapy, pill counts, rates of prescription refills, serum or urine and hair analyses for drugs or metabolite levels, measurement of biological markers in blood, electronic medication monitors and measurement of physiologic markers.[40;55] In general, objective measures of adherence are more expensive and more complex to undertake than subjective measures, and -unfortunately- still not fully reliable.[40;55] Last, it should be noted that non-adherence is seldom an all-or-nothing phenomenon in that patients are perfectly adherent or not adherent at all.[56]

Interventions to target non-adherence are complex, at the most moderately effective and their effect sinks in only shortly (see for a review[18;57]). Furthermore, there are several types of non-adherence (for example forgetting medication versus deliberately not taking medication) resulting in the development of several adherence enhancing strategies for different patients with several types of non-adherence.[58]

There is ample evidence that non-adherence to antidepressants is frequent in MDD in the acute phase.[59-61] However, little is known about the level of non-adherence and its predictors after the acute phase in MDD. In the chapters 4 & 5, extending the results of chapter 3, we have evaluated (non-) adherence to antidepressant medication and its predictors in the continuation and maintenance phase in patients with remitted recurrent MDD. We hypothesized that non-adherence may be a problem after the acute phase as

well, because in the remitted phase patients might assume that they are no longer 'in need of antidepressants' and might not directly feel the consequences of discontinuing antidepressants.[62]

In chapter 4, after asking if patients had used antidepressants during a defined time period (Chapter 3) they were asked how adherent they had been to this medication. (Non-) adherence was assessed with the Medication Adherence Questionnaire, a well validated and easy to administer (subjective) self-report instrument.[63;64] We found non-adherence prevalences ranging from 40% to 53% with a mean of 47% over a 2-year follow-up period. Over this period 21% of patients was always non-adherent, 48% was intermittently non-adherent and 31% was always adherent. This is in line with non-adherence rates in other chronic diseases[40] but significantly lower than in two other studies on maintenance antidepressant use that reported adherence rates of respectively 85%[6] and 79%.[65] However, the first study[6] predominantly consisted of in-patients (76%), including chronically depressed and not completely remitted patients, and in the last study[65] patients were given an intervention to improve adherence.

As we expected non-adherence at the first measurement occasion predicted earlier time to first recurrence over a 2-year period. Like in other chronic diseases, non-adherence to continuation and maintenance antidepressant treatment was frequent, varied and, was a potential risk of recurrence.[40]

Predictors of non-adherence to antidepressive medication

In chapter 5, based upon inconsistent results of studies focusing on predictors of non-adherence in the acute phase of MDD, we selected a set of potential predictors of non-adherence to antidepressant medication in the continuation and maintenance phase of MDD (patient-related, disease-related and treatment-related). In univariate analyses using a stringent significance level ($p<.005$, to correct for chance capitalization caused by multiple testing), we found no independently related predictors of non-adherence over a 2-year period. In a multivariate analysis a prediction model emerged compromising a higher level of personality pathology (PDQ-4+ total score) and a higher level of education as predictors of non-adherence. This final model however, explained about 15% of the variation in non-adherence.

Thus far, the only study of non-adherence in recurrently depressed patients could not identify any demographic or clinical predictors of non-adherence.[65] We therefore compared our results to results of non-adherence prediction studies in the acute phase of antidepressant treatment in MDD. In correspondence to our finding, personality pathology and personality characteristics have been found as predictors of non-adherence in several of these studies.[66;67] Tedlow et al. found in the acute phase of treatment that depressed outpatients treated with fluoxetine who dropped out because of non-adherence had higher rates of histrionic and narcissistic personality disorders (DSM-III) than completers.[67] They suggested that these two personality disorders might be a barrier to

establish a positive patient/doctor relationship. In a depressed outpatient sample Cohen et al. found that extraversion (NEO PI-R, and specifically the Activity facet within the Extraversion dimension) was a negative predictor of non-adherence to antidepressants.[66] Their explanation was that patients with such a personality characteristic are too busy or too engaged to remember to take their medication. However, exploration in our sample on specific personality disorders did not reveal an association with specific personality symptom clusters, possibly due to small numbers.

