Depression in general practice

Underrecognition? Overtreatment? Adequate care!
The infrastructure for the NESDA study is funded through the Geestkracht program of the Netherlands Organisation for Health Research and Development (ZonMw, grant nr. 100001002) and is supported by participating universities and mental health care organizations (VU University Medical Center, GGZ inGeest, Arkin, Leiden University Medical Center, GGZ Rivierduinen, University Medical Center Groningen, University of Groningen, Lentis, GGZ Friesland, GGZ Drenthe, Scientific Institute for Quality of Healthcare (IQ healthcare), Netherlands Institute for Health Services Research (NIVEL) and Netherlands Institute of Mental Health and Addiction (Trimbos)).

Financial support for the publication of this dissertation was kindly provided by: Department of General Practice, University Medical Center Groningen

**ISBN:** 978-94-6108-383-8

Cover artwork: Bas Brand
Lay-out: Ellen Piek & Bas Brand
Printed by: Gildeprint Drukkerijen – Enschede

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Depression in general practice
Underrecognition? Overtreatment? Adequate care!

Proefschrift

ter verkrijging van het doctoraat in de
Medische Wetenschappen
aan de Rijksuniversiteit Groningen
op gezag van de
Rector Magnificus, dr. E. Sterken,
in het openbaar te verdedigen op
maandag 4 februari 2013
om 14.30 uur

door

Ellen Piek

geboren op 5 augustus 1983
te Groningen
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                             Prof. dr. R.A. Schoevers
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Chapter 1

General Introduction
Depression
With a lifetime prevalence of around 20% major depressive disorder ("depression") is a common disease and it is associated with a large amount of morbidity due to its highly recurrent and chronic nature(1). It is projected that by 2020 depression will cause the highest amount of morbidity in developed countries, and will be second only to cardiovascular disease worldwide(1). In 2030 depression will probably be leading the disease burden list (2).

Diagnosis and classification
A patient is diagnosed with depression according to the Diagnostic and Statistic Manual of Mental Disorders, currently the text revision of the fourth edition (DSM-IV-TR). The DSM-IV-TR defines major depressive disorder as a condition with depressed mood and/or anhedonia (the inability to experience pleasure from usually pleasurable activities), and at least five symptoms in total, with a minimum duration of two weeks. The other possible symptoms are changes in appetite and/or weight, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue and/or energy loss, feelings of guilt and/or worthlessness, trouble concentrating and/or deciding, thoughts of death and/or suicidal thoughts or plans. The symptoms may not be caused by another physical or psychiatric disease or by drug use. The depressive episode may not be part of a manic-depressive disorder. The symptoms are not a logical consequence of certain recent events, such as bereavement and they cause significant suffering and/or dysfunction in daily life.

Depression can be mild, moderate or severe and may have melancholic, atypical or psychotic features. Melancholic features are anhedonia, lack of mood reactivity (no improvement of mood in response to positive events), excessive guilt and vegetative symptoms: severe weight loss or loss of appetite, psychomotor agitation or retardation, early morning awakening and worse mood in the morning. In contrast, atypical features are presence of mood reactivity (mood does improve in response to positive events) and "reversed vegetative symptoms", namely increased appetite and/or weight and increased sleepiness. Patients with psychotic features experience severe depression with delusions and hallucinations, they often also have agitation. Women are twice as likely to get a depression compared to men. Fifty percent of those with a depression in the general population recover within three
months (3). Others take longer to recover or have (frequent) relapses or recurrences. A minority (15-20%) has a chronic depression, i.e. lasting over two years (3).

**Treatment of depression**

Depression treatment may comprehend several modalities. Watchful waiting or guidance by the general practitioner (GP) is an effective strategy in the first three months of a depression, as a substantial percentage of patients, also in primary care, have a spontaneous recovery within three months. This holds especially true for patients with a first mild depressive episode. In patients with longer lasting, more severe or recurrent depression, treatment is recommended. Treatment can be largely divided into two strategies: antidepressant drugs and various forms of psychotherapy. Both modalities have been shown to be effective in acute treatment as well as in continuation treatment to prevent relapses; both in primary and in secondary/tertiary care settings (4,5). Guidelines for the treatment of depression in primary care such as the 2003 NHG-standaard depressive disorder from the Dutch Society for General Practitioners (NHG) recommend treatment with antidepressant drugs in case of major depressive disorder dependent on degree of dysfunctioning and/or suffering and on patient preference. After response to the antidepressant, treatment should be continued for at least six months, in order to prevent relapse (return of symptoms of the index episode). In case of a recurrent or chronic depression, maintenance treatment can be considered for one or more years) to prevent recurrences (the appearance of next episodes). In case the patient has a preference for psychological treatment, the GP may refer the patient for this treatment (6).

**Depression in general practice**

Most patients with depression are treated in primary care (7,8). It is therefore important to optimize recognition and treatment of depression in primary care, in order to prevent morbidity and also costs due to loss of work hours and long-term treatment.

In studies before the year 2000 recognition of depression and care for depressed patients in primary care was found to be poor (9-13). Many patients with depression were not recognized and diagnosed as such in primary care, and many of those who were diagnosed did not receive treatment or were treated inadequately, e.g. with too low dose of an antidepressant, at time in most cases a tricyclic
antidepressant (9-11,14). However, in these years the first selective serotonin reuptake inhibitors (SSRIs) made their appearance on the market for the treatment of depression and many projects and postgraduate programs for GPs focusing on diagnosis and treatment of depression were initiated with the ultimate goal to improve recognition and treatment for depressed patients in primary care.

Unfortunately, recent reports in the media and scientific literature still claim that recognition and treatment of depression in primary care is poor (13,15-22). The scientific literature mainly reports underrecognition and undertreatment, while the public media recently spoke about overrecognition and overtreatment (23-26). These discrepancies point out the importance of assessing current care, in order to find areas for improvement and future research.

This thesis set out to study current care for depressed patients in primary care, focusing on both recognition and treatment of depression in primary care.

Netherlands study of depression and anxiety
All studies from this thesis, with the exception of the literature review presented in chapter 4, were performed using data from the Netherlands Study of Depression and Anxiety (NESDA, www.nesda.nl) Chapters 2,3 and 5 used baseline data on the primary care respondents, chapter 6 used data on primary care patients from baseline, two-year- and four-year follow-up.

NESDA is a large prospective cohort study on depression and anxiety disorders among 2981 respondents between 18 and 65 years of age, recruited from the community, primary and secondary mental health care settings. Detailed information on the objectives and methods of NESDA were published elsewhere (27). In short, recruitment in primary care for NESDA was as follows. A screening questionnaire was sent to a random sample of 23,750 patients (registered with 65 GPs), who consulted their GP in the past four months irrespective of the reason for consultation. The screener (consisting of the K-10 with 5 added questions about anxiety) was returned by 10,706 persons (45%). The non-responders showed no bias with regard to psychopathology (28). Those screening positive were approached for a telephone interview consisting of the Composite International Diagnostic Interview (CIDI) short-form (CIDI-SF), which has proven diagnostic quality for screening purposes (29,30). Respondents fulfilling criteria for a current disorder on the CIDI-SF were invited to participate, as were a random selection of screen negatives (both
from the written screener and the CIDI-SF). In total 1610 persons were recruited who underwent an extensive baseline interview, including the CIDI. The GP was not aware of the results of the screening or of the interview.

**Outline of this thesis**

By exploring different aspects, this thesis will outline the current care for depressed patients in primary care. The first step in depression care is recognition of the disorder. Recently, a lot of attention has focused on recognition of depression in primary care. In the 1980s and 1990s several studies reported that recognition by general practitioners (GPs) was poor. However, it is quite difficult to study recognition in primary care, as in the Netherlands where all patients are registered with a single GP (practice), they do not necessarily visit the GP for their depressive symptoms. Therefore, it is important to know which depressed patients do visit their GP without being recognized as such. In chapter 2 we present our study of recognition and determinants of recognition and will further discuss this topic.

The next step in depression care is treatment, of which we investigated several aspects. First, we studied referral of depressed patients to a mental health specialist. We were especially interested whether GPs based their referral decisions on the criteria of their own guideline criteria or on other factors (Chapter 3).

Next we studied the major treatment option for GPs: the use of antidepressants. Most antidepressants are prescribed by GPs and not by physicians in secondary care. Moreover, when started with an antidepressant, many patients continue them for months or even years.

Chapter 5 focuses on the use of antidepressants in primary care, with a focus not on possible undertreatment (as done many times before) but on possible overtreatment with, i.e. whether they are prescribed to patients without a justification according the Dutch primary care guideline for depression. Chapter 4 discusses guideline recommendations and evidence for maintenance treatment with antidepressants in primary care, while chapter 6 describes the characteristics of patients on maintenance treatment with antidepressants.

Chapter 7 summarizes all results, and discusses the findings from this thesis in the light of findings from past and present research and the new Dutch general
practitioners guideline depressie (NHG-standaard depressie) that was published in 2012. The chapter ends with implications for clinical practice and future research.
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Chapter 2

Determinants of (Non-)Recognition of Depression by General Practitioners:
Results of the Netherlands Study of Depression and Anxiety
Determinants of (Non-)Recognition of Depression by General Practitioners: Results of the Netherlands Study of Depression and Anxiety

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Journal of Affective Disorders 2012;138:397-404

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Determinants of (non-)recognition

Patient case A “Recognition of depression”

Mr. A. consulted me with classic depression symptoms: he was sad and unable to enjoy previous enjoyable activities. In addition he had trouble sleeping although he felt tired. He had no appetite and had lost some weight. Concentrating was also a problem. He did not have any thoughts about death or suicide. Until that day he had even been able to work, although he had experienced these symptoms for about six weeks. He was given information about depression and treatment. In addition, we talked about daily structuring, since he had taken sick leave as of the day of first consultation. Part of his daily routine would be to walk for an hour. We made a follow-up appointment the next week.

Unfortunately, not every patient presents him/herself with this classical picture of depression. Presenting with somatic symptoms or atypical depressive symptoms is not uncommon and can be the cause of non-recognition. In the following chapter determinants of non-recognition are discussed.
Abstract

Background
Although most depressed patients are treated in primary care, not all are recognized as such. This study explores the determinants of (non-)recognition of depression by general practitioners (GPs), with a focus on specific depression symptoms as possible determinants.

Methods
Recognition of depression by GPs was investigated in 484 primary care participants of the Netherlands Study of Depression and Anxiety, with a DSM-IV diagnosis of depression in the past year. Recognition (yes/no) by GPs was based on medical file extractions (GP diagnosis of depressive symptoms/depressive disorder and/or use of antidepressants/referral to mental health care). Potential determinants of (non-)recognition (patient, depression, patient-GP interaction, and GP characteristics) were bivariately tested and variables with a p-value <0.2 entered into a multilevel multivariate model. Subgroup analysis was performed on 361 respondents with more reliable GP diagnosis data.

Results
60.5% of patients were recognized by their GP. Patients who did not consult their GP for mental problems, and without comorbid anxiety disorder(s) were less often recognized. In the subgroup, where 68.7% was recognized, in addition to these, decreasing number of symptoms of depression and increased appetite were associated with decreased recognition. No GP characteristics were retained in the final model.

Limitations
Some data on recognition were collected retrospectively.

Conclusions
In addition to patients without a comorbid anxiety disorder or who did not consult their GP for mental problems, GPs less often recognized patients with fewer depression symptoms or with increased appetite. Recognition may be improved by informing/teaching GPs that also increased appetite can be a symptom of depression.
Introduction
Depression is a common condition, associated with a large burden for patients and society due to its chronic or recurrent nature (1). Most patients with depression are treated in primary care, although often in a non-specific way (2,3). Adequate recognition and treatment can decrease the burden of disease (4-6). It is reported that general practitioners (GPs) recognize depression poorly, perhaps due to their more physical and demand-led orientation (7-9). However, various definitions of ‘recognition’ were used in these studies. Those that applied a cross-sectional design and relied solely on GP diagnosis at time of consultation found lower recognition rates compared to studies that used medical file extraction over extended time periods (10,11).

Recognition alone does not necessarily imply appropriate treatment (12). However, it seems obvious that recognition of a patient as having depression or as ‘a psychological case’, or at least a discussion of the symptoms, is essential for adequate treatment. Documentation of an International Classification of Primary Care (ICPC) code of depression in the GP’s records might not be required to ensure appropriate treatment, as GPs might decide not to diagnose depression because they (or the patient) might consider a diagnosis of depression as stigmatising (13). Also, not all GPs code every consultation with an ICPC code. Finally, not every patient with depression needs (immediate) treatment. With a reasonable chance of spontaneous recovery within three months, several guidelines recommend ‘watchful waiting’ or a minimal intervention as an option during the first months, especially for patients with a first and mild depression (14-16). On the other hand, many patients with depression do need treatment, and recognition alone might not be sufficient to ensure adequate follow-up and treatment in these patients (4-6). Therefore a definition of recognition measuring ‘active recognition’ i.e. receiving treatment such as antidepressants or a referral to mental health care might be more suitable.

When it is established which patients remain unrecognized, GPs can be advised to focus on these groups, which in turn, might improve recognition. Although some studies examined determinants of recognition of depression, the results were ambivalent and the sample sizes small. As possible determinants, mostly depression severity and demographics were investigated.

Some studies reported that depression severity predicts recognition (7,9,17,18), or that patients presenting with mental problems were better recognized...
Determinants of (non-)recognition

(7,19,20). Patient characteristics such as age, gender, ethnicity and marital status have also been investigated, but with mixed results. Some found that women and older persons were identified more easily, whereas others found no differences (7,21-23). An elderly primary care sample showed that clinical clues to better identify depression were female gender, the presentation of vague symptoms, and gastrointestinal symptoms (24). Another study performed in the Netherlands found that not only patients with low severity of depression, but also those without chronic somatic comorbidity, with lower educational level and with fewer visits to the GP, were at higher risk for non-recognition (25).

Physician factors such as gender, experience, depression interest and courses on depression were also investigated, again with mixed results. Wittchen et al. found that physician experience of more than 5 years increased recognition. Tylee and Walters found that interest in psychiatry and empathy increased recognition, while pre-occupation with organic disease decreased recognition (7,17).

Only one recent study investigated the different symptoms of depression as possible determinants, and found that only ‘loss of self-confidence’ was associated with recognition (7).

It is unclear which determinants predict GP’s recognition of depression when using a broader, longitudinal measured definition of recognition and examining a wide spectrum of potential predictors.

The main aim of the present study was to identify determinants of (non-)recognition of depression by GPs (longitudinally measured) in patients with DSM-IV diagnosed depression. Characteristics of the patient, depression, patient-GP interaction and GP were investigated. Of the depression characteristics, we focused on the influence of specific depression symptoms on recognition rate. We hypothesized that GPs would less often recognize less severe cases (including patients without suicidal tendency), those who did not present with mental problems, and/or patients with few(er) visits to their GP.

**Methods**

This study was conducted with data from the Netherlands Study of Depression and Anxiety (NESDA, www.nesda.nl), a large prospective cohort study (n=2981) on the course of depression and anxiety disorders among respondents aged 18-65 years, recruited from the community, primary care and secondary mental health care.
Detailed information on the objectives, study population and methods of NESDA has been published (26).

**Study sample and reference standard**

The present study included only those respondents recruited from primary care with (at baseline) a major depressive disorder (MDD) or dysthymia in the past year (n=503) according to the DSM-IV criteria and measured with the Composite International Diagnostic Interview (CIDI). In the Netherlands, access to secondary (mental) health care is not possible without referral by a GP. Moreover, all inhabitants are listed with a single GP (practice).

Details on the recruiting methods have been published (26). Briefly, a screening questionnaire was sent to a random sample of 23,750 patients (registered with 65 GPs) who consulted their GP in the past four months irrespective of the reason for consultation. The screener was returned by 10,706 persons (45%). The non-responders showed no bias with regard to psychopathology (27).

Those screening positively were approached for a telephone interview consisting of the CIDI short-form (CIDI-SF), which has proven diagnostic quality for screening purposes (28,29). Respondents fulfilling criteria for a current disorder on the CIDI-SF were invited to participate, as were a random selection of screen negatives (both from the written screener and the CIDI-SF). In total 1610 persons were recruited who underwent an extensive baseline interview, including the CIDI (30,31). The GP was not aware of the results of the screening or of the interview. Of these 1610 persons, we included only those with a MDD or dysthymia in the past year: i.e. 503 patients registered with 64 GPs.

In addition to the interview/questionnaire data, we also used data from the GP’s electronic patient file (EPF) and from questionnaires filled in by the GPs (available for all 64 GPs). Excluded were 15 respondents who refused permission to use their EPF data (as we could not determine the GP’s diagnosis in these cases), and four respondents with missing values on one or more of the determinants studied. Finally, 484 respondents were included in this study.

Figure 1 displays the recruiting process of this study in detail.
**Figure 1** Recruiting flow-chart*


CIDI-SF = Composite International Diagnostic Interview – Short Form
MHO = Mental Health Organization
MDD = Major Depressive Disorder
Dysth = Dysthymia

**Definition of recognition by GPs**

We used a definition of recognition by GPs (hereafter called ‘recognition’) constructed from extraction from the EPF (extraction period: 1 year before until 1 year after the baseline interview). This method is similar to that of Joling et al., who used different indicators of recognition to construct the most reliable definition (best combination of sensitivity (0.693) and specificity (0.811)) of recognition of depression by GPs (32).
The CIDI diagnosis from the baseline interview was used as reference standard for the diagnosis of depression. The following indicators were used: 1) *Use of antidepressants* (measured by report in the EPF), 2) *Referral to mental health care* (psychologist, psychiatrist, psychotherapist, social worker or professional at an institute for mental health care; referral letter available in the EPF), 3) presence of *ICPC P03* (depressive symptoms) or *ICPC P76* (depressive disorder) or *other relevant P-code* (P indicating a psychological problem) in the EPF.

These three indicators were combined to construct the most sensitive definition of recognition; i.e. if any of these indicators were present, we considered this patient “recognized” (yes/no). Sensitivity of this definition was 0.605.

ICPC codes were missing in all GP contacts for 123 respondents (25.4%). Because of this, respondents that did not receive antidepressants or referral, i.e. in particular the less severe cases, might have been defined as not recognized. We performed subgroup analysis in a subsample with at least one contact with the GP with an ICPC code. Sensitivity of the definition in this subgroup was 0.687.

**Determinants of recognition**

A detailed description of the measures applied in NESDA has been published (26).

*Patient characteristics* including demographic data (age, gender, education in years), number of chronic diseases and self-reported disability due to these diseases (yes or no) were assessed during the baseline interview.

*Depression characteristics* including current and lifetime diagnosis based on the DSM-IV, the number of and all separate symptoms, and number of previous episodes, were assessed with the CIDI during the baseline interview. Severity was measured with the Inventory for Depressive Symptomatology (IDS), and suicidal tendency with the Beck Suicide Ideation Scale (33,34).

*Patient-GP interaction characteristics* were assessed at the baseline interview; the number of contacts with the GP and whether any contact about mental problems had taken place was based on self-report. The Perceived Need for Care Questionnaire (PNCQ) and the Trimbos/iMTA questionnaire for Costs associated with Psychiatric Illness (Tic-P) were administered to assess the need for care (e.g. perceived need for psychotherapy) and the care received (35). Based on the answers to these questionnaires we constructed the variable ‘perceived need for more or other care’ (yes or no).
Finally, *GP characteristics* (years of experience as a GP, special interest in depression, training in psychiatry and/or depression/anxiety in the past year) were derived from the GPs’ questionnaires.

**Ethical considerations**
The study protocol of NESDA was centrally approved by the Ethical Review Board of the VU University Medical Center and subsequently by the local review board of each participating center. After receiving full verbal/written information about the study, written informed consent was obtained from all participants before baseline assessment. A full ethics statement of NESDA has been published (26).

**Statistical methods**
Descriptive statistics were used to describe the study population and the number of respondents recognized, with the Statistical Package for the Social Sciences version 16.0 (SPSS Inc., Chicago, USA). The definition of recognition (constructed with the 3 indicators described above) was used as the dependent variable ‘Recognition’ (yes/no) in the subsequent analyses. The prediction of all independent variables on our dependent variable ‘Recognition’ was analysed with bivariate logistic regression. All variables with a bivariate correlation with a *p*-value <0.2 were then selected for the multivariate logistic regression. To prevent multicollinearity, we excluded from these one of each pair of continuous variables with a mutual correlation >0.7 and dichotomous variables with ≤ 5.0% of respondents in one of the categories.

To determine which variables independently predicted recognition, logistic multilevel analysis was conducted using MLwiN 2.23. Multilevel analysis was used because the patients in this study were nested within the GP practices. Multilevel models are hierarchical systems that estimate regression coefficients and their variance components while at the same time correct for the dependency of the measurements. The first level was defined as patient, the second level as GP. The outcome variable represented the logit of the probability (i.e. natural log of the odds) of recognition of depression by the GP. Regression coefficients were transformed into odds ratios by taking the EXP[regression coefficient]. The Wald test was used to obtain a *p* value for each regression coefficient. The Wald test was also used on the variance parameters to obtain an indication of the necessity for allowing a random intercept or regression coefficient into the model (36). Based on a stepwise
backward selection procedure a final model was fitted consisting of only significant factors that constituted the predictors for recognition of depression by the GPs in the present study.

Results
Study sample
Table 1 lists the characteristics of the study sample. Compared with the total NESDA sample (mean age 41.9 years; 33.6% male), the present sample was slightly older (mean 44.7 years) and with fewer males (29.8%). As expected in a sample with depression in the past year, the average number of depression symptoms was high (7.7). Several symptoms were very common (depressed mood, loss of interest, fatigue and trouble concentrating; all >90%), whereas others were less so: e.g., change in appetite (more appetite 37.8%; less appetite 47.3%) or weight (weight gain 22.1%; weight loss 28.3%), psychomotor agitation (46.7%), psychomotor retardation (50.8%), feelings of worthlessness/guilt (82.9%), problems with sleep (trouble sleeping 79.3%; sleeping too much 37.6%; early awakening 42.8%) and thoughts of death (63.2%).

The average age of the 64 GPs was 48.7 (SD 8.4) years, 56% were male, and their average length of GP experience was 18 years. In the past year, 69% had followed a course on psychiatry and 48.3% on depression and/or anxiety; 36% had a special interest in depression.
Table 1 Characteristics of primary care participants with major depression/dysthymia (n=484) and GPs (n=64).

<table>
<thead>
<tr>
<th>Patient characteristics/comorbidity</th>
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<tbody>
<tr>
<td>Age in years, mean (SD)</td>
<td>44.7 (11.8)</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>144 (29.8%)</td>
</tr>
<tr>
<td>Education: no. of years</td>
<td>11.7 (3.4)</td>
</tr>
<tr>
<td>Comorbid anxiety</td>
<td>318 (65.7%)</td>
</tr>
<tr>
<td>No. of chronic somatic diseases, mean (SD)</td>
<td>1.2 (1.2)</td>
</tr>
<tr>
<td>Disability due to chronic somatic diseases</td>
<td>291 (60.1%)</td>
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<table>
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<tr>
<th>Depression symptoms</th>
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<tr>
<td>Feeling depressed/sad/empty</td>
<td>446 (92.1%)</td>
</tr>
<tr>
<td>Anhedonia/loss of interest</td>
<td>455 (94.0%)</td>
</tr>
<tr>
<td>Fatigue/loss of energy</td>
<td>453 (93.6%)</td>
</tr>
<tr>
<td>Trouble sleeping</td>
<td>384 (79.3%)</td>
</tr>
<tr>
<td>Sleeping too much</td>
<td>182 (37.6%)</td>
</tr>
<tr>
<td>Waking up 2 hours early</td>
<td>207 (42.8%)</td>
</tr>
<tr>
<td>More appetite</td>
<td>183 (37.8%)</td>
</tr>
<tr>
<td>Weight gain</td>
<td>107 (22.1%)</td>
</tr>
<tr>
<td>Less appetite</td>
<td>229 (47.3%)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>137 (28.3%)</td>
</tr>
<tr>
<td>Psychomotor retardation</td>
<td>246 (50.8%)</td>
</tr>
<tr>
<td>Psychomotor agitation</td>
<td>226 (46.7%)</td>
</tr>
<tr>
<td>Feelings of worthlessness/guilt</td>
<td>401 (82.9%)</td>
</tr>
<tr>
<td>Trouble concentrating/deciding</td>
<td>469 (96.9%)</td>
</tr>
<tr>
<td>Thoughts of death</td>
<td>306 (63.2%)</td>
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<table>
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<tr>
<th>Other Depression Characteristics</th>
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<tbody>
<tr>
<td>Depression severity (IDS), mean (SD)</td>
<td>29.9 (12.0)</td>
</tr>
<tr>
<td>No. of symptoms (CIDI), mean (SD)</td>
<td>7.7 (1.2)</td>
</tr>
<tr>
<td>Major depressive disorder/dysthymia (MDD)</td>
<td>469 (96.9%)</td>
</tr>
<tr>
<td>Chronic depression in past 5 years</td>
<td>99 (20.5%)</td>
</tr>
<tr>
<td>Suicide attempt in the past</td>
<td>96 (19.8%)</td>
</tr>
<tr>
<td>Suicidal thoughts in the past week</td>
<td>90 (18.6%)</td>
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<tr>
<th>Patient–GP Interaction Characteristics</th>
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<tbody>
<tr>
<td>Contact with GP in past 6 months</td>
<td>440 (90.9%)</td>
</tr>
<tr>
<td>No. of contacts with GP past 6 months, mean (SD)</td>
<td>3.5 (4.3)</td>
</tr>
<tr>
<td>Contact with GP about mental problems</td>
<td>243 (50.2%)</td>
</tr>
<tr>
<td>Perceived need for more or other treatment</td>
<td>308 (63.6%)</td>
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<thead>
<tr>
<th>GP characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>GP gender (male)</td>
<td>33 (55.9%)</td>
</tr>
<tr>
<td>GP age in years, mean (SD)</td>
<td>48.7 (8.4)</td>
</tr>
<tr>
<td>GP experience as GP (in years)</td>
<td>18.0 (9.8)</td>
</tr>
<tr>
<td>GP special depression interest (yes/no)</td>
<td>21 (35.6%)</td>
</tr>
<tr>
<td>GP training in psychiatry past year (yes/no)</td>
<td>42 (71.2%)</td>
</tr>
<tr>
<td>GP training depression/anxiety past year (yes/no)</td>
<td>31 (52.5%)</td>
</tr>
</tbody>
</table>

All numbers are number of participants with characteristic (percentage) unless otherwise specified.

