Major depressive disorder in primary care: screening, diagnosis and treatment
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CHAPTER 1

General introduction
General introduction

Background

Major Depressive Disorder (MDD) is a mental disease with a relatively high prevalence and a great impact for both patients and caregivers. In the United States a nationally representative survey, the National Comorbidity Survey\(^1\), showed that approximately 1 in 5 women and 1 in 8 men will experience a Major Depressive Episode (MDE)\(^2\) during their lifetime.\(^3\) The 12-month prevalence of MDD was estimated at 6.7%.\(^4\) In the Netherlands, the Nemesis-2 study, a study executed in the general population, estimated the lifetime prevalence of MDD at 18.7% (13.1% male; 24.3% female) and the 12-month prevalence at 5.2% (4.1% male; 6.3% female).\(^5\)

MDD often has a recurrent course, especially if the effectiveness of acute treatment is insufficient and residual symptoms remain.\(^6\) These residual symptoms are among the most important predictors of relapse.\(^7\)-\(^9\) In the absence of prophylactic psychopharmacological or psychotherapeutic treatment, the recurrence rate can rise to about 80%\(^10\) and up to 15% of patients will develop chronic depression.\(^6,11\)

Prevalence in primary care

Most of the professional care for depressed patients is provided in primary care (PC) by general practitioners (GPs).\(^12\)-\(^14\) The point prevalence of MDD in this setting is estimated to be between 10 and 15%.\(^15\)-\(^18\) A World Health Organization (WHO) study on psychological problems in PC across 14 countries showed for instance that 14% of the PC patients suffered from MDD.\(^19\) The Depression 2000 study, a major epidemiological study executed in 412 primary care settings in Germany, revealed a point prevalence of 10.9%.\(^20\) Furthermore, evidence shows that in a primary care setting 40% of the patients with MDD relapses within 10 years.\(^21\)

Under-recognition and undertreatment

As said the GP plays a key role in the management of depressive disorders, being the first point of contact for the recognition, diagnosis and increasingly also for the treatment of depression. However, there is extensive evidence that, among patients with clinically significant depression, around 50% goes unrecognized by their GP.\(^22\)-\(^29\) Moreover, the National Depressive and Manic-Depressive Association consensus statement on the undertreatment of depression mentioned “overpowering evidence” that patients diagnosed with MDD are being critically undertreated.\(^30\) This corroborates findings from other studies that only about one third of the recognized MDD patients in the US received some type of treatment.\(^1,31\) An even smaller portion of recognized patients...
received treatments that could be considered adequate according to the practice
guidelines of the American Psychiatric Association\textsuperscript{32,33} and the Agency for Health Care
Policy and Research.\textsuperscript{24,34-37} In 2001-2002, a second US survey of mental disorders, The
National Comorbidity Survey Replication (NCS-R), was conducted to update information
on the prevalence and clinical significance of DSM-IV disorders, and to study patterns
of treatment and treatment adequacy. They found that only a quarter of patients with
MDD were adequately treated.\textsuperscript{12}

In the Netherlands, a same pattern is found. A recent Dutch study showed that only
36\% of the MDD patients visiting the GP were recognized as suffering from MDD.\textsuperscript{38}
Furthermore, the Nemesis-2 study showed that only 51\% of the patients with MDD
made use of general health care facilities in the past year. Fernandez et al\textsuperscript{39} studied the
adequacy of primary care and specialized care treatment for anxiety and depressive
disorders in Europe, including the Netherlands. They found that 23\% of the patients
in primary care was adequately treated according to the guidelines.\textsuperscript{33,40,41} The under-
recognition of MDD by GPs and the undertreatment and/ or inadequate treatment of
MDD patients (i.e. not according to the guidelines) urges a need for improvement.

**Screening and diagnosing depression in primary care**

To improve the care for depressive disorders it seems we have to increase the recognition
of MDD by GPs. An explanation for the under-recognition is that patients suffering
from MDD often consult their GP with a non-depressive reason for encounter. Many
of these patients present themselves with (non- specific) somatic complaints and not
with complaints that may arouse the GPs suspicion of a possible MDD.\textsuperscript{23} Furthermore,
several studies showed that quite some patients are reluctant to display emotional
problems\textsuperscript{42,43} which further impedes the diagnostic process.