In contrast to our finding that a high level of education was associated with non-adherence to antidepressants in MDD, previous studies in the acute phase found the opposite, i.e. a high level of education was associated with good adherence.[59;68-71] It has been described that in chronic conditions patients with an external locus of control are more likely to be adherent.[72] Furthermore, a positive relation has been found between high intelligence and internal locus of control.[73] As an explanation for our finding, we hypothesize that in this specific sample of patients participating in a preventive CT trial, a higher level of education was associated with a higher internal locus of control resulting in non-adherence.

Given the fact that our findings are in part deviant from results in the acute phase of MDD and add up to an explained variance of no more than 15%, we conclude that we did not succeed in identifying a comprehensive and practical set of clear predictors of non-adherence to antidepressants in the continuation and maintenance phases in remitted, recurrently depressed patients.

There are indications that other factors, not included in this study, may influence patients' medication use. Some reported predictors of adherence to prescribed antidepressant medication not incorporated in our study are: attitudes towards medication or health beliefs (Health Belief Model[74]), perceived stigma,[75-77] and doctor-patient communication style.[78-80] Potentially, inclusion of these factors could lead to a model that better predicts non-adherence.

The original Health Belief Model by Rosenstock in 1966[74] was constructed with four core beliefs of individuals based on their perceptions: perceived susceptibility (an individual's assessment of their risk of getting the condition), perceived severity (an individual's assessment of the seriousness of the condition, and its potential consequences), perceived barriers (an individual's assessment of the influences that facilitate or discourage adoption of the promoted behavior), and perceived benefits (an individual's assessment of the positive consequences of adopting the behavior). Research including 1200 participants has shown that patients' beliefs about prescribed medication could be grouped in two core themes: 1) beliefs about necessity and 2) concerns about prescribed medication (dependency, long-term side effects and also 'stigma').[81]

It is suggested that adherence is influenced by a cost-benefit assessment in which necessity of medication is balanced against concerns about the medication. Horne en Weinman showed that among patients with chronic diseases medication beliefs were more powerful predictors of (non-) adherence than clinical and sociodemographic factors.[81] Prins et al. recently reported in a review that depressed patients had more positive beliefs about antidepressants than healthy people.[82] On the other hand, they found that most patients prefer psychological treatment instead of medication, a majority of patients view antidepressants as addictive and many perceive stigma. Stigma refers to the negative social evaluation associated with a particular label, such as a mental illness, in this case depression. However, fear of stigmatization could play a role both in psychological treatment and in treatment with antidepressants.

Unfortunately, despite the abovementioned studies, there is still little evidence that one of these additional factors is the key for success in understanding the process of becoming non-adherent to prophylactic AD treatment. Moreover, it is doubtful whether these additional predictors of non-adherence will be of clinical relevance since these models incorporate variables that are difficult and time-consuming to assess for doctors. In conclusion, until now, prediction of non-adherence to preventive antidepressant treatment in remitted recurrently depressed patients seems a complex, multifactorial and until now only limitedly successful process.

Clinical implications and suggestions for further research:

Although the current Dutch MDD guideline advices to continue antidepressant treatment for recurrently depressed patients after remission for one to five years, our results indicate that not all recurrently depressed patients are either willing or able to use maintenance antidepressant treatment and that even in those who do use prescribed antidepressants non-adherence is still a problem. Our study results also show that antidepressants might not prevent recurrence in all recurrently depressed patients.

To improve the effectiveness of continuation and maintenance antidepressant treatment in recurrently depressed patients further research is warranted. First, process research that examines underlying mechanisms of ineffectiveness versus effectiveness of continuation and maintenance antidepressant treatment and randomized controlled trials studying its optimal length and dose are badly needed.

Second, clinicians should try to tailor relapse/recurrence prevention strategies for individual patients by selecting those patients that are willing and motivated to use maintenance antidepressant treatment and those that are not. Lately, there has been interest for shared decision making (SDM) between doctors and patient, which puts more emphasis on the patient's preference. SDM is believed to bring about patient involvement, which may improve their medication adherence and thereby improve outcome.[83;84] Consequently, if patients are not willing to continue antidepressant use, doctors and

other health care professionals should consider discussing alternative non-medicinal treatments like the preventive CT[38] we studied, Mindfulness Based Cognitive Therapy (MBCT)[38;85-87] or Wellbeing Cognitive Therapy[38;88] (for a meta-analysis see Vittengl et al.[89]).

