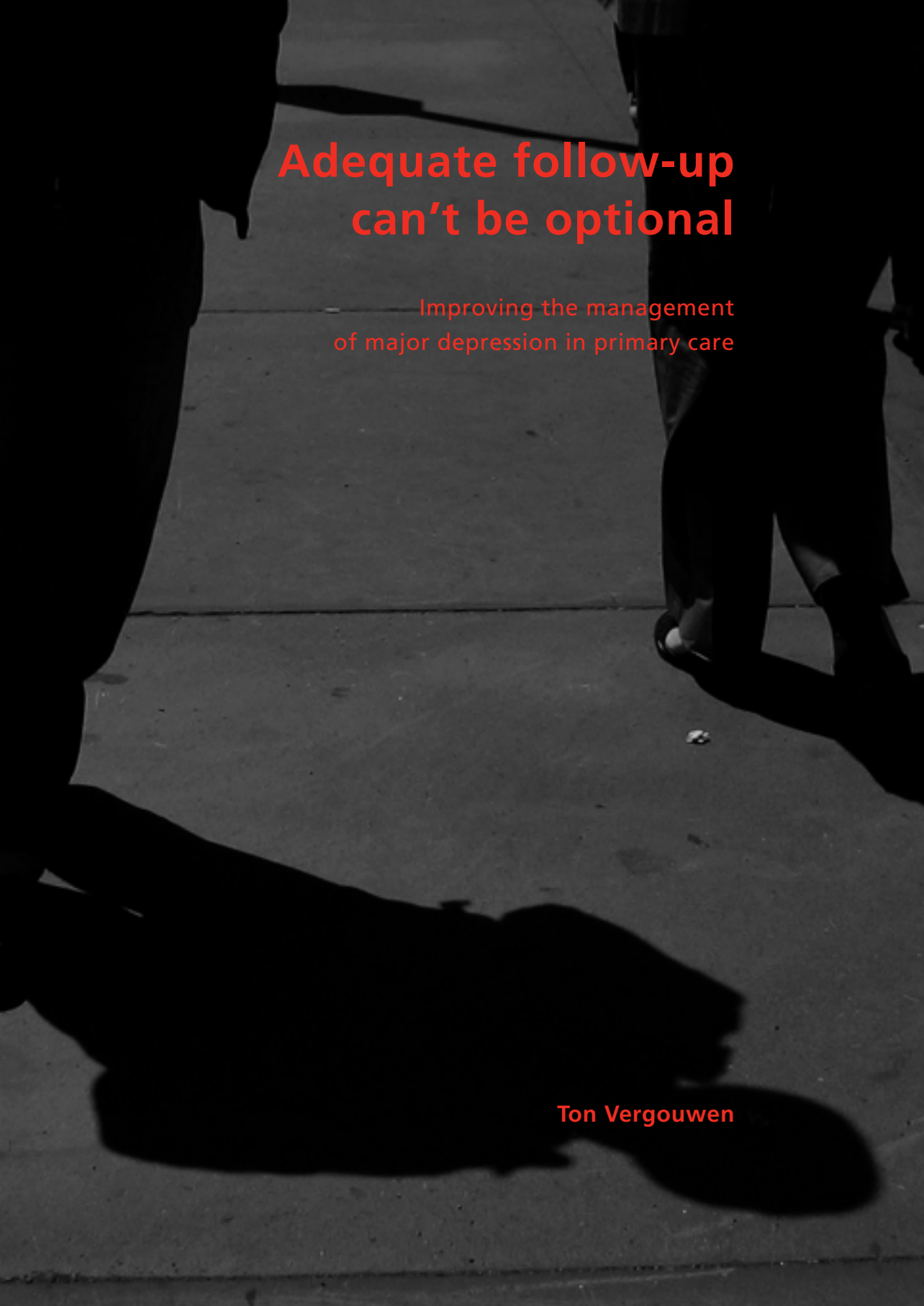

Adequate follow-up can't be optional

Improving the management of major depression in primary care

Ton Vergouwen

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Adequate follow-up is niet vrijblijvend

Verbetering van de behandeling van depressie in de huisartsenpraktijk

(met een samenvatting in het Nederlands)

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit Utrecht
op gezag van de Rector Magnificus,
Prof. Dr. W.H. Gispen,
ingevolge het besluit van
het College voor Promoties
in het openbaar te verdedigen
op dinsdag 17 januari 2006
des middags te 4.15 uur

door

Antonius Cornelius Maria Vergouwen

geboren op 6 mei 1963 te Goes

Promotoren: Prof. dr. G.F. Koerselman
Prof. dr. Th.J.M. Verheij

Co-promotor: Dr. H. Burger

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Contents

Introduction

1

This thesis is based on a systematic review and the OPTIMIND™-study. The aim of the studies was to gain more insight into the possibilities to improve the treatment of major depression in primary care. The systematic review focussed on studies investigating interventions aiming to improve patient adherence to antidepressants, and depression outcome. The OPTIMIND™-study compared the rate of adherence to antidepressant medication, and depression outcome between a depression care program (DCP) and a systematic follow-up program (SFP). In addition, the possibility to improve negative attitudes towards antidepressant medication was investigated. We also examined the possibility to predict an unfavorable outcome (i.e. non-remission by week 10) by studying candidate predictors of non-remission, and examining the relationship between initial symptom improvement and non-remission.

Background

Major depression and consequences

Major depression represents an important and worldwide public health problem (1;2). It is associated with more functional disability than most chronic medical illnesses (3;4;5). In the year 2020 major depression will be the second leading cause of disability, only to be surpassed by ischaemic hearth disease (6). Major depression tends to become a chronic condition with high relapse and recurrence rates (7). It is also associated with an increased reporting of medically unexplained somatic symptoms (8;9;10;11). Seriously depressed patients have been found to utilize health care services three times as often as nondepressed controls (12;13;14). Major depression also negatively influences the outcome of comorbid medical illnesses such as cardiovascular diseases, and diabetes (10) and may even be a risk factor for new occurrence of these conditions (15;16). The high utilization of health care services, loss of work productivity and absenteeism lead to enormous economic costs (17;18).

Major depression in primary care

Depression is the third most common reason for consultation in primary care (19). A review by Katon et al (20) showed that the prevalence increased from two to four percent in the community to five up to ten percent in primary care. A significant part of mental disorders in primary care is not transient and self-limiting. Ormel et al (21) found that at least 50% of mental disorders had a chronic or intermittent course. Mean episode duration after the index consult was about nine months, and mean total episode duration amounted to 14 months. Katon et al (20) demonstrated that depression persisted over 6 to 12 months in one-third to one-half of the cases. Goldberg et al (22) also found that about 50% of patients still meet the criteria for depression after one year. Yet, in a sample of patients initiating antidepressant

medication in primary care, the proportion of patients continuing to meet the criteria for major depression fell rapidly to approximately 10% and remained around that level throughout the follow-up of 24 months (23). However, many patients not meeting the criteria anymore may still suffer from significant symptoms, posing them at risk for relapse or recurrence, continuing functional impairment and somatic comorbidity, e.g. cardiovascular disease. Therefore, remission, i.e. absence of syndromal criteria and none or only minimal symptoms, is the goal of treatment, not just response. In the aforementioned study, the proportion meeting criteria for remission rose gradually to approximately 45%. Schulberg et al (2) observed that only 20% of primary care patients treated with usual care was asymptomatic after 8 months. De Almeida Fleck et al (25) also found a relatively low proportion of people achieving remission at follow-up (9 months) across six countries; rate of remission was 35%. Differences between studies in remission rates may reflect differences in populations as a result of differences in screening or selection procedures, or level of treatment. In conclusion, major depression cannot be viewed as a benign condition for the majority of primary care patients.

Major depression treatment in primary care

Major depression requires long-term treatment. Treatment options include a variety of antidepressants with proven clinical efficacy in reducing symptoms and in preventing relapse and recurrence (26;27;28) as well as psychotherapy (29;30). General practioners are responsible for the majority of antidepressant prescriptions in the Netherlands, and in 2001 the number of patients taking these drugs increased by 61% compared to 1996 (31). Especially the use of selective serotonin reuptake inhibitors (SSRIs) has increased. However, there exists a rift between treatment recommendations and clinical practice realities (32). Despite available effective treatment modalities and guidelines for the treatment of depression (33;34;35;36) , quality of treatment is often poor (5;37;38): among patients initiating therapy, few receive levels of treatment consistent with research evidence and expert guidelines (39;40). Less than one quarter of primary care patients with depressive disorders receive adequate acute-phase treatment (39;40;41). Duration of treatment is inadequate, and patient follow-up and support are suboptimal. Even when appropriate treatment is recommended, adherence to treatment is a major problem. Observational studies showed discontinuation rates of 28% at one month and of 44% - 52% at three months (42;43;44). Adherence to antidepressant medication is necessary for positive patient outcome.

Consequences of undertreatment are chronicity, relapse or recurrence, and long-term disability (23;45;46). For these reasons, proper treatment of depression in primary care is warranted as formulated by the World Health Organization strategy for mental health (6).

Interventions to enhance depression treatment in primary care

Improving outcomes for patients with major depression is not as simple as prescribing a new treatment. The whole management of depression needs to be enhanced (47). Active follow-up, monitoring of patient outcome, and patient education seem important (26). Given the high non-adherence rates, interventions to improve adherence to pharmacotherapy are particularly critical. Barriers to patient adherence include lack of knowledge in the nature of depression, and of antidepressant medication. Negative attitudes towards antidepressants may also jeopardize adherence.

The management of depression may benefit from adaptation of practice conditions that more closely mimic trial conditions in which follow-up visits are scheduled and structured, and outcomes are assessed using standardized instruments (32). Numerous investigators developed interventions, of which several improved adherence to antidepressants and depression outcome more than usual care. Ingredients of these interventions were patient education, counseling, and appropriate feedback from nurses and mental health specialists working as primary care extenders (48;49;50). However, time restraints and limited availability of these treatment modalities preclude intensive treatment for most patients in everyday practice. Change is hard work, and programs to change the management of patients suffering from major depression should be feasible in everyday practice. Most interventions had multiple ingredients, making it difficult to establish which the active ones are. The abovementioned issues warrant investigating which ingredients of depression care programs are effective.

Prediction of outcome

Many primary care patients do not timely remit, even when treatment is adequate. Because non-remission of the index depressive episode is one of the most consistently cited presages of poor long-term prognosis (51;52), and its risk can be reduced by adequate treatment (53;54), it is important to recognize patients with a high probability of non-remission before treatment. These patients can be treated more intensively from the start, and ultimately, their prognosis may improve as a result. Several primary care studies reported patient characteristics that seemed to be related to non-remission. However, in most of these studies remission at week 16 to week 24 was the outcome. This duration is far beyond the acute phase in depression treatment in which remission should be attained (55). In addition, the joint predictive value of these characteristics and the possible clinical implications were not addressed (56), not clarifying what, if anything, clinicians could do with the results. None of the previous studies investigated the discriminative power of the predictive models nor adjusted for over-optimism (57).

Symptoms change in relation to outcome

In spite of the widespread use of SSRIs in primary care, little is known about how long it takes to see their full effect. Acknowledging the absence of empirical data, Schulberg et al (26), in an Agengy for Health Care Policy and Research update, indicated the need for research identifying "the time point at which to augment or change the initial acute treatment." Current guidelines suggest that if a partial response has not occurred after 4 to 6 weeks, treatment should be changed (26;35;36). Others suggest that lack of response by 4 weeks bodes poorly for a beneficial outcome (58). However, guidelines are primarily based on the literature from pharmacotherapy randomized controlled trials conducted in psychiatric care setting, and on the experience of a group of experts. Therefore, it is of clinical relevance to investigate the relation of symptoms change to desired outcome (i.e. remission) during the acute treatment phase in primary care settings. While many studies addressed the question what precedes lack of response, the clinically most important question is what precedes non-remission.

Attitudes towards antidepressant medication

Negative attitudes towards antidepressants are widespread in patients under antidepressant medication (59;60). These attitudes are positively associated with adherence (61;62), which makes it relevant to develop and investigate interventions aiming at improving these negative attitudes.

Study aims and thesis design

With these aforementioned issues in mind, we undertook a systematic review of studies investigating interventions aiming at improving adherence and depression outcome. We also developed a depression care program that was feasible in primary care practices in the Netherlands. The program targeted GP, patient, and structure of follow-up. We decided to compare the DCP with a systematic follow-up program, and not with usual care. Usual care generally does not meet the recommendations given in guidelines (5;37), and is therefore from a clinical point of view an unacceptable comparator.

The effects on adherence to antidepressant medication, depression outcome, and attitudes towards antidepressant medication were compared. In addition, prediction of an unfavorable depression outcome was investigated, relating baseline characteristics and symptoms change respectively, to non-remission by week 10.

Specific aims

At the time we started with the systematic review of interventions aiming to enhance the management of depression, such a review was not yet published. Our aim was: (i) to identify the interventions applied to enhance

management of depression; (ii) to identify the ingredients of the interventions; (iii) to evaluate the effectiveness of the different methods on adherence and depression outcome (chapter 2.1).

The main purpose of this study was to investigate the effect of a depression care program in comparison with a systematic follow-up program on adherence to antidepressants and depression outcome. This comparison should answer whether a complex intervention is more effective than systematic follow-up (chapter 2.2).

Since several studies reported on predictors of outcome in primary care patients suffering from major depression, without addressing the practical consequences, the third aim was to develop a prediction rule that would be applicable in clinical practice. Predictors of non-remission by week 10 were investigated and the development of a prediction rule was illustrated (chapter 3.1)

Mostly, prediction research addresses the relation of baseline characteristics to treatment outcome. In clinical practice, symptoms change is used to predict treatment outcome. The fourth aim was to investigate the rate of improvement at week 2 and week 6 in relation to remission by week 10 (chapter 3.2).

Many patients have negative attitudes towards antidepressant medication. These attitudes are associated with poor adherence, which may result in poor depression outcome. The fifth aim of this study was to investigate whether attitudes of depressed primary care patients can be changed. For that purpose, a depression care program was compared with a systematic follow-up program (chapter 4).

Chapter 5 presents a general discussion, which summarizes and concludes the main findings. Limitations of the studies are discussed and future research programs are proposed.

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Improving adherence to antidepressants: A systematic review of interventions

2.1

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J Clin Psychiatry 2003;64:1415-1420

Abstract

Background

Effectiveness of antidepressant medication is reduced by patients' non-adherence. Several interventions to improve adherence in patients diagnosed with unipolar depression were tested.

Objective

To systematically review the effectiveness of interventions that aimed to improve adherence to antidepressant medication in patients suffering from unipolar depression.

Method

Systematic review of English-language articles of randomized controlled trials obtained by a computerized literature search of Medline, PSYCINFO, EMBASE, and the Cochrane Controlled Trials Register.

Results

Educational interventions to enhance adherence failed to demonstrate a clear benefit on adherence and depression outcome. However, collaborative care interventions tested in primary care demonstrated significant improvements in adherence during the acute and continuation phase of treatment and were associated with clinical benefit, especially in patients suffering from major depression who were prescribed adequate dosages of antidepressant medication.

