Suffering in silence: studies on screening for major depressive disorder in primary care
Wittkampf, K.A.

Citation for published version (APA):
1

General Introduction
General introduction

Background
This thesis is about major depressive disorder (MDD) as it is diagnosed and treated by general practitioners (GPs) in the Netherlands. According to the recent Nemesis-2 study, executed in the general Dutch population, MDD has a 12-months prevalence of 5.2%.

Worldwide, the estimated proportion of the population suffering from MDD in their lifetime is between 7 and 16%. Clearly, MDD is a common disorder in general practice in the Netherlands.

The incidence and prevalence of MDD in primary care settings vary widely among different studies performed in the last decades. It not only depends on country, but predominantly on the structure and level of (mental) health care, on variations in definition of depressive disorder (e.g. DSM-IV, ICD-10), diagnostic procedures and variation in reporting. In the Netherlands, most studies have used the DSM-IV definition of MDD. In this thesis we will confine ourselves to that tradition.

Not only epidemiological, but also clinical diagnosis of MDD in primary care settings can be difficult. Eighty percent of patients with MDD consult their GP with non-specific physical complaints without spontaneously mentioning the psychological nature of their problems. Studies indicate that up to 50% of patients with MDD are not recognised by GP’s.

This is supported by a recent meta-analysis of 37 primary care studies of GPs’ ability to detect depression without specific help from severity scales, diagnostic instruments, education programs, or other organisational approaches. The Nemesis-2 study demonstrated that this low detection rate resulted in a treatment for MDD in only 50.5% of patients in the past 12 months. Conversely, only 7.9% of all patients with MDD, treated as well as not treated, reported an unfulfilled need for MDD care for their MDD. This discrepancy between factual treatment and unmet needs for care might be explained by the fact that under-recognition of MDD is more related to mild depressive disorder than to moderate or severe MDD. Milder forms are more likely to recover spontaneously and often remain undetected and untreated. Regardless of this low percentage of unfulfilled need for care and the spontaneous recovery of these milder forms, the high prevalence of MDD in combination with the high level of underdiagnosis and under-treatment suggests a need for screening programs for MDD in primary care, and continues to do so.

Studies on Screening for Depressive Disorder in primary care
Screening for MDD in primary care is intended to improve detection, management and more importantly successful treatment of MDD. Several randomised studies however, have failed to demonstrate improvement in patient outcomes by screening. Industry sponsored observational studies generally were more positive. A recent Cochrane meta-analysis of MDD screening concluded that
there is substantial evidence that routine screening questionnaires for depression have minimal impact on the detection of MDD by GPs. In addition, no effect on clinical outcome of MDD was found at 6 and at 12 months after screening. A two-stage procedure, consisting of screening combined with a treatment trial, might be effective, but this needs to be evaluated in a larger randomised prospective trial.\textsuperscript{15} Embedding screening in a disease management program may have a positive effect on depressive symptoms.\textsuperscript{16} This effect was found in three trials that recruited patients through a GP screening program and offered enhanced care, consisting of face to face education of patients, telephone support, medication, psychotherapy, and structured follow-up. GPs were also offered guidelines, education, and face-to-face support. Clearly, screening was only one element of this complex intervention, and therefore positive outcomes cannot be attributed to screening alone. In addition, no cost-effectiveness analysis was undertaken and it remains unclear how many patients have to be screened in order to find and treat successfully one additional patient with MDD. Thus, former studies indicate that screening alone does not result in improved care and outcome. However, MDD screening embedded in a disease management programme including diagnosis and evidence based treatment, might lead to improved patient outcome.

Obviously, the lack of uniformity in strategies and study outcomes hampers implementation of strategies for reducing under-detection and under-treatment of MDD in primary care. An approach to evaluate current MDD screening is to use the criteria of Wilson and Jungner\textsuperscript{17}. These criteria were developed already 4 decades ago to ensure a positive net effect of screening programs. Ever since, these criteria, with or without adaptations to different settings and different target disorders, have been used to evaluate screening programs before implementation. However, none of the screening programs (e.g. breast cancer and cervix carcinoma) that have been offered to patients in the Netherlands fulfil at all these screening criteria\textsuperscript{18}. 
Wilson and Jungner criteria for MDD screening in primary care.

Box 1. Wilson and Jungner classic screening criteria

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a "once and for all" project.

Screening programs aimed at MDD fulfill some of these criteria. If screening is part of a disease management program including diagnosis, treatment and follow up, then more criteria are fulfilled, but many of the above criteria require further study.

