Major depressive disorder in primary care: screening, diagnosis and treatment
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CHAPTER 8

General discussion
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The main aim of the project, of which this thesis is a part, was to study the effectiveness of an integrated Disease Management Program (DMP) for depression in primary care (PC). The DMP consisted of identification of patients, screening of these patients with the Patient Health Questionnaire (PHQ)\(^1\), assessment of diagnosis with the Structured Clinical Interview for DSM-IV Axis I disorder (SCID-I)\(^2\), feedback of the diagnosis to the general practitioner (GP) and randomization to one of three available evidence based treatments. To optimize detection and to improve patient outcomes, we followed the recommendations of the National Institute of Health and Clinical Excellence (NICE)\(^3\), to screen groups at risk for Major Depressive Disorder (MDD) and to embed the screening procedure in a Disease Management Program.

In an early phase of this project it became clear that an integrated study of such a complex program was not feasible (in practical terms) and too ambitious. We therefore decided to divide the project in a set of sub-studies. Together these studies had to give answers to our questions regarding the three separate steps of the Disease Management Program: screening, diagnosis and evidence based treatment for patients with MDD in PC. This final chapter discusses the main conclusions that can be drawn from our studies and offers recommendations for future research and implications for clinical practice.

In this thesis the following research questions were addressed:

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 is it 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?
4. Is the Patient Health Questionnaire-9 (PHQ-9) measurement invariant with respect to ethnicity?
5. Is a protocolized brief cognitive behavioural therapy (CBT) more effective than optimized general practitioners’ care (GPC) for PC patients with MDD?
The screening program

The first research question addresses the first step of the Disease Management Program, namely screening. We investigated whether selective screening for MDD, in three high-risk groups (frequent attenders (FAs); patients with mental health problems (MHPs); and patients with unexplained somatic complaints (USCs)) in primary care resulted in better detection of patients with an until then unrecognized MDD, combined with subsequent treatment initiation. Three health centres with 12 GPs and 15996 enlisted patients participated. From these 15996 patients we selected 2005 patients (12.5% of the total enlisted patient group) in the age of 18-70 years that met the criteria for belonging to one or more of the three high-risk groups. MHPs and FAs were selected by using the electronic database of the participating GPs, USCs were selected by GPs using their appointment list of the last four weeks. Considering our definitions of the three high-risk groups, MHPs and USCs had visited their GP over the last three months and FAs visited them frequently over the last year. Of these 2005 patients the GPs excluded 318 patients (e.g. patients with known MDD, patients suffering from schizophrenia or bipolar disorder), resulting in 1687 patients that were invited for the screening program with the PHQ.

Effect of screening on detection

Past and recent studies have shown that patients with MDD often consult the GP with a non depressive reason for encounter. Many of them present themselves with (non-specific) somatic complaints, with psychosocial problems or with chronic illnesses and not with mental health complaints (e.g. loss of interest, sadness). This somatic or psychosocial presentation is an important explanation for under-recognition of MDD in primary care. Screening was advocated as one solution to this under-recognition. Patients in our three groups were at higher risk for MDD because, as a result of the problems they had to cope with (e.g. psychosocial problems, chronic illnesses and unexplained physical symptoms), they experienced more psychological distress, increased functional impairment and decreased health related quality of life which may have induced MDD or they were already suffering from MDD and presented themselves (intentionally or unintentionally) with various complaints and/or with relatively vague complaints.

With the selection of our high-risk groups we thus targeted our screening program at patients that were at high-risk for MDD and were difficult to identify as suffering from MDD. The screening program yielded a total of 29% screener (PHQ) positives, which resulted after a structured clinical diagnostic interview (SCID-I) in a MDD month prevalence of 9.1% (extrapolated value when screening the total high-risk group =11%).
Before the screening procedure 7% of the patients was already excluded because they were known by the GP as suffering from MDD. This resulted in a total MDD month prevalence in these high-risk groups of (11+7) 18%. This means that two third of the MDD patients (11/18) was not (yet) captured by the GP as suffering from MDD. We concluded that screening in these high-risk groups leads to better detection of MDD. However, our aim was not only to improve detection, but also to improve treatment initiation and subsequently improve patient outcomes.