A number of solutions have been proposed to increase the recognition of MDD in
primary care. One is training GPs and practice nurses in recognizing and diagnosing
MDD.\textsuperscript{44} Another solution that has been proposed is the use of brief self report
screening instruments, which enable recognition.\textsuperscript{45} Screening is an appealing solution
because brief instruments, that are easy to administer and score, are available
and acceptable to patients.\textsuperscript{46} However, several studies showed that screening in
unselected GP patients has insufficient efficiency.\textsuperscript{47-49} This is caused by the relatively
low prevalence (i.e. 10-15\%) of depression in unselected patient groups. Low
prevalence results, even when a screener has acceptable sensitivity and specificity, in
a low positive predictive value (i.e. the probability that a patient with a positive test
result actually has the disease). A low positive predictive value makes the screener less acceptable to clinicians, because of the high number of false positives (these patients will be followed up unnecessarily).\textsuperscript{50}

**Patients at high-risk for depression**

Screening GP patients that are both at a higher risk for MDD and are difficult to identify as suffering from MDD, seems a promising and efficient way to prevent under-recognition. Until now, no studies have investigated the effectiveness of a screening program for depression in such high-risk groups. In this thesis we will address the question whether this selective screening for MDD in high-risk groups in PC is effective in terms of detection and treatment initiation.

In our study we selected, on the basis of literature, three (partly overlapping) groups thought to be at relatively high-risk for depression based on the daily GP practice: 1) patients with mental health problems (MHP), 2) patients who frequently attend their GP (FA)\textsuperscript{51-54} and 3) patients with unexplained somatic complaints (USC)\textsuperscript{55-57} Patients with mental health problems (MHPs) consult their GP for a wide range of mental health problems (e.g. anxiety, worrying, sadness, stress, feeling down, insomnia) and/or psychosocial reasons (financial problems, work-related problems, relational or interpersonal problems). Frequent attenders (FAs) comprise different subgroups in terms of their reasons for encounter, for example patients suffering from a chronic illness, patients with a psychiatric or psychological problem, patients with an illness that needs regular/frequent care or patients with psychosocial problems\textsuperscript{58,59}. FAs are often defined as the 10% most frequently consulting patients within a time frame of one year, adjusted for sex and age.\textsuperscript{54,60} Patients with unexplained somatic complaints (USC) consult the GP for physical symptoms for which no clear organic pathology can be found after medical evaluation by the GP.

Patients in these three groups are at higher risk for MDD because, as a result of the problems mentioned above, they experience more psychological distress, increased functional impairment and decreased health related quality of life which may induce MDD\textsuperscript{61-64} or they are already suffering from MDD and frequently attend the GP with various complaints or attend the GP with relatively vague complaints.

**Patient Health Questionnaire (PHQ)**

A number of screening instruments for MDD are available.\textsuperscript{22,46} Of these instruments, only the Patient Health Questionnaire (PHQ) was developed for screening, diagnosing as well as for monitoring the severity of depression. Furthermore it is based on the Diagnostic and Statistical Manual (DSM-IV) criteria.\textsuperscript{2} The PHQ was developed around
1999 as a self-report version of the Primary Care Evaluation of Mental Disorders (PRIME-MD)\textsuperscript{65} and is also able to detect other DSM-IV disorders that are prevalent in primary care (e.g. panic disorder, other anxiety disorder, somatoform disorder). Nowadays, the PHQ has been translated into more than 25 languages and is used all over the world.

The PHQ-9 is the 9 item subscale for MDD.\textsuperscript{65,66} Williams \textit{et al}.\textsuperscript{46} concluded that the PHQ-9 was comparable to or better than other screening measures for depression. A recent systematic review concluded that the PHQ-9 has good sensitivity and specificity for detecting depressive disorders; that the optimal cutoff point is $\geq 10$; that the cutoff points of 5, 10 and 15 represent mild, moderate and severe symptom levels and that its sensitivity to change is well-established.\textsuperscript{67} Another systematic review also found that the PHQ-9 is a valid instrument to detect patients with a Major Depressive Episode (MDE), but concluded that in samples with a low pretest probability of depression, the PHQ-9 is not suitable for diagnosing MDE, because of the risk of overdiagnosis.