The first criterion is met: MDD is an important health problem. Depression is the most common mental disorder in the general population. In 2002 it was the fourth most common cause of loss of disability-adjusted life years (DALYs) in the world, and by 2030 it is projected to become the most common cause in high-income countries. Depression qualifies as a major health problem with great consequences in terms of disability and early death across the world. Reductions in quality of life are comparable to those seen in major chronic physical diseases.

There are different accepted treatments for patients with MDD (criterion 2) and facilities for diagnosis and treatment are available if screening is part of a disease management program (criterion 3). In primary care in the Netherlands, the NHG-guideline has been developed especially for GP-practice and a multidisciplinary guideline for MDD in adults has been developed for primary and secondary care. In the UK, the NICE-guideline on the treatment and management of depression in adults has been developed for primary and secondary care. Treatment options, proposed in these guidelines, are based on the type, severity, and natural course of MDD and preference of patient and clinician. Besides self-management, psycho education, exercise and Internet therapies, the main treatment options for MDD are antidepressant medication, psychotherapy, or a combination of both. These treatments could be provided by the GP or by
psychologists and in case of psychiatric comorbidity, severe dysfunction, unsuccessful treatment or suicidality, the GP may refer to more specialized psychiatric care. This disease management could be considered as an accepted and available treatment for MDD.

Screening criterion 4 (there should be a recognisable latent or early symptomatic stage) is applicable to prevention programs aimed at illnesses with a clear and recognizable latent stage (prevention of cervical cancer) and not at screening programs that aim to improve the recognition of the illness itself. In this thesis we will focus on screening for MDD and not on a latent or early symptomatic stage of MDD. It still is very difficult to predict which patients with mild depressive symptoms will recover spontaneously and which patients will develop MDD and need specific psychiatric treatment. Because of this uncertainty about the course of mild depressive symptoms, sometimes labelled as minor depression, this combination of symptoms could barely be considered as an early stage of MDD. We conclude that this criterion is not applicable to this thesis because we aim to screen for the disorder itself.

Screening criterion 5 and 6 concern the screening test. Criterion 5 is specified by the UK screening committee as: *The screening test should be safe, simple, precise, and validated; a suitable cut-off value should be defined and agreed.*

For MDD screening several instruments are available. One of these instruments is the Patient Health questionnaire (PHQ). Recently, this instrument and all other depression screeners were evaluated by Williams et al who reported similar operating characteristics, but differences in administration time, ease of scoring and the ability to serve additional purposes, such as monitoring severity and screening for conditions other than depression.

Of these instruments, the Patient Health Questionnaire (PHQ) was the only instrument that was directly based on the DSM-IV criteria and developed especially for primary care screening, diagnosis and monitoring of depression severity. Moreover, this instrument could be used to detect other DSM-IV disorders that are relevant in primary care. The PHQ consists of a somatoform section, a depression section, a panic disorder section, other anxiety section, an alcohol abuse section, an eating disorder section and a life event/stress section. Because of its additional objectives, this relatively new screening instrument has become very popular and has been translated into more than 25 languages. The US Preventive Task Force evaluated 41 screening studies and found that the PHQ was one of the best tools (highest combination of sensitivity and specificity) for primary care. Although the PHQ is widely used and validated in different primary care populations, there is large variation in sensitivity, due to relatively low number of patients with MDD.
Each (sub-)population generates its own test-characteristics and therefore test-characteristics need to be validated for primary care sub-populations. Furthermore, only a limited number of studies considered its additional objectives (screening for other DSM-IV disorders besides MDD, its diagnostic features and possibility to measure severity) and yielded different conclusions. More study considering these additional screening objectives is therefore needed.

The acceptability of the screening test (criterion 6) has not been studied before. In fact the complete screening program has to be acceptable for the target population. Patient participation is a cornerstone of successful screening and as such one of the indispensable conditions described by the UK National screening committee. Concerning the acceptability of the screener used in waiting room patients, the developers of the PHQ reported a positive outcome. According to the validation and utility study of Spitzer et al, waiting room patients were willing to fill in the PHQ before consulting the GP. The majority (88%) of patients were comfortable answering the questions on the PHQ. Likewise, 89% of patients believed that the questions were helpful in improving diagnosis and treatment of their problems by their GP.