**Effect of screening on treatment initiation**

Contrary to our finding that screening for MDD in three high-risk groups in primary care resulted in better detection, it did not result in improved treatment initiation. Less than a quarter (23.9%) of the newly detected MDD patients proceeded to the treatments offered. For this low rate we have the following three explanations:

a. Treatment ineligibility

Even though the GPs in our study excluded all patients with known MDD from the 2005 selected high-risk patients before we executed the screening program, half of the newly detected MDD patients already received a treatment. Because they already received such a treatment they were ineligible for our treatment trial. A plausible explanation is that these patients received the treatment for symptoms of a mix of common mental disorders (e.g. depressive-, anxiety-, adjustment – and/or pain complaints). Unfortunately, we have not further investigated the indication for these treatments.

Another explanation for the high number of patients already receiving treatment, may be that GPs in our study did recognize MDD and offered treatment, but failed to register the MDD diagnosis as such. Joling *et al* demonstrated that GPs are attentive to mental health problems in most depressed patients, but that registration with diagnostic codes is weak. This indicates that the International Classification of Primary Care codes (ICPC codes), the standard for registration of complaints in GP, is not adequately used by GPs.

It is also plausible that GPs, after the high-risk group selection and subsequent exclusion of patients with a known MDD, diagnosed some of the selected high-risk patients with MDD and started treatment before the screening procedure started.

A final explanation is that a difference in definition between the DSM-IV classification and ICPC classification may have led to the high number of patients already receiving treatment. For mild MDD the ICPC classification uses a symptom diagnosis like depressed feelings while the DSM-IV uses an illness diagnosis like MDD. Patients with mild MDD
according to the SCID-I (but a symptom diagnosis according to the ICPC) probably, despite of the ICPC symptom diagnosis, received a depression treatment from the GP. Later, during the exclusion phase of the selection period, these patients were not identified by them as suffering from known (mild) MDD.

b. Treatment refusal

Of the newly detected MDD patients that did not already receive treatment 40% refused the depression treatments we offered (i.e. before the randomization procedure). Another 11% of the newly detected MDD patients did not show up for the follow up appointment with the GP that was made in order to discuss the treatment options and randomization procedure. Wittkampf et al. investigated the views of the patients participating in our screening program who were diagnosed by the SCID-I with (unrecognized) MDD, but refused treatment. In her qualitative study the following themes were identified for treatment refusal:

1. Concerns about stigmatization. Fear of stigmatization (e.g. being on benefits, crazy, weak) and patronizing attitudes are themes that often come up in qualitative research on the views of patients on depression.

2. The belief that the experienced symptoms are a normal reaction to everyday life and major life events. This theme corroborates other research findings. Patients are often unwilling to emphasize on feelings of depression and rather express their complaints as being unable to cope with everyday problems or social roles. Patients come up with a wide range of explanations for their complaints such as events in childhood, multiple daily demands or domestic violence.

3. Doubts about the need and effectiveness of treatment. Patients in our study felt that external factors had caused their symptoms and that treatment for MDD would not fit their need. Furthermore, the majority of patients is reluctant to take antidepressants. Reasons for this are the conviction that antidepressants are addictive, worry that antidepressants suppress ‘normal’ grief, and prior negative experiences with antidepressants.

The above findings imply that the patients participating in our screening program that were finally diagnosed with till then unrecognized MDD, had difficulties accepting the diagnosis MDD as an explanation for their complaints (and preferred other explanations) and therefore refused treatment. This important issue addresses the distinction between ‘normal’ human suffering and the illness depression. According to the DSM-IV the diagnosis is symptom based with little reference to a cause. This may result in inappropriate treatment when normal human emotional reactions are treated as illness.
A number of researchers have therefore stressed a more stringent distinction between ‘normal’ human suffering and the illness MDD.\textsuperscript{27,28} Taking the cause of the complaints into consideration is not only more acceptable to the patient, it may also distinguish between patients that need depression specific treatments and those that may be more in need of talking about what happened. The very recent update of the Dutch College of General Practitioners Practice Guideline (The NHG guideline Depression)\textsuperscript{29} also links up with this idea by stating that, with regard to treatment, it is important to distinguish between depressive symptoms and the illness depression and to come to a mutual agreement on the definition of the problem.