Conclusion

We found evidence to support the introduction of interventions to enhance adherence with antidepressant medication in primary care, not only because of better adherence but also because of better treatment results. Because collaborative care interventions require additional resources, a better understanding of the mode of action of different programs is needed to reduce avoidable costs. The effectiveness of educational interventions needs more evidence.

Introduction

Depressive illness is a public health issue of major significance (1). Lifetime prevalence is estimated at about 15% (2) and most depressive patients are treated in general practice (3,4). Despite proven efficacy of antidepressant medication, many depressed patients do not receive an adequate dosage and duration of treatment (5). Shortcomings in depression treatment are frequently noted in both primary care and specialized care (6). These may result in serious consequences such as treatment failure, chronic course, complications, high medical care utilization, and impairment in work functioning and other activities (7,8). Effectiveness of antidepressants is also reduced by patients' non-adherence. Observational studies found discontinuation rates of 28% at one month and 44% to 52% at three months (9,10).

Adherence to antidepressant medication is essential to the outcome of depression treatment. However, Haynes et al. (11) concluded, in a review of interventions to enhance adherence in chronic illnesses like asthma, hypertension, and schizophrenia, that current interventions are not very effective. Studies of programs that aimed to improve adherence with antidepressants were not included. In depressive disorders, education and active participation of patients in the treatment process were presented as cornerstones to enhancing treatment adherence (12). Other investigators argued that multifaceted interventions targeting patient, physician, and structural aspects of care have the potential to improve adherence and depression outcome (13).

Recently, two review articles on adherence to antidepressant medication were published (14;15). There are a number of significant shortcomings in these papers, however. Pampallona et al (14) included several studies in patients suffering from psychiatric disorders not limited to unipolar depressive disorders who were treated with different classes of psychotropic medication (16;17;18;19) as well as a study investigating adherence to referral, but not adherence to medication (19) The authors did not give important details on characteristics of the reviewed studies, and results of a statistical comparison of adherence outcomes between groups were not reported. Lingam and Scott (15) included only two randomized controlled trials of interventions aiming to improve adherence with antidepressant medication in patients with unipolar depressive disorders (13;20). Although adherence is a means to an end (21), these two reviews did not report on depression outcome.

In view of the shortcomings of the previous reviews we decided to review the randomized controlled trials on interventions to improve adherence with antidepressants from the perspective of the studies and to report on effectiveness, adherence, and depression outcome.

Methods

The studies used for this systematic review were obtained by a computerized literature search of four databases. The search strategy was as follows:

MEDLINE (1966 to January 2002): ((patient compliance OR patient dropout OR treatment refusal OR patient education OR adherence) AND (clinical trial OR randomized controlled trial OR controlled trial) AND (depressive disorder OR depression)) [all fields].

PSYCINFO (1984 to January 2002): ((random OR clinical OR control OR trial) AND (adherence OR compliance OR noncompliance OR dropouts OR patient education) AND (depression OR major depression OR affective disorders OR dysthymic disorder)) [all fields].

EMBASE (1980 to January 2002): ((patient compliance OR patient dropouts OR illness behavior OR treatment refusal OR patient education) AND (clinical trial OR controlled study OR randomized controlled trial) AND depression) [all fields].

Cochrane Controlled Trials Register: ((random*) AND (complian* OR adheren* OR pharmacotherapy OR regimen* OR educat*) AND (medicat*) AND (depression OR depressive disorder)) [no restrictions].

Additional reports were identified from the reference lists of retrieved reports and the review article of Pampallona et al (14). Only English-language publications in peer-reviewed journals were considered for inclusion.

Articles were selected if they reported a randomized controlled trial of an intervention aimed at improving adherence to prescribed antidepressant medication in patients with unipolar depression. Studies on interventions that did not target the patient directly (e.g. studies of implementing practice guidelines or training physicians) were not included. No selection on quality of studies was made. Important methodological issues will be addressed in the discussion. Data extraction was done by one author (ACMV) and cross-checked by another author (AB).

Results

The search strategy retrieved 21 studies. The study of Finley et al (22) was not included because adherence rates were not yet available. Another identified study (23) reported on the 19-month follow-up of two studies included in this review (13;24). This left 19 studies to be included. The characteristics and results of the studies are shown in table 1. More detailed information is available on request.

There were many differences across studies, preventing a quantitative comparison between groups. Results are therefore summarized qualitatively. We decided to discuss the studies performed in psychiatric outpatient clinics separately from those performed in primary care.

There were no studies in hospitalized depressive patients. Inclusion and exclusion criteria differed among studies, and assessment of depressive disorder was not uniform. The sample size of the studies ranged from 14 to 1356 participants. The total number of patient participating in the studies was 5232. The interventions were not uniform. We classified the studies into two broad categories of treatment modality: patient education and collaborative care.

Patient education ranged from notifying patients of possible side-effects (25;26) to an information leaflet that was read and explained to the patient during the initial visit (28), and to personalized information mailed directly to patients (31;32).

Collaborative care, on the other hand, was defined as a systematic approach that improves patient education and with an active role of mental health professionals or other care extenders, such as nurses, in primary care (34). Collaborative care interventions are multimodal, i.e. affecting patient and physician as well as the system of care. Increased patient education, longer and more frequent visits, surveillance of adherence to medication regimens, primary care training in the treatment of depression, and feedback and recommendations given by care extenders were frequently used components. Practice nurses aimed to enhance treatment adherence by discussion and encouragement - particularly by providing explanation and reassurance about side-effects of medication (33) or counseling that addressed daily routine, lifestyle, attitudes to treatment, and the reasons for treatment and by giving advice about the use of reminders and cues to take the medication (20).

Telehealth care was also used. It consisted either of emotional support and focused behavioral interventions provided in ten 6-minute calls during 4 months by primary care nurses (36) or of assessments including current use of antidepressants, side effects, and severity of depressive symptoms and sometimes general support and encouragement by care managers in two phone calls. After each telephone assessment, doctors received a feedback report and treatment recommendations (38).

Several interventions had an integrated role of the psychiatrist in primary care (13;24;34;37). In one study (38), the psychiatrist supervised the telehealth care case managers. Psychologists providing brief psychotherapy were integrated in one intervention (24). In another study (36), a psychologist supervised the practice nurses.

Control groups were treated with 'usual care', meaning that no services other than standard ones were provided to the patients and doctors. In most cases, usual care for depression involved prescription of antidepressant medication and 2 to 3 visits over the first 3 months of treatment (24). One study (20) also contained an attention control group. Patients in this group received only one interview to assess the effect of closer monitoring by the research team on adherence.

Assessment and definition of adherence were variable among the studies. While a recent study comparing methods of assessing adherence with medication found the electronic pill container, which records each opening of the container, to be the most informative (41), only one study used electronic monitoring to check reliability of patient-reported adherence. Fourteen studies reported the depression outcome (13,20,24,30-40). Follow-up ranged from 2 weeks to 12 months. Percentage of study completers ranged from 38% to 100%.

Adherence outcome

Psychiatric outpatient studies

Five (25-28,30) of the six (25-30) psychiatric outpatient studies tested education as adherence-enhancing intervention and three of these studies (25;26;28) failed to demonstrate differences in adherence between groups. Myers and Calvert (28) found a statistically significant better adherence in the information group at week 3, but at week 6 this difference had disappeared. In another study, Myers and Calvert (27) demonstrated a significantly better adherence with medication in patients who received the combination of verbal and written information about side effects of antidepressant medication. The study of Altamura and Mauri (30) also reported a better adherence in the intervention group, but the statistically significance was not reported. The study of Myers and Branthwaite from 1992 (29) was the only study that tested the influence of the number of doses to be taken per day and the effectiveness of allowing patients to choose their own dosage regimen. Adherence was significantly better in only those patients who were allowed to choose and selected the three-times-a-day dosage.

Primary care studies

Of thirteen primary care studies (13,20,24,31-40), eleven studies (13,20,24,33-40) tested a collaborative care intervention, and three studies (20,31,32) tested educational interventions. The study of Peveler et al (20) had three intervention arms: (1) leaflet, (2) drug counseling by a nurse, and (3) leaflet and drug counseling by a nurse. The leaflet is considered an education intervention, and the drug counseling arms are considered collaborative interventions because general practitioners and nurses worked together.

Of the collaborative care studies (13,20,24,33-40), nine studies, including the counseling arms of the study of Peveler et al (20), showed significant differences in adherence between intervention and usual care groups (13,20,24,34,35,37-40). In the intervention groups, adherence was approximately 25% higher than in the usual care groups (13;24). Rost et al (40) found that the intervention increased pharmacotherapy use in patients beginning a new treatment episode but no effect in recently treated patients. The stu-

dies of Wilkinson et al (33) and Hunkeler et al (36) failed to demonstrate a difference in adherence between the intervention and usual care goups. Simon et al (38) found that an organized program, consisting of care monitoring, follow-up by telephone, feedback to doctors, and practice support by a care manager, resulted in significant improvements of antidepressant medication use and in a better clinical outcome. A program limited to monitoring and feedback, using computerized data (antidepressant dosage and repeat prescriptions, number of follow-up visits, and arranged visits), had no significant effect compared with usual care.

The studies of Mundt et al (31), Atherton-Naj et al (32) and the leaflet arm in the study of Peveler et al (20) tested an education intervention. All failed to demonstrate differences in adherence.

Depression outcome

Psychiatric outpatient studies

Only one psychiatric outpatient study reported the depression outcome (30). A significant greater reduction in depression score was found in the intervention group.

Primary care studies

All primary care studies (13,20,24,30-40) measured depression outcome. Only two studies, one education study (31) and one collaborative care study (33), failed to demonstrate a significant difference in depression outcome between groups. Rost et al (40) demonstrated that the intervention increased improvement in depressive symptoms in patients beginning a new treatment episode, but not in recently treated patients. Peveler et al (20) found clinical benefit only in patients with major depression and doses above 75 mg dothiepin. Katon et al (13;24) also demonstrated clinical benefit in patients with major depression, but not minor depression (42).

Discussion

Searching for randomized controlled trials that evaluated interventions aiming to enhance adherence with antidepressant medication, we found 19 studies that met the inclusion criteria. The limitations of a qualitative review should be taken into account. Such reviews compare studies that are based on patients from different populations and different geographic locations and performed in varying time periods. Studies on interventions that did not target the patient directly (e.g. studies of implementing practice guidelines or training physicians) were not included. The impact of interventions to improve physicians' compliance with guidelines is quite relevant in itself but is not a topic of this review.

In the psychiatric outpatient studies, only educational interventions were tested. Only the study of Myers and Calvert (27), which combined verbal with written information, resulted in a better adherence. It is, however, important to bear in mind that two of the studies of Myers and Calvert (25;26) that failed to show differences in effect had a very short follow-up (2 weeks). The study of Altamura and Mauri (30) is methodologically flawed because it did not correct for other medication, which is indispensable when measuring drug levels, and only 14 patients were included. The meaning of the better depression outcome in the intervention group in the study of Altamura and Mauri (30) is unclear, given the aforementioned methodological limitations. The study of Myers and Branthwaite al from 1992 (29) did not analyze differences in depression outcome between the intervention groups but rather between adherent and non-adherent patients. There was no evidence that better adherence was associated with a better therapeutic result, possibly because those patients who were improving most tended to abstain from further treatment. Also, the prescribed dosages of antidepressant medication were rather low.

All primary care studies that tested educational interventions to enhance adherence failed to demonstrate a benefit over the control condition. However, the study of Atherton-Naj et al (32) also had a small sample size (N = 45) that possibly precluded the finding of significant differences. The primary aim of this latter study was to investigate the feasibility of the intervention. The negative results of the study of Mundt et al (31) particularly raise questions because this study included 246 patients, precluding a type II error. In this study, however, the intervention consisted of written time-phased educational information mailed directly to the patient that may have been too impersonal or too confronting. Such a procedure may cause a detrimental effect on adherence and possibly nullified the positive influence of education on adherence. Moreover, this study used an interactive voice-response telephone system to obtain assessment data and may thus have introduced another impersonal characteristic.

In primary care studies, nine collaborative care interventions demonstrated significant improvements in rates of adherence during the acute and continuation phase of treatment (≥ 6 months). A pilot study to test the feasibility of the intervention (33) failed to demonstrate a better adherence in the intervention group. Probably this study was underpowered (N = 61). Hunkeler et al (36) also failed to demonstrate a difference in adherence between intervention and control group, while this study included 302 patients. All collaborative care studies in which a better adherence was achieved in the intervention groups compared with the control groups demonstrated better depression outcomes, especially in patients suffering from major depression. The study of Hunkeler et al (36) also demonstrated significantly better depression outcome in the intervention group, despite the lack of difference in adherence to antidepressant medication between groups.

Most of the studies testing collaborative care interventions are multimodal, affecting patient, physician and system of care, which makes it impossible to discern quality of care from patient behavior. In fact, these are integrally linked. These studies targeted both at improving patient education and improving physician quality of care through lecture, reading materials, and appropriate feedback from nurses and mental health specialists working as primary care extenders. Probably the improvements in adequate antidepressant medication found in these studies resulted from a combination of improved quality of care (e.g. the prescription of antidepressant was done more carefully) and the patients' adherence. More complex interventions were not tested in psychiatric outpatient clinics. This needs further attention, because patients treated in specialty care differ from those treated in primary care.

In general, informed consent, repeated monitoring of patient status, and physicians' heightened awareness of non-adherence may have provided a prompt to continue treatment in both groups, thereby minimizing effects that might have occurred. Despite this, especially collaborative care interventions tested in primary care demonstrated significant improvements in rates of adherence and depression outcome during the acute and continuation phase of treatment (≥ 6 months). Given the poor methodology of the studies that tested patient education, the lack of evidence of effect certainly does not mean that there is no effect at all. For instance, the combination of verbal and written information about side-effects of antidepressant medication resulted in a better adherence (27), and patients reporting more educational messages concerning medication and discussions of behavioral strategies from their doctor were more likely to adhere to medication (10).

The favorable findings regarding interventions to improve adherence with antidepressants are in contrast to the negative conclusion of Haynes et al systematic review (11), as mentioned in the introduction. The inclusion criteria in that review were very strict (e.g., at least 80% follow-up of each group studied and, for long-term treatments, at least six months follow-up with positive initial findings), and, as a consequence, the review included no study on interventions to improve adherence to antidepressants.

In conclusion, we found evidence to support the introduction of interventions to enhance the process of care of patients with major depression in primary care. Because collaborative care programs require additional resources (43), the specificity of the interventions needs to be improved. It is recommended that future studies investigating interventions to improve adherence to antidepressant medication attempt to elicit the effects of individual components of the intervention in addition to the effect of the entire intervention.

Since some patients with major depression achieve a favorable outcome with usual care, a stepped-care strategy targeting only those patients whose depression has not resolved within a 2-months period of usual care may be a

viable option (34). This would involve targeting interventions to patients with persistent symptoms. More evidence is also needed on effectiveness of different forms of patient education, e.g. from well-designed randomized controlled trials.