Recognition

In 293 out of 484 respondents (60.5%) depression was recognized according to our definition in the total sample. In the subgroup of individuals with ICPC data in 248 out
of 361 respondents (68.7%) depression was recognized. Based on a sensitivity analysis, this subgroup population generated a higher recognition rate. If ICPC data had been complete in all respondents, probably even more patients would have been recognized.

Determinants of recognition

Bivariate analysis

Using bivariate multilevel logistic regression (Table 2), seven variables were significantly (p<0.05) associated with recognition. Decreasing depression severity and decreasing number of depression symptoms were associated with poorer recognition, and dysthymia was less often recognized compared with MDD. Recognition became also less likely when patients had no contact or fewer contacts with the GP in the past 6 months, or no contacts about mental problems. Finally patients without comorbid anxiety disorders were recognized less often. None of the depression symptoms or GP characteristics was found to be significant.
### Table 2 Results of bivariate multilevel logistic regression

<table>
<thead>
<tr>
<th>Patient characteristics/comorbidity</th>
<th>Total sample (n=484)</th>
<th>Subgroup with ICPC (n=361)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odds ratio</td>
<td>p-value</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.001</td>
<td>0.901</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>0.869</td>
<td>0.501</td>
</tr>
<tr>
<td>Education (no. of years)</td>
<td>1.001</td>
<td>0.972</td>
</tr>
<tr>
<td>Comorbid anxiety disorder</td>
<td>1.586</td>
<td>0.021</td>
</tr>
<tr>
<td>No. of chronic somatic diseases</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>Disability due to chronic somatic diseases</td>
<td>1.069</td>
<td>0.728</td>
</tr>
<tr>
<td>Depression symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeling depressed/sad/empty</td>
<td>1.141</td>
<td>0.705</td>
</tr>
<tr>
<td>Anhedonia/loss of interest</td>
<td>1.857</td>
<td>0.114</td>
</tr>
<tr>
<td>Fatigue/loss of energy</td>
<td>1.586</td>
<td>0.229</td>
</tr>
<tr>
<td>Trouble sleeping</td>
<td>1.317</td>
<td>0.177</td>
</tr>
<tr>
<td>Sleeping too much</td>
<td>1.276</td>
<td>0.216</td>
</tr>
<tr>
<td>Waking up 2 hours early</td>
<td>1.275</td>
<td>0.213</td>
</tr>
<tr>
<td>More appetite</td>
<td>0.775</td>
<td>0.191</td>
</tr>
<tr>
<td>Weight gain</td>
<td>0.887</td>
<td>0.597</td>
</tr>
<tr>
<td>Less appetite</td>
<td>0.905</td>
<td>0.597</td>
</tr>
<tr>
<td>Weight loss</td>
<td>0.992</td>
<td>0.970</td>
</tr>
<tr>
<td>Psychomotor retardation</td>
<td>1.397</td>
<td>0.077</td>
</tr>
<tr>
<td>Psychomotor agitation</td>
<td>1.025</td>
<td>0.896</td>
</tr>
<tr>
<td>Feelings of worthlessness/guilt</td>
<td>1.553</td>
<td>0.076</td>
</tr>
<tr>
<td>Trouble concentrating/deciding</td>
<td>1.234</td>
<td>0.696</td>
</tr>
<tr>
<td>Thoughts of death</td>
<td>0.966</td>
<td>0.859</td>
</tr>
<tr>
<td>Other Depression Characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression severity (IDS score)</td>
<td>1.019</td>
<td>0.018</td>
</tr>
<tr>
<td>No. of symptoms (0-9)</td>
<td>1.177</td>
<td>0.047</td>
</tr>
<tr>
<td>MDD/dysthymia (MDD)</td>
<td>2.241</td>
<td>0.184</td>
</tr>
<tr>
<td>Chronic depression in past 5 years</td>
<td>1.297</td>
<td>0.279</td>
</tr>
<tr>
<td>Suicide attempt in the past</td>
<td>1.149</td>
<td>0.564</td>
</tr>
<tr>
<td>Suicidal thoughts in the past week</td>
<td>1.114</td>
<td>0.659</td>
</tr>
<tr>
<td>Patient –GP Interaction Characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contact with GP in past 6 months</td>
<td>2.705</td>
<td>0.003</td>
</tr>
<tr>
<td>No. of contacts with GP past 6 months</td>
<td>1.096</td>
<td>0.002</td>
</tr>
<tr>
<td>Contact with GP about mental problems</td>
<td>3.547</td>
<td>0.000</td>
</tr>
<tr>
<td>Perceived need for more/other treatment</td>
<td>0.906</td>
<td>0.619</td>
</tr>
<tr>
<td>GP Characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP age (years)</td>
<td>1.004</td>
<td>0.790</td>
</tr>
<tr>
<td>GP gender (male)</td>
<td>1.031</td>
<td>0.905</td>
</tr>
<tr>
<td>GP experience as GP (years)</td>
<td>1.007</td>
<td>0.590</td>
</tr>
<tr>
<td>GP training in psychiatry past year</td>
<td>1.669</td>
<td>0.074</td>
</tr>
<tr>
<td>GP training depression/anxiety past year</td>
<td>0.954</td>
<td>0.857</td>
</tr>
<tr>
<td>GP special depression interest</td>
<td>0.902</td>
<td>0.707</td>
</tr>
</tbody>
</table>

Dependent variable recognition, defined as: diagnosis of depression or depressive symptoms or other psychiatric ICPC code by GP/use of antidepressant and/or referral to mental health care. All variables are yes/no unless otherwise specified. p-values < 0.2 are printed italic as these variables were selected for multivariate analysis. Major Depressive disorder
**Multivariate analysis**

Next, multivariate multilevel logistic regression was performed (Table 3) including all significant characteristics from the bivariate analyses as well as characteristics with a p-value of 0.05 to 0.20. Two variables were retained in the final multivariate model. Discussing mental problems with the GP was a strong predictor of recognition: patients who did not discuss their mental problems with the GP were much less likely to be recognized as having a depression. In addition, patients without a comorbid anxiety disorder in the past year were less likely to be recognized. None of the depression symptoms or GP characteristics remained significant in the final model.

**Table 3** Results of multilevel logistic regression analysis of all participants (n=484) with dependent recognition

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio</th>
<th>95% CI for odds ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comorbid anxiety disorder past year</td>
<td>1.565</td>
<td>1.043 - 2.348</td>
<td>0.030</td>
</tr>
<tr>
<td>Contact with GP about mental problems</td>
<td>3.532</td>
<td>2.378 - 5.248</td>
<td>0.000</td>
</tr>
</tbody>
</table>

 Definition of recognition: diagnosis of depression or depressive symptoms or other psychiatric ICPC code by GP/use of antidepressant and/or referral to mental health care.

**Ancillary (subgroup) analysis**

We repeated the analysis on the subsample of 361 respondents with at least one ICPC coded GP-contact. In this subsample the same seven variables were significantly (p<0.05) associated with recognition using bivariate analysis.

Multivariate multilevel logistic regression was also performed for this subsample. The final model in this analysis consisted of four variables. Again, patients not discussing their mental problems with the GP and patients without a comorbid anxiety disorder in the past year were less likely to be recognized. This subgroup also identified a decreasing number of depressive symptoms and increased appetite as predictors of poorer recognition (table 4).

**Table 4** Results of multilevel logistic regression analysis of subgroup with ICPC code (n=361) with dependent recognition

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio</th>
<th>95% CI for odds ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comorbid anxiety disorder past year</td>
<td>1.837</td>
<td>1.106 - 3.052</td>
<td>0.019</td>
</tr>
<tr>
<td>Contact with GP about mental problems</td>
<td>3.564</td>
<td>2.205 – 5.762</td>
<td>0.000</td>
</tr>
<tr>
<td>Number of symptoms of depression</td>
<td>1.313</td>
<td>1.064 – 1.619</td>
<td>0.011</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>0.553</td>
<td>0.331 – 0.922</td>
<td>0.023</td>
</tr>
</tbody>
</table>

 Definition of recognition: diagnosis of depression or depressive symptoms or other psychiatric ICPC code by GP/use of antidepressant and/or referral to mental health care.
Determinants of (non-)recognition

Discussion

Summary of main findings

Several characteristics of the patient, depression and patient-GP interaction were found to be associated with (non-)recognition. Remarkably, no GP characteristics were retained in the final model. As expected, especially patients without contact with the GP about mental problems were less often recognized. Notably, those without a suicide attempt in the past or suicidal thoughts in the past week were not less well recognized. Therefore, our hypotheses were partially confirmed. The presence of a comorbid anxiety disorder led to better recognition.

It is likely that our definition of recognition was not sensitive enough to detect all recognized cases in the total sample because of missing ICPC codes. The sensitivity analysis showed that in the subgroup of individuals with ICPC codes, in addition to the other predictors, increased appetite was associated with poorer recognition. As increased appetite is an atypical symptom of depression, this suggests that GPs are more attentive to patients with typical features of depression than to those without (or with atypical features). None of the other depression symptoms were significantly associated with recognition.

Moreover, all the GP characteristics were non-significant; for the GP demographics, this was not unexpected. However, we (for example) expected that training in psychiatry, and especially depression, would lead to better recognition. It should be noted that probably many (if not all) GPs had received training in psychiatry in the past (although not all in the past year). As a consequence, training in psychiatry during the past year was confounded by previous trainings.

Strengths and limitations

The present study has several strong points. First, our reference standard for depression diagnosis was the CIDI and not a self-report questionnaire, making comparison with GP recognition more reliable. Second, recognition was not based on GP-coded diagnosis only but on a wider definition, thereby increasing sensitivity. Also, recognition was not measured cross-sectionally as in most studies (in which GPs filled in a questionnaire about each patient), but longitudinally by evaluating EPF data over a 2-year period. We believe information gathered during this period provides a more accurate estimation of the depressed population in primary care. Many patients do not seek help from the GP right at the start of an episode and may
therefore go unrecognized in cross-sectional studies. Also, we expected many GPs not to code a depression at their first encounter with a patient. Since they may initiate a watchful observation period in the hopes symptoms subside without administering an active treatment and labelling the patient as depressed. These patients would also go unrecognized in a cross-sectional study. Fourth, the data collected within NESDA are extensive, enabling to examine many possible determinants of recognition. Finally, the GPs were unaware of the CIDI diagnoses; all had to rely on their own judgment for diagnosis and treatment, which prevents a GP assessment biased by the interviews.

Some limitations also need addressing. First, our group constructed our outcome variable ‘recognition’; we did not ask GPs directly whether they had recognized their patients as being depressed. Although asking about recognition can lead to higher recognition, because of increased awareness. Next, we did not take into account whether the respondent had discussed (or had wanted to discuss) depression with their GP. Third, some data on recognition (e.g. referral to mental health care) were collected retrospectively. In addition, the ICPC codes were missing in about 30% of the GP contacts, making them less reliable for assessing recognition. We dealt with this limitation by performing a subgroup analysis on the group of patients with at least one contact with the GP with an ICPC code. Fourth, our definition of recognition was partially based on the use of antidepressants and referral to mental health care. As a consequence, we partially measured ‘active recognition’. Not all patients need treatment and some do not want treatment (or even a diagnosis of depression) because they consider it as stigmatising (13). We perhaps missed patients that were recognized by their GP as being depressed but who did not receive treatment (neither a prescription for an antidepressant or a referral to mental health care) or were fitted with an ICPC diagnosis of depression, but on the other hand recognition alone might not be sufficient to ensure adequate follow-up and treatment (4-6).

Comparison with literature
As our definition of recognition differed from those used in other studies, our percentage of recognized cases (60.5%) did too: Mitchell et al. 33.6% and Klinkman et al. 35% (9,10,18). It was however comparable to that of Wittchen et al., who reported that 59% (ICD-10) to 75% (DSM-IV) of the patients in their study were
recognized (7). The results of a later study on recognition of depression in primary care, by Joling et al. indicated that the used definition of recognition influences the percentage of recognition found (32).

**Patient characteristics:** In the present study age did not affect recognition, in contrast to others who found that older patients were better recognized (7). This may have been the result of including only patients between 18 and 65 years of age in our study. We did not find any gender differences either, in line with the results of Rifel et al. (21). Patients without comorbid anxiety disorders were less often recognized. Comorbid anxiety and depression are common and have a worse prognosis compared to depression or anxiety alone (37). It could be that these patients are more symptomatic and are therefore easier to recognize for the GP. In the current study however, this could also be an artefact. Our definition included the ICPC codes for feelings of anxiety and anxiety disorder. This is justifiable, as a substantial proportion of our population had comorbid anxiety disorder and depression and a correct ICPC code might not be required to ensure appropriate treatment. This brings us to the other part of the definition, i.e. the use of antidepressants and referral to mental health care, both of which are accepted treatment modalities for anxiety disorder as well. This in turn could lead to the increased recognition of patients with comorbid anxiety disorder.

**Depression characteristics:** Less severe depression was less recognized in many studies (7,9,17,18). And although less severe depression was also less often recognized in our bivariate analysis, we found no significant independent association in the multivariate model. This is interesting, as we had expected severity to predict recognition. Perhaps patients with more severe depression presented more often with mental problems or more often suffered from comorbid anxiety disorders, thereby minimizing or neutralizing the independent effect of severity in the multivariate model. In our subgroup a decreasing number of depression symptoms led to decreasing recognition.

In the present study, no specific depression symptoms were associated with (non-)recognition in the total sample, while in the subgroup increased appetite led to worse recognition. The effect of specific symptoms on recognition was also investigated by Wittchen et al. (7). In their multivariate analysis only ‘loss of confidence’ remained significant; however, because this item is in the ICD-10 but not in the DSM-IV it was not investigated in our study. Wittchen et al. found no other
associations between recognition and specific depression symptoms. Clearly this issue, with two different results, warrants further investigation.

Patient-GP-interaction characteristics: In line with studies by Menchetti et al, Wittchen et al. and Furedi et al., as expected, we found that patients presenting with mental problems were better recognized (7,19,20).

None of the GP characteristics was associated with recognition, whereas Wittchen et al. found that physician experience of more than 5 years increased recognition and Tylee et al. reported that interest in psychiatry also increased recognition (7,17).

Implications for clinical practice and future research
In addition to the reason for the encounter, and comorbid anxiety disorder, the number of symptoms of depression and increased appetite were associated with (non-)recognition of depression in primary care. Mental problems as the reason for encounter experienced the strongest correlation with recognition. It would therefore seem logical to prompt patients to present their mental problem to the GP. However, the GP’s routine workday may be more somatically oriented than they are aware of. In a ±10-minute consultation, GPs often assess/exclude several somatic illnesses and manage the care of frequently multi-morbid patients. Such a busy schedule may not be optimal for an open discussion of sensitive issues sometimes charged with guilt and/or shame. A separate directly accessible pathway to cognitive behavioural therapy (as implemented in the UK) might be a better option. The fact that GPs less often recognized patients with atypical features such as increased appetite, suggests that recognition may be improved by emphasising to GPs that depression may also have atypical features. More studies on the effect of specific depression symptoms on the recognition of depression are needed to confirm (or contradict) the current findings.
Acknowledgement

The infrastructure for the NESDA study (www.nesda.nl) is funded through the Geestkracht program of the Netherlands Organisation for Health Research and Development (Zon-Mw, grant number 10-000-1002) and is supported by participating universities and mental health care organizations (VU University Medical Center, GGZ inGeest, Arkin, Leiden University Medical Center, GGZ Rivierduinen, University Medical Center Groningen, Lentis, GGZ Friesland, GGZ Drenthe, Scientific Institute for Quality of Healthcare (IQ healthcare), Netherlands Institute for Health Services Research (NIVEL) and Netherlands Institute of Mental Health and Addiction (Trimbos Institute).
References


Determinants of (non-)recognition


Chapter 3

Referral of Patients with Depression to Mental Health Care by Dutch General Practitioners: an Observational Study
Referral of Patients with Depression to Mental Health Care by Dutch General Practitioners: an Observational Study

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Biomed Central Family Practice 2011;12:41

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Patient case B “Referral of a depressed patient”

Mr. B. made an appointment because of depressive symptoms after a break-up with his girlfriend. She did not want to have any contact with him anymore. Mr. B. had a depression after a similar life event in the past and recognized the symptoms. He felt very sad, was unable to enjoy anything and unable to work. Most days he would do nothing but lie in bed and sometimes try to call his ex-girlfriend. When I asked him about thoughts about death, he told me he thought a lot about dying. He did think about suicide, but did not want to do this, because he did not want to hurt his mother and sister. I made an appointment with a psychiatrist for him the next day.

In case of suicidal intentions the Dutch General Practitioners Guideline Depression (NHG-standaard depressieve stoornis) recommends to refer patients, such as in this case, to secondary mental health care. Unfortunately, mr. B. committed suicide a few months later despite intensive therapy in secondary care.

Chapter 3 describes whether general practitioners take the guideline recommendations for referral to primary and secondary mental health care into account when making decisions about referral.
Abstract

Background

Depression is a common illness, often treated in primary care. Guidelines provide recommendations for referral to mental health care. Several studies investigated determinants of referral, none investigated guideline criteria as possible determinants.

We wanted to evaluate general practitioner’s referral of depressed patients to mental health care and to what extent this is in agreement with (Dutch) guideline recommendations.

Methods

We used data of primary care respondents from the Netherlands Study of Depression and Anxiety with major depressive disorder in the past year (n=478). We excluded respondents with missing data (n=134). Referral data was collected from electronic patient files between 1 year before and after baseline and self report at baseline and 1-year follow-up. Logistic regression was used to describe association between guideline referral criteria (e.g. perceived need for psychotherapy, suicide risk, severe/chronic depression, antidepressant therapy failure) and referral.

Results

A high 58% of depressed patients were referred. Younger patients, those with suicidal tendency, chronic depression or perceived need for psychotherapy were referred more often. Patients who had used ≥2 antidepressants or with chronic depression were more often referred to secondary care. Referred respondents met on average more guideline criteria for referral. However, only 8-11% of variance was explained.

Conclusion

The majority of depressed patients were referred to mental health care. General practitioners take guideline criteria into account in decision making for referral of depressed patients to mental health care. However, other factors play a part, considering the small percentage of variance explained. Further research is necessary to investigate this.
Introduction

Most patients with depression are treated in primary care (1,2). Primary care guidelines for the treatment of depression, including the Dutch guideline, recommend antidepressants and/or various forms of psychotherapy (3-7). When psychotherapy or counselling is indicated, a general practitioner (GP) can choose to counsel the patient himself or refer the patient to another health professional (3). In case of depression with psychotic features, a depressive episode in the course of bipolar disorder, a severe depression with social impairment or high suicide risk, or insufficient response to two or more antidepressants or other treatment, most guidelines recommend referral to secondary care (3-7). In addition, most guidelines recommend referral for psychological interventions in certain cases, although criteria differ between guidelines (3-7). Finally, patients with seasonal affective disorder may be referred for light therapy (3). For the current study, we used the Dutch primary care depression guideline, which is comparable to international primary care depression guidelines.

A few studies investigating referral behaviour of GPs suggest that multiple factors play a role in whether or not a patient is referred to mental health care, including disease characteristics (diagnosis, severity of symptoms, psychiatric comorbidity, personality characteristics, somatic comorbidity), patient characteristics (age, gender, race, education, insurance policy), whether the patient presented with psychological complaints, and lastly characteristics of the GP (e.g. organization of practice, experience of the GP, and degree of urbanization) (8-15). However, none of these studies evaluated specifically the criteria for referral as mentioned in the guidelines.

The aim of this study was to evaluate the referral practice by GPs to primary (i.e. psychologist, psychiatric nurse or social worker affiliated with the GP practice) and secondary mental health care (i.e. psychiatrist or psychotherapist in free practice, or health care professional affiliated with hospital/ institute for mental health care), of patients with depression who had visited their GP, irrespective of the reason, during the past four months. First, we wanted to know how many patients with depression were referred to primary and secondary mental health care. Second, if any differences existed between non-referred and referred patients, and between patients referred to primary and secondary mental health care. Third, we wanted to
Referral of patients with depression

know if the Dutch guideline recommendations for referral to primary and secondary mental health care corresponded with clinical practice.

We hypothesized that all criteria for referral mentioned in the Dutch guideline would independently increase the likelihood of referral. We had no hypothesis as to where most patients would be referred i.e. primary or secondary mental health care.

Methods
This study was conducted with baseline- and 1-year follow-up data from the Netherlands Study of Depression and Anxiety (NESDA, www.nesda.nl), a large prospective cohort study (n=2981) on the course of depression and anxiety disorders among respondents aged 18-65 years, recruited from the community, primary care and secondary mental health care, that started in 2004. Detailed information on the objectives and methods of NESDA were published elsewhere (16).

In The Netherlands access to secondary (mental) health care is impossible without a referral from a GP. Moreover, in The Netherlands all patients are listed with a single GP or GP practice.

At baseline an extensive interview was conducted. At 1-year follow-up all respondents filled in an elaborate questionnaire. In addition, we used data collected from the electronic patient file (EPF) of the GP for the period of one year before until one year after the baseline interview. Finally, we used data from questionnaires filled in by the GPs themselves.

Study sample
Details on recruiting methods were published elsewhere (16). In short a screening questionnaire was sent to a random sample of 23,750 patients from 65 GPs, who consulted their GP in the past four months irrespective of reason for consultation. The screener was returned by 10,706 persons (45%). Those screening positive were approached for a telephone interview consisting of Composite International Diagnostic Interview (CIDI) short form, which has proven diagnostic quality for screening purposes (17,18). Those fulfilling criteria for a current disorder on the CIDI short form were invited to participate in NESDA, as was a random selection of screen-negatives (both from the written screener and telephone interview). In total 1610 persons were recruited, and underwent an extensive baseline interview,
including the CIDI (19,20). The GP was not aware of the results of the screening and interview.

From these, we included in our study only respondents with a major depressive disorder in the past year (n=478).

We excluded respondents who did not give permission to use their EPF (n=15) or did not fill in the 1-year follow-up questionnaire (n=98), as we did not have full referral data on these respondents. We also excluded respondents of whom the GP had not filled in the GP questionnaire (n=21), as we would be unable to determine the influence of GP characteristics on referral in these cases. We thus included 344 respondents in our analysis. Excluded respondents were on average younger and had a higher Inventory of Depressive Symptomatology (IDS) score at baseline.

Definition of referral
We constructed the variable “referral”, indicating whether or not referral had taken place. Referral was considered present when a letter to or from a mental health professional was present in the EPF or when the respondent reported contact with a mental health professional in the past 6 months at baseline as measured with the PNCQ and Tic-P and in the past year with the Tic-P at 1-year follow-up.

We also created a variable indicating whether referral had been to primary (i.e. a psychologist, psychiatric nurse or social worker affiliated with the GP practice) or secondary mental health care (i.e. a psychiatrist or psychotherapist in free practice, or any health care professional affiliated with a hospital or institute for mental health care). Exact content of treatment by each mental health professional could not be determined.

Indicators/guideline criteria for referral
A detailed description of all measures can be found elsewhere (16). Demographic data (age, gender, education) were assessed during the baseline interview. Current and lifetime diagnoses of MDD based on DSM-IV were assessed with the CIDI, as well as duration of symptoms and number of previous episodes, we constructed from these data the variable chronic depression defined as >12 months with depression in the past two years. Suicidal tendency (suicidal ideations past week, suicide attempt ever) was measured with the Beck Suicide Ideation Scale (21). Current and past use
of antidepressants were based on self report, we derived from these data, which patients had stopped two or more antidepressants.

During the baseline interview number of chronic somatic diseases was recorded. The Perceived Need for Care Questionnaire (PNCQ) and Trimbos/iMTA questionnaire for Costs associated with Psychiatric Illness (Tic-P) were administered during the baseline interview to assess need for care and care received (22). From these questionnaires we used the answers to the questions of perceived need for psychotherapy and perceived need for any other treatment.

Finally, we used several GP and practice characteristics (years of experience as a GP, self-reported interest in depression, presence of a social worker, social psychiatric nurse or psychologist in the GP practice), derived from the GP questionnaires. Table 1 shows a summary of indicators/guideline criteria used.

<table>
<thead>
<tr>
<th>Guideline criteria for referral</th>
<th>Other patient characteristics</th>
<th>GP/practice characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stopped two or more antidepressants</td>
<td>Age</td>
<td>Years of experience as a GP</td>
</tr>
<tr>
<td>Perceived need for (more) psychotherapy/counselling</td>
<td>Gender</td>
<td>Special interest in depression</td>
</tr>
<tr>
<td>Perceived need for more or other treatment other than psychotherapy/counselling</td>
<td>Presence of chronic somatic diseases</td>
<td>Presence of mental health professional in GP practice</td>
</tr>
<tr>
<td>More than 12 months with depression in past two years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suicidal ideations past week or suicide attempt ever</td>
<td>Comorbid anxiety disorder past year</td>
<td></td>
</tr>
</tbody>
</table>

**Ethical considerations**

The study protocol of NESDA was approved centrally by the Ethical Review Board of the VU University Medical Center and subsequently by local review boards of each participating center. After full verbal and written information about the study, written informed consent was obtained from all participants at the start of baseline assessment. A full ethics statement of NESDA is found elsewhere (16).

**Statistical methods**

Results were presented with descriptive statistics: qualitative variables with absolute and relative frequencies, quantitative variables with means and standard deviation. Differences between two groups were tested with Chi square test (qualitative
variables) and Student's t test (quantitative variables). Logistic regression was used to estimate association of referral with observed parameters. Differences were considered significant when the p-value was <0.05. All variables with a bivariate correlation with p-value ≤0.150 were eligible for multivariate analysis. We excluded from these variables one of each pair with a mutual correlation >0.7 and dichotomous variables < 5.0% of respondents in one of the groups. For this multivariate analysis, logistic regression was used, with the dichotomous variable “referral” as dependent variable. We used a manual stepwise backward method to remove non-significant variables.

All statistical analyses were performed with the “Statistical Package for the Social Sciences” version 16.0 (SPSS Inc., Chicago).

Results

Study sample

Of the 344 respondents with MDD, 241 were female and 103 were male with an average age of 45.5 years (SD 11.7).

Referral

199 (57.8%) were referred to mental health care and 145 (42.2%) were not. Of the 199 referred, 93 (46.7%) were referred to primary mental health care and 106 (53.3%) to secondary mental health care.