A questionnaire that can be helpful in making this distinction is the Four-Dimensional Symptom Questionnaire (4DSQ).\textsuperscript{30,31} This questionnaire measures four symptom dimensions: distress, depression, anxiety and somatisation. It may set the base for a conversation in which patient and GP can express their thoughts and ideas on the complaints. This may avoid directly labeling symptoms to illness and leads to more consideration for the patient’s story and consequently to the most suitable treatment.

c. Characteristics of the high-risk groups and treatment refusal

Characteristics of our group of high-risk patients (this is particularly the case for patients with USC and FA patients) may also have played a role in refusing a treatment for MDD. Patients that are frequently attending their GP, our FA high-risk group, may be suffering from a chronic illness or an illness that needs regular/frequent care or psychosocial problems. Patients with USC have a tendency to express their psychological distress physically and have a strong conviction that their experienced complaints are caused by or related to physical problems. This may lead to difficulties with accepting a treatment for a psychiatric problem\textsuperscript{32,33} and to reduced treatment outcomes.\textsuperscript{34}

Even though the GPs in our program gave psycho-education on the diagnosis MDD and the available treatment options and offered a brochure on MDD provided by the Dutch College of General Practice, this information was not enough for these patients to pursue a treatment for this psychiatric disorder. This implies that for these high-risk patients diagnosed with unrecognized MDD a different approach is needed than purely diagnosing and offering treatment.

\textbf{In conclusion}

The screening program led to more detection of MDD, but did not result in improved treatment initiation. Fifty percent of the newly detected MDD patients already received treatment and 40% of the patients that did not already receive treatment, refused treatment. Difficulty with the acceptance of the diagnosis MDD and characteristics of
the high-risk groups were identified as main reasons for treatment refusal. On the basis of these results we conclude that the screening program, as part of a DMP, did not fit the perception of these high-risk patients and therefore was not effective in terms of treatment initiation.

**Different interventions for depressed high-risk patients**

A next question is then whether different approaches or treatments may be available and useful for depressed patients with USC and FA patients. Since we expect patients presenting with MHP to have less problems accepting a treatment for MDD, we will focus on interventions for patients with USC and FA patients.

*a. Interventions for patients with USC*

Interventions for patients with USC have focused on reattribution, a process of attributing physical symptoms to a psychological cause through negotiation and patient-centered communication.\(^{35}\) The reattribution model has been adopted by many researchers for use in training programs on the diagnosis and treatment of patients with USC.\(^{36-39}\) To improve the clinical outcomes for patients with USC diagnosed with MDD, Morriss et al\(^{40}\) designed a training package for GPs based on the reattribution model.\(^{41}\) Depressed patients with USC who after the reattribution intervention acknowledged the diagnosis of MDD showed an improvement in depressive complaints and general functioning, while the patients who dismissed the diagnosis of MDD showed considerably less improvement.\(^{40,42}\) So, training GPs clinically benefited depressed patients with USC who acknowledged the diagnosis of MDD.

In the Netherlands another training program was designed to improve the ability of GPs to recognize and manage depression in patients with USC, sleeping problems and chronic complaining.\(^{43}\) The training consisted of eight sessions of 2.5 hours each aimed at depression. Each session consisted of a discussion on normal practice and difficulties, lectures and video consultation, introduction on guidelines, role playing and evaluation. The training included the reattribution model, management of patients with chronic complaining behavior and techniques for motivating patients for referral to mental health care. The training increased guideline congruent treatment of MDD and improved short-term patient outcomes.\(^{44}\)

Recently Heijmans et al\(^{45}\) performed a qualitative analysis of narrative reviews and scientific editorials to review important and effective elements in the treatment of patients with USC in primary care. They assembled a focus group of experts (GPs participating in the guideline committee on USC in primary care of the Dutch College of General Practitioners) and interpreted the findings. The experts indicated
that an integrated approach in which creating a safe therapeutic environment, generic interventions (e.g., motivational interviewing, explanation giving) and specific interventions (cognitive therapy (e.g. reattribution) and pharmacotherapy) are combined is most useful. According to the experts the consultation process can best be viewed as both a conversation and continuing negotiation between the GP and the patient where there are no certainties about the cause of the complaints.\textsuperscript{45}

The recent Dutch Multidisciplinary Guideline Medically Unexplained Physical Symptoms and Somatoform Disorder\textsuperscript{46} links up with this in stating that a different perspective of looking at the complaints leads to a disagreement in treatment choice. The guideline therefore recommends care based on risk profiles and stepped care (i.e. start a treatment with the least invasive intervention that is supposed to be effective) in which the patient starts at an appropriate level and treatment setting.