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Table 1. Study characteristics and results

Psychiatric outpatient studies

Study	Intervention*	Adherence**	Depression outcome**
Myers et al (25)	ed	n.s.	n.r.
Myers et al (26)	ed	n.s	n.r.
Myers et al (27)	ed	Combination verbal and written information > verbal information	n.r.
Myers et al (28)	ed	n.s.	n.r.
Myers et al (29)	ed	doctor prescribed vs patient chosen regimes: n.s. dosage once a day vs three times a day: n.s. Patients who were allowed to choose and chose the three-times-a-day regime showed a significant better adherence.	n.r.
Altamura et al (30)	ed	n.r.	I > UC

*(ed) educational intervention; (cc) collaborative care intervention

** significance set at $p \leq .05$

(I) intervention; (UC) usual care

(n.s.) non significant

(>) significant better than

(n.r) not reported

Study	Intervention*	Adherence**	Depression outcome**
Mundt et al (31)	ed	n.s.	n.s.
Atherton-Naj et al (32)	ed	n.s.	I > UC
Peveler et al (20)	ed	n.s.	n.r.
Peveler et al (20)	cc	I > UC	Patients with major depression and adequate doses > other patients
Wilkinson et al (33)	cc	n.s.	n.s.
Katon et al (13)	cc	Major depression: I > UC Minor depression: I > UC	Major depression: I > UC Minor depression: n.s.
Katon et al (24)	cc	Major depression 4-month: I > UC 7-month: trend (I > UC; p = .07) Computerized data: n.s. Minor depression 4-month: I > UC 7-month: I > UC Computerized data: trend (I > UC; p = .08)	Major depression: I > UC Minor depression: n.s.
Katon et al (34)	cc	3-month: I > UC 6-month: I > UC Computerized data: I > UC	3-month: I > UC 6-month: trend (I > UC; p = .08) Remission: 3-month: I > UC 6-month: I > UC
Katon et al (35)	cc	I > UC	I > UC Relapse: n.s.
Hunkeler et al (36)	cc	n.s.	I > UC
Katzelnick et al (37)	cc	I > UC	I > UC
Simon et al (38)	cc	I > UC	I > UC
Wells et al (39)	cc	I > UC	I > UC
Rost et al (40)	cc	I > UC	I > UC

*(ed) educational intervention; (cc) collaborative care intervention
** significance set at $p \leq .05$
(I) intervention; (UC) usual care
(n.s.) non significant
(>) significant better than
(n.r) not reported

A cluster randomized trial comparing two interventions to improve treatment of major depression in primary care.

2.2

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Abstract

Background

Many patients with major depression are non-adherent to antidepressant medication and do not receive care according to current guidelines. There is increasing evidence that treatment of depression in primary care can be improved. Comparison between effective interventions may help to establish the active ingredients of such interventions.

Methods

In a randomized trial two interventions to improve treatment of major depression in primary care were compared 1) a depression care program, targeting general practitioners (GPs), patients, and systematic follow-up, and 2) a systematic follow-up program. Thirty GPs were randomized and 211 primary care patients with current major depression were included. All patients were prescribed a selective serotonin reuptake inhibitor (SSRI). Outcome measures included adherence to antidepressant medication, and depression outcome.

Results

No significant differences in adherence rates and treatment outcome measures were demonstrated between interventions at week 10 or week 26. Adherence rates were high and treatment outcome was favourable.

Conclusions

The depression care program was not superior to the systematic follow-up program. Systematic follow-up in depression treatment in primary care seems to be an intervention *per se*, having the potential to improve adherence and treatment outcome.

Depressive illness is a public health issue of major significance (1). Most depressive patients are treated in primary care (2;3) where effectiveness of antidepressants is severely compromised by non-adherence (4), and low quality of care (5).

Various studies have demonstrated that adherence and depression outcome can be improved by interventions supporting the prescription of antidepressants (6;7;8). Ingredients of these interventions were patient education, counselling, improved quality of care, and appropriate feedback from nurses and mental health specialists working as primary-care extenders (e.g. 9;10;11). Another common component within successful interventions seemed to involve systematic follow-up of patients (i.e. regular visit schedule, and structured visits) (7;8;12). In one study (13), systematic follow-up was the main focus of the intervention. It demonstrated significantly improved outcomes at modest costs, in comparison with usual care. Therefore, the favourable effects of the interventions using a combination of ingredients could be due to either the interventions as a whole, or to the effects of systematic follow-up. In addition, it remains unclear whether complex interventions are more effective in comparison with systematic follow-up.

The objective of this study was to compare Optimind™, a depression care program (DCP) that incorporated several ingredients, with a systematic follow-up program (SFP) in primary care.

Method

Subjects

Patients were eligible for the study if they met the following criteria: primary clinical diagnosis of depression fulfilling the criteria of a major depressive episode according to DSM-IV (14); at least 18 years of age; no renal or hepatic dysfunction. Subjects had to give written informed consent prior to participation. For diagnostic psychiatric screening the MINI International Neuropsychiatric Interview (MINI, version 2.1 (15) was used, a semi-structured interview based on DSM-IV (14). Exclusion criteria were: benzodiazepines not stabilized at a maximum level of 10 mg diazepam or equivalent rate at least four weeks prior to start of treatment; use of other psychopharmacological medication; a history of schizophrenia or bipolar disorder; previously unresponsive to selective serotonin reuptake inhibitor (SSRI) therapy (for depression or other indications); women who were pregnant, lactating or not using adequate contraconception; a history of seizures (except for febrile seizures in childhood); meeting DSM-IV criteria for substance abuse (alcohol or drugs) within 3 months prior to the start of the trial, respectively substance dependence within 6 months; any serious medical condition that would, in the opinion of the GP, preclude the administration of a SSRI; a current

serious suicidal or homicidal risk in the GP's judgement; and current psychological or psychotherapeutic treatment.

Design

Following approval of the Medical Ethics Committee, STEGMETC, this multicenter, cluster randomized, openlabel, parallel group study was carried out between September 1999 and January 2001. Thirty GPs participated. After agreement to participate, GPs were randomly assigned to either the DCP, or the SFP. Random treatment assignment was placed in advance in a set of sealed, opaque envelopes by an individual who was not involved in the opening of the envelopes. When a GP was randomized, the GP's name and the number of the envelope were recorded before the envelope was opened.

General practitioners

The GPs were trained in applying the MINI interview by means of interrater sessions. The GPs were allowed to prescribe any of the five SSRIs that were available when the study was carried out (citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline) in at least the minimum effective dose.

Depression care program

In depressive disorders, education of patients and their participation in the treatment process are cornerstones to enhance treatment adherence (16). Health beliefs of patients should also be addressed (17). Several investigators found that interventions enhancing both patient education and participation, and improving physician quality of care, combined with appropriate feedback and systematic follow-up of patients have the potential to improve adherence and depression outcome (7;8). With this knowledge, the following intervention that targeted patients, GPs, and follow-up was developed (see figure 1 for the important characteristics of the programs). Prior to every scheduled visit (7 visits in 26 weeks), the DCP patients received a newsletter by mail. These letters reviewed the biology and symptoms, as well as risk factors for depression. The importance of antidepressant medication was emphasized, and its effects and side-effects were discussed. In addition, the need to continue treatment for up to six months was explained. Patients were also provided vignettes of depressive patients successfully treated with antidepressant medication. The social stigma of depressive patients, the misconceptions about the potential to become dependent of antidepressant medication, and the false belief that depression is a sign of weakness were challenged. The importance of social support was addressed. Patients were instructed to discuss the topics of the newsletters with their GPs to increase their participation in the treatment. Patients were also asked to complete homework assignments: 1) to fill out a

questionnaire addressing the perceived costs and benefits of treatment with antidepressant medication, 2) to plan activities, and 3) to discuss their illness and treatment with significant others to enhance social support.

Prior to each visit, the GPs received a summary of the content of the newsletter and the homework assignments and were stimulated to discuss the topics and homework assignments with the patient. The GPs were asked to help patients clarify the potential benefits of taking antidepressant medication and to challenge perceived costs of taking antidepressant medication. This instruction and the first homework assignment were designed to build on general principles of motivational interviewing (18). Follow-up was structured as in the systematic follow-up program (see next subsection).

Systematic Follow-up Program

The DCP was compared with a SFP (figure 1). Patients and GPs in the SFP received no letters, homework, nor instructions. The SFP targeted only the structure of care: follow-up visits were scheduled and structured, and patients were assessed with the same frequency and with the same instruments as the patients in the DCP group.

Measures

(a) Adherence with antidepressant medication was assessed during the visits at weeks 2, 6, 10, 14, 18, 22, and 26, by pill counts. When a patient did not return pills, the patient's self-reports were used. Early adherence was defined as > 70% medication intake during the first 10 weeks. Late adherence was defined as > 70% medication intake during the full 26 weeks.
(b) The MINI was assessed at baseline and week 26.
(c) Clinical Global Impression (CGI) (19) was assessed at baseline and all the following visits.
(d) The Beck Depression Inventory (BDI) (20) was assessed at weeks 2, 6,10, 18, and 26.
(e) The Symptom Checklist-90-Revised (SCL-90-R) (21) was assessed at weeks 2, 10, 18 and 26.

The GPs did assessments of adherence, MINI, and CGI. The BDI and SCL-90-R are self-rating questionnaires.

During each visit, the process of care in the DCP group was assessed by GPs filling out a questionnaire on patient compliance with various components of the DCP intervention.

Dropouts were defined as patients who were lost to follow-up, because adherence and treatment outcome could not longer be assessed. Patients

who stopped their antidepressant medication on their own initiative without suffering from relevant side-effects, were considered to be non-adherent, and were not considered as dropouts.

Outcomes

The primary outcome in this study was adherence to antidepressant medication at week 26. Secondary outcomes were adherence to medication by week 10, and depression severity and general psychopathology by weeks 10 and 26.

Sample size

The required sample size was estimated assuming a 20% difference in adherent patients between the DCP and SFP group (80% versus 60%), a 20% dropout rate, a two-sided alpha of 0.05 and a power of 80%. The assumed percentage of adherent patients in the DCP is higher than the percentages of adherent patients found in the intervention conditions in previous studies investigating depression management programs because these studies defined adherence as > / = 84% of pills taken (9;22), which is more stringent than our definition (> 70%). The assumed percentage of adherent patients in the SFP group is higher than the percentages found in the usual care conditions of the aforementioned studies (9;22) because of the difference in defining adherence and because we expected that patients in the SFP group would be more adherent compared to a usual care condition. Further, we adjusted the sample size for randomization on practice level (23;24). The sample size sestimation had to be corrected by means of a correction factor that depends on the variation between the GPs and the mean number of patients per GP. The correction factor is defined as $C = 1 + K * [\sigma B^{*}\sigma B/\sigma P^{*}\sigma P]$. The mean number of patients per GP (K) was 7, and the variation between GPs was estimated between 50% and 70%. This results in a standard deviation (σB) of 0.05. σP is the standard deviation of the results of the same GP. The expected percentage of adherent patients in the DCP was 80% (0.80), and in the SFP 60% (0.60). Therefore, σP = 0.46. The result is $C = 1 + 7^{*}[0.0025/0.21] = 1.08$. This means that the estimated 200 patients needed to be multiplied by 1.08, resulting in 216 patients, 108 per group.

Statistical analyses

The two treatment groups were first compared with respect to the most important prognostic indicators. Subsequently, the frequency of early and late adherence was compared between the treatment groups. Further,

change in severity of depression and general psychopathology from baseline to 10 weeks and from baseline to 26 weeks was compared between the groups. If necessary, adjustments for unequally distributed prognostic indicators were made using linear regression for continuous, and logistic regression for dichotomous variables. These analyses were carried out using the Statistical Package for the Social Sciences (SPSS) version 10.0 (SPSS Inc., Chicago, IL, USA).

The patient data in this trial are clustered within the randomized GPs. In addition, repeated measurements were made over time in the same subject. Therefore, the outcomes were additionally analysed using multilevel statistical models. These models were fitted with the MIXED procedure in SAS release 8.02 (SAS Institute, Carey, NC, USA) for continuous outcomes, and the MlwiN package version 1.2 (Centre for Multilevel Modelling, London, UK) for the dichotomous outcomes. Associations were expressed as odd ratios and mean differences for dichotomous and continuous data respectively. These parameters were supplied with a 95% confidence interval (CI). The level of significance (alpha) was 0.05 (two-sided).

Results

Overall, 211 patients were randomized, of which 34 patients completely dropped out of the study (figure 2). Reasons for dropout were diverse, e.g. adverse events, referral to a psychologist or psychiatrist, and non-attendance. Another 35 did not have follow-up ratings on the psychopathology scales by week 26, mostly because they stopped antidepressant medication earlier and were therefore considered to be non-adherent. These patients were no longer followed up.

A comparison between the treatment groups concerning prognostic patient characteristics at study entry is given in table 1. Panic disorder, agoraphobia, and generalized anxiety disorder were somewhat more prevalent in the SFP group.

Adherence

Analysis of adherence rates between the DCP group and SFP is given in table 2. At week 10 and week 26, no differences in adherence rates were found between the DCP group versus the SFP group. Adjustment for the unequally distributed panic disorder, agoraphobia, and generalized anxiety disorder did not change the results.

When at week 26 dropout was also considered non-adherence, the adherence rate was 67/110 (61%) and 54/101 (54%) in the SFP and DCP group, respectively (odds ratio 0.7 (95%CI 0.4; 1.3)).

Depression outcome

In both treatment groups the depression scales showed a decrease by week 10 and continued to decrease between week 10 and 26 (table 3). Neither at week 10 nor at week 26 were these changes different between the groups. Analysis of responder rates (BDI score reduction of ≥ 50%) between the DCP group and the SFP group at week 10 and week 26 showed no differences. At week 26, 70% of patients in both conditions were responders (odds ratio 1.0 (95%CI 0.5; 2.1)).

When at week 26 dropout was considered nonresponse, the responder rates were 51/110 (46%) and 47/101 (47%) in the SFP and DCP group respectively (odds ratio 1.0 (95%CI 0.6; 1.7)).

Using BDI score as a variable indicating remission (score of ≤ 8 asymptomatic; score of > 8 symptomatic; 25), again no significant difference between treatment groups at week 10 or week 26 was found. At week 26, 58% of patients were in remission in the DCP condition, and in the SFP condition 64% of patients (odds ratio 0.8 (95%CI 0.4; 1.5)).

When at week 26 dropout was considered non-remission, the remission rates were 48/110 (44%) and 39/101 (39%) in the SFP and DCP group, respectively (odds ratio 0.8 (95%CI 0.5; 1.4)).

SCL-90-R outcome

Analysis of change in SCL-90-R global severity index scores, measuring general psychopathology, from baseline to the end of week 10, and baseline to the end of week 26, demonstrated no significant differences between treatment groups (table 3).