Comparison between non-referred and referred respondents

We compared referred and non-referred respondents on the guideline criteria and patient and GP/practice characteristics (table 2). Suicidal tendency, chronic depression (≥12 months with depression in past two years) and perceived need for psychotherapy were more often present in the referred group, these patients were on average younger. None of the GP or practice characteristics were significantly different between groups.
Table 2 Differences between respondents with and without referral to mental health care

<table>
<thead>
<tr>
<th>Guideline criteria</th>
<th>No referral</th>
<th>Referred</th>
<th>Total</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>145 (42.2%)</td>
<td>199 (57.8%)</td>
<td>344 (100%)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Stopped two or more antidepressants</td>
<td>10 (6.9%)</td>
<td>23 (11.6%)</td>
<td>33 (9.6%)</td>
<td>1.76 (0.81 – 3.83)</td>
<td>0.147</td>
</tr>
<tr>
<td>Perceived need for (more) psychotherapy/counselling</td>
<td>59 (40.7%)</td>
<td>118 (59.3%)</td>
<td>177 (51.5%)</td>
<td>2.12 (1.37 – 3.28)</td>
<td>0.001</td>
</tr>
<tr>
<td>Perceived need for (more) treatment other than psychotherapy/counselling</td>
<td>81 (55.9%)</td>
<td>110 (55.3%)</td>
<td>191 (55.5%)</td>
<td>0.98 (0.64 – 1.50)</td>
<td>0.914</td>
</tr>
<tr>
<td>More than 12 months with depression in past two years</td>
<td>31 (21.4%)</td>
<td>63 (31.7%)</td>
<td>94 (27.3%)</td>
<td>1.70 (1.04 – 2.80)</td>
<td>0.035</td>
</tr>
<tr>
<td>Suicidal ideations past week or suicide attempt ever</td>
<td>35 (24.5%)</td>
<td>79 (39.7%)</td>
<td>114 (33.3%)</td>
<td>2.03 (1.26 – 3.27)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

**Patient characteristics**

<table>
<thead>
<tr>
<th></th>
<th>No referral</th>
<th>Referred</th>
<th>Total</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age*</td>
<td>47.10 (11.93)</td>
<td>44.32 (11.48)</td>
<td>45.49 (11.74)</td>
<td>N/A</td>
<td>0.031</td>
</tr>
<tr>
<td>Gender, male</td>
<td>38 (26.2%)</td>
<td>65 (32.7%)</td>
<td>103 (29.9%)</td>
<td>0.73 (0.46 – 1.18)</td>
<td>0.197</td>
</tr>
<tr>
<td>Chronic diseases</td>
<td>102 (70.3%)</td>
<td>127 (63.8%)</td>
<td>229 (66.6%)</td>
<td>0.74 (0.47 – 1.18)</td>
<td>0.205</td>
</tr>
<tr>
<td>Comorbid anxiety disorder past year</td>
<td>89 (61.4%)</td>
<td>128 (64.3%)</td>
<td>217 (63.1%)</td>
<td>1.13 (0.73 – 1.77)</td>
<td>0.577</td>
</tr>
</tbody>
</table>

**GP characteristics**

<table>
<thead>
<tr>
<th></th>
<th>No referral</th>
<th>Referred</th>
<th>Total</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years of experience as a GP*</td>
<td>18.21 (10.49)</td>
<td>19.89 (9.88)</td>
<td>19.18 (10.16)</td>
<td>N/A</td>
<td>0.133</td>
</tr>
<tr>
<td>Special interest in depression</td>
<td>40 (29.9%)</td>
<td>52 (27.8%)</td>
<td>92 (28.7%)</td>
<td>0.91 (0.56 – 1.48)</td>
<td>0.690</td>
</tr>
<tr>
<td>Presence of mental health professional in GP practice</td>
<td>101 (69.7%)</td>
<td>147 (73.9%)</td>
<td>248 (72.1%)</td>
<td>1.23 (0.77 – 1.98)</td>
<td>0.390</td>
</tr>
</tbody>
</table>

N = absolute number of respondents; (%) = percentage within variable referral; OR = Odds Ratio; (95% CI) = 95% Confidence Interval for Odds ratio, p-value is from chi-square test
* Numbers are mean (standard deviation); p-value is from independent samples t-test

Next, we tested whether the number of criteria present would predict the chance of referral. Indeed, referred respondents met significantly more criteria (median 2.00) than non-referred respondents (median 1.00), p=0.000. Respondents with one or more criteria had an odds ratio of referral compared to respondents without any criteria of 2.70 (95% CI for odds ratio 1.49 – 4.87). Relation between referral and number of criteria is graphically depicted in figure 1.
Comparison between respondents referred to primary and secondary mental health care

We compared the groups referred to primary and to secondary mental health care (table 3). Having stopped two or more antidepressants and chronic depression, were more common in respondents referred to secondary mental health care.
Referral of patients with depression

| Table 3 Differences between respondents referred to primary and secondary mental health care |
|---------------------------------|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                | Primary mental health care       | Secondary mental health care | Total           | OR (95% CI)     | p-value         |
| N (%)                          | 97 (46.2%)                      | 113 (53.8%)                | 210 (100%)      | N/A             | N/A             |
| Guideline criteria             |                                 |                              |                 |                 |                 |
| Stopped two or more antidepressants | 5 (5.4%)                        | 18 (17.0%)                  | 23 (11.6%)      | 3.60 (1.28–10.12) | 0.011          |
| Perceived need for (more) psychotherapy/counselling | 54 (58.1%)                      | 64 (60.4%)                  | 118 (59.3%)     | 1.10 (0.62 – 1.94) | 0.740          |
| Perceived need for (more) treatment other than psychotherapy/counselling | 47 (50.5%)                      | 63 (59.4%)                  | 110 (55.3%)     | 1.43 (0.82 – 2.52) | 0.208          |
| More than 12 months with depression in past two years | 20 (21.5%)                      | 43 (40.6%)                  | 63 (31.7%)     | 2.49 (1.33 – 4.67) | 0.004          |
| Suicidal ideations past week or suicide attempt ever | 32 (34.4%)                      | 47 (44.3%)                  | 79 (39.7%)      | 1.52 (0.86 – 2.70) | 0.153          |
| Patient characteristics        |                                 |                              |                 |                 |                 |
| Age*                           | 43.42 (11.64)                   | 45.10 (11.34)               | 44.32 (11.48)   | N/A             | 0.304           |
| Gender, male                   | 29 (31.2%)                      | 36 (34.0%)                  | 65 (32.7%)      | 0.88 (0.49 – 1.60) | 0.677           |
| Chronic diseases               | 57 (61.3%)                      | 70 (66.0%)                  | 127 (63.8%)     | 1.23 (0.69 – 2.19) | 0.487           |
| Comorbid anxiety disorder past year | 54 (58.1%)                      | 74 (69.8%)                  | 128 (64.3%)     | 1.67 (0.93 – 3.00) | 0.084           |
| GP characteristics             |                                 |                              |                 |                 |                 |
| Years of experience as a GP*   | 20.97 (9.33)                    | 18.94 (10.28)               | 19.89 (9.88)    | N/A             | 0.147           |
| Special interest in depression | 23 (26.4%)                      | 29 (29.0%)                  | 52 (27.8%)      | 1.14 (0.60 – 2.16) | 0.696           |
| Presence of mental health professional in GP practice | 65 (69.9%)                      | 82 (77.4%)                  | 147 (73.9%)     | 1.47 (0.78 – 2.78) | 0.232           |

N = absolute number of respondents; (%) = percentage within variable referral; OR = Odds Ratio; (95% CI) = 95% Confidence Interval for Odds ratio, p-value is from chi-square test
* Numbers are mean (standard deviation), p-value is from independent samples t-test

Logistic regression analysis

Finally, we tested all variables from table 1 bivariately against the dependent variable “referral”. Age and gender were tested, in order to control for them in the model, if they where significant. All variables with a bivariate p-value ≤0.150 were entered into the model, after step-wise backward deletion, only need for (more) psychotherapy and suicidality remained significant, when controlled for age. This model explained eight to eleven percent of variance (table 4).

| Table 4 Results of multivariate binary logistic regression analysis with referral as dependent variable |
|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------|-----------------|-----------------|
|                                | Odds ratio* | 95% Confidence interval | P-value |                        |
| Age                            | 0.974       | 0.955 – 0.994            | 0.010  |                        |
| Stopped two or more antidepressants | 1.634       | 0.706 – 3.784            | 0.252  |                        |
| Perceived need for (more) psychotherapy/counselling       | 1.865       | 1.187 – 2.930            | 0.007  |                        |
| More than 12 months with depression in past two years       | 1.713       | 0.995 – 2.948            | 0.052  |                        |
| Suicidal ideations past week or suicide attempt ever        | 1.810       | 1.098 – 2.985            | 0.020  |                        |

* Odds ratio for referral in case criterion present, except for criterion age, where odds ratio represents odds for referral with each year increase in age.
Discussion

Summary of main findings

The majority (210/363; 57.9%) of patients with depression in primary care was referred to a mental health professional while GPs seem to apply the guideline criteria when making decisions about referral. Our hypothesis that all guideline criteria independently increased referral chance, was rejected, still suicide risk, chronic depression and patient preference for psychotherapy rendered referral more likely. Failure of treatment (chronic depression and/or stopped treatment with ≥2 antidepressants) led more often to referral to secondary mental health care.

Strengths and limitations of the study

Our study has several strong points. First, as a screening method was used to recruit participants and independent interviewers interviewed all respondents, GPs were unaware of the psychiatric diagnosis. They could only rely on their own judgement in their treatment decisions, including referral. Second, the use of a structured interview (CIDI) for diagnosis. Third, with the extensive interview of NESDA, almost all relevant criteria for referral could be assessed.

There are also limitations. First, the specific Dutch situation where GPs are gatekeepers to mental health care, rendering it unclear if these results can be generalized to countries with other referral systems. Second, we were unable to examine certain criteria presented in the guideline, such as comorbid personality disorders (also a guideline criterion for referral), as these were not assessed in NESDA. Third, missing data on diagnoses in 30% of the GP EPFs, rendering it impossible to clarify the influence of “recognition” on referral practice. Fourth, we were unable to investigate the influence of symptom severity on referral, as referral was initiated at a different point in time for each participant, while symptom severity was measured at baseline and 1-year follow-up only. The symptom severity at time of referral could be very different from the symptom severity at any of these set points in time.

Comparison with existing literature

Referral rate in our study (almost 58% of patients with MDD in the past year) was high compared to the previous studies. Kendrick et al. reported an overall percentage of 22.8%, including patients with minimal or mild depressive symptoms according to
either the 9-item Patient Health Questionnaire or the depression subscale of the Hospital Anxiety and Depression Scale (23). In the study by Wang et al. 26% of patients with a “mental health visit” and 25% with any visit to their GP were referred to a psychologist or psychiatrist (14). Finally, Grembowski et al. found that 23% of patients with depressive symptoms were referred, while 38% had contact with a mental health specialist, as this was also possible without referral (24). These differences are probably a result of different populations of patients and methods for diagnosing depression: GP diagnosis, questionnaires such as Hospital Anxiety and Depression Scale or structured interviews like the CIDI, and different definitions of referral and mental health care. Kendrick et al. included patients with minimal or mild depressive symptoms; Grembowski et al. patients with depressive symptoms, from both groups at least some patients would probably not fulfil criteria for MDD as used in our study (23,24). Wang et al. only considered referrals to psychiatrists or psychologists, while we also investigated social workers, social psychiatric nurses, psychotherapists and professionals in institutes for mental health care (14). Lastly, the study by Grembowski et al. was performed in the United States where a referral from a GP is not required to see a specialist (24).

Although none of the studies investigated all of the determinants we did, several of our determinants were investigated by others. Younger age was associated with more referral in our study, and in the study of Wang et al. and Grembowski et al. (14,24). The incidence of comorbid anxiety disorder did not differ between groups, in line with the study by Simon et al. (25). Referral rates for males and females were the same in our study in concordance with the studies of Miller et al. and Simon et al., but in contrast to the studies by Grembowski et al. and Kendrick et al. (23-26). Chronic somatic disease did not significantly differ between referred and non-referred patients in our population either, in contrast to the study of Kendrick et al. and Miller et al. (23,26).

Implications for future research and clinical practice

Our study shows that Dutch GPs use guideline criteria in their decision to refer depressed patients to mental health care. However, the small percentage of explained variance by the guideline criteria for referral in our multivariate model suggests that there is room for further improvement in clinical practice. If GPs would adhere strictly to the guidelines, a higher percentage would have been expected. At
the same time, the small percentage of explained variance opens a door toward future research: it shows that also other factors (including patient factors) play a part in the decision making process. Future research should focus on investigating these factors. If we better understand why patients are referred (or not referred), courses on recognition and treatment of depression could educate GPs in these areas so that they might be able to take even better care of their patients. Also, while recommendations towards the need for secondary mental health care in depression are quite clear in most guidelines, the indications and possibilities of primary mental health care are less so. This could also be an interesting field of research.
Acknowledgement

We would like to thank all respondents for their participation and Klaas H Groenier, PhD for his statistical assistance for this paper.

The infrastructure for the NESDA study (www.nesda.nl) is funded through the Geestkracht program of the Netherlands Organisation for Health Research and Development (Zon-Mw, grant number 10-000-1002) and is supported by participating universities and mental health care organizations (VU University Medical Center, GGZ inGeest, Arkin, Leiden University Medical Center, GGZ Rivierduinen, University Medical Center Groningen, Lentis, GGZ Friesland, GGZ Drenthe, Scientific Institute for Quality of Healthcare (IQ healthcare), Netherlands Institute for Health Services Research (NIVEL) and Netherlands Institute of Mental Health and Addiction (Trimbos Institute).
References


(5) Institute for Clinical Systems Improvement. ICSI Health Care guideline: Major depression in Adults in Primary Care; 2009. Available at: http://www.icsi.org/depression_5/depression_major_in_adults_in_primary_care_3.html.


Determinants of (non-)recognition


Chapter 4

Guideline Recommendations for Long-term Treatment of Depression with antidepressants in primary care - a critical review
Guideline Recommendations for Long-term Treatment of Depression with antidepressants in primary care - a critical review

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European Journal of General Practice 2010;16:106-112

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Patient case C "Guideline recommendations for maintenance treatment with antidepressants"

Mrs. C. had an episode of major depressive disorder in the past. In addition, and prior to that episode, she was diagnosed with a dysthymic disorder that had lasted for many years. She was a housewife with a disabled husband and a son with psychological problems that still lived with his parents. Her husband and son were both not very talkative and tended to fight quite a lot. At first glance the dysthymic disorder seemed to stem from her surroundings. She was advised to search for hobbies out of the house and talk with friends to cope with the situation at home. Unfortunately, she did not achieve remission with these advises. Psychological therapy (counselling and psychotherapy) were tried. Nonetheless, she remained dysthymic. In 2010 we decided to try treatment with an antidepressant. After only a few weeks of sertraline 50mg she started to feel better, and after 8 weeks she told me she was 'happy'. At home things ran smoother as well, as she would less often react irritated to her husband and son.

At the moment she consults me every six months to discuss her mood and the need for further continuation of the antidepressant. Unfortunately, she is very anxious to stop the sertraline. According to the guideline, this could be considered overtreatment. From the view of Mrs. C. who has had a dysthymic disorder for many years it is understandable that she is anxious and maybe even unwilling to stop. I estimate that attempts at tapering off an antidepressant without the patients full consent are likely to fail. In this case, we discuss the medication twice a year and maybe in the future a good moment will be found to stop the sertraline.

In this chapter it becomes clear that although most guidelines would not recommend maintenance treatment in this case, evidence concerning (indications for) maintenance treatment is scarce.
Abstract

Background
Long-term treatment with antidepressants is considered effective in preventing recurrence of major depressive disorder (MDD). It is unclear whether this is true for primary care. We investigated whether current guideline recommendations for long-term treatment with antidepressants in primary care are supported by evidence from primary care.

Methods
Data sources for studies on antidepressants: PubMed, Cochrane Library, Embase, PsycInfo, Cinahl, articles from reference lists, cited reference search. Selection criteria: adults in primary care, continuation or maintenance treatment with antidepressants, with outcome relapse or recurrence, (randomized controlled) trial/naturalistic study/review. Limits: published before October 2009 in English.

Results
Thirteen depression guidelines were collected. These guidelines recommend continuation treatment with antidepressants after remission for all patients including patients from primary care, and maintenance treatment for those at high risk of recurrence. Recommendations vary for duration of treatment and definitions of high risk. We screened 804 literature records (title, abstract), and considered 27 full-text articles. Only two studies performed in primary care addressed the efficacy of antidepressants in the long-term treatment of recurrent MDD. A double-blind RCT comparing mirtazapine (n=99) and paroxetine (n=98) prescribed for 24 weeks reported that in both groups 2 patients relapsed. An open study of 1031 patients receiving sertraline for 24 weeks, who were naturalistically followed-up for up to 2 years, revealed that adherent patients had a longer mean time to relapse.

Conclusions
No RCTs addressing the efficacy of maintenance treatment with antidepressants as compared to placebo were performed in primary care. Recommendations on maintenance treatment with antidepressants in primary care cannot be considered evidence-based.
Introduction

Major depressive disorder is a common illness. According to the WHO major depressive disorder will be one of the leading causes of disability worldwide by 2020, second only to ischemic heart disease (1). The high level of disability associated with depression is mainly caused by its chronic or recurrent course (2,3). To prevent chronicity, relapses or recurrences after remission has been achieved during treatment of the acute episode, guidelines recommend long-term treatment with antidepressants (AD) (4-6). Two recent meta-analyses based on a considerable number of placebo-controlled trials in which patients were randomized to either continuation of AD or placebo during the first three months after remission, have shown that continuation treatment with AD significantly decreases relapse rates within the first three months after randomization (7,8). This evidence supports the recommendation for continuation treatment with AD during the first months after remission to prevent relapse. Far less research has investigated the efficacy of longer-term maintenance treatment for prevention of recurrence (7,8). Although guidelines also recommend maintenance treatment with AD for several years, or even lifelong, for patients with previous recurrences the scientific basis for these recommendations is meagre, since only few studies have addressed the efficacy of AD in patients randomized more than three months after remission (4-6,8). For registration of an AD (e.g. by the European Agency for the Evaluation of Medicinal Products) the manufacturer is required to provide efficacy data from placebo-controlled acute treatment studies as well as continuation studies lasting up to six months (http://www.emea.europa.eu/pdfs/human/ewp/051897en.pdf).

The majority of patients with depression are treated in primary care (9). One may assume that treatment of depression might not be that different between primary and secondary care, but without proof we cannot simply extrapolate the guidelines from secondary care to primary care. Also, some studies did find, although small, differences between patients in primary and secondary care. For example, psychotic features and suicidality are less often present in primary care (10). Second, primary care patients with depression seem to be less accepting of treatment, possibly leading to a lower effectiveness (11). Third, patients in primary care less often receive psychotherapy (12). As the majority of studies of long-term AD treatment have been carried out in secondary care, their generalizability to primary care...
Guideline recommendations for antidepressant treatment

remains uncertain (7,8).

We sought to investigate the current depression guideline recommendations on long-term treatment with AD in primary care in order to determine if the recommendations are supported by studies representative of the primary care population. This review therefore addressed the following questions. 1. What is, according to current guidelines, the recommended duration of treatment with AD after remission for patients with major depressive disorder treated in primary care? 2. Are these recommendations for long-term treatment with AD in primary care supported by evidence from literature?

Methods

Guideline recommendations

For the first question our aim was to collect current guidelines, from Europe and English-speaking countries in other parts of the world, which provided recommendations for primary care about AD treatment in major depressive disorders. Therefore, we searched PubMed, Cochrane, PsycInfo, Embase, Cinahl, and the National Guideline Clearinghouse as well as with the search machine Google with the keywords “depression”, “guideline” and “treatment”. In addition we searched the website of WONCA for links to primary care organizations in European countries; on the websites of these organizations we searched for depression guidelines. We excluded guidelines that were based on other guidelines and guidelines over ten years old.

Studies on efficacy of long-term treatment with AD in primary care

For the second question, we used four systematic search strategies. First, we searched PubMed, Embase, PsycInfo, Cinahl and the Cochrane library with keywords and free text words. Articles written in English and published until October 2009 were included. We used the following inclusion criteria: participants: adult primary care patients (no children and not only elderly people aged >64 years); intervention: continuation or maintenance treatment with antidepressant agents in primary care; comparison: placebo or no comparison; outcome: relapse or recurrence of depression; study design: randomized controlled trial, controlled trial, open trial, clinical trial, naturalistic study, (systematic) review, all with a duration of at least six months. The search string in PubMed was as follows: Depressive disorder,
Guideline recommendations for antidepressant treatment

major (Mesh) AND Antidepressive agents (Mesh) AND ("Primary Health Care"[Mesh] OR "Physicians, Family"[Mesh] OR "Family Practice"[Mesh] OR "primary care" OR "general care" OR "general health care" OR "general practice" OR "general practitioner"). In the other databases we used comparable search strings.

In order to exclude the possibility that we might have missed articles with the chosen strategy, especially because not all primary care studies mentioned that they were performed in this setting, we did two additional searches in one database (PubMed) by adding the text word “depression” and without all search terms referring to “primary care”, respectively. Either search did not reveal any additional paper. Third, we used the so-called “snowball method” whereby we searched the reference lists of all retrieved articles for possible other relevant articles. Finally, we used Web of Science searching for articles citing the retrieved articles from our original search.

Data extraction
The search results were first screened on title and abstract for studies on long-term treatment with AD of major depressive disorder in primary care. All retrieved articles were obtained and the full text articles were read using the inclusion criteria described earlier.

Studies in specific groups of depressed patients (e.g. post-stroke depression, post-myocardial infarction depression), in children (aged less than 18 years) or the elderly (aged above 65 years) were excluded because depression course and response to AD can be different in these patients (13-15). We excluded duplicates after retrieval of full text articles, because of practical reasons.

All searches were performed by the first author, who also did most of the title and abstract screening. She consulted the other authors in case she doubted about an article. Eventual full text article selection and data extraction was done during a meeting with all authors.

Results
Guideline recommendations for long-term treatment with AD in primary care
We collected 13 depression guidelines specifically addressing or at least mentioning treatment of depression with AD in primary care. An overview of the recommendations in the guidelines for the long-term treatment with AD in primary care is found in table 1 (4-6,16-25). Although all guidelines recommended
Guideline recommendations for antidepressant treatment

continuation treatment with AD after remission for all patients, recommendations for duration of continuation treatment varied from 4 to 12 months. Maintenance treatment of varying durations (between 1 year and lifelong) was recommended for patients at high risk of recurrence, which each guideline defined differently. Almost all cited references in guidelines were based on studies carried out in secondary or tertiary care settings; most of these studies randomized patients within 3 months after remission and the difference between antidepressant and placebo was already achieved within 3 months after randomization (4-6,16-25). Relapse risk was 25% in the first year after remission, 42% after two years, 60% after five years and 50-85% after 15 years (3,26). The risk of relapse or recurrence increased after each subsequent episode (26).

None of the guidelines specified whether recommendations for primary care should be different than those for secondary care and no guideline referred specifically to any controlled study performed in primary care.

Studies on efficacy of long-term treatment with AD in primary care

The database searches identified a total of 716 titles, including duplicates, because titles were retrieved in more than one database. Reference checking and the cited reference search rendered a total of 88 records. Screening titles and abstracts yielded 27 potentially relevant articles after removing duplicates (see Figure 1).
### Table 1: Guideline recommendations for long-term treatment with antidepressant of depression in primary care

<table>
<thead>
<tr>
<th>Guideline Panel</th>
<th>Publication</th>
<th>Country</th>
<th>Duration continuation treatment*</th>
<th>Duration maintenance treatment**</th>
<th>Indications maintenance treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deutsche Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde (DGPPN)</td>
<td>2009</td>
<td>Germany</td>
<td>4 to 9 months</td>
<td>2 years, maybe longer</td>
<td>I, II</td>
</tr>
<tr>
<td>Institute for Clinical Systems Improvement (ICSI)</td>
<td>2009</td>
<td>United States</td>
<td>6 to 12 months</td>
<td>3 years to lifelong</td>
<td>I, II, V, VI, VII, consider for IV</td>
</tr>
<tr>
<td>British Association for Psychopharmacology</td>
<td>2008</td>
<td>Great Britain</td>
<td>6 months</td>
<td>&gt;= 5 years, indefinitely?</td>
<td>I, II, III, IV</td>
</tr>
<tr>
<td>Heyrman J, Declercq T, Rogiers R et al. (CEBAM)</td>
<td>2008</td>
<td>Belgium</td>
<td>6 months</td>
<td>&lt;= 1 year</td>
<td>I, III</td>
</tr>
<tr>
<td>New Zealand Guidelines Group</td>
<td>2008</td>
<td>New Zealand</td>
<td>6 months</td>
<td>2 years</td>
<td>I</td>
</tr>
<tr>
<td>National Institute for Clinical Excellence</td>
<td>2007</td>
<td>Great Britain</td>
<td>6 months</td>
<td>Minimum 1 to 2 years</td>
<td>I, II, III</td>
</tr>
<tr>
<td>World Federation of Societies of Biological Psychiatry (WFSBP)</td>
<td>2007</td>
<td>Diverse</td>
<td>6 to 9 months</td>
<td>Standard 3 years</td>
<td>I, II, III, IV, V, VI, VII</td>
</tr>
<tr>
<td>Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS)</td>
<td>2005/2006</td>
<td>France</td>
<td>4 to 12 months</td>
<td>Not mentioned</td>
<td>(Discuss in case of) I, II, IV, VII</td>
</tr>
<tr>
<td>Helsedirektoratet</td>
<td>2005</td>
<td>Norway</td>
<td>6 months</td>
<td>Not mentioned</td>
<td>Discuss with patient in I, III</td>
</tr>
<tr>
<td>Landelijke stuurgroep richtlijnontwikkeling in de GGZ</td>
<td>2005</td>
<td>Netherlands</td>
<td>6 months</td>
<td>&gt;= 1 year, consider 3-5</td>
<td>I</td>
</tr>
<tr>
<td>Camden &amp; Islington</td>
<td>2003</td>
<td>Great Britain</td>
<td>4 to 6 months</td>
<td>&gt;= 5 years, indefinitely?</td>
<td>I</td>
</tr>
<tr>
<td>Nederlands Huisartsen Genootschap (NHG)</td>
<td>2003</td>
<td>Netherlands</td>
<td>6 to 9 months</td>
<td>1-5 years, incidentally longer</td>
<td>I, II</td>
</tr>
<tr>
<td>CANadian Network for Mood and Anxiety Treatments (CANMAT)</td>
<td>2001</td>
<td>Canada</td>
<td>6 months</td>
<td>Minimum 2 years</td>
<td>I, II, V</td>
</tr>
</tbody>
</table>

* In months from time of remission  
** In years from end of continuation treatment  
I Recurrent depression  
II Episode characteristics (long/severe/chronic)  
III Residual symptoms/stressors or lack of support  
IV Concurrent other DSM-IV axis I or II disorder  
V Age <30 or >60-65  
VI Rapid relapse or recurrence in the past  
VII Family history of major depressive disorder
Of these, 18 articles were excluded because they did not concern the efficacy of long-term treatment with AD in primary care or did not have relapse risk as an outcome measure; two studies were not performed (solely) in primary care; and one article, which was the only study from primary care frequently referred to in guidelines, proved to be a retrospective case-note-audit conducted in primary care, not addressing the relationship between AD use and relapse (27). We were unable to acquire four articles. In summary, after reading the full-text articles, two publications remained (28,29). Neither of them was a placebo-controlled study performed in primary care that addressed the efficacy of AD in the prevention of relapse or recurrence in major depressive disorder.