\textit{b. Interventions for FA patients}

Studies have shown that solely diagnosing and treating FA patients with MDD, without any additional intervention, may be insufficient in reducing depressive symptoms.\textsuperscript{47,48} Katzelnick \textit{et al}\textsuperscript{49} found that a systematic primary care-based treatment program, consisting of (1) GP education on assessment of depressive symptoms and treatment initiation, (2) patient education on MDD and (3) antidepressive medication, was able to increase the number of (guideline congruent) treatments and improve depressive symptoms of FA patients.

One other intervention for distressed FA patients has been described by Katon \textit{et al}.\textsuperscript{50} They evaluated a psychiatric consultation liaison program consisting of a diagnostic interview (the Diagnostic Interview Schedule (DIS) by a psychiatrist with the GP present, a jointly formulated treatment plan and a mutually accepted course of action consisting of pharmacotherapy and referral. However, after one year they found no significant difference in improvement of symptoms. The above seems to highlight the importance of GP and patient education.

\textbf{Implications for treatment initiation in high-risk patients with MDD}

On the basis of our results and the literature we propose a number of implications to increase treatment initiation in high-risk patients with MDD. We recommend GPs to actively create a safe therapeutic environment in which there is room for the patient’s own story and explanations of the symptoms. The GP validates the worries of the patient about their symptoms and simultaneously explores signs of psychological distress, and the GP responds to emotions in order to bring up the subject of emotional suffering. Good communication techniques are an important factor in creating such a safe therapeutic
environment. Training GPs (or practice nurses) in communication skills, motivational interviewing techniques and/or cognitive techniques like reattribution may be useful in motivating these patients to start a treatment.

Further, educating GPs in the assessment of depressive symptoms and management of these high-risk patients in the daily practice might improve clinical outcomes. Finally, GPs should be aware of the fact that the majority of patients do not prefer antidepressants (ADs). An important question is which effective treatment can be offered instead of ADs. In the last part of this thesis we provide an answer to this question by investigating the relative effectiveness of two PC treatment options for patients with MDD.

**Have we missed patient groups with MDD?**

Our three high-risk groups comprised 12.5% of the total GP population between 18-70 years of the participating health centers. This raises the question, whether there are other groups in PC, besides our three high-risk groups, that would further increase the yield of our screenings program.

Next to the high-risk groups we have chosen, other target groups considered at high-risk for depression have been described in the literature. The National Institute of Health and Clinical Excellence guideline on MDD and recently the Task Force on Community Preventive Services recommended to target screening at patients with invalidating somatic illnesses, patients with a history of depressive episodes and elderly patients with cognitive dysfunction.

We believe we have incorporated the first group, patients with invalidating somatic illnesses, in the selection of FAs and/or MHPs, because these patients visit their GP on a regular basis for care associated with their illness and/or have mental health problems caused by the decreased health related quality of life associated with the disabling illness. However, it might be possible that there is a (small) group of patients with an invalidating illness that does not fall in the top 10% of FA or does not attend their GP with MHPs related to their invalidating illness. So we might have missed these patients, but the risk is small.

During designing our study we have not considered patients with a history of depressive episodes as a high-risk group for under-recognition, because we believe that their earlier experience with depression would help them and/or their GP to earlier recognize a new depressive episode and proceed to treatment. However, we have not studied this belief. Elderly patients with cognitive dysfunction were not incorporated in our study on the effectiveness of an integrated DMP because we expected them to respond differently
to the offered treatments than adult patients with MDD. Furthermore, these patients are traditionally examined in separate trials.

**Screening and diagnosing with the Patient Health Questionnaire (PHQ)**

We will now look at some aspects of the screening instrument, the PHQ. Although the PHQ is widely used and validated in different PC populations, each population generates its own test characteristics (sensitivity and specificity). Establishing the test characteristics of our high-risk population is therefore important. The depression module of the PHQ, the PHQ-9, is the most researched module and only a limited number of studies considered the validity of other modules of the PHQ.

The second and third research question of this thesis address the validity of two modules of the PHQ: the PHQ-9 and PHQ-Panic Disorder (PHQ-PD) and address the influence of co-morbid psychiatric disorders on the test characteristics of these two modules.

The PHQ-9 has been extensively used in research and clinical settings. To be able to attribute differences in PHQ-9 scores between groups with different cultural backgrounds to differences in the level of depression, the instrument has to possess measurement invariance. So, the fourth research question addresses measurement invariance of the PHQ-9 with respect to ethnicity.

In order to answer these three questions, we expanded the number of participating health centers. In total six health centers with 23 GPs and 31915 enlisted patients participated. Of these 2314 high-risk patients were invited and received the PHQ.