Third, in patients that have the intention to use antidepressants clinicians continuously have to be aware of non-adherence, especially in patients with inadequate disease control. They have to break the taboo and persist in discussing (non-) adherence to antidepressants with their patients as part of the treatment plan.
Finally, further research should focus on the process of becoming non-adherent to antidepressants in the longest phase of antidepressants use. Given the state of our knowledge, a combination of quantitative and qualitative research would probably be most effective. Only then, new efforts to better predict non-adherence should be undertaken. In the future tailored interventions (ideally simple, quick and inexpensive) to enhance adherence with an enduring effect should be developed for individual recurrently depressed patients. One could even consider applying these interventions preventively.

Progress has already been made with respect to adherence-promoting interventions for other diseases and health problems, which may provide clues for future interventions to improve adherence to antidepressants in the continuation and maintenance phase. In patients with schizophrenia Short Message Service (SMS) has been used to overcome non-adherence based on forgetfulness.[18;90] In patients with tuberculosis preliminary results suggest that SMS messaging in combination with economic incentives largely improves adherence.[18;91] A food infection prevention study showed that information plus 'disgust' generating photos of the consequences (vomiting persons, mouldy food) of not following advices of hygienic food preparation plus behavioral cues during preparing the food decreased the risk of contamination sharply.[18;92] In line with this experiment it would be interesting to study if, for example, a picture of a depressed face on antidepressant medication pillboxes plus warnings of the consequences of antidepressant non-adherence can enhance adherence.

In summary, results in several fields of research (public, physical and mental health) and new technologies can possibly help us to understand and optimize the effect of maintenance antidepressant treatment to prevent relapse/recurrence in recurrently depressed patients. Nevertheless, non-adherence should be considered as a reality that is not completely solvable.

Prediction of recurrence

For a better understanding of the course of recurrent MDD it is important to identify risk factors for recurrence and determine their relative importance. In chapter 6 we described that besides a high number of previous episodes we found two potentially modifiable predictors of recurrence in remitted recurrently depressed patients over a 5.5-year follow-

up period: coping (a more avoidant way of dealing with problems and a smaller 'refocusing on positive matters' coping capacity) and residual depressive symptoms.

Our findings support several experts' opinions and recent therapeutic developments. As stated by Brewin, CT possibly does not directly modify negative information in memory, but potentially aims at creating more positive competitor representations.[93] One such competitor, the coping style 'refocusing on positive matters', might produce changes in relative activation of positive representation as opposed to negative representation in such a way that the positive ones are assisted to win the retrieval competition. Refocusing on positive matters can be seen as a form of distraction, which is considered a more adequate way of coping than rumination The latter is also thought of as a type of avoidance. Distraction implies turning attention away from unpleasant thoughts or events to reduce negative feelings, while rumination is an emotion-focused coping style that implies directing attention toward negative feelings and thoughts.[81;93] Our results are in line with results of research on the mechanisms of effectiveness of CBT in depression[94] and recent developments on Rumination-Focused CBT.[94;95] These treatments focus on "switching patients from less helpful to more helpful styles of thinking" (i.e. less avoidant) through the use of functional analysis, experiential/imagery exercises and behavioral experiments.

Although a substantial part of the variation in recurrence (29%) was explained by the final model, the larger part of it still remained unexplained. As a result, recurrence remains difficult to predict and stays a complex and only partially understood phenomenon. Suggestions for further results are given below.

Clinical implications and suggestions for further research

Recurrence prevention therapies should focus on modifiable factors. More specifically, they might try to stimulate 'refocusing on positive matters' and diminish an avoidant way of dealing with problems. Psychological preventive interventions with cognitive elements, such as preventive CT, Mindfulness-Based Cognitive therapy (MBCT), Rumination Focused Cognitive Behavioral Therapy, and Wellbeing-therapy focus on promoting coping strategies,[38;85;86;88;96-99] but their working-mechanisms are not fully determined yet. The promotion of more helpful coping strategies might be the essential ingredients in all these preventive strategies. Future psychotherapeutic research should therefore examine whether these are essential ingredients in preventive strategies. Furthermore, research is needed with interview-based stress and coping measures as potentially modifiable predictors for recurrence because the (well validated) self-report measures we used are subject to social desirability. Additionally, to prevent relapse in remitted patients, mild residual symptoms should be treated more aggressively. The latter is currently studied in research groups of Jarret and Hollon (personal communication).