One study was an RCT involving 197 patients comparing the efficacy and tolerability of mirtazapine (n=99) and paroxetine (n=98) during 24 weeks in patients with a major depressive episode. Only 91 patients (46.1%) completed the study, while remission was obtained in 35 patients (35%) receiving mirtazapine and 22 patients (22%) receiving paroxetine. After remission, in both groups 2 patients relapsed before the end of the study at 24 weeks. The authors did neither mention how many patients were actually followed after remission nor for how long (29).

The second study involved 1031 primary care patients with DSM-IV major depression who had been participants in another study (30). All patients were treated with sertraline for 24 weeks, which resulted in remission in 59% of patients. Patients (including non-remitters and non-responders) were naturalistically followed-up for up to 2 years. During this follow-up the general practitioner made all decisions about treatment. Depression outcome was compared for patients who were adherent to treatment with AD versus non-adherent patients. Overall relapse or recurrence rates were not statistically different between groups, but adherent patients (mean time to relapse 302 days) had a longer mean time to relapse or recurrence than non-adherent patients (mean time to relapse 249 days) (28).
Guideline recommendations for antidepressant treatment

Discussion

Our main findings are that the available guidelines do not specify that recommendations in primary care might be different from recommendations in secondary care with respect to continuation and maintenance treatment with AD. Moreover, there is a paucity of research investigating the efficacy of long-term treatment with antidepressants in primary care.

A limitation of this review is that we were unable to acquire all existing guidelines. Furthermore, we could not acquire all potentially interesting full text articles. Finally, we limited our search to articles published in the English language. The strength of this review is the comparison between guideline recommendations and evidence. Guidelines are used in everyday practice of primary care, and they are often thought to contain a high level of evidence. However, it is not always clear whether primary care guidelines are based on evidence from primary care.

Overall, guidelines recommend the continuation of treatment with AD for all...
patients for a period of 4, 9 or even 12 months. Maintenance treatment for a longer period (i.e. between 1 year and lifelong) is recommended for patients at high risk of recurrence, which each guideline defines differently. However, the guidelines do not specify that recommendations are actually based on studies in secondary or tertiary care.

Our systematic search did not identify any placebo-controlled RCT to support the efficacy of continuation or maintenance treatment with AD in primary care. The two studies we found provided only circumstantial evidence suggesting that long-term treatment with AD can reduce relapse or recurrence rates (28,29). This raises the question on which studies the guidelines base their ‘level 1’ evidence. Guidelines refer to many studies with respect to optimal duration of treatment with AD after having achieved remission. In their recent meta-analysis of 30 placebo-controlled RCTs on long-term treatment with tricyclic antidepressants (TCAs) or selective serotonin reuptake inhibitors (SSRIs), Kaymaz et al. found a significant relapse-reducing effect of antidepressants compared to placebo at 3, 6, 9, as well as 12 months of follow-up. However, they also showed that the difference between antidepressant and placebo was achieved within 3 months after randomization, while no additional reduction in risk was observed at further follow-up (8). With the exception of two very small trials including a total of 32 patients, there were no studies in which patients were randomized after 3 months of remission (8). Thus, it can be concluded that the recommendations for the use of antidepressants in continuation treatment (i.e. during the first 3-6 months after remission to prevent relapse) are evidence based. However, good quality evidence is lacking for recommendations on the category of patients for whom maintenance treatment is appropriate, and on the duration of maintenance treatment. Furthermore, guideline recommendations for long-term treatment are only based on studies in patients treated in secondary care or specialized research settings and not for patients treated in primary care. Although one could argue that there are no strong arguments that recommendations on maintenance treatment with antidepressants in primary care should be different form secondary care, we conclude that they cannot be considered evidence-based. Hence, clinicians should be cautious with too strictly following the guidelines and instead may adjust the indication for long-term treatment to fit each patient’s need. Finally, we conclude that further studies on the long-term treatment with antidepressants in primary care are warranted.
Conclusion
Whereas depression guidelines recommend long-term (maintenance) treatment with antidepressants for both primary and secondary care patients with recurrent depressive episodes, it remains unclear whether these recommendations apply for patients in primary care.
Guideline recommendations for antidepressant treatment

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Guideline recommendations for antidepressant treatment


Chapter 5

Most Antidepressant Use in Primary Care is Justified; Results of the Netherlands Study of Depression and Anxiety
Most Antidepressant Use in Primary Care is Justified; Results of the Netherlands Study of Depression and Anxiety

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PLoS ONE 2011;6:e14784

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Patient case D "Overtreatment with antidepressants"

In the daily lists of repeat prescriptions was a prescription for paroxetine 20mg for Mrs. D. According to her file she had had an severe episode of major depressive disorder about 10 years ago after her first husband had suddenly died. Her psychiatrist had prescribed her the paroxetine then. She was asked to make an appointment to discuss current situation and possible phasing out of the paroxetine. During the consultation she told she had been fine ever since she had started the paroxetine. Her live at that moment was very stable, she had remarried about 18 months before. She had never really thought about stopping the paroxetine and was a bit anxious about it, afraid it would lead to a new episode of depression. After some discussion and counseling, she decided to try and phase it out. She used 10mg for a month and then stopped the paroxetine. Six months later her mood had been stable. Mrs. D. is a good example of a patient that is overtreated with antidepressants, although she started with a good indication.

In this chapter overtreatment with antidepressants according to the guideline is described.
Abstract

Background
Depression is a common illness, often treated in primary care. Many studies have reported undertreatment with antidepressants in primary care. Recently, some studies also reported overtreatment with antidepressants. The present study was designed to assess whether treatment with antidepressants in primary care is in accordance with current guidelines, with a special focus on overtreatment.

Methods
We used baseline data of primary care respondents from the Netherlands Study of Depression and Anxiety (NESDA) (n=1610). Seventy-nine patients with treatment in secondary care were excluded. We assessed justification for treatment with antidepressant according to the Dutch primary care guidelines for depression and for anxiety disorders. Use of antidepressants was based on drug-container inspection or, if unavailable, on self-report. Results were recalculated to the original population of primary care patients from which the participants in NESDA were selected (n=10,677).

Results
Of 1531 included primary care patients, 199 (13%) used an antidepressant, of whom 188 (94.5%) (possibly) justified. After recalculating these numbers to the original population (n=10,677), we found 908 (95% CI 823 to 994) antidepressant users. Forty-nine (95% CI 20 to 78) of them (5.4%) had no current justification for an antidepressant, but 27 of them (54.5%) had a justified reason for an antidepressant at some earlier point in their life.

Conclusions
We found that overtreatment with antidepressants in primary care is not a frequent problem. Too long continuation of treatment seems to explain the largest proportion of overtreatment as opposed to inappropriate initiation of treatment.
Introduction
Depression is a common disorder that is associated with a great amount of morbidity because of its highly recurrent and chronic nature (1). Most patients with depression are treated in primary care (2,3). Guidelines on the treatment of depression in primary and secondary care consider treatment with antidepressants and/or psychotherapy indicated for all patients with major depressive disorder (MDD) (4-10). According to these guidelines the treatment should be continued for 6 months after remission (continuation treatment) of a first episode, while it should be continued for one or more years (maintenance treatment) in patients with a recurrent MDD or chronic depression (4-10).

Various studies reported that treatment of depression in primary care is not according to guideline recommendations (11-16). Most studies reported undertreatment, especially with antidepressants of patients with MDD (11-16). However, in recent years there has also been a lot of attention for overtreatment with antidepressants (17-19). The fact that in the last 6 months of 2005 760,000 people in the Netherlands (population 16.500.000) were prescribed an antidepressant, according to the Dutch Foundation for Pharmaceutical Statistics (SFK, www.sfk.nl) led to discussions in the Dutch media and among professionals. High numbers were recently also reported in the US and UK, which also led to discussions (20-22). A few studies on overtreatment with antidepressants suggested that this is mainly due to prescription of these drugs to patients with milder forms of depression, such as dysthymia (Dysth) or minor depression (miD) (17,18,23-26). Especially the prescription of antidepressants to patients with miD is controversial, as there is no evidence for the efficacy of antidepressants in this condition (27-29). On the other hand, even patients without a depression might receive antidepressants for another justified indication such as anxiety disorders and pain, for which several antidepressants are also registered.

The aim of this study was to evaluate whether the statements reported in the media and a few articles in the literature about widespread overtreatment with antidepressants were true. Therefore, we wanted to assess to what extent the use of antidepressants is in accordance with the Dutch primary care guideline for depression (which is comparable to other international guidelines) as well as for anxiety disorders, with a focus on overtreatment.
Methods
This study was conducted with baseline-data from the Netherlands Study of Depression and Anxiety (NESDA, www.nesda.nl), a large prospective cohort study on depression and anxiety disorders among respondents aged between 18 and 65 years, recruited from the community, primary care and (secondary) mental health care. Detailed information on the objectives and methods of NESDA were published elsewhere (30).

Study sample
For this study we selected from the NESDA database only those respondents who were recruited in primary care. In short the recruitment in primary care was as follows. A screening questionnaire was sent to a random sample of 23,750 people from 65 general practitioners (GPs) who had consulted their GP in the past four months, irrespective of reason for consultation. In the Netherlands patients are listed with a single GP or GP practice. The GP is the gatekeeper to secondary care; access to secondary (mental) health care is impossible without a reference from a GP.

The screening questionnaire consisted of the Kessler-10 (K-10), which has proven screening qualities for affective disorders, and five additional questions asking about the presence of specific anxiety disorders (31,32). A positive score was defined as a validated K-10 score of ≥20, or a positive score on any of the five anxiety questions (32). Almost half of the sample (n=10,706; 45%) returned the screener. Responders to the screener were slightly more often female and older than non-responders (30,33). Although having to take small age and sex differences into account, we consider this sample representative of patients consulting their GP in the Netherlands (33).

Those who screened positive (n=4592) were approached for a telephone interview with the short form sections of the CIDI (CIDI-SF), which has proven screening qualities with a high sensitivity for detecting mental disorders (34). Specifically trained research staff (mainly psychologists and research nurses) conducted the telephone interview.

All persons who screened positive on the CIDI-SF (n=898), as well as 196 out of 278 randomly selected persons with a positive K-10 plus, but not fulfilling CIDI-SF criteria and a random selection of 516 screen negatives (healthy controls)
participated in the baseline assessment of NESDA (n=1610), which consisted of a face-to-face interview.

The 79 respondents already receiving treatment for psychiatric conditions in secondary care (defined as more than one contact with either an institute for mental/psychiatric health care or an independent psychiatrist) were excluded from our study sample, yielding a total sample of 1531 respondents for the present analyses.

**Description of Procedures or Investigations undertaken**

**Measures**

As part of the screening procedure, all respondents filled out the *K-10 plus*. Demographic data (age, gender, ethnicity, education) were assessed during the baseline interview.

Current and lifetime diagnoses of MDD, Dysth, current diagnosis of mID, comorbid anxiety disorders (social phobia, panic disorder, agoraphobia, generalized anxiety disorder) based on DSM-IV were assessed with a structured interview, the *World Health Organization Composite International Diagnostic Interview – lifetime version 2.1 (CIDI)*, which is considered the gold standard for diagnosing depressive and anxiety disorders in large epidemiological studies (35-37). Specifically trained research staff (mainly psychologists and research nurses) conducted the baseline interview including the CIDI.

From the data of the CIDI interview, in which all depressive symptoms were listed separately, we created a variable for *depressive symptoms*, defined as having had one or more DSM-IV symptoms of depression during at least two weeks lifetime with at least either anhedonia or depressed mood, without fulfilling the criteria for diagnosis of MDD or dysthymia. From this data we also created a variable “chronic MDD”, defined as having had a lifetime diagnosis of MDD and 24 months of (probably uninterrupted) symptoms of depression in the past five years as recorded with the *life chart method*. The life chart is a method for recalling depressive symptomatology, the respondent was asked during the interview to mention several important (personal) events from the last several years and was subsequently asked to recall if there was some depressive symptomatology at that point. The life chart has been proven useful to assess the course of illness in patients with mood disorders (38-40).
Overtreatment with antidepressants

Outcome variables

Whether respondents used antidepressants was based on drug container inspection of all drugs used in the past month at baseline and classified according to the World Health Organization Anatomical Therapeutic Chemical (ATC) classification. If respondents had forgotten to take the medication to the interview, their use was based on self-report (done for 35.3% of all subjects). The use of two different methods for assessing antidepressant drugs was not a problem in the current study, as we were not interested in patient compliance, for which self report and drug container inspection can give very different results, but only in physician prescription behaviour. We therefore used the drug container inspection only to assess which medications were used and not for pill counts. Use of antidepressants included selective serotonin reuptake inhibitors (ATC-code N06AB), tricyclic antidepressants (N06AA) and other antidepressants (N06AF/N06AX). St John’s wort was not considered an antidepressant.

Justification for treatment with an antidepressant

To determine the justification for treatment with an antidepressant, we followed the recommendations from the guidelines for depression and for anxiety disorders of the Dutch General Practitioner’s Association (NHG) (7,41). Treatment was considered justified when it was mentioned in the guideline as (one of the) first step option(s) and considered possibly justified when it was mentioned as (one of the) second step option(s). For depressive disorders the depression guideline recommends the use of an antidepressant during six months after response for a first episode of MDD as one of the first step treatment options, although dependent on the degree of suffering or dysfunction. As dysfunction is a criterion for the diagnosis of MDD and patients consulted their physician, we assumed that probably most had at least some degree of suffering or dysfunction. Therefore, we considered treatment with antidepressants justified when a respondent had suffered an episode of MDD in the past year. In case of recurrent or chronic MDD the guideline recommends one to five years of maintenance treatment, with the option for longer in patients with previous recurrences after withdrawal of antidepressants. Therefore, treatment of chronic or recurrent MDD for up to two years was considered justified, all treatment longer than two years was considered possibly justified. In case of dysthymia an antidepressant is mentioned in the depression guideline as (one of the) second step option(s) and
therefore considered possibly justified. Antidepressants were not considered justified for depressive states not fulfilling criteria for MDD or dysthymia.

As antidepressants are also registered for the treatment of anxiety disorders, we also considered treatment with antidepressants justified in case the guideline recommendations from the anxiety disorder guideline were followed. This guideline recommends treatment with an antidepressant in case of the presence of an anxiety disorder in the last year, with the option (i.e. possibly justified) to continue the treatment for a longer period.

Overtreatment was considered present when a respondent received an antidepressant without justification or possible justification, i.e. without a non-recurrent (i.e. single) episode of MDD or dysthymia in the past year, or an anxiety disorder or recurrent MDD or chronic depression in lifetime.

Ethical considerations
The study protocol of NESDA was approved centrally by the Ethical Review Board of the VU University Medical Center and subsequently by local review boards of each participating center. After full verbal and written information about the study, written informed consent was obtained from all participants at the start of baseline assessment. A full ethics statement of NESDA is found elsewhere (30).

Statistical methods
Descriptive statistics and frequencies were used to describe the use of AD and psychological treatment. We recalculate the found numbers and percentages of justified and unjustified treatment with antidepressants in our sample to the original population of 10,677 persons who returned a completed K-10 plus screener questionnaire. This backward projection was done in several steps, which can be derived by reading Figure 1 from the bottom up, or from table 1.
In the first step, we split our sample into four groups; no use of an antidepressant, justified use, possibly justified use and unjustified use. We will refer to these groups as “justification groups”. After that, we registered the number of screen-positives and screen-negatives in each of the justification groups. These numbers were then multiplied by a correction factor (respectively total screen-positives divided by screen-positives in sample (4592/1024) or total screen-negatives divided by number of screen-negatives in our sample (6085/506)) to calculate the estimated number of persons from each justification group in the original screen-positive and screen-negative groups. Finally, we added up the estimated numbers screen-positives and negatives for each justification group.

A 95% confidence interval (95% CI) was calculated for all estimated numbers. This was done by first calculating the standard error of the proportion with the proper mathematical formula. This number was then multiplied by 1.96 and subtracted and added to the proportion in order to get the 95% CI of the proportion, which could then be recalculated to the 95% CI of the absolute number by multiplying by n.
We used a Chi square statistic to test for significant differences in justification for an antidepressant between antidepressant users with no/mild/moderate/severe MDD.

All statistical calculations were performed using SPSS for Windows Release 16.0.

### Table 1 Results of recalculation of justified and unjustified antidepressant use to screener population

<table>
<thead>
<tr>
<th></th>
<th>Study sample (n=1531)</th>
<th>Screen positive (n=4592)</th>
<th>Screen negative (n=6085)</th>
<th>Screener population (n=10,677)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitely justified</td>
<td>95 (47.7%)</td>
<td>94 * 4.5$^{(1)}$ = 422</td>
<td>1 * 12.0$^{(2)}$ = 12</td>
<td>434 (394-474)$^{(3)}$</td>
</tr>
<tr>
<td>Possibly justified</td>
<td>93 (46.7%)</td>
<td>92 * 4.5$^{(1)}$ = 413</td>
<td>1 * 12.0$^{(2)}$ = 12</td>
<td>425 (385-465)$^{(3)}$</td>
</tr>
<tr>
<td>Unjustified</td>
<td>11 (5.5%)</td>
<td>11 * 4.5$^{(1)}$ = 49</td>
<td>0 * 12.0$^{(2)}$ = 0</td>
<td>49 (20-78)$^{(3)}$</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>199 (100%)</td>
<td>197 * 4.5$^{(1)}$ = 884</td>
<td>2 * 12.0$^{(2)}$ = 24</td>
<td>908 (823-994)$^{(3)}$</td>
</tr>
</tbody>
</table>

$^{(1)}$ Correction factor screen-positives group: total number of screen-positives divided by number of screen-positives in the study sample (4592/1024=4.5)

$^{(2)}$ Correction factor screen-negatives group: total number of screen-negatives divided by number of screen-negatives in the study sample (6085/506=12.0)

$^{(3)}$ 95% Confidence Interval

### Results

#### Study sample

The average age of the population was 45.8 years, 1054 (68.8%) of respondents were female and 477 (31.2%) male.

The diagnoses of the respondents with lifetime depression/depressive symptoms (n=1064, of whom 651 with a comorbid anxiety disorder) were as follows: 807 respondents had a lifetime MDD of whom 428 in the past year; 23 had a lifetime Dysth without history of MDD of whom 16 in the past year; and 234 had a lifetime miD or depressive symptoms in lifetime without a history of MDD or Dysth, of whom 44 had a miD in the past month (incidence in last year unknown). The diagnoses of the respondents with a lifetime anxiety disorder (n=762) were: 345 patients with social phobia; 344 patients with a panic disorder (with or without agoraphobia); 131 patients with agoraphobia; and 330 patients with a generalized anxiety disorder (324 patients had more than one anxiety disorder).

#### Justified and non-justified treatment

Of the respondents with a depression/depressive symptoms (MDD, dysthymia, miD or depressive symptoms, n=1064), 189 (17.8%) used an antidepressant, of whom 75 (39.7%) had a justification, 68 (36.0%) a possible justification and 46 (24.3%) did not have a justification.
However, of the 46 antidepressants users with a depression/depressive symptoms without a justification for treatment with an antidepressant (non-recurrent MDD, miD or depressive symptoms) nine had only a depression/depressive symptoms and 37 had a lifetime anxiety disorder (26 in the past year), which means that the antidepressant may have been prescribed for the anxiety disorder rather than the depression. This means that in only nine patients (4.5%) with a depression/depressive symptoms treatment was not justified.

Of the 111 respondents with a lifetime anxiety disorder without a depression/depressive symptoms eight patients (10.1%) used an antidepressant, in three this was justified and in five possibly justified.

Only 2 (0.6%) of the 356 respondents without a lifetime depression or anxiety disorder used an antidepressant. This treatment obviously was not justified.

Table 2 shows a summary of justified and not justified treatment in our sample. In total 11 respondents used an antidepressant without a definite or possible justified reason. Eight of them used a SSRI, one a TCA (at low dose) and two another antidepressant; the duration of antidepressant use varied from 0 to 120 months, with a median of 48 months. Nine of these respondents had a depression/depressive symptoms (six a single episode of MDD more than one year ago, three miD or depressive symptoms). They represent 0.77% of the 1175 respondents with a lifetime depression or anxiety disorder. The other two represent 0.56% of the 356 respondents without a depression/depressive symptoms or anxiety disorder. Thus, 6 of the 11 respondents (54.5%) had a justified reason for treatment with an antidepressant at some earlier point in their life because of an episode of MDD.

Table 2: Treatment with antidepressants and justification for treatment

<table>
<thead>
<tr>
<th></th>
<th>No AD</th>
<th>AD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unjustified</td>
<td>566 (98.1%)</td>
<td>11 (1.9%)</td>
<td>577</td>
</tr>
<tr>
<td>Possibly justified</td>
<td>225 (70.8%)</td>
<td>93 (29.3%)</td>
<td>318</td>
</tr>
<tr>
<td>Definitely justified</td>
<td>541 (85.1%)</td>
<td>95 (14.9%)</td>
<td>636</td>
</tr>
<tr>
<td>Total</td>
<td>1332 (87.0%)</td>
<td>199 (12.9%)</td>
<td>1531</td>
</tr>
</tbody>
</table>

Treatment was considered definitely justified in case of a MDD in the past year, or recurrent or chronic MDD with antidepressant treatment ≤ 24 months, or an anxiety disorder in the past year.

Treatment was considered possibly justified in case of dysthymia in the past year, or a recurrent or chronic MDD with antidepressant treatment > 24 months, or an anxiety disorder over one year ago.

All other antidepressant treatment was considered unjustified.

All numbers are absolute number of respondents (percentage of total respondents in row)

AD=antidepressant
Table 3 shows the relation between severity of depression at baseline and antidepressant use. This table shows that antidepressant users with a mild (recurrent) MDD are less often classified as definitely justified AD use. We performed a Chi square test comparing the justification groups for antidepressant users with moderate to severe (recurrent) MDD to antidepressant users with no MDD or mild (recurrent) MDD. The difference was significant (p=0.015), antidepressant users with moderate to severe (recurrent) MDD more often had a justified reason for the use of an antidepressant compared to antidepressant users with no MDD or mild (recurrent) MDD.

<table>
<thead>
<tr>
<th></th>
<th>Definitely justified AD users (n,%)</th>
<th>Possibly justified AD users (n,%)</th>
<th>Unjustified AD users (n,%)</th>
<th>Total (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDD Single Mild</td>
<td>7 (24%)</td>
<td>6 (21%)</td>
<td>16 (55%)</td>
<td>29</td>
</tr>
<tr>
<td>MDD Recurrent Mild</td>
<td>12 (39%)</td>
<td>19 (61%)</td>
<td>N/A</td>
<td>31</td>
</tr>
<tr>
<td>MDD Single Moderate</td>
<td>19 (54%)</td>
<td>7 (20%)</td>
<td>9 (26%)</td>
<td>35</td>
</tr>
<tr>
<td>MDD Recurrent Moderate</td>
<td>9 (64%)</td>
<td>5 (36%)</td>
<td>N/A</td>
<td>14</td>
</tr>
<tr>
<td>MDD Single Severe</td>
<td>11 (33%)</td>
<td>8 (24%)</td>
<td>14 (42%)</td>
<td>33</td>
</tr>
<tr>
<td>MDD Recurrent Severe</td>
<td>17 (53%)</td>
<td>15 (47%)</td>
<td>N/A</td>
<td>32</td>
</tr>
<tr>
<td>Dysthymia</td>
<td>N/A</td>
<td>8 (100%)</td>
<td>0 (0%)</td>
<td>8</td>
</tr>
<tr>
<td>miD/depressive symptoms</td>
<td>N/A</td>
<td>N/A</td>
<td>7 (100%)</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>75</td>
<td>68</td>
<td>46</td>
<td>189</td>
</tr>
</tbody>
</table>

N/A= not applicable

Respondents with a recurrent MDD and possibly justified AD use had a possible justification because they had used an antidepressant for more than 2 years.

Use of antidepressants in the primary care population

With the selection procedure as described in the method section, we can calculate what our findings mean for the total population of respondents (n=10,677) who returned the K-U10 plus (table 1).

In our sample there were 188 antidepressant users with justified antidepressant use of whom 95 (50.5%) with a definite justified reason, and 93 (49.5%) with a possible justified reason: 2 among the respondents with a negative K-U10 plus (n=6085, of whom 506 participated in the study) and 186 among the respondents with a positive K-U10 plus (n=4592, of whom 1023 participated).

Recalculated to the respondents who completed the K-U10, there are 24 (95% CI 0 to 57) antidepressant users with a definite or possibly justified reason in the screen-negative group and 835 (95% CI 726 to 943) in the screen-positive group.
All 11 respondents who used an antidepressant without a definite or possible justified reason had a positive K-U10 plus. The total number of antidepressant users without a justified reason among all respondents with a positive K-U10 plus can be recalculated at 49 (95% CI 20 to 78). As there were no antidepressant users without indication with a negative K-U10 plus, the total number of respondents who used an antidepressant without indication among all 10,677 people who completed the K-U10 plus, is also 49 (95% CI 20 to 78). K-U10 plus results were unknown for one respondent without antidepressant use.

Combining the results of antidepressant users with and without justification, recalculated to the sample of 10,677 GP patients from 65 GPs who had consulted their GP in the past four months irrespective of reason for consultation and did return a completed screening questionnaire, 908 (8.5%), (95% CI 823 to 994), used an antidepressant of whom 859 (94.6% of the antidepressant users) with a definite (n=434, 47.8%) or possible (n=425, 46.8%) justification in accordance with the guideline and 49 patients (5.4% of the antidepressant users) without justification.