**Patient Health Questionnaire-9 (PHQ-9)**

We investigated the accuracy of the PHQ-9 in diagnosing and detecting depressive disorder in a high-risk population of primary care patients using the SCID-I diagnosis as criterion.

**Screening**

The cutoff point that is most widely used to indicate a positive case of depressive disorder is a PHQ-9 sum score of 10 or higher. When applying this cutoff point for screening purposes to our high-risk population we found a sensitivity (SE) of 0.93 and a specificity (SP) of 0.85 using the SCID-I diagnosis as criterion. Furthermore, with this cutoff point we found a positive predictive value (PPV) of 0.47 and a negative predictive value (NPV) of 0.99. When applying a cutoff point of 15 we found a SE of 0.65 and a SP of 0.96. PPV with this cutoff point was 0.69 and NPV was 0.95. We can conclude that for screening...
purposes in these three high-risk groups the PHQ-9 is a valid instrument. For screening purposes one wants to obtain a high detection rate. Therefore we recommend to use the cutoff point of ≥10 when screening in these three high-risk groups since this yields the highest SE (0.93).

**Diagnosis**

In order to assess the accuracy of the PHQ-9 in diagnosing depressive disorder, we made use of the diagnostic algorithm\(^1\). When applying this algorithm, we found a SE of 0.68 and a SP of 0.95 using the SCID-I diagnosis as criterion. In the high-risk population we found a month prevalence of depressive disorder of 12.3%. This resulted in a PPV of 0.67 and a NPV of 0.96. A PPV of 0.67 is too low for diagnostic purposes. Thirty three percent of all PHQ-9 positive patients will be wrongly diagnosed as depressed. So, for every two depressions one false positive must be followed up and follow-ups are costly and time consuming. We can conclude that the PHQ-9 is not an optimal instrument for diagnosing depressive disorder in this population.

**Influence of co-morbidity**

Co-morbidity of somatoform, anxiety and depressive symptoms, the so called “SAD triad”, is a well known phenomenon in PC. Studies of Hanel et al\(^5\) and Lowe et al\(^6\) showed that the overlap in symptoms of those three disorders occurs in more than 50% of PC patients. We studied the influence of co-morbid anxiety- and somatoform disorders on the test characteristics (e.g. SE, SP) of the PHQ-9 using the SCID-I diagnosis as criterion. The month prevalence of depressive disorder in patients with a positive PHQ score on the anxiety and/or panic module was 49.5%. When applying the diagnostic algorithm for diagnostic purposes we found a SE of 0.85 a SP of 0.83, a PPV of 0.83 and a NPV of 0.85.

The month prevalence of depressive disorder in patients with a positive PHQ score on the somatoform disorder module was 33.6%. When applying the diagnostic algorithm we found a SE of 0.91, a SP of 0.85, a PPV of 0.75 and a NPV of 0.95.

A co-morbid anxiety- or somatoform disorder increases the SE and the PPV of the instrument. A higher PPV results in a smaller percentage of PHQ-9 positive patients that will be erroneously diagnosed with depressive disorder. However, a PPV of 0.75 is still too low and requires further diagnostic testing. We can conclude that also in subgroups with an anxiety or somatoform disorder the PHQ-9 is not an optimal instrument for diagnosing depressive disorder in this population.

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\(^1\) A positive outcome on the categorical algorithm requires that five or more of the nine depressive symptom criteria are present more than half of the days in the past 2 weeks (suicidal thoughts count if present at all), and one of these symptoms has to be depressed mood or anhedonia (see appendix 1).
Patient Health Questionnaire –Panic Disorder (PHQ-PD)

The PHQ-PD is the subscale of the PHQ for panic disorder. We investigated the accuracy of the PHQ-PD in diagnosing and detecting panic disorder using the SCID-I diagnosis as criterion in the same high-risk population of PC patients. The original algorithm is most widely used to indicate a positive case of panic disorder. In our three high-risk groups, when applying this original algorithm we found a SE of 0.44 and a SP of 0.94. Modified algorithms of the questionnaire led to a significant improvement of SEs compared to the original algorithm (0.61 and 0.66 respectively). When applying just the screenings question we found a SE of 0.71 and a SP of 0.83. We can conclude that for screening purposes in these three high-risk groups the PHQ-PD is a moderate instrument.