STRENGHTS AND LIMITATIONS

Strengths and limitations of the studies in this thesis were already addressed in each chapter and so we only summarize the most important ones.

Strengths

First, our sample comprises a relatively large cohort of remitted recurrently depressed patients with at least two previous depressive episodes that was followed prospectively for 2 and respectively 5.5 years with structured interviews based on DSM-IV. Second, patients were remitted on medication and/or psychological therapy or no treatment at all, without restrictions on medication status at entry to the study, and were living in different parts of the Netherlands, which both enhance generalizability of the findings. And third, we have used internationally accepted, validated and reliable instruments.

Limitations

First, we applied a prospective cohort approach to the data of patients who originally participated in a randomized controlled preventive CT-trial. Where possible, the analyses were performed on the total sample, not including early drop-outs (CT plus TAU, n = 172; early drop-outs n = 15). Because we tested in all studies if the intervention (CT) modified or confounded the relation on the outcomes and if so performed the analyses only in the control group (n = 84), it is unlikely that bias influenced our results.

Second, our findings may be influenced by selection bias. The patients in the studies prescribed in this thesis, although remitted, were willing to participate in a preventive CT trial and therefore probably had, in comparison with other recurrently depressed patients, a reduced HRQOL. Additionally, they might have had less confidence in the effect of maintenance pharmacotherapy resulting in a diminished use of antidepressants and higher non-adherence rates. On the other hand, 51% used antidepressants at study entry.

Third, the DELTA study was not designed to examine the effect of maintenance antidepressant treatment on recurrence, which was an important issue of this thesis. Yet, to date a prospective randomized design, comparing maintenance antidepressant treatment to intermittent use and no use (with and without an additional preventive psychological therapy), was not considered ethical.

Fourth, we used several self-report instruments instead of more objective tools. On the other hand, all of these self-report instruments are validated and widely used all over the world. Finally, studies included in this thesis did not include patients with only one previous depressive episode and the dataset available for this thesis did not include a number of important potential predictors of non-adherence and recurrence. For example the role of neurobiological factors, like cortisol[100-102] fatty acids[103;104] and polymorphisms

of the serotonin transporter gene,[105] as predictors of relapse/recurrence are interesting to investigate. However, this was beyond the scope of this thesis. Currently, we are studying the influence of these neurobiological factors in the DELTA study group.

CONCLUDING REMARKS FOR CLINICAL PRACTICE

Remitted recurrently depressed patients have a very high likelihood of getting another recurrence of their illness within a few years time. HRQOL of these patients is decreased over all domains and this reduction is related to depressive symptoms. The large majority of the patients did not receive or use adequate continuation and maintenance antidepressant treatment after remission. Despite continuation and maintenance antidepressant use, 60% relapsed over 2 years. Only one third was fully adherent and non-adherence was predicted by a higher level of personality pathology and a higher level of education. Finally, time to recurrence was predicted by the number of previous episodes, coping style and residual depressive symptoms.

As a result, recurrently depressed patients deserve continuous, long-term, specialized, and dedicated care for recurrence prevention, which should include:

1. assessment of their perceived HRQOL
2. assessment and treatment of their (sub-syndromal) residual symptoms
3. tailored preventive therapy:
    - maintenance antidepressant therapy and /or
    - psychological therapy, like preventive CT, with a focus on modifiable coping strategies
4. in case of maintenance antidepressant therapy, continuous attention for (non-) adherence

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Summary

SUMMARY

Major depressive disorder (MDD) is a disease with a high recurrence rate. This thesis focuses on the following aspects of the clinical course of recurrent depression: health related quality of life (HRQOL), long-term use of antidepressive medication, adherence to antidepressive medication, and predictors of a new episode in recurrent depression. The presented studies in this thesis are based on data obtained in the Depression Evaluation Longitudinal Therapy Assessment (DELTA) study, a project aimed at the prevention of recurrence of MDD with cognitive group therapy. A sample of 172 patients with recurrent depression, remitted on various types of treatments (including AD), was followed prospectively for 5.5 years after remission. The aims of the studies presented in this thesis are introduced in *chapter 1*.