Conversely, the acceptability of an MDD screening program, including diagnosis and treatment, is not very well studied in the target population. Indirect evidence of poor acceptability comes from two sources. Participation in screening tests for MDD is generally low when they are offered in primary care settings: 30-60% of patients in primary care decline to participate in screening interviews offered by researchers or clinic nurses during routine attendance. Studies have shown that patients experience difficulties with being diagnosed as having MDD. A remarkable difference exists between the conventional medical view and the patients’ view of the concept of MDD. Most patients attribute their complaints to external psychosocial problems. As a consequence, they find it difficult to accept that they are diagnosed with MDD, which they consider a disease-focused concept. This probably has to do with patients’ views that MDD is not the right label for their problems, a negative view of MDD related to fear of stigmatization, doubts about the purpose of labelling, feelings of shame and scepticism about the benefits of therapy, in particular drug treatment. These studies are performed in patients diagnosed as depressed by their GP and not in a screening program. More research is required to explore patient’ views on MDD screening and screening outcome in primary care.

Criterion 7 states that the natural history of MDD, including development from latent to declared disease, should be adequately understood. The natural history of MDD has certainly been studied widely, but an important difficulty of MDD is the heterogeneity of its natural course caused by different factors such as psychosocial circumstances, psychiatric comorbidity and heterogeneity of the illness
As described above (at criterion 4), this thesis aims at screening for MDD and not for some early stage of MDD. This does not alter the fact that the heterogeneity of the natural course of MDD itself will have impact on the outcome and on the effectiveness of screening for MDD. In this thesis we will not study the course of MDD and its relation with the effectiveness of screening, but in the general discussion we will address this criterion and speculate whether further research is necessary.

Criterion 8 (there should be an agreed policy on whom to treat as patients) is met sufficiently if the DSM-IV criteria of MDD are used for diagnosis. Which patients with MDD actually need treatment depends on the severity of the symptoms. From all patients in primary care that fulfil the diagnostic criteria for MDD, 50% recover within three months without specific psychiatric treatment. Recent Dutch multidisciplinary treatment guideline advices to follow up patients with MDD for three months before starting with specific psychiatric treatment (psychotherapy and/or medication) except for severe MDDs. This ‘stepped care’ policy should therefore be part of a MDD disease management program in primary care.

Finally, the cost-effectiveness of screening for MDD needs more research (criterion 9) and case finding should be a continuing process (criterion 10). The process of screening for MDD should be part of a disease-management program that is a continuing process to improve MDD-care in primary care, as stated by the NICE-guideline. The MDD screening effort and costs should be balanced in relation to the improvement in patient outcome. Therefore it is important to study the effectiveness of screening, the efforts and costs to perform such a program, and the number of patients that have to be screened in order to diagnose one extra patient with MDD, and the number needed to screen to cure one extra patient from a MDD.

In summary: after discussing these Wilson and Jungner criteria it is clear that 4 criteria need further research:

1. The screenings instrument (criterion 5): the test-characteristics of the PHQ in specific populations, the ability of the PHQ to screen for other DSM-IV disorders besides MDD, the ability to diagnose MDD and its possibility to measure severity of MDD.
2. The acceptability of the screening program for the target population (criterion 6).
3. The natural history and course of MDD revealed by screening (criterion 7) (outside the scope of this thesis).
4. The (cost-)effectiveness of the screening program in a high-risk population (criterion 9).

Besides these, there are two other subjects that require more research:
5. The target population of screening for MDD.
6. The meaning of psychiatric comorbidity of patients with MDD in a screening program.
These additional issues will be discussed in the following paragraphs.

**Global versus targeted screening**
The NICE guideline on MDD advises primary care MDD screening in a preselected high-risk population only. This advice was based on consensus and has not been evaluated since. One of the main problems of screening an unselected primary care population is the relatively low positive predictive value of MDD screening tests, despite acceptable sensitivity and specificity. This low positive predictive value leads to a high number of false positives. Screening for MDD in a high prevalence group will increase the positive predictive value of a positive test, thereby increasing the efficiency of screening.

Of course the next question is which particular patients in primary care are at high-risk for unrecognized MDD. Several groups with large mutual overlap have been described. The NICE-guideline referred to the review of Palmer and Coyne suggesting three groups with increased prevalence of MDD: patients with disabling somatic diseases; patients with depressive episodes in the past, and elderly patients with cognitive impairments like dementia. Other groups that have been described in the literature are patients who visit their GP frequently, patients with unexplained somatic complaints, and patients who consulted their GP with psychosocial problems. The additional value of screening a preselected high-risk population for MDD instead of an unselected population has not been empirically evaluated.