In conclusion

The PHQ-9 and (in lesser degree) the PHQ-PD are suitable for screening in our three high-risk groups. If these instruments are used for screening in this high-risk population, they should be followed by diagnostic procedures (e.g. the SCID-I). The use of the PHQ-9 and the PHQ-PD as diagnostic instruments may result in a large number of false positives and is not recommend.

Measurement invariance of the PHQ-9

To answer the fourth research question, data of the validation study of the PHQ was used. From this data we selected two contrasting cultural groups, Surinam Dutch and Dutch and assessed measurement invariance by comparing four categorical single factor models with an increasing number of restrictions, representing an increasingly stronger measurement invariance assumption. We conclude that, in relation to the two

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2b All of the first four questions of the PHQ-PD (see appendix 1) are answered with “yes”, and presence of four or more somatic symptoms during an anxiety attack.

3c (i) At least three of the first four questions are answered with “yes,” other coding criteria unchanged; (ii) At least two of the first four questions are answered with “yes,” other coding criteria unchanged.

4d "In the last four weeks, have you had an anxiety attack—suddenly feeling fear or panic?"
cultures we studied for this purpose, the Surinam Dutch and the Dutch, the PHQ-9 was measurement invariant for ethnicity in women and partially measurement invariant for ethnicity in men. Given a certain level of depression, Surinam Dutch males were less likely to endorse the item ‘psychomotor’ problems than Dutch males. This is in line with Huang et al who found evidence of partial measurement invariance of the PHQ-9 in four of the largest racial/ethnic groups in the United States. They concluded that, even though they found evidence of partial measurement invariance, the PHQ-9 measures a common concept of depression in the different cultural groups.

The partial measurement invariance we found may result in somewhat lower mean PHQ-9 total scores in Surinam Dutch males compared to Dutch given a comparable depression severity. In screening terms, this may lead to more false negatives in Surinam Dutch males. We expect, however, this difference to be minor, since it concerns only one item and the percentage of endorsement of this item in our sample is low (19.9%) compared to the item endorsement of the other 8 items (mean endorsement 29.4%; range= 9.7- 45.2%). Hence, we believe the PHQ-9 measures a common concept of depression in these groups and can be used for screening in Surinam Dutch and Dutch patients without adjustment of the cutoff point.

Assessment of measurement invariance is not only important when looking at differences between cultures, but is also important when looking at differences between males and females, differences between patients from different age classes and differences between groups at different measurement points. In these cases it is also possible that the difference in PHQ total scores does not reflect a true difference in depressive symptomatology. Clinicians should be aware of this. We recommend clinicians to assess measurement invariance as much as possible before interpreting outcomes.

**The last step of the DMP: evidence based treatment**

The last research question addresses the relative effectiveness of two PC treatment options in their most optimal form (i.e. according to the guidelines). We investigated, in a multicenter randomized trial, whether 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 the clinical guidelines. In order to improve the generalizability of the results, we decided to divert from the original protocol and discard the high-risk groups. For the inclusion procedure we asked GPs to refer patients in the age of 18-70 years whom they considered to be suffering from MDD to the study centre. Forty GPs, with 109 general practitioners
participated. During the recruitment phase, 175 patients were referred of whom 121 met the inclusion criteria and agreed to participate in the trial.

The overall results of the trial show that psychologists are equally capable of treating MDD patients as GPs and maybe even better since the trend in our study appears to consistently favour the brief CBT group. Despite using a GPC protocol consisting of supportive contacts which could be combined with an antidepressant (AD) (i.e. GPs were free to choose whether they prescribed an AD), GPs prescribed ADs to 48% of the patients. In the brief CBT group comparable outcome was accomplished with an eight session CBT and a small percentage of AD prescriptions (11%). This smaller percentage of AD prescriptions is an advantage of brief CBT, especially in the light of the ongoing debate on the effectiveness and applicability of AD in patients with milder forms of depression. Overall, there seems to be a smaller indication area for AD.

Also without the above advantages, CBT may offer some additional advantages over AD:

a. CBT produces no medication side effects;

b. CBT may provide the patient with the feeling of being part of improving their problems;

c. CBT is able to adjust maladaptive cognitive coping skills (e.g. catastrophizing, self blame);

d. CBT has a preventive effect on recurrence: a large majority of patients with MDD experience more than one Major Depressive Episode (MDE) and the risk of recurrence (i.e. a new episode of affective illness following recovery) progressively increases with each successive MDE. CBT has been found to have an enduring effect that reduces the risk of symptom return after the treatment has stopped. Even brief versions of CBT may have long-term preventive effects on recurrence. ADs have also been found to reduce the risk of symptom return and patients with recurrent MDD may benefit from continued treatment with ADs. However, CBT has been found to have a prophylactic effect on recurrence after treatment is stopped, while ADs have to be continued to reach comparable prophylaxis.