Chapter 2 describes health related quality of life (HRQOL) in recurrently depressed patients. In this study recurrently depressed patients reported a lower HRQOL than individuals recruited from the general Dutch population, both for the physical and mental health domains. Given the fact that all our patients were remitted, this indicates that a positive clinical outcome, is not necessarily accompanied by a full functional recovery of quality of life. One of the explanations for this finding was the finding that changes in the level of HRQOL were related to changes in the level of mild residual depressive symptoms in these patients. An increase in the level of depressive symptoms corresponded with a decrease in all 8 domains of the SF-36, the HRQOL scale we used. This finding indicates that residual symptoms should be treated aggressively.

Chapter 3 describes patterns of long-term (continuation and maintenance) use of antidepressive medication. In our sample 76% of the patients was treated with antidepressive medication for their last depressive episode before entering the study, of whom 62% was still using antidepressive medication at study entry. Of the latter group 42% continued antidepressive medication either until the first recurrence or during the full 2-year follow-up period. About one third (38%) used antidepressive medication intermittently while the remaining patients (20%) did not use antidepressive medication anymore. About two thirds of the 'continuous users' used antidepressive medication in an adequate dosage (≥ 20 mg fluoxetine equivalent). Consequently, the large majority of our sample (77%) did not use adequate antidepressive medication in the continuation and maintenance phase. Furthermore, we found that despite continuous use of antidepressive medication, 60% of these patients relapsed within two years. This relapse rate was comparable to the rate of the 'intermittent users' (64%), even after controlling for the effect of minimal required dosage and non-adherence. The relapse rate in 'non-users' (26%) was significantly lower compared to the two other user-groups. Since we did not randomize on use of antidepressants, we have to treat these results with caution. Replication is necessary within a study that randomizes on antidepressant use.

After determining *whether* patients had used antidepressive medication during a defined time period in chapter 3, *chapter 4* describes *how* adherent they had been to this medication. At the different adherence assessment points, we found non-adherence prevalences ranging from 40% to 53% with a mean of 47% over a 2-year follow-up period. Over this 2-year period 21% of patients was always non-adherent, 48% was intermittently non-adherent and 31% was always adherent. Like in other chronic diseases, non-adherence to continuation and maintenance AD treatment was frequent and varied over time. So doctors have to be continuously aware of this silent problem and should keep talking about is with their patients, not only in the acute phase, but also in the continuation and maintenance phases.

Chapter 5 describes patient-related, disease-related and treatment-related predictors of non-adherence to antidepressive medication in the continuation and maintenance phase of MDD. We found that a higher level of personality pathology and a higher education level both increase the probability of becoming non-adherent over a 2-year period.

Chapter 6 describes predictors of recurrence of depression in remitted recurrently depressed patients over a 5.5-year follow-up period. We present a prediction model which in addition to a high number of previous episodes, comprises two potentially modifiable predictors of recurrence: i.e., coping related factors (a more avoidant way of dealing with problems and a smaller 'refocusing on positive matters' coping capacity) and residual depressive symptoms.

In *chapter 7* the findings of the previous chapters are discussed. In conclusion it is advised that recurrently depressed patients deserve continuous, long-term, specialized, and dedicated care for recurrence prevention which should include: assessment of HRQOL, assessment and treatment of residual symptoms, tailored preventive therapy (maintenance antidepressant therapy and/or psychological therapy, like preventive cognitive therapy, with a focus on modifiable coping strategies) and in case of maintenance antidepressant therapy, continuous attention for (non-) adherence.

Samenvatting

SAMENVATTING

Major depressive disorder, hier aangeduid als 'depressie', is een ziekte die dikwijls terugkomt. Dit proefschrift richt de aandacht op kwaliteit van leven, langdurig gebruik van antidepressiva, therapietrouw (adherence) en risicofactoren van terugval. De onderzoeken in dit proefschrift zijn gebaseerd op gegevens uit the Depression Evaluation Longitudinal Therapy Assessment (DELTA) study, een studie met als doel het voorkomen van terugval bij depressie door middel van cognitieve therapie in groepsverband. Een groep van 172 patiënten die meerdere depressies achter de rug hadden gehad en opgeknapt waren met diverse behandelingen is 5.5 jaar gevolgd. In *hoofdstuk 1* komen de doelen van de onderzoeken die in dit proefschrift gepresenteerd worden aan de orde.