Discussion

Summary of main findings

The main finding of our study is that overtreatment with antidepressants did not appear to be a very frequent problem in Dutch primary care. Of all GP patients (and after excluding patients who were treated in secondary care including hospitals, institutes for mental health care and psychiatrists with private practices) 8.5% received an antidepressant. When compared with the guidelines of the Dutch General Practitioner’s Association (NHG), 94.6% of the antidepressant use was in accordance with the guideline (47.8% definitely and 46.8% possibly) while only 5.4% was not. The latter was for the large part not due to treatment of mild forms of depression or patients without psychiatric diagnoses, but to non-justified long continuation of antidepressant treatment in patients who at some earlier point in their life had a justified reason for treatment with an antidepressant.

Strengths and limitations

The current study has several very strong points. First, we used a screening method to recruit participants, which did not affect the awareness of patient’s psychiatric status for GPs in our study. This means that the GPs could only rely on their own
diagnostic judgments also for their prescription of antidepressants. The second strength of this study is its large sample size, which is rather rare in a primary care study. The third strength is that all patients were diagnosed based on a structured interview and not on the GPs’ records.

However there are also limitations. First, the last mentioned strength is also a weakness, as the structured interview we used (the CIDI) does not assess the degree of suffering and dysfunction, which should be part of the GPs’ consideration for antidepressant treatment according to the guideline recommendations. Second, the representativeness of the population may be limited. The GPs in this study, and thus their patients, may not be representative for all Dutch primary care practices, as these practices/GPs agreed to participate in the NESDA study, and thus have interest in psychiatric research. This may be associated with a better compliance to the guidelines for depression and for anxiety disorders. Next to that, according to the SFK about 760,000 Dutchmen were prescribed an antidepressant (about 6.3% of the adult population) in the last 6 months of 2005. In our primary care sample we recalculated that 8.5% used an antidepressant. This higher percentage may be explained by the fact that respondents were selected among the patients who consulted their GP in the last four months. The non-response to the screening questionnaire did not seem to be biased with regard to psychopathology (33).

Fourth, we did not have access to the full electronic patient file from the GPs. Therefore we did not know why they prescribed an antidepressant. This might have been of interest, as antidepressants can also be prescribed for other indications than depression or anxiety disorder. Some antidepressants including TCAs at low dose for example are used for neuropathic pain. However, if any effect, this would result in an even lower estimation of overtreatment with antidepressants in our sample. In addition, we could not determine the ground on which the GPs based their treatment decisions, therefore we could not determine if a decision to (dis)continue an antidepressant was according to guideline recommendations. This applies especially to the category ‘possibly justified’ in patients who had recovered from a recurrent depressive episode more than two years ago, as we do not have information as to why the antidepressant was continued in these patients. Among them are definitely patients who continue their antidepressants for good reasons, e.g. patients who had stopped their antidepressant after a recurrent episode and who developed a new recurrence, and patients who tapered off and subsequently developed minor
Overtreatment with antidepressants

symptoms and therefore restarted medication. This limitation also means that we were unable to estimate the severity of symptoms at the time the antidepressant was started. Table 3 showed that some respondents with a mild episode of MDD received treatment with antidepressants. The guideline at time of the study does not differentiate between mild and moderate to severe depressive episodes in its recommendations, but more recent guidelines do. For example the new Dutch multidisciplinary depression guideline is much more conservative and recommends reserving treatment with antidepressants for patients with more severe depressive states (42). It is unclear whether the patients with mild symptomatology at baseline had more severe symptomatology at the time the antidepressant treatment was initiated.

A final limitation is the cross-sectional design of the study, as a result of which the start of symptoms and time of remission could not be determined precisely. We allowed treatment with antidepressants in case of a MDD in the past year. In some cases treatment probably should have been stopped before the interview, because the patient had been in remission for (more than) 6 months. Because of the cross-sectional design, we also had to rely on recall of symptoms of depression and anxiety during the past year and for lifetime diagnoses. Several researchers have questioned the reliability of retrospective recall of symptoms during a single interview in persons with a history of depression (43,44).

Comparison with literature
Several previous studies also looked at rates of overtreatment, with various outcomes. The major contrast with our study is that these studies only looked at relative small groups of GP patients and did not allow recalculation of the results to the total population of GP patients. Two of the previous studies found high rates of overtreatment: 25% (Sihvo et al.) and even 35% (Berardi et al.) (17,18). Berardi et al. described a group of 361 primary care patients of whom 82 used an antidepressant. They only considered treatment with antidepressants indicated for current depression, ignoring possible continuation or maintenance treatment and other indications for the use of antidepressants like anxiety disorders. This is a rather limited definition, as continuation treatment is a well-established part of depression treatment and many antidepressants are also registered for anxiety disorders. Sihvo et al. described a group of 526 patients who used an antidepressant. They adopted a
definition of overtreatment slightly broader than ours. Treatment was considered “non-psychiatric” in case there was no CIDI diagnosis of MDD, Dysth, anxiety disorder (generalised anxiety, social phobia, panic disorder or agoraphobia), bipolar disorder or alcohol dependence in the last 12 months.

The third previous study (Cameron et al) reported a small percentage (exact percentage not mentioned) of overtreatment in a Scottish primary care sample of 120 antidepressant users (19). They did not have a diagnosis based on a structured interview, but used a cut-off score of the Hospital Anxiety and Depression Scale (HADS). Of their sample 45 had “no depression”, 34 had a “possible depression” and 41 had “probable depression.” In the respondents with “no depression”, they reported that 32 had a history of depression (as recorded by the GP), 5 had anxiety disorder, 5 had neuropathic pain and for only 3 it remained unclear why they received an antidepressant.

It can be argued that our definition of non-justified antidepressant use is rather small, and that in reality more patients in our sample did not actually need an antidepressant. First, we defined lifelong treatment non-justified only for patients without a definite or possible justification. This created the problem of how to classify the category ‘possible justified’ for treatment beyond two years of patients with a recurrent depression, while most guidelines recommend several years and only for a (non-specified) subgroup lifelong treatment. Second, also in case of anxiety disorders it could be argued that lifelong treatment is unnecessary in many if not most cases. Third, the diagnosis chronic MDD was based on the self-report of 24 months (of probably uninterrupted) symptoms of depression in the past five years according to the life chart and a lifetime diagnosis of MDD. It could very well be that these patients had no chronic MDD, but just symptoms of depression during two or more years. This would mean that in more patients antidepressants would be unnecessary. When we would have classified all possible justified cases as overtreatment the percentage would indeed rise substantially: from 5.4% to 52.2%, which is much higher than Berardi et al. and Sihvo et al. and clearly illustrates the importance of a clear definition of overtreatment. We think however that our definition including life long treatment for patients with recurrent depressive episodes is justifiable, considering the high recurrence rate of depression, especially after multiple episodes (45,46). As discussed above, at least part of the respondents with a possible justification will have a very good reason for the use of an antidepressant. Moreover, there could be
patients without a justified reason for the use antidepressants, for whom the physician (or the patient himself) found an antidepressant needed, e.g. because of residual symptoms after a single episode of MDD. One could also argue that, although not indicated according to the guideline, this is justified treatment.

If indeed the percentage of overtreatment is lower in the Netherlands than in other countries: what would be the explanation? A possible explanation is the difference in primary care systems. In the Netherlands, the GP is the gatekeeper to secondary and mental health care; patients need a reference from the GP before they can consult mental health care. Secondly, Dutch GPs have been trained during the last years in how to diagnose and treat depression and anxiety disorders, as part of the implementation of the Dutch primary care guidelines. This also implies that our results probably cannot be generalized globally, as primary healthcare systems vary across countries.

Another explanation for the difference could be that antidepressant use in our study was based on drug-container inspection in most patients and on self-report in a minority of cases, while the Dutch Foundation for Pharmaceutical Statistics (SFK, www.sfk.nl) data are based on pharmacy prescription data. From previous studies it is known that many patients do not pick up their prescription or do not take their medication (47,48).

In this study we focused on overtreatment with antidepressants, and therefore we looked at whether patients received an antidepressant without a justified reason. However, “justified” does not mean “needed”. Patients with a mild or even moderately severe episode of MDD do not necessarily need treatment (either an antidepressant or psychotherapy), although they do have a justified reason for treatment with an antidepressant. New guidelines like the recent 2009 update of the Dutch multidisciplinary guideline for depression recommend reserving antidepressants for patients with moderate to severe depression (42). Therefore, an alternative interesting question is: who needs an antidepressant, and how many of the patients who need an antidepressant do actually receive an antidepressant. This however, was not the focus of our study as undertreatment of depression has already been the focus of many studies in the past (11-16). Moreover, the NESDA study is not suitable for answering this question. It is a naturalistic study and part of the study population did not seek any help. It is therefore impossible to determine which patients are
“undertreated” by their GP and which did not seek help for their psychological complaints.

Implications for clinical practice and future research
In conclusion, the current study provides a unique insight into the justification of the prescription of antidepressants in Dutch primary care. In contrast to the scarce literature, the rate of overtreatment with antidepressants in the present study was low. Another interesting finding is that overtreatment is not so much due to treatment of mild forms of depression or patients without psychiatric diagnoses, but rather to an excessive duration of antidepressant treatment in patients with remitted (recurrent) MDD. This latter finding presents several implications for clinical practice. First, projects on optimizing treatment with antidepressants in primary care, should not focus on reducing overtreatment but on identifying patients who do not need antidepressants anymore. Second, GPs should be aware that apparently many patients tend to continue the antidepressant over many years. Which of these patients might be able to stop the antidepressant is unclear. Therefore, further studies addressing this question are warranted before starting campaigns to reduce the use of antidepressants in primary care.

Acknowledgement
The infrastructure for the NESDA study (www.nesda.nl) is funded through the Geestkracht program of the Netherlands Organisation for Health Research and Development (Zon-Mw, grant number 10-000-1002) and is supported by participating universities and mental health care organizations (VU University Medical Center, GGZ inGeest, Arkin, Leiden University Medical Center, GGZ Rivierduinen, University Medical Center Groningen, Lentis, GGZ Friesland, GGZ Drenthe, Scientific Institute for Quality of Healthcare (IQ healthcare), Netherlands Institute for Health Services Research (NIVEL) and Netherlands Institute of Mental Health and Addiction (Trimbos Institute).
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Overtreatment with antidepressants


Chapter 6

Long-term Users of Antidepressants in Dutch General Practice: Characteristics and Consequences.
Maintenance Users of Antidepressants in Dutch General Practice: Characteristics and Consequences

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Patient case E "Maintenance treatment with antidepressants"

Mrs. E. visits my practice for her half-yearly appointment. She uses paroxetine since 2008. In 2008 she had a major depressive disorder with a comorbid anxiety disorder. She attempted to stop the paroxetine in 2010, which resulted in a recurrence of mainly anxiety symptoms. She is very reluctant to try it another time. Mrs. E. is one of many patients with comorbid depressive and anxiety symptomatology that use maintenance treatment with antidepressants.

In the following chapter we describe the patients on maintenance treatment with antidepressants and relate characteristics of these patients to guideline recommendations for maintenance treatment (whether they are evidence-based or not).
Abstract

Background
There is hardly evidence on maintenance treatment with antidepressants in primary care. Nevertheless, depression guidelines recommend maintenance treatment i.e. treatment to prevent recurrences, in patients with high risk of recurrence, and many patients use maintenance treatment with antidepressants. This study explores the characteristics of patients on maintenance treatment with antidepressants in general practice, and compares these characteristics with guideline recommendations for maintenance treatment.

Methods
We used data (baseline, two-year and four-year follow-up) of primary care respondents with remitted depressive disorder (≥6 months) from the Netherlands Study of Depression and Anxiety (n=776). Maintenance treatment was defined as the use of an antidepressant for ≥12 months. Multilevel logistic regression was used to describe the association between sociodemographic, clinical and care characteristics and use of maintenance treatment with antidepressants.

Results
Older patients, patients with a lower education, those using benzodiazepines or receiving psychological/psychiatric care and patients with a concurrent history of a dysthymic or anxiety disorder more often received maintenance treatment with antidepressants.

Limitations
Measurements were not made at the start of an episode, but at predetermined points in time.

Conclusions
Since patients with chronic or recurrent depression do not use maintenance treatment with antidepressants more often, characteristics of patients on maintenance treatment do not fully correspond with guideline recommendations. However, patients on maintenance treatment appear to be those with more severe disorder and/or more comorbidity.
Introduction
Depression is a common condition that has a chronic or recurrent course in a significant proportion of cases (1). Most patients are treated in primary care (2,3). Treatment in primary care may consist of counselling by the general practitioner, various forms of psychotherapy and/or antidepressants (4). Many studies have provided evidence for continuation of antidepressants after remission to prevent relapses. Far less evidence is available for treatment after this continuation phase, to prevent recurrences, known as maintenance treatment (5,6). Most guidelines do recommend maintenance treatment, of various durations, in a subgroup of patients with high risk of recurrence. However, the various guidelines, such as the NICE guideline depression in adults, the ICSI Health Care guideline major depression in adults in primary care and the Dutch General practitioners guideline depression (NHG-standaard Depressieve stoornis) use different indicators for patients at increased risk of recurrence (5,7-11). Almost all guidelines recommend maintenance treatment with antidepressants in case of recurrent depression, some also after a first episode if it was a severe or chronic episode. Less frequently the following criteria are used in some guidelines: residual symptoms, stressors or lack of support, concurrent other DSM-IV axis I or II disorders, age <30 or >65, rapid relapse or recurrence in the past and family history of major depressive disorder (5).

In a previous paper based on data from the Netherlands Study on Depression and Anxiety (NESDA), we reported that only 5.4% of patients receiving antidepressants in Dutch primary care, do use their antidepressant without a justified indication according to the primary care guidelines depression and anxiety (12). In the same study we found that over half of the patients without a current justification had started to use antidepressants with a justification in the past. Apparently, a proportion of patients using antidepressants, decide to continue them for years after recovery.

Currently, we do not know which of these patients should indeed be advised to continue using their antidepressant to prevent recurrences and which patients could “safely” be advised to discontinue them. Studying the patients of our previous study in more detail may shed some light on the reasons behind their decision to continue or to discontinue their antidepressant. More specifically, we were interested to know whether patients using antidepressants as maintenance treatment have ‘valid’ reasons for that. Therefore, we decided to compare sociodemographic, clinical and
care characteristics of remitted patients (in remission for at least six months) with and without maintenance treatment (antidepressant use ≥12 months). Subsequently we compared these characteristics with guideline recommendations for maintenance treatment. We hypothesized a priori that most patients on maintenance treatment would meet one or more guideline criteria (Dutch primary care guideline depression 2003) for maintenance treatment such as a recurrent or chronic depression and that these patients more often would have a comorbid anxiety disorder than patients without maintenance treatment.

**Methods**
This study was conducted with data from NESDA (www.nesda.nl), a large prospective cohort study (n=2981) on the course of depression and anxiety disorders among respondents aged 18-65 years, recruited from the community, primary care and secondary mental health care. Detailed information on the objectives, study population and methods of NESDA has been published (13).

**Study sample**
The current study used data from the baseline, two-year and four-year follow-up measurements/interviews of NESDA on only respondents recruited from primary care. We decided to use data on these respondents only since we wanted a representative primary care sample. Recruitment was described in detail elsewhere (13). Briefly, recruitment in primary care went as follows. A written screener was sent to 23,750 primary care patients that consulted their general practitioner in the past four months, irrespective of the reason for consultation. The screener was returned by 10,706 persons (45%). The non-responders showed no bias with regard to psychopathology (14). Those screening positive were approached for a telephone interview consisting of the Composite International Diagnostic Interview Short Form sections (CIDI-SF), which has proven diagnostic quality for screening purposes (15,16). Respondents fulfilling criteria for a current disorder on the CIDI-SF were invited to participate, as were a random selection of screen-negatives, both from the written screener and the CIDI-SF. In total, 1610 persons were recruited, who underwent an extensive baseline interview, including the CIDI (17,18). The GP was not aware of the results of the screening or the interview. After two years and after four years the interview, including the CIDI was repeated.
We included those patients that had recovered from a major depressive disorder at least more than 6 months ago according to the CIDI at that moment (either baseline interview, two-year follow-up or four-year follow-up), i.e. those with a lifetime major depressive disorder but not in the past 6 months (n=776). Some patients fulfilled the criteria for inclusion on multiple occasions e.g. at baseline and two-year follow-up. We included them separately for each interview moment. In total we had 1571 observations of remitted depression.

Definition of maintenance treatment and other long-term treatment
All depression guidelines mentioned in the introduction recommend continuation treatment with antidepressants, after having achieved remission with an antidepressant, to prevent relapses. The recommended duration for continuation treatment varies between four and twelve months. Maintenance treatment is defined as all treatment with antidepressants beyond this period. Therefore, in our analysis we define maintenance treatment as all treatment with antidepressants ≥12 months in patients with depression that has been in remission for at least six months. With short-term use we refer to all use of antidepressants for less than 12 months.

Determinants of maintenance use
A detailed description of all measures applied in NESDA has been published (13). All characteristics were measured at each interview.

Sociodemographic characteristics including age, gender and education were self-reported by the patient during the interview, work status was assessed with the Trimbos/iMTA questionnaire for assessment of Costs associated with Psychiatric illness (19-21).

Clinical characteristics including current and past (last 6 months, last year, lifetime) diagnoses of MDD and dysthymia, comorbid anxiety disorders (panic disorder with and without agoraphobia, agoraphobia, social phobia and generalised anxiety disorder) were all assessed with the CIDI and severity of depression with the IDS (Inventory of Depressive Symptomatology) and of anxiety with the BAI (Becks Anxiety Inventory) (22,23). The presence of suicide attempts in the past was measured with the Beck Suicide Ideation Scale (24).

Chronic depression, defined as a CIDI diagnosis of depression and symptoms of depression for more than 24 months and recurrent depression defined as more
than one episode of MDD in the past, were assessed during the interviews using the CIDI and life chart data. The life chart is a method for recalling depressive or anxious symptomatology, the respondent was asked during the interview to mention several important (personal) events from the last several years and was subsequently asked to recall if there was some depressive (or anxious) symptomatology at that point. The life chart has been proven useful to assess course of illness in patients with mood disorders (25-27).

Personality traits (neuroticism and extraversion) were assessed with the Neuroticism-Extraversion-Openness-Five-Factor-Inventory (NEO-FFI). The number of chronic somatic diseases was derived from the Trimbos/iMTA questionnaire for assessment of Costs associated with Psychiatric illness (19-21).

**Care characteristics:** During the interviews the respondents were asked if they had had contact with the GP in the last six months, the number of contacts with the GP in the last six months, if any of these contacts with the GP had been about mental problems, the type of help they received (information, a referral to a specialist/mental health care professional, psychotherapy, practical support, skills-training, other help or no help), if they had perceived need for more or any other form of treatment and if they had had contact with primary (social worker, social psychiatric nurse, first line psychologist, psychotherapist) or secondary (psychiatrist, professional from a mental health care organisation) mental health care.

The respondents had been asked to bring all medication they had used in the past month to the interview; the use of antidepressants and benzodiazepines was then recorded by the interviewer according to the World Health Organization Anatomical Therapeutic chemical (ATC) classification. 35.3% of all respondents had forgotten to bring their medication; antidepressant use was based on self-report in these subjects. Use of antidepressants included selective serotonin reuptake inhibitors (ATC-code N06AB), tricyclic antidepressants (N06AA) and other antidepressants (N06AF/N06AX). St. John’s wort was not considered an antidepressant. Past use of antidepressants and duration of use of currently used antidepressants was based on self-report.

**Ethical considerations**
The study protocol of NESDA was approved centrally by the Ethical Review Board of the VU University Medical Center and subsequently by local review boards of each
Characteristics of maintenance antidepressant users

participating center. After full verbal and written information about the study, written informed consent was obtained from all participants at the start of baseline assessment. A full ethics statement of NESDA is found elsewhere.

**Statistical methods**

The Statistical Package for the Social Sciences version 20.0 for Mac was used for the descriptive statistics to describe the study population (IBM Statistics, Chicago, USA). The definition “maintenance antidepressant treatment” as described above was used as the dependent variable. We chose to dichotomize this outcome variable (maintenance antidepressant use; n=271 versus no antidepressant use or acute/continuation antidepressant use n=1302) since a dichotomous outcome measure simplifies interpretation of the results and enabled us to calculate chances in terms of percentages on patient level in the final prediction model.

The prediction of all independent variables on our dependent variable “maintenance antidepressant treatment” were analysed with bivariate multilevel logistic regression. To prevent multicollinearity, we excluded from these one of each pair of continuous variables with a mutual correlation >0.7 and dichotomous variables with ≤5.0% of respondents in one of the categories.

To determine which variables independently predicted maintenance treatment or other long-term treatment logistic multilevel analysis was conducted using MLwiN 2.25. Multilevel models are hierarchical systems that estimate regression coefficients and their variance components while at the same time correct for the dependency of the repeated measurements (baseline, two-year and four-year follow-up measurements). The first level was defined as observation (within patient), the second level as patient (between patients). The outcome variables represented the logit of the probability (i.e. natural log of the odds) of maintenance antidepressant treatment of depression. Regression coefficients were transformed into odds ratios by taking the EXP[regression coefficient]. The Wald test was used to obtain a p value for each regression coefficient. The Wald test was also used on the variance parameters to obtain an indication of the necessity for allowing a random intercept or regression coefficient into the model (28). Based on a stepwise backward selection procedure, a final model was fitted consisting of only significant factors that constituted the predictors for long-term/maintenance treatment with antidepressants in the present study.
Results

Study sample
The first column of Table 1 lists the characteristics of the study sample. Several dichotomous characteristics had ≤5% in one category and were excluded and not listed in this table (the use of a tricyclic or other antidepressant, whether the respondent had received skills-training, practical support, other help or no help and long-term use of antidepressants in the past).

Antidepressant and long-term antidepressant use
Out of 1610 primary care respondents, 776 had remitted depression (lifetime MDD and no depression in the past six months), these respondents had a total of 1571 measurements of remitted depression. 1261 times no antidepressant was used, in 41 occasions an antidepressant was currently used for less than 12 months and 271 cases there was maintenance treatment with antidepressants (antidepressant use ≥12 months).

The characteristics of each of these three groups are listed in the right three columns of table 1.
## Characteristics of maintenance antidepressant users

<table>
<thead>
<tr>
<th></th>
<th>All measurements (1571)</th>
<th>No antidepressant use (1261)</th>
<th>Acute/continuation antidepressant use (41)</th>
<th>Maintenance antidepressant use (271)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sociodemographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age in years, mean (SD)</td>
<td>48.1 (11.8)</td>
<td>47.5 (12.1)</td>
<td>45.2 (9.6)</td>
<td>51.3 (9.5)</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>1136 (72.3%)</td>
<td>912 (72.3%)</td>
<td>30 (73.2%)</td>
<td>195 (72.0%)</td>
</tr>
<tr>
<td>Education (high)(^1)</td>
<td>700 (44.6%)</td>
<td>598 (47.4%)</td>
<td>16 (39.0%)</td>
<td>88 (32.5%)</td>
</tr>
<tr>
<td>Working</td>
<td>1014 (64.5%)</td>
<td>823 (65.3%)</td>
<td>25 (61.0%)</td>
<td>168 (62.0%)</td>
</tr>
<tr>
<td><strong>Clinical characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. chronic somatic diseases, mean (SD)</td>
<td>0.9 (1.1)</td>
<td>0.9 (1.0)</td>
<td>1.0 (1.2)</td>
<td>1.0 (1.2)</td>
</tr>
<tr>
<td>IDS(^2) (moderate-severe)</td>
<td>272 (17.3%)</td>
<td>198 (15.7%)</td>
<td>15 (36.6%)</td>
<td>60 (22.1%)</td>
</tr>
<tr>
<td>BAI(^3) (moderate-severe)</td>
<td>174 (11.1%)</td>
<td>126 (10.0%)</td>
<td>8 (19.5%)</td>
<td>40 (14.8%)</td>
</tr>
<tr>
<td>Neuroticism, mean (SD)</td>
<td>34.2 (7.7)</td>
<td>33.9 (7.7)</td>
<td>38.1 (7.1)</td>
<td>35.3 (7.8)</td>
</tr>
<tr>
<td>Extraversion, mean (SD)</td>
<td>37.6 (6.7)</td>
<td>38.0 (6.5)</td>
<td>35.9 (7.3)</td>
<td>36.0 (7.0)</td>
</tr>
<tr>
<td>Suicide-attempt</td>
<td>113 (7.2%)</td>
<td>89 (7.1%)</td>
<td>4 (9.8%)</td>
<td>20 (7.4%)</td>
</tr>
<tr>
<td>Dysthymia lifetime</td>
<td>453 (28.8%)</td>
<td>323 (25.6%)</td>
<td>13 (31.7%)</td>
<td>117 (43.2%)</td>
</tr>
<tr>
<td>Recurrent MDD</td>
<td>888 (56.5%)</td>
<td>712 (56.5%)</td>
<td>23 (56.1%)</td>
<td>153 (56.5%)</td>
</tr>
<tr>
<td>Chronic depression</td>
<td>252 (16.0%)</td>
<td>191 (15.1%)</td>
<td>5 (12.2%)</td>
<td>56 (20.7%)</td>
</tr>
<tr>
<td>Anxiety(^4) lifetime incl. &lt;6 months</td>
<td>434 (27.6%)</td>
<td>324 (25.7%)</td>
<td>22 (53.7%)</td>
<td>88 (32.5%)</td>
</tr>
<tr>
<td>Anxiety(^5) lifetime incl. &lt;12 months</td>
<td>1070 (68.1%)</td>
<td>811 (64.3%)</td>
<td>32 (78.0%)</td>
<td>229 (84.5%)</td>
</tr>
<tr>
<td>Care characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contact with GP &lt;6 months</td>
<td>1232 (78.4%)</td>
<td>982 (77.9%)</td>
<td>34 (82.9%)</td>
<td>217 (80.1%)</td>
</tr>
<tr>
<td>No. of contacts GP &lt;6 months, mean (SD)</td>
<td>2.2 (2.5)</td>
<td>2.1 (2.3)</td>
<td>3.3 (3.6)</td>
<td>2.6 (3.4)</td>
</tr>
<tr>
<td>Contact GP about mental disorder</td>
<td>219 (13.9%)</td>
<td>140 (11.1%)</td>
<td>24 (58.5%)</td>
<td>56 (20.7%)</td>
</tr>
<tr>
<td>Received information</td>
<td>249 (15.8%)</td>
<td>171 (13.6%)</td>
<td>20 (48.8%)</td>
<td>59 (21.8%)</td>
</tr>
<tr>
<td>Received psychotherapy</td>
<td>199 (12.7%)</td>
<td>128 (10.2%)</td>
<td>21 (51.2%)</td>
<td>51 (18.8%)</td>
</tr>
<tr>
<td>Perceived need for more or other treatment</td>
<td>346 (22.0%)</td>
<td>252 (20.0%)</td>
<td>24 (58.5%)</td>
<td>71 (26.2%)</td>
</tr>
<tr>
<td>Psychological/psychiatric care past six months(^5)</td>
<td>511 (32.5%)</td>
<td>358 (28.4%)</td>
<td>33 (80.5%)</td>
<td>121 (44.6%)</td>
</tr>
<tr>
<td>Past antidepressant use</td>
<td>127 (8.1%)</td>
<td>100 (7.9%)</td>
<td>7 (17.1%)</td>
<td>20 (7.4%)</td>
</tr>
<tr>
<td>Benzodiazepine use</td>
<td>178 (11.3%)</td>
<td>105 (8.3%)</td>
<td>10 (24.4%)</td>
<td>63 (23.2%)</td>
</tr>
<tr>
<td>SSRI(^6) current</td>
<td>248 (15.8%)</td>
<td>N/A</td>
<td>29 (70.7%)</td>
<td>219 (80.8%)</td>
</tr>
</tbody>
</table>

All numbers are number of participants with characteristic (percentage) unless otherwise specified.