The group that had all follow-up assessments of the BDI and SCL-90-R at week 26 (N=142, 67%) was similar to the total group with respect to the proportion female gender (68.3%), mean age (45.3), baseline BDI (21.3), baseline SCL (1.2), CGI (4.4) and comorbidity (46.8% previous depression, 12.9% panic disorder, 12.2% agoraphobia, 12.0% social anxiety disorder, 3.6% obsessive compulsive disorder, 5.0% posttraumatic stress disorder and 22.3% generalised anxiety disorder).

The results of the multilevel analyses were nearly identical and were, therefore, not presented.

Process of care in the DCP condition

During all visits, a mean of 88% of patients stated that they had read the information. Questions concerning the information were asked by 22% of patients. With regard to the homework assignment, 58% of patients stated that they completed it, and at 70% of the follow-up visits the homework was discussed. Of the GPs, 89% read the information.

Discussion

To our knowledge this study is the first in primary care to compare a DCP with a SFP. Adherence rates and treatment outcomes were favorable, with no differences between the programs.

In this trial 'naturalistic' in- and exclusion criteria were used and the participating primary-care settings were well distributed across the Netherlands, representing the average Dutch practice in size and type. The characteristics of our sample correspond well with what is already known of the epidemiology of psychiatric disorders in primary-care settings (26).

We hypothesized that the DCP would be more effective in comparison with the SFP. This was not the case. As is apparent from the confidence intervals, differences in effectiveness between the interventions cannot be excluded. However, the point estimates for all outcomes studied were close to unity so that important differences seem unlikely. Possible explanations for the lack of differences should be considered. 1) There may have been a selection in recruiting the participating GPs: most of them had shown interest in psychiatric research earlier (27). This may have led to more experience in treating depression in comparison with the average GP, possibly explaining the favorable results in both interventions. In addition, GPs were informed about the objectives of the study. This may have contributed to a heightened awareness of non-adherence and non-response. 2) Another explanation might be that GPs and patients in the DCP group did not comply with the instructions. Given the results of the process of care assessment, compliance with some components of the DCP was lower than intended, possibly making the intervention less effective. Process of care in the SFP was not assessed. Therefore, we do not know what the GPs and patients in the SFP condition discussed during the visits. However, it is very unlikely that the patients in the SFP condition received interventions like the ones in the DCP group. Therefore, it seems reasonable to assume that there was a contrast between interventions. 3) The SFP in which patients and GPs had scheduled follow-up visits and assessments with explicit attention to adherence and symptoms change was effective in itself. This is in line with data consistently indicating that systematic follow-up is associated with better adherence and treatment outcomes (13;28). The level of care in the SFP was considerably above that usually provided in daily practice. This may well have created a ceiling effect, precluding the finding of differences between the two groups. The high adherence rate and favorable treatment outcome in the SFP group (see below) support this explanation. 4) No data were available on patients who discontinued treatment. Therefore, dropout could have biased the results. Sensitivity analyses, however, showed a very modest potential for bias due to loss to follow-up.

Lacking a usual care condition, the high adherence rates and good treatment outcome do not prove that the DCP and the SFP were effective.

High adherence rates might also be explained by the measurement of adherence using pill counts and patient reports, because such measurement methods may overestimate adherence (29). However, our adherence rates seem to be consistent with those in intervention groups in other primary-care trials (9;22). Moreover, naturalistic primary-care studies using a less stringent definition adherence (i.e. continuing antidepressant medication, irrespective of percentage of taken pills), also measured by patients' reports, found that only 66% of the patients continued their antidepressant medication within one month (30), and only 50% of patients during a 6-month period (31). The adherence rates in our study are much higher.

The treatment outcomes in our trial were favorable. This can be expected when patients are mildly ill and have a good prognosis. However, all patients included in our study suffered from major depression, and had a mean BDI score of approximately 23 (a score of >/= 15 is considered 'fully symptomatic') (25). Furthermore, patients with psychiatric or somatic comorbidity were not excluded. Depression outcome scores in our present study are in line with those of previous studies, in which 70% of intervention patients became responders (9;22). In the usual care conditions of these studies only 43% of patients responded. Moreover, Schulberg et al. (32) found remission rates in standardized treatment conditions that were in line with our results. Compared to usual care, these remission rates were significantly higher. Considering these indirect comparisons, we believe that the programs investigated in this study were effective.

Our aim was to develop interventions that could be investigated in primary-care offices. Therefore, adherence was assessed by using pill counts and patient reports, and depression score was assessed by a self-rating questionnaire (BDI). However, the duration, frequency, and intensity of the visits may not be feasible in many primary care practices. This may limit the generalizability of our study results. Nevertheless, systematic follow-up by non-medical personnel in collaboration with GPs might be a cost-effective alternative (7;13;33).

In conclusion, in primary care patients suffering from major depression treated with SSRIs, a DCP as well as a SFP was associated with equal adherence and treatment outcome. Systematic follow-up seems to be an intervention *per se*, having the potential to improve adherence and depression outcome. Clinical effectiveness and cost-effectiveness should guide the optimal management of depression in primary care. Therefore it is recommended that future studies continue to elicit the separate effects of the components of interventions to improve depression treatment. In these studies, assessment of the process of care is needed in order to evaluate what really happened and might have worked. SFPs should also be compared with usual care.

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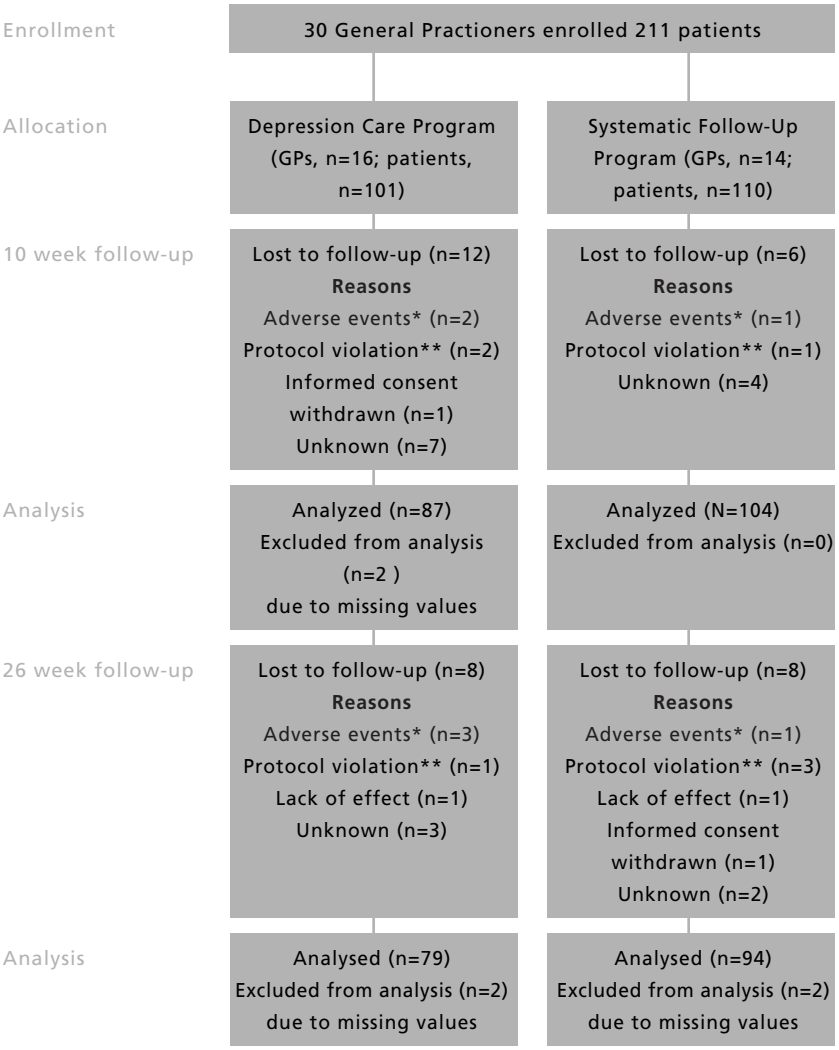
Figure 1. Elements of interventions to improve depression treatment

intervention	Evidence based antide-pressant dose	Enhanced patient education	Enhanced GP education	Stimulating active parti-cipation of GP and patient in the treat-ment process	Self-mana-gement support	Systematic follow-up
DCP	Yes	Yes	Yes	Yes	Yes	Yes
SFP	Yes	No	No	No	No	Yes

Figure 2. Flow Diagram of Patient Progress Through the Trial



* No serious adverse events related to SSRIs were reported

** Protocol violation was defined as switching medication to a non-SSRI antidepressant, or referral to a psychologist or psychiatrist.

Table 1. Baseline characteristics of the patients [1]

	Depression care program (N = 101)	Systematic follow-up program (N = 110)
Demographic		
Age (yr.)	42.1 (14.4)	43.9 (14.3)
Female(%)	71.3	63.6
Employed(%)	56.7	60.1
Unfit for work(%)	12.0	7.7
Caucasian(%)	96.0	95.5
Clinical		
BDI	22.7 (8.4)	22.6 (9.8)
SCL-90 R global severity index	1.3 (0.6)	1.3 (0.6)
CGI	4.4 (0.9)	4.4 (0.8)
Previous depression(%)	40.7	45.7
Panic disorder (%)	5.1	14.3
Agoraphobia (%)	9.2	13.3
Social anxiety disorder (%)	12.2	13.3
Obsessive compulsive disorder (%)	4.1	3.8
Posttraumatic stress disorder (%)	8.2	5.7
Generalised anxiety disorder (%)	17.3	26.7

[1] Standard deviations are given in parentheses

Table 2. Primary endpoints

	Depression care program ($N_{baseline}$=101)	Systematic follow-up program ($N_{baseline}$=110)	Odds ratio (95% CI)
Adherent up to week 10	75/87 (86%)	90/104 (87%)	1.0 (0.4;2.2)
Adherent up to week 26	54/79 (68%)	68/94 (72%)	0.8 (0.4;1.6)

Table 3. Secondary endpoints*

	Depression care program (N = 101)	Systematic follow-up program (N = 110)	Mean difference (95% CI)	Odds ratio (95% CI)
Change in BDI score week 0-10	-11.3	-11.1	-0.2 (-2.9;2.4)	-
Change in BDI score week 0-26	-13.6	-13.6	0.0 (-2.8;2.8)	-
Change in SCL score week 0-10	-0.59	-0.57	-0.02 (-0.17;0.13)	-
Change in SCL score week 0-26	-0.75	-0.68	-0.07 (-0.24;0.11)	-
Change in CGI score week 0-10	-1.81	-1.88	0.07 (-0.31;0.45)	-
Change in CGI score week 0-26	-2.84	-2.80	-0.04 (-0.39;0.31)	-
BDI 50% reduction week 0-10	45 (58%)	52 (57%)	-	1.0 (0.6;1.9)
BDI 50% reduction week 0-26	47 (70%)	51 (70%)	-	1.0 (0.5;2.1)
BDI <=8 (remission) week 10	36 (46%)	43 (46%)	-	1.0 (0.6;1.9)
BDI <=8 (remission) week 26	39 (58%)	48 (64%)	-	0.8 (0.4;1.5)

* Based on 172 and 142 patients at week 10 and 26, respectively

Predicting non-remission from major depression in primary care

3.1

Development of a risk score for clinical practice

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submitted

Abstract

Objectives

Studying candidate predictors of non-remission at week ten in primary care patients suffering from major depression who are treated with selective serotonin reuptake inhibitors (SSRIs). Developing and testing a risk score for use in daily practice.

Design

Prospective cohort study.

Setting

Primary care practices in the Netherlands

Participants

147 patients with major depression

Main outcome measures

The presence or absence of non-remission at week ten. Candidate predictors of non-remission at week ten as obtained from the medical record and questionnaires were studied by using a multivariate logistic regression analysis. The ability to discriminate between patients with and without remission was quantified.

Results

Baseline depression severity, comorbid anxiety disorder, chronic somatic illness, PDQ-R total score (> 26), being unfit for work, and employment status predicted non-remission by week ten fairly good. The ROC area of the predictive model had a value of 0.67 (95% confidence interval 0.59;0.75).

Conclusions

The results in this study suggest that prediction of non-remission using baseline characteristics is feasible and can be helpful.

Introduction

Major depression is a highly prevalent condition with far-reaching consequences for the individual patient, as well as for society. Despite antidepressant treatment, many patients do not timely remit. Non-remission of the index depressive episode is one of the most consistently cited presages of poor longterm prognosis (1;2) but its risk can be reduced by adequate treatment (3;4). If patients with a high probability of non-remission can be recognized before treatment, these patients can be treated differently from the start, and ultimately, their prognosis may improve as a result. To this end, predictors of non-remission need to be identified. As most patients with major depression are treated in primary care, predictors should be suitable and valid for this setting.

In primary care, patient characteristics that seem to be related to non-remission are duration of index depressive episode before antidepressant treatment started (5), severity of depression (6), coexisting anxiety disorder (5;7;8), personality pathology (9;10), chronic somatic illness (6;11), and being unemployed (12). However, findings are not consistent across studies and non-remission was predicted far beyond the duration of the acute treatment phase in which remission should be attained (13). Moreover, the joint predictive value of these characteristics and the clinical implications were not addressed in these studies (14).

Within a randomized controlled trial studying the effects of a depression care program (DCP) (15), in 147 primary care patients with a major depression, we sought to elucidate predictors of non-remission. In addition, we developed a practically applicable score that allows the clinician to allocate a probability of non-remission to each individual patient.

Methods

Data were obtained from a multicenter open label cluster randomized controlled trial performed in 30 primary care practices in the Netherlands, including patients suffering from major depression according to DSM-IV (16). Subjects had to provide written informed consent prior to participation. Exclusion criteria were: treatment with benzodiazepines not stabilized at a maximum level of 10 mg diazepam or equivalent rate at least four weeks prior to start of treatment; use of other psychoactive medication; a history of schizophrenia or bipolar disorder; substance abuse or dependence; previous unresponsiveness to SSRI therapy; and current psychological or psychotherapeutic treatment. Following approval of the medical ethics committee, the study was carried out between September 1999 and January 2001. The GPs were randomly assigned to either a depression care program (DCP), or a systematic follow-up program (SFP). The GPs were allowed to prescribe any of

the five SSRIs that were available at the time the study was carried out (citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline) in at least the minimum effective dose.

The DCP aimed at teaching cognitive behavioral skills to manage depression, counseling to improve medication adherence, and stimulating active participation of GPs and patients in the treatment process. The SFP focused on the structure of care: follow-up visits were scheduled and structured, during which patients were assessed with the same frequency and with the same instruments as the patients in the DCP group.

Predictors

When a small data set is analyzed with logistic regression to provide individualized estimates of an adverse outcome (i.c. non-remission), prespecified full models are preferred. Therefore, external knowledge should be incorporated as much as possible in the modeling process (17). Consequently, in our study the choice of candidate predictors was based on the literature mentioned in the introduction, and no selection on statistical grounds was applied.