**Screening for MDD only or also on comorbid psychiatric disorders**
Many studies concerning screening on MDD are focused on MDD only as if this is a one-dimensional problem. In primary care this one-dimensional approach is a simplification and a potential barrier for screening success. The heterogeneity of MDD is enormous. Most patients suffer from a wide variety of somatic and psychiatric problems and the combination of MDD and generalized anxiety disorder, panic disorder, somatoform disorder or alcohol abuse is common. Many of these conditions have overlapping symptoms and this probably modifies the scores on MDD-screening instruments, making the screening less specific. Conversely, but beyond the scope of this thesis, psychiatric comorbidity influences the course of MDD and effectiveness of treatment.
Main problems
There still is a need for screening on MDD because of under-recognition and under-treatment in primary care, but evidence for the effectiveness of screening for MDD in primary care is lacking. Screening in unselected populations is ineffective because of low disease prevalence which causes a low positive predictive value.45 Screening for depression in a preselected high-risk population is proposed as a solution to increase disease prevalence and effectiveness of screening. Many different groups of primary care patients with higher prevalence of MDD are proposed in the literature, but until now no studies are available about the effectiveness of screening for depression in any of these high-risk populations in primary care.

The additional features of the mood module of the PHQ (PHQ-9) concerning its diagnostic skills and severity measurement have not yet been validated in a Dutch high-risk population in primary care. Moreover, the PHQ is also developed for screening on other psychiatric disorders but there is little evidence about the psychometric properties of these other modules of the PHQ. Finally, there are no studies about the acceptability of the screening program for the target population. The participation to screening programs is generally low (about 50%). This raises doubts about the acceptability of screening for MDD for patients. There is no information about the patient's view on screening for MDD.

Research questions

High-risk population
1. Which patients are at high-risk for depressive disorder in primary care?
2. What is the prevalence of psychiatric disorders in high-risk population in primary care?

Screenings instrument
3. What are the psychometric properties of the mood module of the PHQ (PHQ-9)?
4. Is the PHQ-9 valid to use as a screener, a diagnostic instrument as well as a measure of severity of MDD?
5. What are the test characteristics of the PHQ panic-module and the PHQ somatoform module?

Screening program
6. Is screening for MDD in a high-risk population effective?
7. How acceptable is a screening program for MDD to the target population?
Structure of thesis

Part I
This thesis consists of three parts. The first part concerns the high-risk population that will be used for our screening program. In this part we describe this population, its characteristics and the difficulties of general practitioners in caring for these patients. We focus on the psychiatric comorbidity in this population and on our justification to select these patients for MDD screening.

Part II
The second part of this thesis concerns multiple aspects of the screening instrument, the Patient Health Questionnaire. First we systematically review the literature about the diagnostic accuracy of the mood module of the PHQ (PHQ-9) and perform a meta-analysis to provide the summary sensitivity and specificity of the PHQ-9.

Secondly we perform a validation study of the PHQ-9 in our high-risk population. This study aims to determine the accuracy of the Patient Health Questionnaire (PHQ-9) in (1) screening, (2) diagnosing and (3) measuring severity of depressive disorder in high-risk groups for depressive disorder in family practice. In this study we also analyze the influence of comorbid psychiatric disorders on the test-characteristics of the PHQ-9.

Thirdly, we study the validity of the panic module of the PHQ (PHQ-PD) in this high-risk population and aim to test whether modified evaluation algorithms could improve the operating characteristics of this questionnaire. In addition, the influence of psychiatric comorbidity on the test characteristics of the panic module is evaluated.

Finally we determine the specificity, sensitivity, and reliability of the somatoform disorder module of the PHQ (the 15-symptom Patient Health Questionnaire, PHQ-15) for detection of somatoform disorders in a high-risk primary care population.

Part III
The third part of this thesis concerns the screening program. First we aim to evaluate the effectiveness of selective screening for MDD in the high-risk population. We calculate the number of patients needed to screen to treat one additional patient for MDD.

Secondly, we describe the characteristics of patients with MDD in our high-risk population in order to find predictors that might improve the selection of a high-risk population. This might provide opportunities to develop a more efficient screening program for depression in primary care.
The last chapter of this third part concerns the patients’ view on screening for MDD. We describe a qualitative study with patients who participated in our screening program and were diagnosed with MDD. In this study we aim to improve our understanding of the views of these patients in order to clarify the reasons for acceptance or rejection of a screening program for the target population.
References