In all dichotomous variables 0=no/characteristic not present, 1=yes/characteristic present.

\(^1\) Low-average (elementary (not completed), general intermediate, lower/intermediate vocational, or general secondary education) versus high (higher vocational, college or university education).

\(^2\) Inventory of depressive symptomatology; depression severity. None-mild disorder versus moderate to (very) severe disorder.

\(^3\) Beck's anxiety inventory; anxiety severity. None-mild disorder versus moderate to severe disorder.

\(^4\) Anxiety disorder (panic disorder with or without agoraphobia, agoraphobia, social phobia or generalized anxiety disorder).

\(^5\) Primary mental health care/psychological care: social worker, social psychiatric nurse, first line psychologist, psychotherapist; secondary mental health care/psychiatric care: psychiatrist, professional from a mental health care organisation.

\(^6\) Selective Serotonin Reuptake Inhibitors.
Determinants of maintenance antidepressant use in remitted patients

Bivariate analysis

After excluding variables with a mutual correlation >0.7 (received psychotherapy because of correlation with psychological/psychiatric care) and exclusion of the variable current SSRI use (this variable would obscure results as most antidepressants users used an SSRI and almost all antidepressant users were maintenance users), we did a bivariate multilevel logistic regression (table 2). Eight variables were significantly (p<0.05) associated with maintenance treatment with antidepressants.

Sociodemographic characteristics: Increasing age led to more maintenance treatment, while a high education decreased the chances for maintenance treatment with antidepressants. Personality characteristics were also associated with maintenance treatment with antidepressants. Increasing extraversion led to less maintenance treatment.

Clinical characteristics: A history of anxiety disorders or dysthymia also led to more maintenance treatment, as did a chronic depression in the past.

Care characteristics: Receiving care from a mental health professional (psychological or psychiatric care) led to increased chance of maintenance treatment with antidepressants. Finally the use of benzodiazepines increased the ‘risk’ of receiving maintenance treatment with antidepressants. Contact with the GP whether or not about mental problems did not reach significance. Also receiving information or a referral to a specialist remained non-significant.
Table 2 Results of bivariate multilevel logistic regression in patients remitted depression with dependent variable ‘maintenance treatment with antidepressants’ (1571 observations in 776 individual patients)

<table>
<thead>
<tr>
<th>Remitted patients (1571 observations)</th>
<th>Odds ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sociodemographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age in years</td>
<td>1.035 (1.018-1.051)</td>
<td>0.000</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>1.016 (0.685-1.507)</td>
<td>0.937</td>
</tr>
<tr>
<td>Education&lt;sup&gt;1&lt;/sup&gt; (high)</td>
<td>1.742 (1.219-2.489)</td>
<td>0.002</td>
</tr>
<tr>
<td>Working</td>
<td>0.863 (0.615-1.212)</td>
<td>0.395</td>
</tr>
<tr>
<td><strong>Clinical characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. chronic somatic diseases</td>
<td>1.065 (0.916-1.239)</td>
<td>0.413</td>
</tr>
<tr>
<td>IDS&lt;sup&gt;2&lt;/sup&gt; (mod/severe)</td>
<td>1.293 (0.874-1.914)</td>
<td>0.199</td>
</tr>
<tr>
<td>BAI&lt;sup&gt;3&lt;/sup&gt; (mod/severe)</td>
<td>1.250 (0.779-2.004)</td>
<td>0.355</td>
</tr>
<tr>
<td>Neuroticism</td>
<td>1.015 (0.993-1.037)</td>
<td>0.173</td>
</tr>
<tr>
<td>Extraversion</td>
<td>0.965 (0.940-0.990)</td>
<td>0.006</td>
</tr>
<tr>
<td>Suicide attempt</td>
<td>1.024 (0.570-1.841)</td>
<td>0.936</td>
</tr>
<tr>
<td>Dysthymia lifetime</td>
<td>2.226 (1.537-3.223)</td>
<td>0.000</td>
</tr>
<tr>
<td>MDD &lt;12 months</td>
<td>1.209 (0.754-1.939)</td>
<td>0.430</td>
</tr>
<tr>
<td>Recurrent MDD</td>
<td>1.043 (0.734-1.481)</td>
<td>0.814</td>
</tr>
<tr>
<td>Chronic depression</td>
<td>1.587 (1.017-2.477)</td>
<td>0.042</td>
</tr>
<tr>
<td>Anxiety&lt;sup&gt;4&lt;/sup&gt; &lt;12 months</td>
<td>1.171 (0.836-1.641)</td>
<td>0.358</td>
</tr>
<tr>
<td>Anxiety&lt;sup&gt;4&lt;/sup&gt; lifetime</td>
<td>2.910 (1.902-4.452)</td>
<td>0.000</td>
</tr>
<tr>
<td><strong>Care characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contact with GP &lt;6 months</td>
<td>1.129 (0.779-1.635)</td>
<td>0.522</td>
</tr>
<tr>
<td>No. of contacts GP &lt;6 months</td>
<td>1.045 (0.987-1.106)</td>
<td>0.129</td>
</tr>
<tr>
<td>Contact GP about mental problems</td>
<td>1.411 (0.938-2.121)</td>
<td>0.098</td>
</tr>
<tr>
<td>Received information</td>
<td>1.406 (0.952-2.077)</td>
<td>0.087</td>
</tr>
<tr>
<td>Received referral</td>
<td>1.496 (0.980-2.285)</td>
<td>0.062</td>
</tr>
<tr>
<td>Received psychotherapy</td>
<td>1.232 (0.859-1.768)</td>
<td>0.256</td>
</tr>
<tr>
<td>Perceived need for more or other</td>
<td>1.174 (0.833-1.654)</td>
<td>0.361</td>
</tr>
<tr>
<td>treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychological/psychiatric care&lt;sup&gt;5&lt;/sup&gt;</td>
<td>1.584 (1.149-2.185)</td>
<td>0.005</td>
</tr>
<tr>
<td>Past antidepressant use</td>
<td>0.660 (0.364-1.198)</td>
<td>0.172</td>
</tr>
<tr>
<td>Benzodiazepine use</td>
<td>2.389 (1.528-3.735)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

In all dichotomous variables 0=no/characteristic not present, 1=yes/characteristic present

<sup>1</sup> Low-average (elementary (not completed), general intermediate, lower/intermediate vocational, or general secondary education) versus high (higher vocational, college or university education)

<sup>2</sup> Inventory of depressive symptomatology; depression severity. None-mild disorder versus moderate to (very) severe disorder

<sup>3</sup> Beck’s anxiety inventory; anxiety severity, none-mild disorder versus moderate to severe disorder

<sup>4</sup> Anxiety disorder (panic disorder with or without agoraphobia, agoraphobia, social phobia or generalized anxiety disorder)

<sup>5</sup> Primary mental health care/psychological care: social worker, social psychiatric nurse, first line psychologist, psychotherapist; secondary mental health care/psychiatric care: psychiatrist, professional from a mental health care organisation, care in the past six months

**Multivariate analysis**

Next, multivariate multilevel logistic regression was performed (table 3). For multivariate analysis, we included all characteristics from the bivariate analyses with p<0.2. Six variables were retained in the final multivariate model. Age (in years),
Characteristics of maintenance antidepressant users

education (0=low-intermediate, 1=high), having a history of dysthymic disorder or an anxiety disorder (0=no, 1=yes), having received psychological or psychiatric care in the past six months and the current use of benzodiazepines (0=no, 1=yes).

Table 3 Results of multivariate multilevel logistic regression in patients with remitted depression (1571 observations in 776 individual patients) with dependent variable “maintenance treatment with antidepressants”

<table>
<thead>
<tr>
<th>Odd ratio</th>
<th>95% CI for odds ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sociodemographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (in years)</td>
<td>1.033</td>
<td>1.014-1.051</td>
</tr>
<tr>
<td>Education(^1) (high)</td>
<td>0.645</td>
<td>0.440-0.945</td>
</tr>
<tr>
<td><strong>Clinical characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysthymia lifetime</td>
<td>1.891</td>
<td>1.290-2.771</td>
</tr>
<tr>
<td>Anxiety lifetime(^2)</td>
<td>2.300</td>
<td>1.474-3.589</td>
</tr>
<tr>
<td><strong>Care characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychological/psychiatric care past six months(^3)</td>
<td>1.644</td>
<td>1.164-2.321</td>
</tr>
<tr>
<td>Benzodiazepine use</td>
<td>2.046</td>
<td>1.283-3.262</td>
</tr>
</tbody>
</table>

In all dichotomous variables 0=no/characteristic not present, 1=yes/characteristic present

\(^1\) Low-average (elementary (not completed), general intermediate, lower/intermediate vocational, or general secondary education) versus high (higher vocational, college or university education)

\(^2\) Anxiety disorder (panic disorder with or without agoraphobia, agoraphobia, social phobia or generalized anxiety disorder)

\(^3\) Primary mental health care/psychological care: social worker, social psychiatric nurse, first line psychologist, psychotherapist; secondary mental health care/psychiatric care: psychiatrist, professional from a mental health care organisation

**Discussion**

**Summary of main findings**

Several characteristics of the patient, disease and treatment were associated with maintenance use of antidepressants in remitted depressed patients. Remarkably, both recurrent depression and chronic depression were not, this hypothesis was rejected. Our other hypothesis that patients with a comorbid anxiety disorder would more often be on maintenance treatment with antidepressants was confirmed. A dysthymic disorder in previous history had the same effect, which was unexpected since acute treatment with antidepressants in this disorder is not first step treatment and should be considered as a trial. It could be that GPs view dysthymic disorder as a mild chronic depression, or that these patients are reluctant to stop their antidepressant because of frequent relapses. Older patients and those with a low or intermediate education more often had maintenance treatment with antidepressants. We think that older patients less often ‘ask’ their GP or another physician if a certain medication can be stopped. Patients with a higher education might favour...
psychotherapy instead of antidepressant treatment, or GPs might think that patients with a lower education are less able to benefit from psychotherapy. The fact that patients on maintenance treatment more often use benzodiazepines is probably related to symptoms of anxiety for which these drugs are frequently prescribed.

Patients on maintenance treatment had received more often psychological/psychiatric care. We expected that this difference was due to the reception of more psychiatric care, since we had expected patients on maintenance treatment to be patients with recurrent, chronic or more severe depression. Therefore we performed a post-hoc analysis and found that patients on maintenance antidepressant treatment had indeed received more psychiatric (19.5% versus 7.3%) and not more psychological (25.0% versus 22.5%) care. These patients could be more severely ill and therefore have a good reason for maintenance antidepressant treatment, or GPs have less insight in patients (previously) treated in secondary mental health care but do repeat their prescriptions as a result of which antidepressant treatment is not critically evaluated.

The number of contacts with the GP and whether the patient had had contact with the GP about mental problems in the last six months were not correlated to maintenance treatment, as we would have expected. An explanation for this could be that patients with a history of depression in general visit their GP frequently and not just those on maintenance treatment with antidepressants.

Severity (IDS) was not significant, probably since severity was not measured at the start of the episode, but instead at predetermined points in time during the interviews, at which time we selected patients in remission, i.e. without current disorder and therefore probably not a high severity score.

Strengths and limitations
The present study has several strong points. First, our study group was large, especially for a primary care study. Second, the data collected within NESDA is extensive, enabling us to examine many possible determinants. Third, since the GP was unaware of the study diagnosis, all treatment decisions were based on their own judgment, preventing bias. Fourth, since we had several measurements, we could quite accurately determine the time of remission and presence of maintenance antidepressant treatment with antidepressants.
This study also has some limitations that need addressing. First, since variables such as depression and anxiety severity were not measured at the start of the episode or start of the antidepressant, we could not be sure that no relationship between severity and maintenance treatment with antidepressants exists. Next to that, although the CIDI was administered at three different times, we could not be sure of the exact moment of remission and therefore had to use a slightly less accurate definition of maintenance treatment (treatment with antidepressants for ≥12 months, while there was no depression in the past six months), because the guideline recommends continuation treatment for all patients for six months.

Comparison with literature
Only few articles report on determinants of maintenance treatment with antidepressants in primary care. A few researchers did study risk factors for non-adherence to continuation and maintenance treatment. Burton et al. studied factors associated with the duration of antidepressant treatment, 40% of their patients continued their antidepressant for more than 180 days. They did not find an association between continuation and sociodemographic factors such as age, gender and socioeconomic deprivation. We did find an association between maintenance treatment with antidepressants and both age and education level. Treatment >180 days could be viewed as continuation or maintenance treatment but is probably in most cases shorter than our definition of maintenance treatment. It could be that the differences arise after longer treatment (29). Holma et al. found several indicators of receiving maintenance treatment in the univariate analyses: number of previous episodes, comorbid somatic disorders and comorbid mental disorders, severity of anxiety, anxiety disorders, positive medication attitude, personality disorder and good adherence during the acute phase of treatment. In their multivariate analysis only good adherence to acute phase antidepressant treatment remained significant, we did not study this, but did find a significant association between maintenance treatment and anxiety disorders as they did in their univariate analyses (30). Finally Ten Doesschate et al. examined potential predictors of non-adherence to continuation and maintenance antidepressant use and found that in multivariate analysis personality (measured with the Personality Disorder Questionnaire-4+) and a higher education were associated with an increasing likelihood for non-adherence. A higher education decreased likelihood of maintenance treatment in our study,
comparable to the result of ten Doesschate et al. (31). The personality characteristic extraversion was only significant in the bivariate analysis in our study.

We could not find any other studies that had studied or found dysthymia and/or benzodiazepine use to increase likelihood of receiving maintenance treatment with antidepressants.

Comparison with guideline recommendations
As mentioned in the introduction, it is also interesting to compare our results with guideline recommendations for maintenance treatment. Depression guidelines, including the Dutch General Practitioners guideline, recommend maintenance treatment with antidepressants for patients at high risk for relapse and/or recurrence or chronic depression. As we stated in a review in 2010, different guidelines have different indicators of patients at high risk for chronic or recurrent course of depression (5). The Dutch guideline we used, used the following indicators: recurrent or chronic depression and/or failure of non-pharmacological treatment, or in case of residual or recurrent symptoms after phasing out antidepressants (4). We would expect these established risk factors for unfavourable course to be determinants of maintenance use.

We were very surprised to find that recurrent and chronic depression were not more common in patients with maintenance antidepressant treatment, since these were the two key indications for maintenance antidepressant treatment in patients with depression according to the Dutch General practitioners guideline (and other guidelines). Since chronic depression was significant in the bivariate analysis it could be that any effect was overshadowed in the multivariate analysis by the fact that these patients e.g. more often received psychological or psychiatric care since chronic depression is also an indication for referral (4). In an article about referral of depressed patients we did indeed find that chronically depressed patients were referred more often (32). Recurrent depression did not reach significance or even a trend towards significance in the bivariate analysis. We found it difficult to explain this unexpected finding. One explanation would be that maintenance treatment is prescribed more often only to patients with a high number of previous episodes instead of to all patients with a recurrent episode. Since recall bias of number of episodes is a problem, we decided not to analyse number of episodes. The new Dutch GP guideline depression (2012) even recommends reserving maintenance
Characteristics of maintenance antidepressant users

treatment with antidepressants for patients with more than three episodes of depression (33).

The presence of an anxiety disorder increased likelihood of receiving maintenance antidepressant treatment. All anxiety disorders tested in this study are legitimate indications for the prescription of an antidepressant and the guideline anxiety disorders recommends to continue the antidepressant for at least six to twelve months after remission (34). A significant proportion of our population probably do not use maintenance antidepressant treatment for remitted depression, but instead with a good indication for an anxiety disorder.

Implications for clinical practice and future research

Not only patients with a comorbid anxiety disorder, but also those with a history of a dysthymic disorder, older patients, lower educated patients and those receiving psychiatric care or benzodiazepines more often use maintenance treatment with antidepressants and remarkably not patients with a recurrent or chronic disorder. GPs should be aware of patients with maintenance antidepressant treatment and individually weigh the risks of stopping versus the disadvantages of continuing the drug, together with the patient. As patients with a dysthymic disorder have a questionable indication for antidepressant use, the dubious advantages and more clear disadvantages of continuing should be critically discussed in these patients. In all patients, but maybe especially in older patients and those with a lower education, it might be necessary for the GP to initiate the discussion about continuation or discontinuation of antidepressant treatment, since these patients seem to use maintenance treatment more often while it is unclear if they have a higher risk of recurrence. Finally, in patients referred back from secondary mental health care on antidepressant treatment, the GP might propose a consultation once or twice yearly, as also proposed in the recent new Dutch GP guideline depression. This consultation could according to the new guideline not only be used to discuss the need to continue the antidepressant, but also to notice signs of impending relapse or recurrence at an early stage.

The role of views of the GP has not yet been studied. It would be interesting if a positive or negative attitude of GPs towards both depressed patients, their views of their task in treating depression and their views of the efficacy and place of antidepressants in depression treatment, influences treatment with antidepressants in
their patients. Next to that, additional analysis is needed among antidepressant users to identify those ‘at risk’ for long-term treatment, since in our group also non-users were present. Finally, another interesting group to study in more detail are patients with persisting depression that have been using an antidepressant for over a year. It would be interesting to find out who these, in some way undertreated, patients are and how we could help these patients to recover.
References


(8) Institute for Clinical Systems Improvement. ICSI Health Care guideline: Major depression in Adults in Primary Care. 2009; Available at: http://www.icsi.org/depression_5/depression_major_in_adults_in_primary_care_3.html.


Characteristics of maintenance antidepressant users


Characteristics of maintenance antidepressant users


Chapter 7

Summary and general discussion
Introduction
Depression is a common condition, causing great amounts of morbidity due to its often recurrent and sometimes chronic course. It is projected that depression will be the second leading cause of disability worldwide by 2020 and the leading cause of disease burden by 2030 (1,2). Most patients with depression are treated in primary care (3,4). This makes the care for depression in primary care a subject of great interest and importance.

In past years both in the media and in the scientific literature there was a lot of attention for depression in primary care. In the (Dutch) media the discussion focused mainly on “overrecognition” and “overtreatment”. It was stated that patients with depressive symptoms, e.g. as a reaction to negative life events, are often incorrectly diagnosed with depression and are often unnecessarily treated with antidepressants, which are not or minimally effective in these patients while also causing serious side effects (5-7). In the scientific literature underrecognition and undertreatment seemed to be the main subject. Many patients with depression remain unrecognized and of those recognized, the large part does not receive adequate treatment e.g. psychotherapy or pharmacotherapy with an antidepressant.

These discussions are not new. In the 1980s and 1990s care for depressed patients in primary care was a frequently studied subject, also in The Netherlands as illustrated by the appearance of many theses.

The aim of this thesis was to investigate current care for depressed patients in primary care. This thesis could thereby form a possible starting point for further improvement in order to decrease burden of this disease. In this chapter we will summarize the findings from chapter 2 through 6 and discuss them in the light of previous as well as recent literature. We will conclude with a discussion about future practice and research.

Main findings
General conclusion
Overall this thesis gives a rather optimistic picture of current care for depressed patients in primary care compared to previous literature and media reports. We conclude that, in general, the care for depression in primary care is, in most cases, adequate, i.e. in accordance with the recommendations of the ruling primary care
summary and general discussion

guideline for depression, as it existed in the years the studies were performed (2004-2009).

Recognition
Recognition was adequate with 60.5-68.7% of depressed patients recognized by the general practitioner (GP) (chapter 2). Patients in this study were 484 participants of the Netherlands Study of Depression and Anxiety (NESDA) who were recruited from 65 primary care practices in and around Amsterdam, Leiden and Groningen and who were found to have a life-time diagnosis of major depressive disorders (MDD). Two risk factors (determinants) for non-recognition were found, of which no mental health related reason for visiting the GP was the strongest. Patients without a comorbid anxiety disorder were less often recognized as well. A subgroup-analysis was performed in a subgroup of 361 patients in which the GP used an International Classification for Primary Care code (ICPC-code) (irrespective of the code used) in at least one contact with the patient. This subgroup therefore had more reliable GP diagnosis data, since in the total study population several GPs did not code any contact, making ICPC diagnosis of depression, which was an important part of our definition of recognition, impossible. In this subgroup, just as in the total study population, patients without a mental health related reason for visiting the GP or without a comorbid anxiety disorder were less often recognized. In addition, patients with fewer depressive symptoms and those with an increased appetite were recognized less often.

Referral
In chapter 3 we describe the referral of 344 depressed primary care patients to mental health care professionals by the GP. Also for this study, baseline data of primary care respondents, in this case with a depression in the past year, from NESDA were used. Interestingly, over half (58%) of depressed patients were referred; this was an unexpected high percentage. Equal percentages were referred to primary (first line psychologist, social psychiatric nurse or social worker affiliated with the GP practice) and secondary (psychiatrist or psychotherapist in free practice, or any health care professional affiliated with a hospital or institute for mental health care) mental health care. With logistic regression we tested whether guideline criteria for referral were independent predictors of referral. The Dutch primary care guideline
recommends to refer to secondary mental health care patients with psychotic features, with bipolar disorder, with severe depression with social impairment or with high suicide risk and patients with no or insufficient response to two or more antidepressants. In addition, several guidelines, including the Dutch primary care guideline, recommend referral for psychological interventions in certain cases, although the criteria differ between guidelines.

In our study, younger patients, those with a perceived need for psychotherapy, those with suicidal tendency and with chronic depression were referred more often. Patients with chronic depression or who had used (and stopped) at least two antidepressants were more often referred to secondary mental health care compared to primary mental health care. Referred patients met on average more guideline criteria for referral compared to non-referred patients. We can therefore conclude that GPs do take guideline recommendations into account in decision making for referral of depressed patients. However, other factors play a role as well, since we could only explain 8-11% of variance.

### Treatment with antidepressants

In chapter 4 we report that guideline recommendations for treatment with antidepressants are thoroughly based on evidence when it comes to acute treatment (i.e. up to three months or until remission) and continuation treatment (from four to twelve months after remission to prevent relapses), also in primary care. In contrast however, evidence for maintenance treatment (the treatment phase after continuation treatment during another one, two or even more years to prevent recurrences) is almost completely lacking in primary care. The guideline recommendations for maintenance treatment in primary care are only based on uncontrolled studies mainly performed in secondary and tertiary care.

In chapter 5 we presented a study showing that overtreatment is not a frequently encountered problem in Dutch general practice. We studied the use of antidepressants in a group of 1531 primary care patients, with and without depression and/or anxiety disorders. Of these patients 199 used an antidepressant at time of interview (baseline measurement of NESDA), of whom 188 (94.6%) with a (possibly) justified indication according to the Dutch depression primary care guideline for depression (and for anxiety disorders), leaving 11 patients without a justification. Six (54.5%) of these patients had a single episode of major depressive
disorder more than one year ago. This means that they did have an indication for the use of an antidepressant in the past, while the antidepressant had been continued too long according to guideline recommendations. The other five patients without a (possibly) justified indication never had a justified indication for the use of an antidepressant. As NESDA was designed to study depression and anxiety, patients with these disorders were oversampled. Therefore we recalculated our findings to the original population of primary care patients \( n=10,677 \). The results were the same, only 5.4% of patients on antidepressants had no (possibly) justified indication for the use of these drugs.

Chapter 6 describes the use of maintenance treatment in a sample of primary care patients. We studied the determinants of maintenance treatment of primary care patients with remitted depression. We used data on primary care respondents from NESDA, from the baseline, two-year- and four-year follow-up measurements \( n=776, 1571 \) observations). Unexpectedly, we had to reject our first hypothesis that patients with a chronic and/or recurrent depression would more often use maintenance treatment. Our second hypothesis that patients with a history of anxiety disorder(s) more often were on maintenance antidepressant treatment was confirmed. Remarkably, also patients with a history of dysthymic disorder had an increased likelihood of maintenance treatment with antidepressants. Patients who used benzodiazepines or had had contact with a mental health professional in the past six months had an increased likelihood of maintenance treatment with antidepressants as well. The difference in mental health care use in the last six months was due to a higher percentage receiving secondary mental health care. The percentage receiving primary mental health care was comparable. Finally, older patients and those with a low or intermediate education had an increased chance of using maintenance treatment.

**Historical overview**

**Discussion about depression care from 1980 till now**

In the 1980s and 1990s, there was a heavy scientific debate about recognition and treatment of depression. This discussion focused mainly on poor recognition and treatment in primary (medical) care, since researchers had just found that the majority of patients with depression presented and were treated in this setting. Many researchers studied risk factors for non-recognition and consequences of non-
recognition as well as treatment standards and adequacy of different treatments for depression in primary care (8-11). Different indicators of adequacy of antidepressant prescription were studied, such as the type of depression for which the antidepressants were prescribed and the dosages prescribed (10,12). Other treatments originating in primary care such as referral to primary and secondary mental health care or to various forms of psychotherapy and the effects of these treatments were less often studied (13,14).

The past decade started with the World Health Report of the World Health Organization in 2001 that focused on mental health. In this report it was stated that depression would be the leading cause of disability in the developed world by 2020, and second only to ischaemic heart disease globally. The awareness of the importance of mental disorders grew. Many researchers started studying mental disorders, including depression. In fact, in the 12 years between 2000 and 2011 almost as many articles on depression have been published in PubMed as in the 30 years before the year 2000. By the time this thesis is published, the number of articles published since 2000 will almost certainly have exceeded the number published between 1970 and 2000.