Depression severity was assessed by the Beck Depression Inventory (BDI), a self-administered questionnaire (18). The total BDI score was divided by ten and was rounded to the nearest integer. The other candidate predictors were assessed by the GPs at baseline and filled out on standard forms. Further, the history of depressive episodes and present comorbid anxiety disorders were assessed by the GPs using the MINI (19). Chronic somatic illnesses were assessed using a standard form that was filled out by the GPs and were defined according to Koike et al (11) : cardiovascular diseases (e.g. angina pectoris, myocardial infarction, hypercholesterolemia, hypertension), cerebrovascular diseases (e.g. cerebrovascular accident, transient ischemic attack), other chronic diseases (e.g. chronic obstructive pulmonary disease, thyroid disease, diabetes mellitus, postmenopausal symptoms, arthritis or rheumatism), and chronic pain (e.g. migraine, or back problems). Comorbid somatic illness was defined as the presence of any of these conditions. Personality pathology was assessed by the PDQ-R, a self-rating scale with 152 true/false questions yielding a separate score for each of the 11 DSM-III-R personality disorders and a total score (20). Prior to the analyses the PDQ-R total score was dichotomized at 26, i.e. near the median. Treatment condition was not considered a potential predictor as DCP and SFP had shown equivalency in the trial (15).

Outcome definition

The outcome was non-remission at week ten. This period was chosen because remission should be attained in this acute treatment phase. If a patient does not attain remission by then, and no attempts have been made

to optimize treatment, the patient should not be considered adequately treated (21;22). Prior to the study we defined non-remission as a BDI score of greater than eight (13).

Statistical analyses

The analysis of the current study was performed in patients with complete data for all variables. The independent contributions of the predictors were quantified using a multivariable logistic regression analysis with non-remission as the dependent variable and the predictors as the independent variables. The reliability (goodness of fit) of the model was assessed using the Hosmer and Lemeshow test.

The model was validated using bootstrapping techniques, i.e. the model was adjusted for over-optimism by applying a shrinkage factor to the regression coefficients (17;23). Subsequently, this model was used to develop a risk score indicating the probability of non-remission. Since regression coefficients themselves are not easily added up to a score, they were transformed to a round number of points as follows. The coefficients reflect the relative weight of each variable in the prediction. Therefore, variable specific points were calculated by a uniform transformation of the coefficients, i.e. division by ten. Next, the number of points was rounded to the nearest integer. The total score for each individual patient was determined by assigning the points for each variable present, and adding them up.

The performance of the risk score was evaluated by determining the observed and predicted risk of non-remission by categories of its values. Further, the score was transformed to dichotomous "prognostic tests" allowing each patient to be classified as high or low risk of non-remission. Sensitivity, specificity, the area under the receiver operating characteristic curve (AUC) (24) as well as the positive and negative predictive value were calculated to assess the discriminatory power of these dichotomous tests for various cutoffs of the risk score. The AUC is an overall measure of discriminatory power of a continuous test with 0.5 indicating no discrimination and 1.0 indicating perfect discrimination. Also the AUC was shrunk by using bootstrapping techniques.

Results

After selection of patients with complete data for all variables, 147 out of a total of 211 were analysed, i.e. 70%. Sociodemographic and clinical characteristics of patients are presented in table 1. The characteristics of these patients were similar to those of patients not included, except for lifetime depression (characteristics of patients not included: age 43.7 (SD 17.3), male gender 30% , employed 59%, being unfit for work 5%, baseline BDI 23,2 (SD

10.2), baseline SCL90-R 1,4 (SD 0.7), previous depression 28%, comorbid anxiety disorder 36%, chronic somatic illness 48%, and PDQ-R total score [> 26] 49%).

At the end of the follow-up period of ten weeks, 82 patients showed non-remission yielding an a priori risk of 56% (82/147).

The results of the adjusted multivariate logistic regression analysis, and of the calculation of the variable specific points is presented in table 2. The p-value from the Hosmer-Lemeshow test was 0.14 indicating no deviance of goodness of fit.

The sum of the points (table 2), assigned according to the aforementioned procedure, yields the risk score. For instance, a depressive patient with a BDI score at baseline of 30, who is suffering from a chronic somatic illness, and is unfit for work will have a risk score of 18 + 1 + 3 = 22.

Evaluation of risk scores

The observed and predicted non-remission frequencies according to score categories are depicted in table 3. The predicted risk of non-remission ranged from 38 to 76% from the lowest to the highest score category, in fair agreement with the observed risks.

The risk scores were subsequently evaluated as dichotomous tests, a positive result indicating high risk and a negative result indicating low non-remission risk. The positive and one minus the negative predictive values (PPV and 1-NPV) for various levels of the risk scores are presented in table 4. In case of a positive test, the risk of non-remission equals the PPV, if negative the risk of non-remission is 1-NPV. For example, using a cutoff of >/=15, the PPV equals 50/68 (74%), 1-NPV equals 32/79 (41%).

The sensitivity indicates the proportion correctly classified as high risk of those who did not remit by week ten; the specificity indicates the proportion correctly classified as low risk of those who did have remission by week 10. E.g., if a value of >/= 15 were used the risk score would have a sensitivity of 61% and a specificity of 72%. In this case, 28% are falsely classified as high risk (false positive), and 39% are falsely classified as low risk (false-negative) respectively (table 4).

The AUC was 0.67 (95% confidence interval 0.59-0.75).

Discussion

To our knowledge, this is the first study in which a risk score for prediction of non-remission from major depression, that can be applied in practice, was developed. The predictors demonstrated to predict non-remission by week ten fairly good. We applied a shrinkage method to a full model including predictors that were solely selected on the basis of external information (17).

The AUC was 0.67, which may appear rather low when compared to results obtained from diagnostic studies. However, this must be put in perspective because in the diagnostic setting the demands for the precision of discrimination, i.e. discrimination between diseased and non-diseased, are generally much higher than for the prognostic setting. Further, the AUC is an overall measure of model performance, not for a specific cutoff value for the predicted risk. In clinical practice, however, a sensible cutoff value must be chosen so that after the test, the probability of non-remission will be so high or low that it helps deciding whether a more effective treatment, e.g. an antidepressant in combination with psychotherapy (25), is needed.

If, for instance, a cutoff value of >/= 15 is used and if a different treatment only and always follows a positive test, at most 74% (PPV) of these patients may benefit from this treatment, and out of the test negative patients, 41% (1-NPV) will have non-remission without having had the opportunity to benefit from the alternative treatment. If we assume that the alternative treatment leads to remission in 35% of the patients (26) who do not remit with SSRI treatment, 44% of our sample would not have remitted, compared with 56% when the prediction rule was not used (see the appendix for the calculation). With this strategy, around 39% (false negatives) of those who had non-remission would not have been treated more intensively, and 28% (false-positives) of those who had remission would have been treated more intensively.

Several limitations of our study need to be addressed. Our analyses are based on patients of whom all baseline variables and depression outcome scores at week ten were available. This may limit generalizability of the results. However, the baseline characteristics of the patients who were included in the analysis were very similar with those of the total sample. A second limitation is that it is not feasible in everyday practice to ask all depressive patients to fill out the PDQ-R and count them up. A simpler assessment tool should be developed to assess personality pathology for use in primary care settings. However, in this study the PDQ-R was the only available assessment tool for personality pathology. Therefore, we dichotomized the PDQ-R total score to use a crude score. Another issue is that other candidate predictors of non-remission, e.g. duration of the index depressive episode, life stress, and social support (22) were not included in the model.

A strength is that all patients were treated with SSRIs combined with standardization of care. This is in contrast to previous studies, in which treatment modalities varied substantially (placebo, usual care, psychotherapy, and antidepressant medication). In addition, none of the previous studies investigated predictors of non-remission in patients treated with SSRIs, currently widely prescribed antidepressants in primary care. In addition, we predicted non-remission by the end of the acute treatment phase, whereas other investigators predicted non-remission far beyond the duration of the acute treatment phase. This difference is relevant from a clinically perspec-

tive, because a favorable treatment outcome should be attained by the end of the acute treatment phase. The major strength is that this study illustrates the development of a risk score and addresses the possible implications in clinical practice, using a recommended strategy (17). The discriminative power of the predictive model was investigated, a score was constructed, and absolute risks were reported according to categories of the score.

In summary, we illustrated the process of developing a risk score. Possible predictors were combined into a scoring method which may be useful in clinical practice. However, before implementation of the model in clinical practice, the actual performance of the risk score should be validated in other samples. In addition, other predictors should be investigated as well.

Appendix

We assumed that 35% of the patients who do not remit with SRI treatment alone, would attain remission with more intensive treatment. If, for instance, a cutoff value of >/= 15 is used and if more intensive treatment only follows a positive test, according to table 4, 68 patients will receive more intensive treatment. These patients can be divided in 50 non-remission patients, and 18 remission patients. It is reasonable to assume that the remission patients will also attain remission with more intensive treatment. Therefore, another 18 patients, 35% of the 50 non-remission patients will attain remission, leaving 32 patients in non-remission. The more intensive treatment of 68 patients with a cutoff value of >/= 15 reduced the non-remission rate in this group from 50/68 = 74% to 32/68 = 47%, a reduction of 27%. In the total sample, this strategy would reduce the percentage of non-remitters from 82/147 = 56% to 64/147= 44%.

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Table 1. Baseline characteristics of the patients*

Demographic	
Age	42.8 (12.9)*
Male gender	50 (34%)
Employed	93 (63%)
Unfit for work	16 (11%)
Clinical	
BDI	22.5 (8.7)*
SCL-total	1.3 (0.6)*
Previous depression	74 (50%)
Anxiety disorder	64 (44%)
Chronic medical illness	66 (45%)
PDQ-R total score > 26	74 (50%)

*standard deviations are given in parentheses

Table 2. Multivariable non-remission predictors

Predictor	Coefficient	Odds ratio (95% confidence interval)	Points
Constant	1.65		
BDI baseline score/10	0.61	1.8 (1.1;3.2)	6
Anxiety disorder	0.16	1.2 (0.6;2.4)	2
Chronic somatic comorbidity	0.11	1.1 (0.5;2.4)	1
PDQ-R total score > 26	0.36	1.4 (0.7;3.1)	4
Previous depression	0.02	1.0 (0.5;2.1)	0
Employed	-0.45	1.6 (0.7;3.5)	-5
Unfit for work	0.26	1.3 (0.4;4.9)	3

Table 3. Remission and non-remission according to score-categories

score	N (%)	Non-remission	Remission	Observed proportion of Non-remission	Predicted proportion of non-remission
< 10	41 (28%)	13 (16%)	28 (43%)	13/41 (32%)	38%
10-15	38 (26%)	19 (23%)	19 (29%)	19/38 (50%)	52%
15-20	36 (24%)	25 (30%)	11 (17%)	25/36 (69%)	65%
>/= 20	32 (22%)	25 (30%)	7 (11%)	25/32 (78%)	76%
Total	147 (100%)	82 (100%)	65 (100%)	82/147 (56%)	56%

Table 4. Prognostic test characteristics for three cut-offs

Risk score	N (%)	False	False negative (%)	PPV* (%) positive (%)	1-NPV** (%)
>/= 10	106 (72%)	16%	60%	65%	32%
>/= 15	68 (46%)	39%	28%	74%	41%
>/= 20	32 (31%)	70%	11%	78%	50%

* PPV positive predictive value

** 1-NPV one minus negative predictive value

Initial rate of improvement and ultimate remission of major depression in primary care

3.2

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Submitted

Abstract

Objective

To investigate the relationship between symptom improvement after two or six weeks and remission after ten weeks in depressed patients treated with antidepressants in primary care.

Design

Prospective cohort study

Setting

Primary care practices in the Netherlands

Patients

172 patients starting selective serotonin reuptake inhibitor (SSRI) treatment for major depression

Main outcome measures

At week two and six, patients were classified as unimproved, partially improved, or improved. For each category we calculated the proportion of remission at week ten.

Results

Of the unimproved or partially improved patients at week six, 29% (95% confidence interval 18 to 43) and 27% (17 to 40) attained remission at week ten, respectively.

Conclusion

These data suggest that in primary care depression treatment with an SSRI should be reconsidered in depressed patients who are unimproved or partially improved by week six.

Introduction

Selective serotonin reuptake inhibitors (SSRIs) form the mainstay of depression treatment in primary care. Yet, some patients benefit insufficiently. In these patients, timely switching to another treatment may result in better outcome (1,2). Earlier studies (3,4,5,6) recommended treatment change if there is no improvement after four weeks. These recommendations were based on analyses in which the treatment objective was defined as response, i.e. a reduction of at least 50% from pretreatment depression severity. The ultimate treatment goal however, is complete remission (7). As it will on average take longer to reach remission than to attain response (8), the aforementioned recommendations should be reconsidered. Only one study (9), performed in specialty care, investigated the relation between initial symptom change and ultimate remission over a sufficiently long period. To date, this relation has not been investigated in primary care.

In the present study, we analysed data from a trial in primary care to investigate whether rate of improvement after two or six weeks of SSRI administration relates to ultimate remission of depression.

Method

We obtained data from a cluster randomized controlled trial performed in 30 primary care practices in the Netherlands. The study design and flow of patients through the trial are described in detail elsewhere (10). The principal aim of the study was to compare the influence on medication adherence and treatment result of either a depression care program (DCP) or a systematic follow-up program (SFP) in SSRI treated patients with a major depressive episode according to DSM-IV. We found no differences in outcome at week 10 and week 26 between these two conditions. Overall, 47% of patients attained remission at week 10.

Data analysis

We examined the rate of improvement at weeks two and six after starting SSRI treatment in relation to remission by week ten. Patients were categorized by criteria for unimproved, i.e. less than 25% improvement on the Beck Depression Inventory (BDI) score, partially improved (i.e. 25% up to 50% improvement on the BDI score), and improved (i.e. 50% improvement or more on the BDI score). The criterion for remission was a BDI score of less than or equal to eight at week ten (11). We calculated the proportion of remission at week ten for each category and provided exact binomial 95% confidence intervals.

Results

In total 211 patients were included in the randomized controlled trial. After selection of subjects with BDI scores available at week ten, 172(82%) remained for the present analysis. Baseline characteristics of these patients are reported in table 1. They were similar to those of the 39 patients not included, except for baseline BDI score (22.2; SD 9.0 versus 25.6; SD 9.9, respectively).

The relation between rate of improvement at weeks two and six with remission at week ten is shown in table 2. Within the categories 'unimproved' and 'partially improved', the proportion of patients attaining remission at week ten decreased from week two to week six. The lowest proportions were observed for the patients who were unimproved of partially improved after six weeks of treatment, 29% (95%CI 18% to 43%), and 27% (95%CI 17% to 40%) respectively.

Discussion

Depressed patients who were unimproved or partially improved after six weeks of SSRI treatment, had the lowest chance to reach remission by week ten. To our knowledge this is the first study in primary care on the relation between initial symptom improvement and ultimate remission.