Hoofdstuk 2 beschrijft de kwaliteit van leven van patiënten die meerdere depressies gehad hebben. In dit onderzoek rapporteerden deze patiënten een lagere kwaliteit van leven dan een groep mensen uit de Nederlandse samenleving. Het feit dat de patiënten in ons onderzoek niet meer depressief waren wijst erop dat herstel van een depressie niet noodzakelijkerwijs samen hoeft te gaan met volledig herstel van de kwaliteit van leven. Een van de verklaringen voor deze bevinding is dat veranderingen van de kwaliteit van leven samenhingen met veranderingen in het niveau van milde depressieve restklachten. Een toename van deze depressieve restklachten ging samen met een verlies van de kwaliteit van leven in alle domeinen van de SF-36, de kwaliteit-van-leven-schaal die wij gebruikten. Deze uitkomst suggereert dat depressieve restklachten agressief behandeld moeten worden.

Hoofdstuk 3 beschrijft patronen van langdurig gebruik van antidepressiva in de onderhoudsfase van behandeling. In onze onderzoekspopulatie gebruikte 76% van de patiënten antidepressiva tijdens de laatste depressie voordat zij startten met de DELTA-studie. Van deze groep gebruikte 62% nog steeds antidepressiva toen de studie van start ging. 42% van deze groep ging door met het gebruik van antidepressiva of tot de eerste terugval of gedurende 2 jaar follow-up; ongeveer eenderde (38%) gebruikte zo nu en dan antidepressiva, terwijl 20% geen antidepressiva meer gebruikte. Ongeveer tweederde van de 'continue gebruikers' slikte antidepressiva in een adequate dosering (meer dan 20mg fluoxetine equivalent). Dus, de meeste patiënten (77%) in ons onderzoek gebruikten hun antidepressiva niet op een adequate manier. Verder vonden we dat ondanks continu gebruik van antidepressiva in de onderhoudsfase 60% van deze patiënten terugviel binnen 2 jaar. Dit terugval percentage was overigens gelijk aan het terugval percentage in de groep die de antidepressiva niet continu gebruikte (64%). Deze resultaten moeten wel voorzichtig geïnterpreteerd worden aangezien de patiënten in dit onderzoek niet gerandomiseerd werden tussen wel en niet gebruik van antidepressiva.

Na het bepalen *of* patiënten gedurende een bepaalde periode antidepressiva gebruikt hadden in hoofdstuk 3, beschrijft *hoofdstuk 4 hoe* trouw de patiënten deze medicijnen innamen. Op de verschillende meetmomenten vonden we therapieontrouw percentages

van 40% tot 53% met een gemiddelde van 47% over 2 jaar. Gedurende deze periode was 21% van de patiënten altijd ontrouw, 48% was nu eens trouw en dan weer niet en 31% was altijd therapietrouw. Net als bij andere chronische aandoeningen komt therapieontrouw in de onderhoudsfase van antidepressivagebruik dus dikwijls voor en fluctueert in de tijd. Daarom moeten dokters continu alert zijn op dit 'stille' probleem en erover blijven praten met hun patiënten, niet alleen in de acute fase (als patiënten depressief zijn), maar ook in de onderhoudsfase als zij opgeknapt zijn.

Hoofdstuk 5 beschrijft patiënt-, ziekte- en behandelinggerelateerde risicofactoren van therapieontrouw van antidepressiva gebruik in de onderhoudsfase bij patiënten met terugkerende depressies. Wij vonden dat meer persoonlijkheidspathologie en een hoger opleidingsniveau risicofactoren waren om therapieontrouw te worden gedurende de 2 jaar.