In 2001 the Dutch government launched a large research program called “Geestkracht” for research on mental disorders in order to increase available knowledge about these illnesses and to improve their treatment. The Netherlands Study of Depression and Anxiety (NESDA) started in 2004 and is funded by the “Geestkracht” program. This study was started with the main aim to investigate the long-term course of depressive and anxiety disorders. Almost 3000 people with and without a disorder from the community, primary care and secondary mental health care were included.

The increasing knowledge on depression also reached the media. The media especially picked up on articles questioning the efficacy of antidepressants, (patient) reports about serious side effects and prescription of antidepressants for mild depressive states (5-7,15,16).

**Recognition of depression in primary care from 1980 till now**

Recognition of depression in primary care was found to be poor in the 1980s and 1990s. In most studies the majority of patients with a depressive disorder remained unrecognized, while at the same time a considerable number of patients not fulfilling
Summary and general discussion

criteria for a depressive disorder, were given the diagnosis depression by the primary care physician (8-11).

Recognition of depression has also been a subject of great interest in more recent years. Compared to the studies published in the 1980s and 1990s, these studies have more encouraging results (17-19). More patients are recognized in primary care, although there are large differences between studies. In some countries recognition still seems poor.

Rate of recognition

In the 1980s, Perez-Stable et al. from the United States (US), found that only just over a third of patients with major depressive disorder was recognized as such by the primary care physician and a considerable number without major depressive disorder was given the diagnosis of depression by the primary care physician (8).

In the 1990s, Klinkman et al. also from the US came to the same conclusion. In their study 35% of depressed patients was diagnosed as such by their primary care physician, while almost 30% of patients without depression, was diagnosed as having depression by their primary care physician (9). Klinkman et al. concluded that false positives and false negatives occupied the middle ground in functioning and symptoms between true positives and true negatives. The primary care physician did diagnose patients with severe depression (9). In 1998, Lecrubier reported in a French study that only 54% of depressed patients were recognized by general practitioners as “psychological cases” and only 15% was recognized as being depressed (10).

In a Dutch study Tiemens et al. considered false-positives and false-negatives in another way. They found that in many cases of psychological/psychiatric illness, the patients were recognized as having a mental disorder, but there was disagreement between the GP and the psychiatric assessment about the correct diagnosis or the severity of the illness. This applied especially to the false-negative cases. Most of the false-positive cases were true false positives (55%) (11). In The Netherlands this gave lead to the development of many refresher courses for GPs on the recognition of depression.

After the year 2000, results became more encouraging. In addition, the focus widened. Recognition was no longer considered in yes and no terms and instead severity of depression and need for treatment were taken into consideration. In 2002, Kessler et al. reported a follow up study in the US on patients with depression
according to a psychiatric assessment. The general practitioners had diagnosed 39% of patients with anxiety or depression at baseline. After three year follow up, 64% of patients with depression at baseline had received a diagnosis of depression. Of the patients without diagnosis, most had a spontaneous recovery. Only 14% had not received a diagnosis while still having a clinically severe condition. The authors concluded that general practitioners fail to recognize one out of every seven patients with treatable depression (20).

Other studies reported similar percentages. In a German study by Wittchen et al. 75% of DSM depressed patients was recognized (of ICD-10 depressed patients 59% was recognized) (17). In an Italian study, Berardi et al. found that almost 80% of depressed patients was recognized in primary care. However, they also found that 45% of patients diagnosed with depression by the primary care physician did not fulf ICD-10 criteria for this diagnosis. Over half of these false-positives had a subsyndromal depression (19).

Finally, in a study in the United Kingdom Mitchell et al. specifically studied accuracy of GPs in diagnosing mild depression and distress. GPs diagnosed only one in three patients with mild depression as such, although their specificity was over 80%. They did better in diagnosing distress, as almost half of patients with distress got this “diagnosis”; specificity was the same, around 80%. They concluded that GPs have more difficulty identifying patients with mild compared to moderate-severe depression. Their other conclusion was that although GPs seem to have considerable difficulty in diagnosing patients with mild depression, the implications are unclear, as some of these patients may not want help or do recover spontaneously (21).

The overall picture from the studies performed in the last decade is that the majority of patients are adequately recognized (17,19-21). In addition, awareness regarding the number of false-positives and the consequences of “overrecognition” and consequent “overtreatment” has risen (11,18,19). False-negatives/false-positives and recognition are studied in more detail, acknowledging the fact that depression often coincides with other psychiatric disorders, especially anxiety disorders and that depressive symptomatology is a spectrum and a distinct difference between healthy and depressed does not (always) exist (9,11).
Determinants of (non-)recognition

Several researchers studied risk factors for non-recognition. In several studies low severity was found to be a risk factor, as was younger age (10,11,21,22). Coyne et al. found that severity was a major indicator of recognition: 73.3% of severely depressed patients were recognized, compared to 18.4% of patients with a mild depression. Younger patients more often remained undetected, as did those without comorbid anxiety disorder. Undetected patients also did less often have several specific depression symptoms such as low energy, feeling worn out or failing to get 6 or more hours of sleep. There was also a trend toward less disturbance of appetite in the undetected group (22).

Lecrubier studied factors influencing recognition as well and found that a psychological reason for encounter with the GP made recognition more likely, as did female gender and older age. Recognition increased with increasing severity. Patients with chronic medical conditions were less often recognized (10).

Tiemens et al. compared patient characteristics of true false-negative patients and concordant positive patients and found that the true false-negatives were on average younger, and visited their physician less often for psychological reasons (11). Reason for encounter was also found by several other researchers to be correlated to recognition. More specifically, a psychological reason for encounter led to higher recognition rates while somatic reasons for encounter led to lower recognition rates (23-25). Patients with both acute and chronic somatic diseases are also less often recognized according to studies by Furedi et al. and Henriques et al. (25,26).

Finally, having had prior episodes was found to be associated with better recognition in the studies by Fernandez et al. and by Wittchen et al. (24,27).

Referral of depressed patients to primary and secondary mental health care from the 1980s till now

In previous literature a consistent small minority of patients with psychological complaints was referred to mental health care. Patients with more serious psychiatric diagnoses such as psychosis were more often referred, as were males and younger patients. The GP referred only 5.5% of patients with depressive or anxiety diagnoses according to Verhaak in 1993 (13). Creed et al. found that the number of referrals to psychiatric services by a general practitioner was negatively correlated to the amount
of detail in the referral letter; while in referrals to psychologists there was a positive correlation (14). The number of referrals has increased by a factor 4.5 from the 1970’s to the late 1990’s (28).

More recent studies focused on barriers preventing referral and patient factors influencing referral. Patients more often had a history of depression and an acute or chronic stressor according to Miller et al. (29). Younger patients were more often or older patients less often referred (30,31). Trude and Stoddard investigated whether primary care physicians experienced barriers in referring to mental health care. They found that over half of primary care physicians did experience barriers in the availability of mental health care (32). Physician factors influencing referral behaviour were therapeutic confidence and personal experience according to Kravitz et al. (33). According to Van den Boogaard et al. severity of depression, marital status and also causal attributions related to intrapsychic fears and childhood were associated by being in therapy for 3 sessions or more. Being in therapy meant that referral had taken place (34). Anthony et al. even state that the decision to refer a patient with depression, is a complex one. Practice setting and environment play a role, but also clinician comfort in treating depression, perceived severity and complexity of the disorder, patient preference and patient financial resources are important (35).

Treatment with antidepressants in primary care from 1950s till now
In 1958, the first two antidepressant drugs were discovered: the first tricyclic antidepressant imipramine by Kuhn and the first monoamine oxidase inhibitor iproniazid by Kline. Within several years more antidepressants were developed and marketed. As these antidepressants could have serious side effects and achieving an adequate dose could be difficult, the numbers of patients using these drugs remained stable at quite a low level. With the introduction of zimeldine, fluvoxamine and especially fluoxetine, the first serotonin reuptake inhibitors (SSRIs), this changed in the 1980s. These drugs had fewer side effects and were easier to be dosed at an adequate level. At the same time the introduction of DSM-III (1980) made it easier to make a diagnosis of depression. As a result the prescription of antidepressants, especially the SSRIs, began to grow and experiences became more widely available. It then became apparent that depressive disorders did not behave like a “common cold” and that antidepressants should not be used just until recovery (“acute treatment”) but instead should be continued after remission for at least several
months ("continuation treatment") to prevent relapses. Continuation treatment was promoted for all patients. Even longer treatment for one of more years ("maintenance treatment") became promoted to prevent recurrences, though only for patients with a high recurrence risk. However, it remained unclear which patients did have an increased risk and how long maintenance treatment should last.

While continuation treatment has been widely studied and guideline recommendations for primary care can be considered evidence based, maintenance treatment cannot (chapter 4). There are several reasons for this. First, studies with long follow-up are expensive. And as in all medical specialties, most research is funded by pharmaceutical companies, whose goal is to make profit from the sales of medications. For registration of an antidepressant, only positive data from acute and continuation studies are needed (36).

This means that when short-term and medium-term results are positive, the antidepressant can be brought on the market. Long-term studies (i.e. studies into the use as maintenance treatment) are at that point not necessary. In the case of antidepressants this is further complicated by the fact that existing guidelines already recommend long-term/maintenance treatment for certain patients (and for some patients even lifelong treatment). Therefore, the expected extra profit for pharmaceutical companies in case of positive results is minimal.

Undertreatment

Undertreatment has long been the focus of almost all research on antidepressant use in primary care. In addition to all studies from the 1980s and 1990s reporting underrecognition, many if not most recognized patients did also not get treatment with antidepressants. For example, Lecrubier reported that among the low 15% of patients with a recognized depression in his study, only about 50% was treated with antidepressants (10). Furthermore, antidepressants were often prescribed at inadequate dosages in a significant percentage of cases as shown in a UK study (12). The same authors also discussed monitoring of patients on antidepressants, as about a fifth of patients that had been taking antidepressants for more than six months had depression at the syndromal level, suggesting insufficient care by the general practitioner.

Simon et al. from the US did a broader study on the treatment of depressed patients (37). They found that 66% of patients with major depressive disorder at
baseline had received some form of treatment (either a visit to a mental health professional and/or a prescription for antidepressants) from their primary care physician. Likelihood of treatment was strongly related to severity of illness, patients receiving antidepressants or using specialty mental health services were more symptomatic and more disabled at baseline. Dosage and duration of antidepressants met current standards (Agency for Health Care and Policy Research; AHCPR) in 61% of cases with an antidepressant prescription (38,39). This seemed like an encouraging result, it should be noted however, that Simon et al. used a prevalent sample of depressed patients. It is well known that most patients that discontinue antidepressants, do so in the first weeks of treatment. These patients are probably underrepresented in their study.

Since the year 2000, more articles about undertreatment of depression were published. Lecrubier wrote in a review of three large epidemiologic studies (WHO-study, INSERM and ESEMeD) that in all three studies, the majority of patients with depression did not receive an antidepressant (85%; 79% and 78.8% respectively) (40). In an Italian study 20.9% of patients who would benefit from an antidepressant, received this treatment (41). Most patients who did receive an antidepressant, received a SSRI at therapeutic dosage, while two thirds of tricyclic antidepressants were prescribed at sub-therapeutic dose (41).

Overtreatment?
Overtreatment has long been an underexposed subject compared to undertreatment. As far as we know, the first studies were done in the UK by Sireling et al. (1985) reporting that only 56% of patients treated with antidepressants by the general practitioner because of depressive symptoms, had a major depressive disorder, while 23% had milder depressive diagnoses (42). In patients receiving other treatments such as benzodiazepines, or who were referred to a social worker, only 19% had a major depressive disorder, while 31% had milder depressive diagnoses (43).

In the last few years, more attention has been focused on overtreatment, as it became apparent that antidepressants have side effects and that, especially in primary care, a substantial percentage of patients recovers spontaneously within the first few months. In the Netherlands the general public got interested in the subject because Trudy Dehue’s best seller “De depressie-epidemie” (The depression epidemic) in 2008 (5). This book describes that depression is not increasingly
common, but just more noted and moreover, considered a disease as opposed to a transient state of mind. She suggested that depression was often overtreated, because patients and physicians alike were influenced by the pharmaceutical industry and antidepressants were readily asked for and prescribed. In her opinion it could not be true that over a million Dutch citizens (8% of the Dutch population) were using an antidepressant with a valid indication. Since then, the media picked up on this subject and television programs like “iedereen depressief” (everybody depressed) were made, as well as a broadcast of the consumer programma “Radar” reporting that antidepressants were prescribed unnecessarily for many kinds of complaints while having serious side effects that were ignored by the pharmaceutical industry and prescribers (6,7). In other countries the media also paid attention to the subject (15,16,44).

As previously mentioned in the paragraph about recognition, several researchers came to the conclusion that not all patients diagnosed with depression by the GP, had a major depressive disorder (MDD). Some researchers also found that some of these “false-positive depressed patients”, i.e. patients without an indication for an antidepressant, actually did receive antidepressants (11,22). A study in Spanish primary care by Pinto-Meza et al. (2008) in 333 primary care patients starting antidepressants after diagnosis of depression by the GP showed that only 118 of these patients had MDD and 15 dysthymia, while 81 had minor depression and 119 other forms of depression (45). At least the prescription of antidepressants to patients with minor depression could be considered overtreatment, rendering a percentage of overtreatment of at least 24%. Sihvo et al. from Finland and Berardi et al. from Italy also found high percentages of overtreatment of 25% and 35%, respectively (19,46). Some of these studies have also methodological limitations. Pinto-Meza made the diagnosis with a telephone interview and did not consider other diagnoses such as anxiety disorders as indications for antidepressant treatment. Berardi et al. did not only not consider anxiety disorders as an indication but also ‘forgot’ continuation treatment as indicated treatment. Sihvo et al. did, but still found a high percentage of overtreatment, all in patients without any known psychiatric disease (19,46). A more recent study by Cameron et al. was the only mentioning “a low percentage” of overtreatment, however, without mentioning an exact percentage (47).
Comparison of the findings from this thesis with previous literature

Recognition

Determinants of recognition

When comparing determinants of (non-)recognition from our study to previous studies, our results were in line with the results of Wilhelm et al., Furedi et al. and Fernandez et al.; patients without a psychological reason for encounter were at risk for non-recognition (23-25).

Of the specific depression symptoms, increased appetite led to decreased recognition although only in the subgroup. In contrast, Coyne et al. reported correlations between low energy/feeling worn out or sleep disturbance and non-recognition and a trend towards less disturbance of appetite in the undetected group (22). We could not fully compare our results to those of Wittchen et al. since we did not study loss of confidence as a symptom (27).

Finally, we found that patients with a comorbid anxiety disorder were more often recognized, although this may have been an artefact caused by our definition of recognition, which included the use of antidepressants and the diagnostic codes for anxiety disorder and feelings of anxiety.

Recognition rate

Comparing the recognition rate in our study to recognition in previous studies, recognition is significantly higher, especially compared to the studies in the 1980s and 1990s. In the older studies only about one third of depressed patients was recognized, while in our study two thirds were recognized. These differences are probably at least partly due to the implementation of guidelines and extra training of the Dutch GPs. Also important is the fact that depression is less of a taboo compared to 20 or 30 years ago. As a result patients are better informed about the diagnosis and more often bring it up as a possible diagnosis themselves. Unfortunately in some countries recognition is still poor according to a recent review by Mitchell et al. from 2009. They performed a meta-analysis about recognition of depression in primary care by pooling results of 41 studies with over 50,000 patients. Overall recognition was 47.3% (41.7-53.0%), although recognition highly varied between studies (6.6%-78.8%) (18). This is probably due to differences between studies in definition of recognition and to differences between countries in training of
primary care physicians and health care systems.

The importance of the definition of recognition is well illustrated by the study of Joling et al. (48). They found that recognition was best defined by a combination of the following indicators of recognition: free text words strongly related to depression and/or the use of antidepressants and/or referral according to the electronic medical record from the GP. The addition of the diagnostic codes for depression and depressive feelings did not further improve diagnostic accuracy. This is a very important finding, as many studies in the past solely used these codes as evidence for recognition. In our study, we used a wide definition of recognition including the diagnostic codes for depression (International Classification for Primary Care; ICPC) and the use of antidepressants or referral according to the electronic medical record. In our opinion this leads to a more accurate estimation of recognition by the GP as Joling et al. demonstrated.

Next to that, large differences exist between countries, which could be due to differences in health care systems. As is obvious from the WHO study and several more recent studies, in some countries (especially in Asia) recognition is still poor, while in Europe recognition seems to have improved (40,49-51). In the Netherlands general practitioners are gatekeepers to secondary care, i.e. patients cannot visit secondary (mental) health care without a referral from their general practitioner. The GP knows his patients and is therefore able to diagnose depression even when a patient consults with all kinds of different (somatic) complaints. If a patient would visit several separate specialists, the whole picture (the depression) is more easily overlooked. Moreover, GPs have to follow a postgraduate training of three years, including a specific training in psychiatry consisting of a three-month internship. Next to that, many postgraduate courses about mental disorders exist. In the last ten years, several guidelines for the treatment of mental disorders in primary care have been updated and together with postgraduate training on mental health have led to better awareness on mental disorders among general practitioners. Short questionnaires have been developed such as the INSTEL-screen (intervention study primary care screenings questionnaire) to help the GP to screen for depression very quickly during their busy consultation hours (52).
Referral

In chapter 3 we found that 58% of patients with depression was referred. In the 1980s and 1990s only a small proportion of patients with depression was referred according to Verhaak (13). It could be that depression was more of a taboo in those days, or that psychiatric care was less accessible. In a later study Verhaak found that percentage of referrals increased by a factor 4.5 from the 1970s until the 1990s (28).

We studied determinants of referral as well and found that GPs base their referral decisions partly on guideline recommendations. Patients with a preference for psychotherapy were referred more often, as were patients with chronic depression, patients with suicidal tendency, younger patients and those with more severe depression. Those with non-response to two or more antidepressants or chronic depression were more often referred to secondary mental health care. These results are in line with those of Kendrick et al., Wang et al. and Van den Boogaard et al. who also found that younger patients and those with more severe depression were referred more often (31,34,53). Patient preference influenced referral not only in our study, but also in the study by Anthony et al. (35). Interestingly, Anthony et al. and Kravitz studied other determinants and found that therapeutic confidence / physician confidence in managing patients with depression and also personal experience were determinants of referral (33,35). Unfortunately, we did not study physician opinions as possible determinants.

Our finding that also non-response to antidepressants was a determinant of referral, was a new finding.

Treatment with antidepressants

Undertreatment

We did not study undertreatment. This was a deliberate decision. At first glance undertreatment seems easy to define. According to many depression guidelines that have been published in the last 10-20 years, all patients with a major depressive disorder could benefit from the prescription of an antidepressant. And possibly some patients with other conditions, such as dysthymia would benefit too. On the other hand, fifty percent of patients in the general population with a depression recover spontaneously within three months. Consequently, several guidelines consider “watchful waiting” or a minimal intervention as an option in the first few months, especially for patients with a first and mild depression (54-56). Hence, patients who
have an indication for the use of an antidepressant, do not necessarily need an antidepressant. Moreover, some patients who are not treated with antidepressants, do actually receive psychotherapy or another form of psychological support, which are also potentially effective strategies for treating depression. Third, a substantial percentage of patients with depression do not visit their GP, or do not present with mental problems, because they do not think they need help for these problems. All these patients could be considered undertreated if we would strictly follow a definition that states that every patient with an indication for an antidepressant should use an antidepressant.

The more recent guidelines such as the new Dutch multidisciplinary depression guideline and the new Dutch general practice guideline depression have added another dimension to this discussion. These guidelines now recommend reserving antidepressants for the patients with more severe MDD instead of all patients with MDD (54,57). This could be viewed as a partial return to the past. Before the DSM-III and IV, physicians discerned several types of depression. Antidepressants were indicated for depression with ‘vital’ (i.e. melancholic) symptoms only. The DSM-III started defining depression as a cluster of a certain number of symptoms, unregardless of which symptoms a patient displayed.

In 1994 the first NHG-standaard (Dutch College of General Practitioners guideline) “Depressive disorder” was published. Although this guideline wrote that antidepressants could be prescribed to all patients with depression, it was recommended to be reticent in prescribing these drugs (58).

The new trend is not prescribing antidepressants in case of certain symptoms (e.g. melancholic symptoms), but in more severe cases, defined as patients with a higher degree of suffering and/or dysfunctioning. Most of the time these patients have more symptoms as well. These changes are based on the most recent literature, showing that patients with mild and even moderately severe depression do not profit more from antidepressants than from placebo (59,60).

Overtreatment

By the time the Dutch media started publishing about overtreatment in primary care, we were already planning the study from chapter 5, since literature about this subject was scarce at the time. Our results were unexpected and for us a real surprise: only 5.4% of antidepressant treatment was not in accordance with recommendations from
current guidelines. Earlier studies had studied overtreatment from two different viewpoints: First, some studies focused on recognition of depression (both false-negatives and false-positives) reporting the use of antidepressants among false-positives. Most of these patients had depressive symptoms, without fulfilling criteria for a MDD. This led to the conclusion that GPs prescribed antidepressants for too mild depressive symptoms/disorders (27,53,61). Second, some studies did focus directly on the prescription of antidepressants and possible overtreatment. The Finnish study by Sihvo et al. and the Italian study by Berardi et al. were already mentioned above. They found a high percentage of overtreatment (19,46). In contrast, Cameron et al. reported that in Scotland overtreatment was not a large problem (47). This is remarkable, as the Scottish primary care/health care system is comparable to that in the Netherlands with the GP as gatekeeper to secondary (mental) health care. Finally, our finding that most overtreatment was due to (too) long continuation of antidepressants in patients with a previous indication/justification according to the primary care guideline, was never reported before, while it is possible that it has also never been taken into account before.

**Future research and practice**

**Future practice**

**New guidelines**

Less than a year before the completion of this manuscript, the second revision of the Dutch general practice guideline depression was published (57). For the first time this guideline not only provides GPs with recommendations for the diagnosis and treatment of patients with major depressive disorder (MDD), but also with recommendations for patients with milder depressive symptoms. Recommendations about antidepressant prescription had been a bit vague in the previous guideline, they could be prescribed to patients with MDD depending on degree of dysfunctioning, degree of suffering and patient preference. In the new guideline it is stated that in all but the most severe cases of depression, treatment should start with baseline interventions (psychoeducation, structuring of daily life, activity planning and monitoring) plus first step interventions (e.g. guided self-help or short psychological interventions). Only when this has proven to be ineffective, antidepressants are an option as well as psychotherapy. Maintenance treatment with antidepressants and/or psychotherapy is recommended after more than three episodes or after a single
severe episode. No specific duration for maintenance treatment is mentioned in the new guideline.

In conclusion, from now on, according to this guideline, GPs should reserve antidepressants for those with (very) severe depression, and to patients with mild/moderate severe depression only after little or no response to other treatments. Some patients could benefit from maintenance treatment, especially after multiple episodes with relapses/recurrences after the discontinuation of antidepressants.

**Recognition**

In chapter 2, we studied determinants of recognition of depression. We found a trend towards less recognition of certain atypical features (increased appetite). It seems that more awareness of atypical features is still needed. Unfortunately, the new general practitioners guideline does not pay specific attention to atypical features.

**Treatment with antidepressants**

When taking into account the results of this thesis, it is unclear how clinical practice for the treatment of depression and especially for the use of antidepressants should change. In our study, almost all patients who use an antidepressant (i.e. prevalent users) have (or had) a major depressive disorder or an anxiety disorder at the time the antidepressant was started. The recommendation from the new guideline not to prescribe an antidepressant to patients with minor depression, already appears to be standard practice. What is partly new compared to the previous guideline, is to restrict prescription to patients with (very) severe MDD and not to start an antidepressant in patients with mild to moderate severe MDD. However, the new guideline allows them also in these patients when baseline interventions and first step interventions have failed. It is unknown how many of the patients with MDD who got an antidepressant in our study, would have fulfilled this additional criterion. Therefore, although the new guideline is far more explicit in it’s recommendations for treatment with antidepressants, it is probable that prescription numbers will not decrease.

In the new guideline, only a little bit more attention is paid to the discontinuation of antidepressants. In the previous guidelines, it was stated that patients should discontinue their antidepressants within four weeks after a continuation period of six months. In the new guideline they add that tapering off
should be dependent on the specific antidepressant used and that attention should be paid to potential relapses.

We think that the new guideline should have paid even more attention to the discontinuation of antidepressants, as we found in chapter 5 that most patients using antidepressants without a current justification/indication according to the guideline, were patients with a history of a single episode of a major depressive disorder. The new guideline e.g. should have stated that periodic consultations are recommended for all patients using antidepressants in which (dis)continuation should be discussed. The new guideline does recommend these check ups for patients referred back to the GP from secondary mental health care. In our opinion these check ups should be recommended for all patients.

**Referral**

It is difficult to give recommendations for referral, since evidence is scarce. It seems that quite a large proportion of depressed patients is referred. We think the guideline recommendations for referral in the new guideline were already followed.

**Future research**

Future research should focus on the subjects that can further improve care for depressed patients in primary care/general practice. In specific, the following subjects could be of interest:

**Recognition of depression**

Improving recognition rate in itself should not be a goal, outcome is more important. In the last few years several researchers already studied the outcome of depression in patients that had gone unrecognized (39,62). They found that outcome was the same for recognized and unrecognized patients. It was stated that unrecognized patients often had less severe depression and therefore a better chance of spontaneous recovery (39,63). In our study in chapter 2 we came across another major issue in studying recognition: the definition. If a depression goes unrecognized in patients not consulting their GP, or consulting only once or maybe even a few times for unrelated subjects, could this be called failure to recognize depression? If we would answer this question with yes, it would mean that screening for depression among all patients visiting the GP would be necessary. Several studies already found
that random screening for depression in general practice does not improve outcome of depression (63,64). Therefore, random screening seems unnecessary and even pointless.

Another point in recognition is the patient perspective. Are patients willing to accept treatment? Do they want to discuss their depression? A study performed with NESDA data by van Beljouw et al., showed that patients without a perceived need for care/treatment often had less severe depression and a better chance of spontaneous recovery (65). It seems that a good proportion of patients is able to make valid judgments about their condition and their ability to sort it out for themselves.

Do we then need research on recognition of depression? The answer still should be yes. Depressive disorder and especially depressive symptoms are very common and cause a lot of suffering and dysfunctioning. Loss of work hours due to depression is very high, bringing with it very high costs for society. Preventing morbidity is important and recognition is the first step. Future research on recognition should focus on exploring barriers to recognition, and determinants of recognition in relation to risk factors for chronic or recurrent course of depression.