There are limitations to the study that may have bearing on its generalizability. Firstly, the analysis is based on patients who completed the period of ten weeks. However, those patients who dropped out were not materially different except for a slightly higher BDI score at baseline, a difference which is not considered clinically relevant. Secondly the results may not be generalizable to specific SSRIs. In our study all SSRIs available in the Netherlands at the time were prescribed, i.e. paroxetine (71%), fluoxetine (5%), citalopram (7%), sertraline (13%), and fluvoxamine (4%). For instance, it was suggested that fluoxetine has a slower onset of action compared with the other SSRIs (12) which may entail a different relation between initial rate of improvement and ultimate remission.

There is some discrepancy between our results and the only available comparator study of Quitkin et al (9). They observed that 41% (95% CI 31%-52%) of unimproved patients and 48% (95% CI 40-57%) of partially improved patients still attained remission. However, differences in study design hamper comparison between the studies. E.g., Quitkin et al (9) recruited patients partly by advertising, and treated them in specialty care. Therefore, the characteristics of patients differed between the studies. All patients were treated with fluoxetine. In addition, they assessed remission at week twelve in stead of week ten. The longer duration of follow up might explain the higher rate of remission (13).

Our results may help GPs considering when to change treatment, and discussing this issue with patients at the start of antidepressant treatment. Changing treatment includes the options of switching to another antidepressant, adding another antidepressant or referral to specialty care. A remaining question is which probability of ultimately reaching remission by week ten is low enough to justify treatment change. Quitkin et al. suggested 30% as a threshold below which treatment should be reconsidered. If we apply this criterion to our study population, the point estimates and their 95% confidence intervals for all patients at week two as well as for patients improved at week six, do not give cause for reconsidering treatment. Treatment with an SSRI should be reconsidered in depressed patients who are unimproved or partially improved by week six, however. This group of patients constituted 57% of our population.

In summary, the results of the present study suggest that treatment with SSRIs should be reconsidered when patients are unimproved or partially improved after a treatment duration of six weeks. Further studies assessing symptoms change and remission at uniform time points in larger samples are recommendable.

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Table 1. Baseline characteristics of the patients [1]

	(N = 172)
Demographic	
Age (yr.)	44.2 (13.6)
Female(%)	68.4%
Employed (%)	62.7%
Unfit for work(%)	10.1%
Clinical	
BDI baseline severity	22.2 (9.0)
SCL-90 R global severity index	1.3 (0.6)
CGI	4.4 (0.7)

[1] Standard deviations are given in parentheses

Table 2. Relation of rate of improvement at week 2*, and week 6* to remission at week 10.

	Week 2 Proportion attaining remission by week 10	**Week 6** Proportion attaining remission by week 10 (95% CI)
Unimproved	37/93 (40%; 95% CI 30-50**)	13/45 (29%; 95% CI 18-43)
Partially improved	25/49 (51%;95% CI 38-64)	14/52 (27%; 95% CI 17-40)
Improved	16/24 (67%; 95% CI 47-82)	52/73 (71%; 95% CI 60-80)
Total	78/166 (47%; 95% CI 40-55)	79/170 (47%; 95%CI 39-54)

* week 2 analysis and week 6 analysis is based on 166, 170 patients respectively, because of missing data

**95% CI; 95% confidence interval

Improving patients' attitudes towards antidepressants

4

The effect of a depression care program

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Submitted

Abstract

Background

Many depressed patients have negative attitudes towards antidepressants, leading to poor adherence and depression outcome. Interventions to ameliorate attitudes are needed.

Method

In a cluster randomized controlled trial two interventions to improve management of major depression in primary care were compared: 1) a depression care program, targeting general practitioners (GPs), patients, and systematic follow-up, and 2) a systematic follow-up program. Thirty GPs were randomised and 211 patients with current major depression were included. All patients were prescribed a selective serotonin reuptake inhibitor (SSRI). Attitudes were assessed at baseline, week ten and week 26. Differences in attitudes change between DCP and SFP were analysed.

Results

Changes in patients' attitudes were more favorable in the DCP condition at week 10 and week 26, compared with a systematic follow-up.

Conclusion

The depression care program ameliorates attitudes towards antidepressants in primary care patients with major depression.

Introduction

Major depressive disorder is associated with severe personal suffering for the affected patients, great distress for their family, and major societal costs (1;2). Antidepressant medication reduces depressive symptoms (3;4), but negative attitudes towards antidepressant medication may lead to poor adherence (5;6) and a consequently increased risk for chronicity (7) and relapse (8). Because negative attitudes in depressed patients are widespread (9;10), interventions for reducing these attitudes are needed.

In community studies, Paykel et al (11), and Jorm et al (12) demonstrated positive attitude changes of an information campaign whereas Hegerl et al (13) found no effects. A recently published randomized intervention study in depressed patients suggested a positive effect of coaching by community pharmacists on attitudes towards antidepressants (14).

In the present study, we investigated whether attitudes towards antidepressant medication responded to a depression care program in primary care.

Method

Data were obtained from a cluster randomized controlled trial performed in 30 primary care practices in the Netherlands, including patients suffering from major depression according to DSM-IV. The design and primary results of this study have been reported elsewhere (15). In brief, GPs were randomly assigned to either a depression care program (DCP), or a systematic follow-up program (SFP). The DCP patients received a newsletter prior to every scheduled visit. These letters educated patients on depression and antidepressant medication. The social stigma of depressive patients, and the false belief that depression is a sign of weakness were challenged. The importance of social support was addressed. Patients were asked to complete homework assignments: 1) to fill out a questionnaire addressing the perceived costs and benefits of treatment with antidepressant medication, 2) to plan activities, and 3) to discuss their illness and treatment with significant others to enhance social support. The GPs were asked to help patients clarify the potential benefits of taking antidepressant medication and to challenge perceived costs of taking antidepressant medication.

In DCP as well as SFP, seven follow-up visits in 26 weeks were scheduled. During the visits, adherence to antidepressant medication, and severity of psychopathology were assessed. The ingredients of both interventions are depicted in figure 1. The GPs were allowed to prescribe any of the five selective serotonin reuptake inhibitors (SSRIs) that were available at the time the study was carried out (citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline) in at least the minimum effective dose. Concurrent psychological or psychotherapeutic treatment was not allowed.

From the results we concluded that overall adherence rates were high and treatment outcome was favorable, with no significant differences between interventions at week 10 or week 26.

Measurements

We constructed a self-administered patient questionnaire based on previous reports on attitudes towards antidepressants (16;17), in which perceived effectiveness, harmfulness, and stigmatization seemed to be relevant attitudes. The questionnaire (appendix A) consisted of 12 statements, clustered in three dimensions: 1) six positive statements (1-6) concerning the **effectiveness** of antidepressants (Cronbach alpha 0.78), 2) three negative statements (7-9) concerning **harmfulness** (Cronbach alpha 0.68), and 3) three negative statement (10-12) addressing **stigmatization** (Cronbach alpha 0.90). Patients responded on a 5-point Likert disagreement-agreement scale.

Data analysis

The analysis of the current study was performed in patients with a baseline measurement and a follow-up measurement at week 10 and week 26.

To study the effect of the interventions on the continuous dimensions of attitude we calculated change scores as the difference between the outcome score at either week 10 or week 26, and the baseline value. To obtain maximum statistical efficiency the significance was determined by performing analyses of covariance (ANCOVA). In these analyses, the outcome scores either at week 10 or at week 26 were related to treatment group while adjusting for the baseline value (18).

Results

The characteristics of the patients included in the analysis are depicted in table 1. No relevant differences between the intervention groups were demonstrated. There were also no relevant differences between DCP and SFP in proportions of patients not included in the analysis (34% versus 32%). Patients excluded from the analysis were slightly younger (age 38.2 years (15.7) versus 45.3 (13.1), and had a somewhat higher BDI score (25.2 (8.9) versus 21.8 (9.1), and a higher score on stigmatization (2.9 (1.1) versus 2.6 (1.2).

As illustrated in table 2, changes in all dimensions were more favorable in the DCP group at both time points. The ANCOVA yielded statistical significant results for the dimensions effectiveness, and harmfulness, both in favor for DCP at week 10 and week 26. For stigmatization no statistically significant differences were found but the trend was similar with a more favorable change in the DCP group.

Discussion

In this study, changes in attitudes towards antidepressants were more favorable in the DCP group as compared with the SFP group. These results suggest that attitudes towards antidepressant medication can be ameliorated by a depression care program in primary care patients with major depression, who start treatment with SSRIs.

Some limitations of the study need to be addressed. The scale we used was not thoroughly validated. Yet, the internal consistency as well as the face validity of our scale seems reasonable. Further, changes were consistently more favorable in the DCP on all three dimensions. Secondly, the impact of the relatively high lost to follow-up rate must be considered. Although it seems reasonable to assume that dropout is related to attitudes towards antidepressants, the proportion of lost to follow-up was similar in both treatment arms and it seems in our view unlikely that the dropout- attitude relationship was different between the intervention arms. Thus, lost to follow up is unlikely to have biased our results. Yet, patients not included in the analyses were slightly younger, had a somewhat higher baseline BDI score, and agreed more to the statements concerning stigmatization and therefore generalizability to this type of patients may be limited.

Our results are in accordance with a previously published randomized trial demonstrating a positive effect of coaching by community pharmacists in depressed patients in primary care (14).

Given the fact that negative attitudes towards antidepressants are widespread among depressed patients (9;10;19), the results give cause for cautious optimism. Adherence, perceived wellbeing, role functioning, and quality of life might be better when patients are comfortable with taking antidepressant medication and don't feel stigmatized (5;20). Based on the results demonstrating that the changes in attitudes were more positive in DCP, one might expect better adherence rates in DCP as well. This was however not the case, as we reported elsewhere (15). This might be explained by the fact that DCP contained various ingredients, of which patient education and the repeated consideration of the costs and benefits of antidepressants addressed attitudes towards antidepressants. These ingredients might have influenced adherence positively via changing attitudes in a positive direction. Possibly, other ingredients had a negative effect on adherence, counteracting the positive effect. Self-management support, consisting of enhancing social support and daily activities might have increased patients' willingness to cope alone without medication. Indeed, most depressive patients in primary care prefer counseling and psychotherapy to antidepressant medication (21). Another explanation may be that the intensive follow-up patient GP contacts in both intervention groups created a ceiling effect in adherence obscuring any differences. Nevertheless, in two observational studies attitudes towards anti-

depressants were positively associated with adherence (19;22). This was also demonstrated in chronic physical illnesses (17). Therefore, investigating which ingredients have the potential to improve adherence via attitudes change, and which ingredients negatively influences this, needs further attention.

In summary, our findings suggest that a depression care program ameliorate attitudes towards antidepressants. Future research ought to determine whether adherence, depression outcome, and other related outcomes such as perceived wellbeing, role functioning, and quality of life improve when interventions are tailored to patients' attitudes.

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Figure 1. Elements of interventions to improve depression treatment

intervention	Evidence based anti-depressant dose	Enhanced patient education	Enhanced GP education	Stimulating active partici-pation of GP and patient in the treat-ment process	Self-manage-ment support	Systematic follow-up
DCP	Yes	Yes	Yes	Yes	Yes	Yes
SFP	Yes	No	No	No	No	Yes

Table 1. Baseline characteristics of the patients [1]

	DCP (N = 67)	SFP (N = 75)
Demographic		
Age (yr.)	44.9 (13.2)	45.7 (13.1)
Female(%)	73.1	64.0
Employed(%)	63.2	61.1
Unfit for work(%)	10.5	8.3
Clinical		
BDI baseline severity	21.5 (7.5)	21.1 (9.7)
SCL-90 R global severity index	1.2 (0.5)	1.2 (0.6)
Previous depression (%)	47.8	44.0
Anxiety disorder (%)	36.9	48.6
Comorbid somatic illness (%)	46.3	54.7

[1] Standard deviations are given in parentheses

Table 2. Attitudes towards antidepressants at week 10 and week 26*

Week 10

	Effectiveness				Harmfulness				Stigmatization			
	DCP	SFP	Diff.	P val	DCP	SFP	Diff	P val	DCP	SFP	Diff	P val
Baseline	3.2	3.3			3.1	2.5			2.9	2.3		
Analysis												
Follow up	3.5	3.3			2.1	2.3			1.9	1.9		
Change score	- 0.3	0.0	- 0.3		1.0	0.2	0.8		1.0	0.4	0.6	
ANCOVA				0.029				0.007				0.108

Week 26

	Effectiveness				Harmfulness				Stigmatization			
	DCP	SFP	Diff	P val	DCP	SFP	Diff	P val	DCP	SFP	Diff	P val
Baseline	3.2	3.3			3.1	2.5			2.9	2.3		
Analysis												
Follow up	3.5	3.2			1.9	2.1			1.7	1.7		
Change score	- 0.3	0.1	- 0.4		1.2	0.4	0.8		1.2	0.6	0.6	
ANCOVA				0.006				0.001				0.136

*Values are means, Diff = Difference, val = value

Appendix A. Attitudes towards antidepressants

Statement

1. Antidepressants are effective in the treatment of depression
2. Depression can be treated with medication
3. Even when I feel better, I will have to continue the antidepressant medication in order to prevent a relapse
4. I will have to take the antidepressant medication for a long time
5. When I feel good, I have to continue the antidepressant medication
6. When I feel substantially better, I have to continue the antidepressant medication
7. I will suffer from bothersome side effects caused by the antidepressant medication
8. Antidepressants are harmful
9. Antidepressants are addictive
10. I am ashamed that I need antidepressant medication
11. I am afraid that others will find me weak when I take antidepressant medication
12. I am afraid that others will find me crazy when I take antidepressant medication

Five responses ranged from strongly disagree (1) to strongly agree (5)

General discussion

5

The aim of the studies described in this thesis was to gain more insight into the possibilities to improve the management of major depression in primary care, with special emphasis on patient adherence, depression outcome and the prediction of an unfavorable outcome. Numerous reports have demonstrated that single initiatives usually do not have an effect (1;2). Ineffective interventions include distribution of guidelines (3), knowledge transfer to doctors that does not increase their skills or change how the healthcare team works (4;5), feedback reports on indicators of quality of care (6), and screening programs (7;8;9;10;11). Therefore, the focus of this thesis is on interventions targeting patient, doctor, and management of depression simultaneously in primary care.

We first undertook a systematic review of studies investigating the effect of interventions on patient adherence and depression outcome in depressive patients. In addition, we performed a cluster randomized trial, comparing a depression care program (DCP) with a systematic follow-up program (SFP) in primary care patients suffering from a major depression. Again, the effects on adherence to antidepressant medication and depression outcome were examined. Also, the possibility to improve negative attitudes towards antidepressant medication was investigated. Further, we examined the possibility to predict an unfavorable outcome (i.e. non-remission by week ten) by studying candidate predictors of non-remission, and examining the relationship between initial symptom improvement and non-remission.

In this chapter the major results are discussed. In addition, I will elaborate on some of the secondary findings of the studies and on methodological issues. Finally, implications for the treatment of primary care patients suffering from major depression and new directions for research will be formulated.