**Implications to manage MDD in PC**

So, how to manage MDD in PC? Our finding, that psychologists are equally capable of treating MDD as GPs and maybe even better, corroborates other findings in PC. This finding, together with the reduction of AD prescriptions in the brief CBT group and the above described advantages of CBT, leads us to recommend brief CBT as first choice treatment for PC patients presenting with MDD in primary care. For a small amount of patients (one in seven) this brief intervention may not be sufficient. For them, other
evidence based psychotherapy like interpersonal psychotherapy (IPT) or ADs may offer good alternatives. The Dutch Multidisciplinary Guideline for Depressive Disorder\(^6\) does not recommend an optimal therapy duration, but states that efforts should be made to achieve the shortest duration of therapy.

On the basis of our results we can conclude that an eight session CBT seems sufficient for the majority of PC patients with MDD. Currently, brief CBT is not a treatment option in the Dutch Multidisciplinary Guideline for Depressive Disorder\(^6\) and the NHG guideline Depression\(^9\), but may fit well within the recent developments in Mental Health Care. The Dutch Mental Health Care has increasingly moved towards the stepped care model. The assumption of stepped care is that many patients benefit from low-intensity treatments and do not need further treatment. In stepped care the patient is first offered the lowest intensity treatment needed which is still likely to provide significant health gain given the severity of the disorder. Patients who do not respond adequately can ‘step up’ to a subsequent higher intensity treatment.\(^6\) Brief CBT may be a suitable low intensity psychological treatment.

**Implications to enhance care for MDD patients in PC**

We further propose a number of implications to enhance the care for MDD patients in PC.

**a. Treatment preferences**

Earlier in this thesis it was shown that patients often refuse to accept the diagnosis of MDD out of fear that the diagnosis will lead to treatment with ADs. Furthermore, when patients start using the prescribed ADs, 50% of them discontinue the use within 6 weeks.\(^6\) This indicates that GPs seem to have faith in medication, while quite some patients are not willing to take them. The Dutch Multidisciplinary Guideline for Depressive Disorder\(^6\) states that the choice between psychological therapy and pharmacotherapy must be made in agreement with the patient. However, patients are often reluctant to display their preferences due to fear of stigma or low self-esteem associated with MDD and GPs are also unlikely to elicit their preferences\(^9\) which altogether leads to dissatisfaction in both patient and GP.

Dwight-Johnson *et al*\(^7\) investigated whether a depression Quality Improvement (QI) program, designed to elicit and join patient and provider treatment preferences, was able to increase (adequate) depression treatment and the likelihood of receiving the preferred treatment. The program consisted of training health care personnel in providing patient education about treatment options and encouraging them to elicit and address patient treatment preferences. The results showed that a larger amount of patients in the QI group than in the usual care group received a treatment and also
the preferred treatment, and that a larger amount of patients in the QI group received a treatment that was in accordance with the guidelines. Furthermore, this QI program was also able to improve the quality of care and mental health outcomes of PC patients with MDD. Informing patients about the available treatment options and motivating them to elicit and address treatment preferences are recommend steps when aiming at enhancing care for patients with MDD in PC.

\[\text{b. Joint prescription of antidepressive medication}\]

Given the increasing rate of AD prescriptions in the last decades, evaluation of the adequacy of AD prescriptions is becoming more and more important. Research has shown that adequacy of AD prescription in PC is suboptimal. Joint prescribing of ADs by a GP and a psychiatrist may be a solution since it has been found to produce significant improvement in rates of adequate AD prescription in MDD patients.

\[\text{c. Monitoring treatment adherence, side effects and outcomes}\]

For treatment to be successful, it is essential to ensure and monitor the patient’s adherence to treatment. Providing information on the symptoms, course and treatment of MDD and addressing barriers to adherence (e.g. lack of motivation, side effects) may be important strategies to enhance adherence to treatment. Next to treatment adherence, the patient should also be systematically monitored to assess their response to treatment. The integration of structured measures of depression severity, side effects and treatment adherence into the care of MDD patients, which has been referred to as measurement-based care, may enhance the quality of care and improve clinical outcomes. The Patient Health Questionnaire, which has been found to be a valid instrument for monitoring depressive symptoms may well be used for this purpose.