In this thesis we will assess the accuracy of the Patient Health Questionnaire-9 (PHQ-9) as (a) a diagnostic instrument for depressive disorder. If this is not the case we will assess the accuracy of the PHQ-9 as (b) a screener for depressive disorder in a Dutch high-risk population (FAs, patients with USC, patients with MHP) in primary care.

\section*{Co-morbidity}

Co-occurrence of psychiatric disorders, especially between mood and anxiety disorders, is common.\textsuperscript{68,69} Many patients suffer for instance from both panic disorder (PD) and depressive disorder.\textsuperscript{70} For instance studies of outpatients with MDD revealed co-morbidity rates of PD of 6.6–17.1%.\textsuperscript{70-74} A recent survey of the burden of disease in Australia in terms of years of life lost due to disability\textsuperscript{75} ranked anxiety & depression as the first overall female burden of disease in women and the third overall male burden of disease in men, implying substantial financial and economical costs to society.

Next to screening for MDD, the PHQ is also designed to screen for panic disorder, other anxiety disorder, somatoform disorder, alcohol abuse, and eating disorder. This makes it a useful instrument in clinical practice where co-morbidity is the rule rather than the exception. However, until now, little research has been done on the psychometric properties of the panic disorder module of the PHQ (PHQ-PD) and the available results are equivocal.\textsuperscript{65,76} Furthermore, the influence of psychiatric co-morbidity on the test characteristics of the PHQ-PD and PHQ-9 is unknown, even though this may result in a decreasing specificity and increasing sensitivity of these PHQ modules. In this thesis we will investigate the validity of the PHQ-PD in detecting and diagnosing PD in the three
high-risk groups and determine the influence of psychiatric co-morbidity on the test characteristics of the PHQ-PD and the PHQ-9.

**Measurement invariance**

Diagnosing depression is a challenging task because of reasons addressed above. In addition, cultural background can also impede the diagnostic process. Cole *et al.* found that a person’s cultural background may bias screening and diagnostic outcomes and thereby they addressed the issue of measurement invariance. A measurement invariant test across different ethnic groups implies that group differences on test scores can be attributed to differences on the underlying variable measured by the test instead of to ethnic differences: for example if Chinese patients have a higher score on a measurement invariant depression test than American patients, the group difference on a test score is attributable to depression and not to some other, unobserved, difference between Chinese and Americans. Using screening or diagnostic instruments that are not measurement invariant for ethnicity may result in over- or underestimation of the prevalence of the disorder or of group differences.

To our knowledge only one earlier study examined measurement invariance for ethnicity of the PHQ-9. They used a generalized Mantel-Haenszel statistic. In this thesis we will also assess measurement invariance for ethnicity of the PHQ-9, but we will use a categorical single factor model, which is able to pick up not only uniform non-invariance, but also non-uniform non-invariance.

**Disease management**

As mentioned earlier, there is not only a problem with the recognition of depression by GPs, but also, in case of recognition, a problem with adequately treating MDD. So, in order for increased recognition (by screening and accurate diagnosis) to result in improved patient outcome, newly recognized MDD patients should be offered evidence based treatments. However, evidence based treatments can only be delivered if GPs or other health care professionals have the necessary skills and resources (i.e. time) to do so. We can therefore conclude that to really improve the management of depression in primary care a broad approach including screening, diagnosis and evidence based treatment (this also incorporates educating GPs in guideline driven care), a so-called Disease Management Program, is needed.

**The APOLLO-D study**

The APOLLO-D study, Academic Primary- care Oriented Longitudinal Outcomes Depression, intended to study the effect of a simple and easy to implement three-step
Disease Management Program (DMP) for MDD in primary care on the total burden of MDD (symptomatology, costs and prevention of chronicity). The three-step DMP comprised:

1. screening in three high-risk groups (patients with mental health problems (MHP), patients with unexplained somatic complaints (USC) and patients who frequently attend their GP (FAs) with the Patient Health Questionnaire (PHQ)65,

2. for those positive on screening this was followed by formal diagnosis with the Structured Clinical Interview for DSM-IV Axis- I disorders (SCID- I)80,81 and

3. for those diagnosed with MDD who did not already receive one of the treatment options or a comparable treatment one of the following three treatment options was available: a) pharmacotherapy with antidepressants; b) structured and supportive care from the GP and c) brief cognitive behavioral therapy by a primary care psychologist.