**Primary care versus secondary care**

Although the number of studies on depression in primary care has increased substantially in recent years, still most recommendations in primary care guidelines stem from studies performed in secondary and tertiary care (66). It is sometimes stated that patients with depression in primary and secondary care are not very different. However, this may not be the case in all countries. In The Netherlands a referral from a GP is necessary to consult secondary (mental) health care. In chapter 3 we showed that the GP takes guideline recommendations into consideration in decision-making about referral. It is therefore, at least in The Netherlands, doubtful if patients in primary and secondary can be considered the same. It could be that recommendations for patients in primary and secondary care should be different. Consequently, future research should focus on the exploration of possible differences between patients and if risk factors for e.g. relapse/recurrence are the same and therefore if treatment should be the same.
The role of the practice nurse for mental health care

A new phenomenon in The Netherlands is the psychiatric nurse working in the GP practice. It would be interesting to study care by these nurses and outcome of patients treated by them. Especially since the new GP guideline recommends short psychological interventions in a large proportion of cases, which can be provided by psychiatric practice nurses. And even more so since the Dutch government limited reimbursement of psychological and psychiatric care since January 2012. Patients now have to pay a contribution per session for psychological care and a fixed contribution for psychiatric care. Care by the psychiatric practice nurses in the GP practices is still fully reimbursed. If care by these nurses is cost-effective and the patient outcomes are good, treatment by the psychiatric nurse in the GP practice will probably play an important role in depression treatment in primary care in the future.
Summary and general discussion

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Chapter 8

Dutch summary / Nederlandse samenvatting
Depressie en behandeling

Algemeen

Depressie is een veelvoorkomende aandoening. Gedurende het gehele leven krijgt ongeveer 20% van de mensen ooit een depressieve stoornis of depressieve klachten. Depressie heeft een grote invloed op de kwaliteit van leven en gaat ook gepaard met veel kosten voor de maatschappij. Dat laatste is niet alleen het gevolg van kosten die gemaakt worden voor behandeling van de depressie, maar vooral ook door verlies van werkcapaciteit. Dit effect wordt versterkt doordat in een flink percentage van de gevallen depressie een recidiverend of chronisch karakter heeft. De meeste patiënten met een depressie worden behandeld in de eerste lijn, dat wil zeggen in de huisartspraktijk, eventueel met hulp van andere zorgverleners in de eerste lijn zoals maatschappelijk werkers en eerstelijns psychologen.

Diagnose en classificatie

De diagnose depressieve stoornis wordt gesteld met behulp van criteria uit de DSM-IV, patiënten moeten tenminste vijf symptomen van depressie hebben, waarvan tenminste één hoofdsymptoom, zie onderstaande tabel. Daarnaast moeten deze symptomen tenminste twee weken aanwezig zijn gedurende de meeste dagen en het grootste deel van de dag. De klachten mogen niet het gevolg van middelengebruik (alcohol, drugs of medicijnen) of een lichamelijke ziekte zijn en moeten lijdensdruk veroorzaken bij de patiënt en belemmeren in activiteiten (werk, sociale contacten). Tot slot mogen de klachten niet het gevolg zijn van rouw bijvoorbeeld na het verlies van een naaste. Indien niet wordt voldaan aan deze criteria voor een depressieve stoornis, maar een patiënt wel één of meerdere symptomen van depressie heeft, kan gesproken worden van een milde depressie of depressieve klachten.

Er zijn diverse indelingen van depressieve stoornis, zo kun je spreken van een milde, matig-ernstige of ernstige episode, maar ook van melancholische, vitale, atypische of psychotische kenmerken. Melancholische depressie wordt gekenmerkt door vitale symptomen zoals gewichtsverlies of verlies van eetlust, bewegingsonrust of juist bewegingsarmoede (bijvoorbeeld weinig mimiek) en slaapproblemen zoals vroeg in de morgen wakker worden. Atypische kenmerken zijn juist het tegenovergestelde: toegenomen eetlust, gewichtstoename, overmatig slapen. Psychotische depressie is een ernstige vorm van depressie waarbij wanen en hallucinaties ontstaan, vaak met een zeer sombere of negatieve inhoud.
Vrouwen krijgen twee keer zo vaak een depressie als mannen. De helft van de mensen die een depressie krijgen, hersteld spontaan binnen drie maanden. Zoals eerder genoemd krijgt een aanzienlijk percentage een recidief. De minderheid (15-20%) heeft een chronische depressie, dat wil zeggen meer dan 2 jaar.

Behandeling van depressie
Zoals eerder gezegd worden de meeste patiënten behandeld in de eerste lijn. Daar een deel van de patiënten spontaan herstelt, wordt in de eerste drie maanden vaak gekozen voor een behandeling bestaande uit informatie en eventueel enkele adviezen betreffende activiteiten en dagindeling. In geval van langer bestaande depressie of een ernstige depressie is intensievere behandeling aangewezen. Grofweg zijn er twee behandelingsmogelijkheden: antidepressiva en diverse vormen van psychotherapie. Beide zijn effectief gebleken. De NHG-standaard depressie (huisartsenrichtlijn) adviseert behandeling met antidepressiva en/of psychotherapie afhankelijk van lijdensdruk en voorkeur van de patiënt. Als voor antidepressiva gekozen wordt, moeten deze altijd nog zes maanden worden gebruikt nadat de patiënt beter is om te voorkomen dat een terugval optreedt, deze behandeling noemen we “terugvalpreventie”. Bij patiënten met een recidiverende of chronische depressie kan gekozen worden de antidepressiva nog langer voort te zetten om ook recidieven te voorkomen, dit wordt onderhoudsbehandeling of “recidief-preventie” genoemd.

Nederlandse Studie naar Depressie en Angst (NESDA)
De meeste studies in dit proefschrift zijn uitgevoerd met data uit NESDA. NESDA is een grote studie waaraan 2981 patiënten tussen 18 en 65 jaar met en zonder depressie en angst deelnemen. Doel is het verkrijgen van meer inzicht in het ontstaan en verloop van angst en depressie. De studie is in 2004 van start gegaan, bij de start, na 1 jaar, 2 jaar, 4 jaar en inmiddels ook na 6 jaar zijn deze mensen onderzocht. Bij elke meting is gekeken naar symptomen van angst en depressie, maar ook naar bijvoorbeeld behoefte aan zorg, lichamelijke ziekten, gebruik van medicijnen waaronder antidepressiva en nog veel meer.
Samenvatting van dit proefschrift

Introductie

In het verleden is vaak geroepen dat herkenning en behandeling van depressie in de eerste lijn onder de maat was. Er is veel literatuur over onderherkenning en onderbehandeling, voornamelijk uit de jaren ’80 en ’90 van de vorige eeuw. De laatste jaren is er, vooral in de media, veel aandacht geweest voor ‘overherkenning’ en ook overbehandeling, dat wil zeggen het aanmerken van mensen zonder depressie als depressief en/of ze behandelen met antidepressiva terwijl daarvoor geen indicatie bestaat.

Doel van dit proefschrift was het onderzoeken van de ‘zorg rondom depressie in de huisartspraktijk’ op dit moment. Dit proefschrift zou daarmee een startpunt kunnen gaan vormen voor het verder verbeteren van de zorg voor depressieve patiënten in de huisartspraktijk.

Herkenning van depressie

Wij vonden dat depressie adequaat werd herkend door de huisarts. 60,5%-68,7% van de patiënten met depressie werd herkend in onze studie in hoofdstuk 2. Wij maten herkenning in een groep van 484 patiënten met depressie uit de nesda-studie. We hebben daarnaast gekeken of er kenmerken waren die de niet-herkende patiënten onderscheidden van de wel-herkende patiënten. Het bleek dat patiënten die naast de depressie ook een angststoornis hadden en diegenen die als reden om naar de huisarts te gaan opgaven dat ze psychische klachten hadden, beter herkend werden dan patiënten zonder angststoornis of psychische reden voor contact met de huisarts. Daarnaast leek te gelden dat bij patiënten met minder depressieve klachten en patiënten met een toegenomen eetlust de depressie minder vaak werd herkend door de huisarts. Het leek daarmee dat de huisarts de ‘ziekere’ patiënten beter herkende dan de minder zieke (minder symptomen, geen bijkomende psychische ziekte), een goed teken, immers hoe ernstiger de depressie, hoe minder kans op spontaan herstel. Opvallend was dat patiënten met een toegenomen eetlust minder goed herkend werden, mogelijk dat huisartsen atypische symptomen zoals toegenomen eetlust minder snel herkennen als symptoom van depressie. Het zou echter ook kunnen dat specifiek toegenomen eetlust door huisartsen gezien wordt als een lichamelijke klacht en niet een symptoom van depressie.
Nederlandse samenvatting

Behandeling van depressie

Verwijzing naar de geestelijke gezondheidszorg

In hoofdstuk 3 hebben we gekeken of het verwijsgedrag van huisartsen bij een groep van 344 depressieve patiënten overeenkwam met de aanbevelingen uit de huisartsenrichtlijn voor depressie (NHG-standaard depressie 2003). Ten eerste bleek dat 58% van de patiënten met depressie door de huisarts werd verwezen naar de geestelijke gezondheidszorg. Dit percentage was veel hoger dan verwacht, in het verleden werden veel lagere percentages gevonden in studies. Het bleek dat huisartsen inderdaad de aanbevelingen uit de NHG-standaard gebruiken bij hun beslissingen rondom verwijzing.

Patiënten die behoefte hadden aan psychotherapie, patiënten met suïcidale neigingen en met een chronische depressie werden vaker verwezen, net als jongere patiënten. Conform de richtlijn werden patiënten met een chronische depressie of zonder effect van twee of meer verschillende antidepressiva vaker naar de tweede lijn (psychiater, instelling voor geestelijke gezondheidszorg) verwezen ten opzichte van de eerste lijn (eerstelijns psycholoog, maatschappelijk werk, sociaal psychiatrisch verpleegkundige in de eerste lijn). Patiënten die verwezen waren voldeden gemiddeld aan meer criteria voor verwijzing uit de NHG-standaard dan patiënten die niet verwezen werden. Uit onze studie bleek tot slot dat andere factoren ook een rol lijken te spelen in het verwijsgedrag van huisartsen.

Behandeling met antidepressiva

In hoofdstuk 4 beschrijven we dat de aanbevelingen in de richtlijnen rondom het gebruik van antidepressiva evidence-based (gebaseerd op bewijs uit wetenschappelijke studies) zijn voor wat betreft behandeling in de acute fase tot remissie (het moment waarop de patiënt beter is) en “terugvalpreventie” gedurende enkele maanden na remissie. Echter, er is geen bewijs voor onderhoudsbehandeling in de eerste lijn. De aanbevelingen hierover in de richtlijnen blijken gebaseerd op ongecontroleerde studies uit de tweede en derde lijn ((academische) ziekenhuizen/psychiatrische ziekenhuizen).

In hoofdstuk 5 gaan we in op de door de media de laatste jaren vermeende overbehandeling met antidepressiva in de Nederlandse huisartsenpraktijk. We concluderen dat dit helemaal geen groot probleem is. Wij onderzochten een groep van 1531 patiënten met en zonder depressie en/of angststoornis uit de
huisartsenpraktijk die in de laatste vier maanden hun huisarts bezochten (ongeacht of dit vanwege psychische klachten was). In deze groep gebruikten er 199 een antidepressivum op het moment van de eerste meting van de nesda-studie. Van deze 199 bleken er 188 (94,6%) een gegronde reden voor dit gebruik te hebben volgens de NHG-standaard depressie en de NHG-standaard angststoornissen. 11 (5,4%) patiënten hadden volgens de NHG-standarden angststoornis en depressie geen indicatie voor het gebruik van een antidepressivum op dat moment. Zes van hen (54,5%) hadden een éénmalige depressieve episode gehad meer dan een jaar geleden. Zij hadden daarmee dus in het verleden een goede indicatie voor het gebruik van een antidepressivum, maar hadden daar volgens de NHG-standaard inmiddels mee kunnen stoppen. De andere 5 patiënten zonder indicatie hadden ook nooit een indicatie gehad. Bij hen was het antidepressivum zonder indicatie/geldige reden volgens de NHG-standaard voorgeschreven. Omdat nesda tot doel had depressie en angst te bestuderen, was er in deze studie ten opzichte van de reguliere huisartsenpopulatie een overschot aan patiënten met een depressie en/of angststoornis. Daarom berekenden wij wat onze resultaten betekenden voor de gehele huisartsenpopulatie waaruit de selectie voor de nesda-studie was gemaakt (10.677 patiënten). De resultaten waren hetzelfde, slechts 5,4% van de patiënten die antidepressiva gebruikten, deden dit zonder een op dat moment geldige indicatie.

Tot slot beschrijft hoofdstuk 6 de kenmerken van een groep patiënten die een onderhoudsbehandeling met antidepressiva gebruikten. Ook in deze studie werden data uit de nesda-studie gebruikt, in dit geval van de eerstelijns patiënten met een depressie die gedurende tenminste een half jaar in remissie was. We vergeleken kenmerken van deze patiënten met en zonder onderhoudsbehandeling met antidepressiva (antidepressivagebruik >12 maanden). Het betrof 776 patiënten, waarin wij 1571 metingen tot onze beschikking hadden, daar we meerdere meetmomenten meenamen in de analyse en sommige patiënten op meerdere meetmomenten aan onze inclusiecriteria voldeden. Van tevoren stelden wij hypotheses op; wij verwachtten dat patiënten die voldeden aan één of meer criteria voor onderhoudsbehandeling uit de NHG-standaard (dat wil zeggen dat zij een chronische of recidiverende depressie hadden) ook vaker een onderhoudsbehandeling met antidepressiva zouden ontvangen. Daarnaast was onze verwachting dat patiënten met een comorbide angststoornis vaker een onderhoudsbehandeling met antidepressiva zouden krijgen. Alleen de laatste
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hypothese werd bevestigd, patiënten met een comorbide angststoornis gebruikten vaker antidepressiva als onderhoudsbehandeling, net als patiënten met een comorbide dysthyme stoornis. Ook oudere patiënten, patiënten met een lagere opleiding, diegenen die ook benzodiazepines gebruikten en patiënten die psychologische of psychiatrische zorg hadden ontvangen in het laatste half jaar gebruikten vaker een onderhoudsbehandeling met antidepressiva. Daar patienten met een recidiverende of chronische depressie niet vaker onderhoudsbehandeling met antidepressiva kregen dan patienten zonder deze kenmerken, konden we concluderen dat het gebruik van een onderhoudsbehandeling antidepressiva niet overeenkomt met de aanbevelingen uit de richtlijn. Het lijkt echter wel alsof het de patienten met een meer ernstige depressie zijn die een onderhoudsbehandeling krijgen, daar wij vonden dat deze patienten vaker een comorbide angststoornis of dysthyme stoornis hadden en ook vaker benzodiazepines gebruikten of psychologische of psychiatrische zorg ontvingen.

Conclusie
De algemene conclusie van dit proefschrift is dat de zorg voor depressieve patiënten in de eerste lijn in de meeste gevallen adequaat is, dat wil zeggen in overeenstemming met de aanbevelingen uit de (toen) geldende richtlijnen.

Wanneer we dit beeld vergelijken met studies uit het verleden blijkt het percentage herkende patiënten flink toegenomen sinds de jaren '80 en '90 van de vorige eeuw, toen slechts ongeveer een derde van de patiënten werd herkend.

Ook de behandeling lijkt een stuk verbeterd. Verwijzing voor depressie en angst was zo'n 30 jaar geleden een uitzondering, terwijl nu meer dan de helft van de patiënten verwezen lijkt te worden. Overbehandeling met antidepressiva is een onderwerp dat nog maar kort in de belangstelling staat. Ten opzichte van studies in andere landen lijkt het alsof Nederlandse huisartsen adequaat antidepressiva voorschrijven, daar slechts in 5,4% van de gevallen sprake was van overbehandeling, ten opzichte van percentages als 25 of zelfs 35% in studies uit andere landen.
Toekomstvisie

Praktijk

Nieuwe richtlijnen

Vlak voor de afronding van dit proefschrift, kwam in juni 2012 de nieuwe NHG-standaard depressie uit. Deze standaard beperkt de indicatie voor het voorschrijven van antidepressiva in het algemeen en onderhoudsbehandeling met antidepressiva ten opzichte van de vorige standaard.

Herkenning

Daar in hoofdstuk 2 bleek dat patiënten met atypische symptomen (toegenomen eetlust) minder goed herkend werden, lijkt meer aandacht voor atypische symptomen nodig. Jammer genoeg wordt hieraan geen aandacht besteed in de nieuwe richtlijn.

Behandeling met antidepressiva

Het is onduidelijk hoe het gebruik of het voorschrijven van antidepressiva door huisartsen zou moeten veranderen wanneer we kijken naar de resultaten van dit proefschrift. In alle behalve de meest ernstige gevallen dient een patiënt met depressie nu eerst begeleiding te krijgen alvorens over te gaan op het voorschrijven van antidepressiva. Het is onduidelijk in welk percentage van de gevallen dit nu het geval is en dus in hoeverre de behandeling moet veranderen.

Antidepressiva afbouwen lijkt wel een punt van aandacht, daar de meeste overbehandeling het gevolg lijkt van het langdurig doorgebruiken van antidepressiva terwijl er geen indicatie meer voor is. Helaas besteedt de nieuwe richtlijn nauwelijks aandacht aan dit onderwerp. Ik vind dat alle patiënten die een antidepressivum gebruiken, moeten worden beschouwd als chronische patiënten en daarom bijvoorbeeld halfjaarlijks voor controle zouden moeten komen. Tijdens deze controle kan dan het gebruik van het antidepressivum besproken worden, naast de actuele situatie om ook alert te zijn op eventuele terugval of recidief.

Verwijzing

Aanbevelingen voor verwijzing zijn niet echt te geven, er is weinig onderzoek naar gedaan. Wij denken dat de aanbevelingen in de richtlijn al opgevolgd worden.
Onderzoek

Toekomstig onderzoek moet zich richten op onderwerpen die de zorg voor depressieve patiënten in de eerste lijn verder kunnen verbeteren.

Onderzoek naar herkenning zou zich moeten richten op factoren die herkenning kunnen verhinderen en kenmerken van patiënten die leiden tot minder herkenning in relatie tot risicofactoren voor ongunstig beloop. Immers, herkenning op zichzelf zou geen doel moeten zijn, het gaat om de uitkomst voor de patiënt.

Daarnaast is onderzoek naar de verschillen tussen depressieve patiënten in de eerste en tweede lijn nodig. Veel aanbevelingen in de richtlijnen voor de behandeling van depressie in de eerste lijn zijn gebaseerd op studies onder patiënten in de tweede lijn. Men beroept zich hierbij op het feit dat deze patiënten niet substantieel zouden verschillen. Echter in veel landen kunnen patiënten rechtstreeks naar de specialist, zonder tussenkomst van een huisarts. In Nederland is dit niet het geval en het is daarmee maar zeer de vraag of ook in Nederland patiënten in de eerste en tweede lijn niet van elkaar verschillen. Wellicht dat de aanbevelingen voor de eerste lijn anders moeten zijn omdat bijvoorbeeld de risicofactoren voor terugval of recidief anders zijn of de te verwachten reactie op behandeling.

Tot slot is de laatste jaren de praktijkverpleegkundige op het gebied van de geestelijke gezondheidszorg in de Nederlandse huisartsenpraktijk in opmars. Er is nog maar weinig onderzoek gedaan naar de (kosten-)effectiviteit van deze vorm van geestelijke gezondheidszorg. Dit is wel belangrijk, daar deze zorg, althans voorlopig, nog volledig wordt vergoed in tegenstelling tot andere eerste- en tweedelijns geestelijke gezondheidszorg.
Dankwoord
Dankwoord

Een makkelijk stukje om te schrijven, dacht ik nog toen ik aan dit dankwoord begon. Nu ik begonnen ben, begin ik te twijfelen. Ik mag natuurlijk niemand vergeten en er zijn de afgelopen jaren veel mensen geweest die op de een of andere manier aan dit proefschrift of mijn persoonlijke ontwikkeling hebben bijgedragen.

Allereerst natuurlijk mijn promotoren; Klaas van der Meer en Willem Nolen. Zonder jullie had ik hier nu niet gestaan. Klaas, bedankt voor het vertrouwen dat je in mij toonde toen ik, inmiddels bijna zes jaar geleden, bij je aanklopte als student geneeskunde met de mededeling dat ik promotieonderzoek wilde gaan doen. Ondanks mijn beperkte ervaring met onderzoek, die op dat moment slechts bestond uit de verplichte wetenschappelijke stage in het kader van de studie geneeskunde, hielp je me aan een aanstelling bij de afdeling huisartsgeneeskunde. Tijdens de bijeenkomsten rondom de voortgang van de artikelen in dit proefschrift, waardeerde ik je creativiteit, waarbij je veel nieuwe ideeën tentoonspreidde. Je zorgde ook altijd dat ik het perspectief van de huisarts voor ogen hield, dat dit proefschrift huisartsgeneesekundig zou blijven en geen pure psychiatrie. Willem, ook jij durfde het aan om dit project te starten met mij als zeer onervaren onderzoekster. In het begin waardeerde ik vooral je tekstuele input, die ik zeker kon gebruiken. Later ben ik ook steeds meer je inzicht in de klinische relevantie van onderzoek gaan waarderen, haarfijn wist je vaak de vinger op de zere plek van een voorgenomen onderzoek te leggen. Aan te wijzen waarom de resultaten weinig zouden bijdragen en suggesties te doen voor een alternatieve werkwijze of een ander doel, zonder de besluiten ooit voor mij te nemen.

Als vanzelfsprekend ben ik natuurlijk ook de leden van de beoordelingscommissie zeer dankbaar voor het beoordelen van dit manuscript, Prof. Dr. H.E. van der Horst, Prof. Dr. P.F.M. Verhaak en Prof. Dr. R.A. Schoevers.

Daarnaast alle co-auteurs van de diverse artikelen die zijn opgenomen in dit manuscript. Brenda Penninx, bedankt voor het ter beschikking stellen van de NESDA database en alle hulp die je gegeven hebt bij de 4 artikelen in dit proefschrift die uit NESDA zijn voortgekomen. Ik kon altijd rekenen op een zeer snelle en kritische
Dankwoord

beoordeling van een concept-artikel. Karlijn Joling wil ik bedanken voor al het voorwerk dat zij deed voor het artikel over herkenning van depressie, onze samenwerking was helaas van korte duur, maar heb ik als zeer prettig ervaren. Hein van Hout en Harm van Marwijk wil ik in dat kader bedanken voor het vertrouwen dat ze me gaven door hun een deel van hun project over herkenning van depressie aan mij uit te bestedend. Witte Hoogendijk, bedankt voor de kritische input in het artikel over overbehandeling met antidepressiva. Boudewijn Kollen, tot wij elkaar ontmoetten dacht ik dat ik de statistiek van mijn artikelen best zelf kon doen. Jij liet mij zien dat je sommige statistiek beter aan een specialist kunt overlaten. Bedankt voor je altijd snelle en nauwkeurige analyses voor de artikelen in hoofdstuk 2 en 6. Tot slot Peter Verhaak, ik hoop in de toekomst nog vele onderzoekstrajecten samen te kunnen starten. Laat het artikel waaraan jij in dit proefschrift hebt bijgedragen daarvan het begin zijn.

Niet te vergeten Klaas Groenier, bij wie ik altijd kon aankloppen voor statistisch advies. En alle medewerkers en deelnemers van NESDA, bedankt voor bieden van deze schat aan informatie.

Doordat ik mijn werkzaamheden veelal vanuit huis heb verricht, heb ik weinig directe onderzoekscollega’s gehad. Toch wil ik alle promovendi binnen NESDA en de afdeling huisartsgeneeskunde op deze plaats bedanken. Zo af en toe kwamen we elkaar tegen en ik heb van jullie veel geleerd over het doen van onderzoek en jullie waren een welkom klankbord voor de frustraties van een promovendus.

Vervolgens alle collega’s uit de diverse huisartspraktijken waar ik de afgelopen jaren heb gewerkt. In het bijzonder Michiel Andriessen, mijn eerste opleider, die door zijn vertrouwen in mij, mijn zelfvertrouwen veel goed heeft gedaan. Je bood me de flexibiliteit die ik voor de combinatie van opleiding en onderzoek zo hard nodig had. Het was een fantastisch jaar in Ommen. Dan Kees Huttenga, mijn huisartsopleider voor het derde jaar, waar ik een week te vroeg kwam voor het kennismakingsgesprek. Toen al vertelde je dat je weinig affiniteit had met de wetenschap. Mijn parttime AIOS-schap vond je echter prima. Waar nodig kon ik mijn uren schuiven voor mijn onderzoek en de broodnodige extra tijd hieraan besteden. Ook nadat ik mijn huisartsopleiding had afgerond heb ik me als waarnemer altijd zeer

Tenslotte de mensen die buiten het werk om hebben bijgedragen aan dit proefschrift. In dat kader natuurlijk allereerst mijn man. Bas, ik kan me de frustraties van het eerste jaar als onderzoeker nog goed herinneren. Hoe vaak heb ik niet achter mijn computer in ons kleine flatje in Almelo op het punt gestaan het op te geven? Elke keer praatte je mij weer moed in, zei je dat het echt wel zou gaan lukken. Nooit had ik toen gedacht hier te staan, en toch, mede dankzij jou, sta ik hier nu toch. Niet alleen het begin was moeilijk, ook bij de laatste loodjes was jij het weer die ondanks je eigen nieuwe en drukke baan mij geholpen hebt de lay-out perfect te maken. Privé hebben we de laatste jaren ook aardig wat voor onze kiezen gehad. Jij bleef, ondanks alles, naast me staan. Samen zijn we hard bezig ook die problemen te overwinnen. Jouw foto op het omslag geeft niet alleen de inhoud van dit proefschrift, maar ook onze huidige privé-situatie akelig goed weer “achter de wolken schijnt de zon!” Dan mijn ouders, omdat ze me altijd gesteund hebben om mijn talenten te ontplooien en dromen te verwezenlijken. Ook mijn schoonouders, mijn beide zusjes Inge en Sanne, mijn schoonzus en zwager wil ik bedanken. Er zijn, en zoals ook jullie weten niet alleen in dit promotie-traject, de afgelopen jaren veel moeilijke perioden geweest. Mede dankzij jullie heb ik het vol kunnen houden en door kunnen gaan.

Een aantal vrienden en vriendinnen wil ik op deze plaats ook nog bedanken voor alle ontspannende momenten die we de afgelopen jaren samen beleefd hebben. Francina en Marc, Marjan en Marcel, Jose, Frank en Lotte, Marten en Lisanne, Loes, Marjet en Patrick en alle anderen die ik nu dreig te vergeten, bedankt daarvoor.
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