\[\text{d. Collaborative Care}\]

In the daily practice of the GP, there usually is no time for extensive patient education, carefully monitoring of symptoms or treatment adherence. In order to overcome this, programs, in which health care staff provides a substantial part of the care, have been developed and have proven to be effective for depressive patients in primary care, like depression care support programs, case management and collaborative care programs. Collaborative Care (CC) is a systematic approach, developed in PC in the US, that improves patient education and integrates mental health professionals, nurses, and care managers into the PC practice to help GPs provide treatment according to the guidelines.
CC usually consists of the following key elements:

1. **Stepped care approach**
2. A depression care manager who educates patients, monitors symptoms, side effects and adherence to treatment. At fixed evaluation moments the care manager determines, on basis of questionnaire results, whether the treatment needs adjustment according to the stepped care principle.
3. **Supervision by a psychiatrist or psychologist for the care manager and GP.** The psychiatrist or psychologist can, for example, recommend changes in medication or teach the care manager or GP motivational interviewing skills.

The Dutch Depression Initiative is a national initiative developed to improve the care for patients with depression and to attain the quality level of the Dutch Multidisciplinary Guideline for Depressive Disorder and the NHG guideline Depression. They implemented a CC model in a primary care, a hospital and an occupational health setting. The CC model comprised of psycho-education, brief problem solving therapy (PST; 6 sessions), a self help book and if necessary ADs. The depression care manager worked together with the GP and a psychiatrist and provided the treatments according to the stepped care principle. This CC model has shown to be effective in improving response, remission and severity of depressive symptoms in PC. One of the identified effective elements in this model was the provision of brief psychological treatment (in this case PST). In the majority of CC models, particularly in the US, providing brief psychological treatment, is unusual. We believe that brief CBT is a treatment that may fit well into a CC model for depressed patients in primary care.

### Implications for future research

**a. What works for whom?**

Both (brief) CBT and ADs are effective treatments for MDD. Interestingly, these treatments presumably exert their effects through different pathways. The response to CBT, for instance, is predicted by reduced medial prefrontal activity and increased amygdala activation, while activity in the serotonergically-mediated medial prefrontal-limbic network is associated with response to selective serotonin reuptake inhibitors (SSRI). Imaging, molecular and genetic data may offer potential biomarkers for the assessment of treatment outcomes. Future studies should focus on identifying differential predictors for CBT and AD to reveal what works for whom.

**b. The relationship between the quality of therapists and patient outcomes.**

Very few psychological therapy trials in PC have examined important quality issues like
therapist experience, therapist qualifications and therapist skills. Despite attempts to eliminate the therapist as an important outcome variable by training therapists, providing supervision and using treatment manuals, some evidence suggests that individual therapists may have an important impact on patient outcome. Crits-Christoph and Mintz\textsuperscript{89}, for example, meta analyzed data from ten clinical trials and found substantial contribution of individual therapists to outcome. Monitoring outcomes on the basis of individual therapists may provide an opportunity to directly manage and improve outcomes in specific PC practices. Furthermore, highly skilled therapists may be identified and asked if they permit videotape recordings of their therapy sessions in order to identify successful elements. These videotapes may then be used in the supervision and training of therapists.

c. Screening instrument for suitability for psychotherapy
In the past decades indicators of suitability for psychotherapy like the possibility of building a therapeutic relation, psychological mindedness and the quality of the patients object relations have been identified.\textsuperscript{90} Furthermore, research has indicated that patients with a higher suitability for psychotherapy have shown relatively more favorable outcomes.\textsuperscript{91} Identifying patients that are suitable and unsuitable for psychotherapy may therefore enhance clinical outcomes. Future studies may focus on developing screening tools that screen for suitability for psychotherapy.

d. Describe the content of usual GP care.
Usual GP care is often a difficult comparison condition since the content of the GP care is mostly not reported or standardized according to clinical guideline recommendations. Most studies do report whether GP care included the prescription of medication and whether GPs were asked to refrain from referral, but do not report the extent of the AD prescriptions and referrals. Future studies should always thoroughly describe the content and interpretation of usual GP care since this would aid in the interpretation of findings.

e. Cost effectiveness
Unfortunately we have not planned an economic analysis of the costs of brief CBT and optimized GPC. Future research in PC is needed to examine the relative cost-effectiveness of both PC treatments in order to put the current findings in context.
REFERENCES