During the first year of the project the design of the study had to be adapted for two reasons. First, in the screening study the point prevalence of MDD in the selected high-risk groups was not 20-30%, as we had expected based on the scientific literature52,55,82,83 , but 18%, of which 7% was already recognized by their GP and 11% detected by screening. Secondly, of those diagnosed with MDD 50% was already receiving one of the offered treatment options, making them ineligible for participation in the treatment trial, while another 25% refused to participate in the treatment trial for various reasons. This resulted in a very small number of patients eligible for the treatment trial. Based on these facts we had to conclude that the DMP could not be cost-effective.

Therefore, we decided to break up the APOLLO-D study and to focus on the separate steps of the DMP independently. We aimed to describe the three high-risk groups (symptomatology and diagnosis), to describe in detail why screening of the high-risk groups could not be cost-effective, to study the accuracy of the PHQ as a screener and diagnostic tool for the DSM-IV diagnoses MDD and relevant co-morbidity (panic disorder and undifferentiated somatoform disorder), to execute a qualitative study focused on the patients’ perspective on depression and depression treatment for MDD patients detected by screening (PHQ and SCID-I), to study measurement invariance for ethnicity of the PHQ-depression module (PHQ-9) and finally to execute a separate two-arm intervention trial (RCT) which will be introduced now.

Treatment of depression in primary care

In the Netherlands, two depression guidelines are available to GPs: the multidisciplinary guideline for depressive disorder (2010)84 and the primary care guidelines for depression85, both offering effective treatment recommendations. Unfortunately,
implementation of the recommendations in the daily GP practice has been slow.\textsuperscript{86} The Depression Breakthrough Collaborative, initiated by the Netherlands Institute of Mental Health and Addiction (http://www.trimbos.nl) and executed from 2006 till 2008, aimed at improving the implementation of clinical depression guidelines in daily practice. The project substantially increased the percentage of patients treated according to the guidelines, especially in the mild to moderate depressed patient group. Seventy-eight percent of the mild to moderate depressed patients and 57% of severely depressed patients were treated according to the guidelines.\textsuperscript{87} These percentages are relatively high when compared to a research in six European countries where the overall proportion of adequately treated patients with anxiety and depressive disorders was only 23% in the primary care setting.\textsuperscript{39} This implies that it is possible to increase the percentage of patients treated according to the guidelines with an approach based on the stepped care principle. The stepped care principle means: start a treatment with the least invasive intervention that is supposed to be effective.

**Treatment guidelines**

The treatment guidelines of the National Institute for Health and Clinical Excellence (NICE, 2010)\textsuperscript{88} and the American Psychiatric Association (APA, 2010)\textsuperscript{89} recommend low intensity psychological therapy and in some cases antidepressants for mild MDD. For moderate and severe MDD guidelines recommend AD, or psychological therapy, or a combination of both.

A recently published algorithm of the United States Departments of Veterans Affairs and Defense for the management of MDD in the primary care setting recommends that the acute phase of outpatient therapy (during which the patient receives medication, psychotherapy or a combination of these modalities) should last for 8 to 12 weeks. In addition, patients with MDD should receive appropriate psycho-education, active monitoring of symptomatology (i.e. ‘watchful waiting’) and lifestyle advices (getting adequate sleep, regular exercise and reducing or eliminating tobacco and caffeine).\textsuperscript{90}

The Dutch multidisciplinary guideline for depressive disorder (2010)\textsuperscript{84} contains a treatment algorithm, based on the stepped care principle. The treatment algorithm is divided into four sub algorithms based on the duration of the episode, the severity of the episode and possible recurrence:

- Depressive episode, mild, first episode shorter than three months
- Depressive episode, mild, first episode longer than three months or recurrent
- Depressive episode, (moderate) severe, first episode
- Depressive episode, (moderate) severe, recurrent.
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For all four algorithms the guideline recommends basic interventions (psycho-education, active monitoring of symptomatology and lifestyle advices). For mild MDD the Dutch guideline recommends first step interventions (e.g. low intensity psychological therapy, activation, bibliotherapy). For moderate to severe MDD the guideline recommends AD, or psychological therapy or a combination. This is in accordance with the APA and NICE guidelines. In general, two treatment options for MDD can be distinguished: psychological therapy and an intervention by the GP, which may include the prescription of antidepressants.