Hoofdstuk 6 beschrijft risicofactoren van terugval bij mensen met terugkerende depressies gedurende een periode van 5.5 jaar. Wij vonden in een voorspellingsmodel, naast meer voorgaande depressies, potentieel veranderbare risicofactoren van terugval, namelijk, copinggerelateerde factoren (een meer vermijdende manier van omgaan met problemen en een beperkter vermogen om je te richten op positieve zaken) en depressieve restklachten.

In *hoofdstuk 7* worden de bevindingen uit de voorafgaande hoofdstukken bediscussieerd. Concluderend, patiënten met terugkerende depressies verdienen continue, langdurige, gespecialiseerde, en toegewijde zorg om terugval te voorkomen. Deze zorg zou ten minste moeten bestaan uit beoordeling van de kwaliteit van leven, evaluatie en behandeling van depressieve restklachten, op maat gesneden preventieve therapie (onderhoudsantidepressiva en/of psychotherapie, zoals preventieve cognitieve therapie, met het focus op veranderbare coping strategieën) en, bij onderhoudsantidepressiva, continue aandacht voor therapie(on)trouw.

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DANKWOORD

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PUBLICATIONS

ten Doesschate MC, Koeter MW, Bockting CL, Schene AH. Health related quality of life in recurrent depression: a comparison with a general population sample.
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ten Doesschate MC, Bockting CL, Koeter MW, Schene AH. Prediction of recurrence in recurrent depression: a 5.5-year prospective study.
Journal of Clinical Psychiatry 2009, in press

CURRICULUM VITAE

Mascha Charlotte ten Doesschate, born January 27th 1974 in Utrecht, The Netherlands
Maried, two children

1993	Graduation Stedelijk Gymnasium in Nijmegen
1993 - 1994	Architecture at the University of Delft (propaedeutics)
1994 - 2001	Medicine at the University of Utrecht
2001 - 2003	Trained as a psychiatrist in Veldwijk in Ermelo
2003 - 2006	Trained as a psychiatrist in the Academic Medical Center in Amsterdam
2003 - 2009	PhD research in the Academic Medical Center in Amsterdam with a ZonMW OOG-Geestkracht grant for education of investigators in Mental Health.
2006 - 2008	Psychiatrist at outpatient clinic, Arkin Mental Health in Amsterdam
2009 - now	Psychiatrist at the department of Eating Disorders, Novarum, Arkin Mental Health in Amstelveen

DE GAPER

Op het omslag van dit proefschrift staan foto's van "D'Oude Gaper" aan de Diezerstraat in Zwolle waar de handel in Drogerijen, Specerijen en Verfwaren van J. ten Doesschate (geboren 16 april 1842, †20 juli 1916) gevestigd was. J. ten Doesschate was de grootvader van mijn grootvader.
Op de foto op de achterflap ziet men voor het linker raam en boven de deur een "Gaper".
De gaper was het uithangteken van drogisten en apothekers.
Een gaper is een beeld van het hoofd van een man, meestal van zuidelijke afkomst, een Moor die zijn mond open doet, alsof hij gaapt. De mond staat echter niet open om te gapen, maar om een medicijn in te nemen.
Rond 1000 jaar na Christus verkochten marskramers in deze streken (het huidige Nederland, België en delen van Frankrijk en Duitsland) hun waren op de jaarmarkten. Een van die marskramers was de kruidenhandelaar. Bij het verkopen van zijn waren werd de marskramer vaak geassisteerd door een Moor. Deze Moren waren afkomstig uit Noord-Afrika. Zij kwamen mee met de kruidenhandelaren die hun producten vanuit het verre oosten naar Europa importeerden. Samen met de kruidenhandelaar voerde de Moor op een verhoging een toneelstukje op om de bezoekers van deze jaarmarkten te overtuigen van de goede kwaliteit van de waren. De kruidenverkoper legde aan het eind van zijn verhaal de "zieke" Moor een pil, een pijpje kaneel, een takje kruiden of een pijpje zwavel op de tong. De Moor verdween van het toneel en trok vliegensvlug zijn mooiste kleed en tulband aan en kwam dansend en zingend op het toneel terug om de bezoekers te laten zien dat hij door dit medicament genezen was. Dit alles om de bezoekers te overtuigen dat zij grote sufferds waren als zij de waren van de handelaar niet kochten.
Bronnen: www.gapers.nl en www.wikipedia.nl.


DROGIST
DROGERIJEN