Interventions to improve depression treatment

The quality of treatment of depressive patients in primary care is generally low (12;13;14;15): among patients initiating therapy, few receive levels of treatment consistent with research evidence and expert guidelines (15;16;17). Less than one-quarter of primary care patients with depressive disorders receive adequate acutephase treatment. Duration of treatment is inadequate, and patient follow-up and support are suboptimal. Even when appropriate treatment is recommended, adherence to treatment is a major problem (18;19). Nonadherence is a major obstacle in the effective treatment of depression. To improve management of depression in primary care, various interventions were studied.

In chapter 2.1 we presented the findings of a systematic review of studies investigating these interventions. The focus was on studies aiming at enhancing adherence to antidepressant medication and improving depression outcome. Most interventions used components of collaborative care.

Collaborative care is a team-based approach that transfers assessment, education, and treatment monitoring activities for depression to nonphysicians, and sometimes provides mechanisms for improved primary care/mental health specialty partnerships (20). It was found that most collaborative care interventions demonstrated significant improvements in rates of adherence to medication, and better depression outcomes during the acute and continuation phase of treatment. These results support the introduction of interventions to enhance the management of depression in everyday practice.

The usefulness of these interventions, however, also depends upon the feasibility in clinical practice. Implementation may be problematic because effective interventions had multiple ingredients, and required intensive support from research teams. This is not compatible with available time, financial restraints, and practice organization in most community settings (21;22). For this reason, it was recommended that quality improvement initiatives direct attention not merely to the design of clinical interventions but also to the systems of care in which the interventions will be implemented. Investigating which components of interventions are effective, and designing interventions that are feasible in a wide variety of primary care practices is warranted to improve the management of depression in daily practice.

In chapter 2.2 we compared the effect of a depression care program (DCP) with a systematic follow-up program (SFP). With the characteristics of effective interventions in mind (chapter 2.1), we developed a program that was thought to be feasible in primary care practices in the Netherlands. The program targeted GP, patient, and organization of follow-up. Collaboration with practice nurses and mental health workers was not feasible in the Netherlands, because these professionals were not yet widely available in primary care practices at the time of our study. We decided not to compare DCP with usual care, albeit all other studies (chapter 2.1.) did so. This was because the quality of usual care is generally poor, and we would not recommend it in clinical practice. We agreed with other researchers (23;24;25) that, from a scientific perspective, usual care should be considered of dubious value as a comparison. We tested DCP against SFP, which is suggested to be an effective intervention per se (26;27). Indeed, Simon et al (6) demonstrated that an intervention in which systematic follow-up was the main focus significantly improved outcomes in comparison with usual care. The SFP in this project was tailored to the recommendations of the Dutch primary care guidelines on management of depression (28), and should be considered as a standard.

The results showed that adherence was high and depression outcomes were favorable, with no differences between the interventions. SFP seemed as effective as a more complicated program. In comparison with usual care, albeit indirect, SFP has the potential to improve adherence and treatment outcome in many patients treated with SSRIs. Therefore, it seems necessary to implement this program.

Several methodological issues concerning the trial should be addressed. When designing a study of treatment effectiveness in routine primary care practices, competing aims of rigorous scientific methodology (internal validity) and generalization of study findings (external validity) should be balanced within the randomized controlled trial (29). In general, the internal validity of randomized controlled trials is high (i.e. drawing conclusions from a treatment used in a particular setting on patients) but clinicians are primarily interested in the generalizability of a trial (24). Do the trial's results apply to their patients?

With regard to our study, the internal validity of the results are strengthened by the use of a cluster randomized controlled trial, minimizing confounding by indication bias. In addition, all participants had to meet the criteria of the *Diagnostic and Statistical Manual of Mental Disorders* fourth edition for major depressive episode, and depression severity was assessed using a reliable and valid questionnaire (30). There are also limitations, of which several were addressed in chapter 2.2. E.g. the measurement method of adherence might have overestimated adherence, and GPs and patients were openly assigned to treatment, possibly biasing the results.

The generalizability of our findings is strengthened by the inclusion of sociodemographically diverse patients, without excluding patients suffering from comorbid disorders. Secondly, the interventions were performed by GPs working in nonacademic primary care practices, representing everyday treatment settings. Thirdly, we did not use treatment manuals. Purifying interventions enhances the study's internal validity, but possibly decreases the generalization of results since rigorously defined treatments administered in the RCT will likely vary from those implemented in daily practice. Generalizability might be weakened by several factors. In our study, GPs and patients were informed about the purpose of the study, and all patients had agreed to be treated with antidepressant medication. This may have resulted in recruitment of motivated GPs and patients. In addition, data collection during the full study duration was not possible for all included patients. Missing values are problematic in research as they may bias the results. We compared the baseline characteristics of patients with complete data, versus those of patients with missing data. This revealed that patients with missing data were younger and had a higher baseline BDI score. Schulberg et al (31) reported the same differences in completers versus dropouts in a primary care study. In order to perform an evaluation of the patterns of missingness, we calculated the mean of the last available values of the BDI scores for the acute treatment phase (10 weeks), and for the full study duration (26 weeks) for both conditions. No differences were demonstrated. Therefore, the comparison of BDI scores between interventions was not likely biased by missing data. Our assumption that the outcome values that were missing, were missing at random, was essential for performing repeated measures

analyses of the continuous outcomes using all patients, not only the complete cases. In conclusion, it is reasonable to assume that our comparisons between DCP with SFP was not biased by missing data, but our results might not generalize to younger patients with more symptom severity.

Unlike all the previous studies, our interventions were not tested against usual care, for reasons already mentioned. Despite the fact that some investigators believe that no difference between treatment conditions cannot distinguish equal effectiveness from equal ineffectiveness in the absence of an inactive control condition, practical clinical trials without a concurrent placebo arm are relatively common. If both interventions have shown unequivocal superiority against placebo, then a trial without a concurrent placebo control condition is generally thought reasonable (25). Based on the literature, we considered it reasonable to assume that DCP and SFP would be superior to an inactive control condition.

The favorable adherence and depression outcomes may partly be explained by the fact that all patients were prescribed SSRIs. Longitudinal patterns of antidepressant prescribing in primary care demonstrated that patients who initiated therapy on a SSRI were more likely to have a prescribed average daily dose and duration consistent with recommended treatment guidelines within the first 6 months of initiating therapy than were patients who initiated therapy on a tricyclic antidepressant (32;33;34;35;36). However, the outcomes of our study are far more favorable than would be expected from comparisons with observational studies (19;35;37).

Prediction of outcome

In antidepressant treatment, remission should be the ultimate treatment goal that should be attained during the acute treatment phase (38;39). This phase lasts approximately 10 weeks (40). Fortysix percent of our sample attained remission at week 10. Nevertheless, approximately half of the participants did not attain remission. From a clinical perspective, it would be interesting to know beforehand for which patients interventions are likely to be insufficient. For these patients alternative interventions should be given to improve their prognosis.

Numerous reports claim predictor variables of treatment success or failure (41). However, most have been only of academic interest, because they lack investigating the possible consequences in clinical practice. In addition, in primary care studies remission at week 16-24 was predicted, whereas remission attained in the acute treatment phase is the ultimate treatment goal after antidepressant medication is started.

Chapter 3.1 illustrates the development of a score from collected baseline characteristics that allows the GP to allocate a probability of non-remission to each individual patient.

Greater illness severity, presence of an anxiety disorder, presence of a chronic somatic illness, PDQ-R total score greater than 26, being unemployed, and being unfit for work predicted non-remission by week ten fairly good. The risk score is the only score available, and has the potential to improve when other relevant predictors are included, such as duration of depressive episode (42), and social support (43). In the future, biological variables, e.g. pharmacogenetic information may also be promising (44).

It is hoped that researchers investigating possible predictors of depression outcome will address the consequences for clinical practice. Otherwise, clinicians might be misled by statistical results.

Given the results of prediction research up till now, baseline variables have a moderate power to predict outcome in clinical practice (41; this thesis chapter 3.1). It seems that outcome can not yet be powerfully predicted before treatment is started. An alternative may be the prediction of an unfavorable treatment course once treatment is started, to prevent persistence with a trial that is likely to fail. Treatment guidelines provide information on when to consider treatment change for patients who are not responding (28;45). However, no primary care studies investigated the relation of symptoms change to ultimate remission in the acute treatment phase. Therefore, the evidence presented in guidelines is of limited value.

In chapter 3.2 we investigate the relation of symptoms change at week two or six to remission at week ten. The data suggest that treatment with SSRIs should be reconsidered after six weeks in depressed patients who are unimproved or partially improved. If these results are replicated in large samples, this will help to improve guidelines.

Attitudes towards antidepressant medication

Negative attitudes towards antidepressants are widespread and may threaten adherence to this medication. Several studies reviewed in chapter 2.1 tried to educate patients on the benefits of antidepressant medication, but none assessed attitudes towards this medication. In our study (chapter 2.2), important ingredients of DCP were patient education and discussing the benefits and costs of antidepressant medication. We assumed that these ingredients might improve attitudes towards antidepressant medication.

In chapter 2.5 a study on the possibility to change attitudes towards antidepressant medication is described. The results demonstrated that the changes in attitudes were more positive in DCP. Based on this result, one might expect better adherence rates in DCP also. This was not the case: no differences between DCP and SFP were found (chapter 2.2). This might be explained by the fact that DCP contained various ingredients, two of which addressed attitudes towards antidepressants. These ingredients might have influenced adherence positively, by changing attitudes in a positive direction. Possibly, other ingre-

dients had a negative effect on adherence, counteracting the positive effect. Self-management support, consisting of enhancing social support and daily activities might have increased patients' willingness to cope alone without medication, thereby counteracting the positive effect. Another explanation may be that the intense follow-up in both interventions created a ceiling effect in adherence. When this was the case, the extra interventions applied in DCP would not increase adherence. Because in two observational studies attitudes towards antidepressants were associated with adherence (46;47), the potential to change attitudes might be promising, especially in patients with negative attitudes towards antidepressant medication. It is warranted to investigate which ingredients of interventions influence adherence positively via positive attitudes changes, and which counteract the positive effect.

Implications for the management of major depression in primary care

Major depression is a serious, often chronic disease. Usual care in primary care patients suffering from major depression generally does not meet guidelines, and needs considerable improvement. Numerous collaborative care interventions, incorporating principles of chronic disease management (48), seem promising. These interventions significantly enhance the quality for depression treatment, leading to better adherence and depression outcomes (chapter 2.1), in combination with positive consequences for productivity, absenteeism (49), and health care costs (50). The costs are within the range of other widely accepted public health improvements (51).

Numerous barriers, however, threaten the implementation of collaborative care interventions in the Netherlands (15) and elsewhere (21;52;53;54). The large gap in the quality of care cannot be closed only by increased efforts of individual practitioners (1). To disseminate interventions widely, strategies are needed to support their implementation and maintenance in primary care practices. Pincus et al (55) described the "6 P" conceptual framework which describes 6 different levels at which barriers occur, and at which interventions can be aimed. We need to consider barriers and interventions at each of the following 6 levels: the patient, the provider, the practice, the health plan, the purchaser, and the population. Depressed patients often encounter stigma, deny the presence of depressive symptoms, have negative attitudes towards antidepressants, and experience the presence of hopelessness. These factors create barriers to seeking and accepting appropriate care. Primary care providers face multiple competing demands for their attention and receive little or no financial incentive to manage depression. Most practices are set up to deliver health care for acute conditions, whereas chronic illnesses such as depression require different strategies. In addition, there is a wide variation in how primary care practices are linked to mental

health specialty support (56), which is also the case in the Netherlands (15). Interventions targeting these first three levels (patient, provider, practice) improved the management of depression, as illustrated in chapter 2.1 and 2.2. However, sustainability of improvements requires attention to the other levels. The organizational and economic context, in which treatment choices are made, must be taken into account (56;57;58). When economic and organizational obstacles remain, interventions to improve the management of depression in the primary care sector stand little chance of long-term success. A challenge for policymakers may be how to link depression care with the management of other chronic conditions, such as asthma, diabetes, and hypertension (56).

Compared with most collaborative care interventions, SFP is relatively simple and already recommended in practice guidelines (e.g. 28). Therefore, and with the results of our trial in mind, it seems necessary to implement this program in patients starting treatment with antidepressant medication. This would guarantee a proper follow-up (59). At the practice level, the monitoring of GPs by a transient research team during the trial could be replaced by computer programs serving as a prompting system that ensures adherence to follow-up visits and enhanced monitoring of outcomes. In the near future, practice nurses could become an option in the follow-up of depressive patients, thereby creating a relatively simple collaborative care intervention (6). This collaborative care is already adopted in the management of other chronic diseases, like diabetes and cardiovascular diseases, which are frequently comorbid with depression. Implementation in the context of many other pressing clinical priorities is challenging.

Implications for the prediction of non-remission

When a clinically relevant and reliable risk score is available, the patients above a predetermined risk score may be treated more intensely (e.g. the combination of antidepressant medication and psychotherapy, collaborative care with a psychiatrist involved, or specialty care). Up till now, it seems that outcome can not yet be powerfully predicted before treatment is started. While awaiting the development of more powerful risk scores based on baseline characteristics, symptoms change is the best alternative. Once treatment is started, rate of symptoms improvement is used in predicting outcome. For clinical practice, treatment guidelines recommending when to change treatment in case of unimprovement or partial improvement are available to help GPs. The most recent practice guideline for GPs in the Netherlands (28) recommends change of treatment in case of ineffectiveness at week four or six. However, the evidence on which this guideline is based is rather weak. Based on our results, we would advice GPs to consider treatment change in patients who are unimproved or partially improved after six weeks of

treatment. Therefore, our results are in line with the Dutch guideline. To be informed on the rate of improvement, the use of severity rating scales is recommended. A self-administered questionnaire, such as the BDI, is a good option for primary care. In addition, at the start of a treatment GPs should inform the patient of how long a trial with a SSRI takes. If the rationale of the trial length is made clear, adherence may improve.

Implications for the possibility to change attitudes toward antidepressants

Recently, it was demonstrated that patients given antidepressants vary widely in adherence. This variation was primarily explained by the balance between their perception of need and harmfulness of antidepressant medication, in that adherence was lowest when perceived harm exceeded perceived need, and highest when perceived need exceeded perceived harm (47). Despite the fact that we did not find differences in adherence to antidepressant medication between DCP and SFP, the result that DCP improved attitudes might be promising for patients with most negative attitudes, for whom SFP might be insufficient, especially when the effective ingredients of DCP can be identified.

Future directions

In the introduction of this thesis, we motivated the studies we performed. With this thesis, more insight in the different aspects of the management of depression in primary care was gained. However, questions remain. Therefore, we end with some recommendations for further research.

New research should expand the knowledge on interventions to improve the management of depression.

- The separate effects of components of these interventions need to be clarified. Because usual care is of low quality, interventions should be tested against a systematic follow-up program.
- Outcome measures should not only include adherence and depression outcome, but also functional outcome, and quality of life.
- Cost-effectiveness and feasibility of interventions are relevant aspects to be addressed.
- When effective interventions that are relatively easy to implement are available, strategies to convince politics and insurance companies are needed.