The best evidence based psychological intervention so far is Cognitive Behavioral Therapy (CBT). A meta-analysis and meta-regression showed small effects favoring CBT over usual GP care for patients with depression irrespective of type (e.g. minor depression, MDD). However, until now, no studies have compared these two treatment options in their most optimal form (both according to the guidelines). In this thesis we will investigate whether a protocolized brief cognitive behavioral therapy (brief CBT) applied by psychologists is more effective than general practitioners’ care (GPC) for PC patients with MDD when the latter is optimized according to clinical guidelines. In order to be able to carry out the treatment trial we had to divert from the original protocol and discard the high-risk groups, since the original screening study showed that the high-risk patients, diagnosed with unrecognized MDD, were reluctant to participate in a treatment trial. For the two-arm intervention trial we used patients with depressive complaints referred by the GP.

Research questions and outline of this thesis

In this thesis we will focus on the screening study, the validation study of the PHQ-9 and the PHQ-panic disorder module (PHQ-PD), the study on measurement invariance for ethnicity of the PHQ-9, and on the two-arm intervention trial (RCT). This thesis will address the following research questions:

1. Is selective screening for MDD in three high-risk groups in primary care effective in terms of detection and treatment initiation?
2. Is the Patient Health Questionnaire-9 (PHQ-9) a valid diagnostic instrument for depressive disorder and a valid screener for depressive disorder in three high-risk groups in primary care? And what is the influence of co-morbid anxiety and somatoform disorder on the test characteristics of the PHQ-9?
3. Is the Patient Health Questionnaire-PD (PHQ-PD) a valid instrument for diagnosing and detecting panic disorder (PD) in three high-risk groups in primary care? And what is the influence of co-morbid depressive- and somatoform disorder on the test characteristics of the PHQ-PD?
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4 Is the Patient Health Questionnaire-9 (PHQ-9) measurement invariant with respect to ethnicity?
5 Is a protocolized brief Cognitive Behavioral Therapy (CBT) more effective than optimized General Practitioners’ Care (GPC) for primary care patients with MDD?

Chapter 2 addresses the first research question. In order to answer this question we performed a prospective cohort study among 2005 high-risk patients from three primary care health centers in the Netherlands. Three high-risk groups of patients were selected: (a) frequent attenders, (b) patients with mental health problems and (c) patients with unexplained somatic complaints.

Chapter 3 addresses the second research question. In order to answer this question, we performed ROC curve analysis, compared the performance of the PHQ-9 as a diagnostic instrument to that of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)- which we used as reference standard-, and studied the influence of co-morbid anxiety and somatoform disorder on the test characteristics of the PHQ-9 by a subgroup analysis of patients who scored positive on the PHQ-anxiety module or somatoform disorder module.

Chapter 4 addresses the third research question. In order to answer this question, we administered the PHQ to our primary care sample of patients at high-risk for psychiatric disorders. The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID- I) was used as the reference standard for the presence of PD. Sensitivity, specificity, and predictive values were calculated. The influence of psychiatric co-morbidity on the test characteristics of the PHQ-PD was assessed with a subgroup analysis of patients who scored positive on the PHQ-depression module or somatoform disorder module.

Chapter 5 addresses the fourth research question. In order to answer this question, we used two strongly contrasting cultural groups (n=1772). Measurement invariance was assessed by comparing four categorical single factor models with an increasing number of restrictions, representing increasingly stronger measurement invariance assumptions.

Chapter 6 describes the study protocol of our randomized trial designed to compare brief cognitive behavioral therapy with general practitioners’ care for depression in primary care.

Chapter 7 addresses the fifth research question. To answer this question, we randomized 121 primary care patients with Major Depressive Disorder to optimized general practitioners’ care or protocolized brief cognitive behavioral therapy (8 sessions). Severity and symptomatology, response and remission were measured with the clinician-rated Hamilton Depression Rating Scale-17 and the patient-rated Patient Health Questionnaire-9.

Chapter 8 summarizes the results, discusses the main conclusions that can be drawn from our studies and offers recommendations for future research and implications for clinical practice.
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Chapter 1


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