Continuing research on possible predictors of outcome is warranted.

- Potential promising predictors, e.g. pharmacogenetic variables should be tested to know beforehand for which patients interventions are likely to be insufficient.

- Practical clinical trials (25) may have the best design to investigate possible predictors of outcome.
- As stated in chapter 3.1 prediction rules should be external validated in another, yet similar population.
- The relation of rate of symptoms change to ultimate remission should be investigated in larger studies, at uniform timepoints.
- Combining baseline variables with symptoms change rate at different time points should be investigated in large studies.

New research on attitudes towards antidepressant medication should be initiated.

- More reliable and valid questionnaires should be developed.
- Subsequent research should determine whether patients' attitudes about medication influences adherence and depression outcomes in a clinically significant amount.
- Interventions having the potential to change attitudes towards antidepressant medication should be developed and investigated.
- Investigating for which subgroup interventions aiming at improvement of attitudes is effective, is important.

Epilogue

"Usual" care of depression is "usually" inadequate. The main conclusion of this thesis is that management of primary care patients suffering from major depression can be enhanced, leading to improved adherence, better depression outcome, and more positive attitudes towards antidepressant medication. In addition, we demonstrated that poor outcome can be predicted with readily available predictors.

The results of our studies have broadened the knowledge on interventions to improve depression management in primary care. Implementation of complex interventions in everyday practice remains a major challenge. Because a systematic follow-up program seems as effective as more complex interventions, it is time to improve usual care by using a systematic follow-up program. This may help a vast amount of patients suffering from major depression. Therefore, adequate follow-up can't be optional.

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Summary

A1

Depressive illness is a public health issue of major significance. Despite proven efficacy of antidepressant medication, the quality of depression management in primary care is still generally insufficient. Few patients receive levels of treatment consistent with guidelines, and effectiveness of antidepressant medication is reduced by patients' nonadherence. This may result in serious consequences such as treatment failure, high medical care utilization, and functional impairment.

In this thesis, we report on our attempts to gain more insight into the possibilities to improve adherence, patients' attitudes towards antidepressant medication, and depression outcome. Furthermore, the possibility to predict poor outcome was studied.

In chapter 2.1, we review the literature on interventions aiming at improving adherence and depression outcome. We included 19 studies. Interventions using enhanced patient education, counseling, improved quality of care, and collaboration with practice nurses and mental health workers, resulted in significant improvements in rates of adherence, and better depression outcomes. Control groups were treated with usual care, involving prescription of antidepressant medication without a systematic follow-up. Consequently, introduction of interventions to enhance management of depression in primary care seems warranted. However, most of the effective interventions consisted of multiple ingredients and required intensive support from research teams, which likely precludes implementation in daily practice. Comparison of effective interventions might therefore help to establish their active ingredients, and, consequently, to develop interventions which are compatible with usual systems of care.

We therefore developed a depression care program (DCP) that was feasible in primary care practices in the Netherlands, where collaboration with practice nurses and mental health workers is not widely present. DCP consisted of enhanced patient education, enhanced GP education, stimulation of participation of GP and patient in the treatment, patient's self-management support, and discussing the costs and benefits of antidepressants. In a cluster randomized trial, described in chapter 2.2, we compared the effects of this program with those of a less complex systematic follow-up program (SFP) in patients suffering from major depression, who were prescribed selective serotonin reuptake inhibitors. We decided to compare DCP with SFP, because the results of only usual care have been proven to be unsatisfactory, and should therefore be considered less relevant as a comparison. Furthermore, SFP is in line with what is recommended in most treatment guidelines. Our study demonstrated that adherence was high and depression outcomes were favorable in both conditions. So, it was concluded that SFP is an effective intervention *per se*.

Management of depression might also improve when clinicians could estimate beforehand which patients presumably will not profit from certain interventions. Such patients should then better be treated with other interventions. In chapter 3.1 we present the development of a prediction rule from collected baseline patient characteristics, which provides the general practitioner with a manageable instrument to allocate a probability of non-remission to individual patients. Greater illness severity, comorbid anxiety disorder, chronic somatic illness, a PDQ-R total personality-score greater than 26, employment status, and being unfit for work predicted non-remission by week ten fairly good. The applicability of such a risk score may even improve when other relevant predictors are included.

Prediction of unfavorable outcome might also be obtained from rating symptoms change after antidepressant treatment is actually started. Most guidelines on the treatment of depression recommend to evaluate treatment results after four to six weeks, and, if necessary, to change treatment. However, the evidence on which such recommendations are based is rather weak. In chapter 3.2 we report on the investigation of the relation between initial symptoms change and remission. Our data show that treatment with antidepressant medication should be reconsidered if patients are still unimproved or partially improved after six weeks. To monitor symptoms change, we recommended the use of a self-administered questionnaire.

Negative attitudes towards antidepressants are widespread and may partly explain variations in adherence between patients. Interventions to improve such attitudes are therefore needed. In chapter 4, we examined the possibility to improve attitudes towards antidepressant medication in depressed primary care patients, using data from the cluster randomized trial described in chapter 2.2. Our findings demonstrate that changes in attitudes were more favorable in the DCP group than in the SFP group. However, as we have been unable to demonstrate any difference in adherence rates as well as in depression outcomes between the DCP and SFP condition, the clinical relevance of these results remains unclear. Supposedly, patients with negative attitudes for whom SFP is insufficient, might profit from a positive attitudes change through the use of active ingredients of DCP. However, this possibility requires further study.

All these considerations taken together, we conclude that the management of major depression in primary care can be substantially improved. This may result in higher adherence rates, more positive patient attitudes towards antidepressant medication, and, ultimately, better outcome of depression treatment. Since systematic follow-up seems to be as effective as more complex interventions, one might rightly state that *systematic follow-up can't be optional anymore*.

Keywords: major depression, primary care, depression care program, systematic follow-up, adherence, prediction, attitudes

Samenvatting

A2

Depressie is een groot gezondheidsprobleem. Ondanks de werkzaamheid van antidepressieve medicatie laat het resultaat van behandelingen in de huisartsenpraktijk vaak te wensen over. Belangrijke redenen daarvoor zijn gebrekkige therapietrouw en onderbehandeling van depressieve patiënten. Het gevolg kan zijn dat de behandeling faalt, met als consequenties chroniciteit, comorbiditeit, hoge zorgconsumptie en disfunctioneren van de patiënt.

In dit proefschrift doen we verslag van onze pogingen om meer inzicht te krijgen in de mogelijkheden om de therapietrouw, de depressieuitkomst en de attitudes van patiënten ten aanzien van antidepressiva te verbeteren. Ook onderzochten we de mogelijkheid om het behandelresultaat te voorspellen.

In hoofdstuk 2.1 bespraken wij eerdere studies, die interventies onderzochten om de therapietrouw en depressieuitkomst te verbeteren. Interventies met uitgebreide patiëntenvoorlichting, counseling, gestructureerde *follow-up* en samenwerking met praktijkverpleegkundigen of andere gezondheidswerkers resulteerden in relevante verbeteringen in de mate waarin patiënten de voorgeschreven antidepressiva innamen, en waarin de ernst van hun depressieve symptomen verminderde. In die studies werden deze interventies vergeleken met een routinebehandeling, die in het algemeen bestond uit het voorschrijven van een antidepressivum, zonder dat de patiënten op een gestructureerde manier werden gevolgd. Uit het literatuuroverzicht blijkt dat routinebehandeling alléén niet voldoet. In de praktijk van alledag is verbetering daarvan echter moeilijk. De interventies die bleken te werken, bestonden immers uit verschillende ingrediënten en werden ondersteund door onderzoeksteams. Dit maakt invoering in de dagelijkse praktijk problematisch. Vergelijking van verschillende interventies kan echter duidelijk maken welke ingrediënten specifiek verantwoordelijk zijn voor betere resultaten. Dat kan helpen bij het ontwikkelen van interventies die wel aansluiten bij de organisatie van de gemiddelde huisartsenpraktijk in Nederland.

Wij ontwikkelden daartoe een *depression care program* (DCP), dat toepasbaar was in Nederlandse huisartsenpraktijken waar praktijkverpleegkundigen of andere gezondheidwerkers vaak niet beschikbaar zijn. Belangrijke ingrediënten van dit DCP waren: informatieverstrekking aan patiënten en huisartsen, stimulering van een actieve bijdrage van de patiënt en huisarts aan de behandeling, opdrachten aan de patiënt om sociale steun te vergroten en activiteiten te plannen, en bespreking met de patiënt van de voor- en nadelen van antidepressieve medicatie. Omdat vast staat dat een routine eerstelijnsbehandeling van depressie tot onvoldoende resultaten leidt, vergeleken we dit DCP programma met een interventie, waarmee de patiënten gestructureerd werden gevolgd (*systematic follow-up program*; SFP). In behandelrichtlijnen voor depressie wordt een dergelijke vorm van systematische *follow-up* ook geadviseerd. In een onderzoek waarin huisartsenpraktijken werden gerandomi-

seerd (hoofdstuk 2.2), kregen alle geïncludeerde patiënten met een depressieve stoornis (*major depressive disorder*) een selectieve serotonine heropnameremmer (SSRI) voorgeschreven. We vonden een grote therapietrouw en gunstige behandeluitkomsten in *beide* interventiegroepen. SFP lijkt dus al een werkzame interventie op zichzelf.

In het algemeen zal de behandeling van depressie eveneens verbeteren, als de behandelaar van tevoren weet, welke patiënten *niet* zullen opknappen van een bepaalde voorgenomen aanpak. Die patiënten zullen dan anders, hopelijk effectiever behandeld kunnen worden. In hoofdstuk 3.1 hebben wij de volgende voorspellers van behandelsucces onderzocht: de ernst van de depressie, de aanwezigheid van een angststoornis, de aanwezigheid van een chronische somatische aandoening, de score op een persoonlijkheidsvragenlijst, eerdere depressieve episodes, het hebben van werk, en arbeidsongeschikt zijn. Met deze gegevens, die voor de start van een behandeling reeds bekend zijn, kan de huisarts aan iedere patiënt een score toekennen, die correspondeert met een bepaalde waarschijnlijkheid dat de behandeling succes zal hebben. De score voorspelde de kans op behandelsucces redelijk goed. Wanneer nog andere voorspellende variabelen beschikbaar zijn, zal de mate waarin de score de uitkomst kan voorspellen, mogelijk nog verbeteren.

Ook als de behandeling reeds is gestart, kan de uitkomst daarvan nog worden voorspeld. Daarvoor kan de mate waarin de ernst van de depressieve symptomen verandert, gebruikt worden. Op basis daarvan wordt in behandelrichtlijnen voor depressie geadviseerd om na 4 tot 6 weken het resultaat van de behandeling te evalueren en de behandeling aan te passen, als de patiënt dan nog onvoldoende is verbeterd. De wetenschappelijke basis voor deze aanbevelingen is echter zwak, omdat de relatie tussen afname van de ernst van depressieve symptomen en het uiteindelijke resultaat niet in eerstelijnsstudies is onderzocht. In hoofdstuk 3.2 doen wij verslag van ons onderzoek daarnaar. Uit de resultaten blijkt dat een behandeling met een SSRI heroverwogen moet worden, wanneer de patiënt *na zes weken* nog niet of slechts gedeeltelijk is verbeterd. Om de verandering van depressie-ernst te meten is een vragenlijst die door de patiënt zelf wordt ingevuld, geschikt.

Negatieve attitudes ten aanzien van antidepressiva zijn wijdverbreid en verklaren in belangrijke mate de variatie in therapietrouw tussen patiënten. Daarom zijn interventies nodig die irreële negatieve attitudes kunnen verbeteren. In hoofdstuk 4 doen wij verslag van een onderzoek naar de mogelijkheid om zulke negatieve attitudes bij depressieve patiënten te beïnvloeden. Wij maakten gebruik van data uit de studie, die in hoofdstuk 2.2 is beschreven. Het bleek dat de patiënten die in de DCP-groep werden behandeld, een gunstiger verandering in attitudes hadden dan de patiënten in de SFP-groep.

Omdat echter geen verschillen werden aangetoond in therapietrouw en behandelresultaat tussen de DCP- en de SFP-groep (hoofdstuk 2.2), blijft de relevantie van deze bevinding vooralsnog onduidelijk. Het zou kunnen zijn dat SFP niet bij alle patiënten met negatieve attitudes tot verbetering van therapietrouw leidt. Zulke patiënten zouden dan profijt kunnen hebben van ingrediënten uit het DCP-programma, die de attitude ten opzichte van de behandeling in positieve richting veranderen. De verwachting is gerechtvaardigd, dat daardoor ook de therapietrouw zal verbeteren. Dit zal echter onderwerp moeten zijn van nader onderzoek.

Op basis van de besproken resultaten concluderen wij dat het resultaat van de medicamenteuze behandeling van depressie in de huisartsenpraktijk kan verbeteren. Systematische *follow-up* van de behandeling lijkt daarvoor een even goed instrument te zijn als meer complexe interventies. In de Nederlandse huisartsenpraktijk is een dergelijke strategie goed in te passen. Het is dan ook tijd om de gangbare routinebehandeling van depressie in de eerste lijn te verbeteren.

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A3

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Dankwoord

A4

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Amsterdam, november 2005

Curriculum vitae

A5

Ton Vergouwen was born on May 6, 1963, in Goes, the Netherlands. He received his secondary school education at the Gertrudislyceum in Roosendaal and graduated in 1981. He studied medicine at the Vrije Universiteit in Amsterdam, receiving his degree as a medical doctor in 1989. First, he was working as a resident in psychiatry, pulmonology, and cardiology. In 1992 he started his specialization in psychiatry at the Academic Hospital of the Vrije Universiteit in Brussels, where he was also trained in neurology. After 4 years, he returned to the Netherlands for his psychotherapeutic training in the Jelgersmakliniek in Oegstgeest.

Since 1997 he works as a psychiatrist. Currently, he is employed in the Sint Lucas Andreas Hospital, a teaching hospital in Amsterdam. He is also editor of Patient Care Neuropsychiatrie en Gedragsneurologie.

Ton Vergouwen werd geboren op 6 mei 1963 in Goes. In 1981 ontving hij het VWO diploma aan het Gertrudislyceum in Roosendaal. Vervolgens studeerde hij tot 1989 geneeskunde aan de Vrije Universiteit te Amsterdam. Na zijn artsexamen werkte hij op afdelingen psychiatrie, longziekten en cardiologie. Hij specialiseerde zich tot psychiater in het Academisch Ziekenhuis van de Vrije Universiteit te Brussel, waar hij ook een jaar neurologie deed. Het keuzejaar psychotherapie volgde hij in de Jelgersmakliniek te Oegstgeest.

In 1997 werd hij geregistreerd als psychiater. Momenteel werkt hij in het Sint Lucas Andreas Ziekenhuis te Amsterdam als psychiater en plaatsvervangend A-opleider. Hij is tevens redacteur van Patient Care Neuropsychiatrie en Gedragsneurologie.