Improving long-term outcome of major depression in primary care

Smit, Jannetje

Chapter 8

Summary and general discussion

Introduction

In this final chapter, I will briefly review the rationale and underlying framework of the research that was presented in this thesis. After summarising the main findings, I will discuss several issues related to the interpretation of the results and their implications. The chapter concludes with recommendations for primary care treatment of depression and future research.

Starting point

The Department of Psychiatry at the University of Groningen in the Netherlands has a long history in primary care research. In a previous study, the effects of a comprehensive PCP training program on improvement of recognition, diagnosis and managing depression were evaluated. Main findings showed that this training improved PCPs knowledge of depression, resulted in better recognition, improved accuracy of diagnosis and increased the proportion of patients receiving treatment according to clinical guidelines (Os *et al.* 1999; 2003). The training also improved patient outcomes, but only on the short -term: at three-month follow-up, depressed patients of trained PCPs had less severe psychopathology and higher recovery rates. Particularly patients with a recent-onset depression were found to benefit from improved physician performance (Tiemens *et al.* 1999 ; Ormel *et al.* 1998). For patients with more persistent depression however, the PCP training did not seem to improve outcome (Os *et al.* 2006).

One explanation for the limited effects was that the training was basically an acute care protocol, containing only a few, rather isolated recommendations made from a chronic care perspective (Tiemens 1999). It was clear that for treatment to be more effective for recurrent and persistent cases, new concepts and approaches were needed. These should not only address the potentially recurrent or persistent nature of depression, but also take account of the specific aspects of the setting in which this treatment is usually delivered. These contextual aspects of primary care practice have been described as “competing

demands" (Klinkmann 1997) and involve the complex ecosystem of patient, clinician and healthcare system.

Treat depression as a chronic illness?

As it became clear that depression is often a disorder that remits, it also became clear that this prognosis should have implications for the contents and goals of treatment. Next to remission as a treatment target, these should include maintaining this recovery over time, and thus the prevention of relapse and recurrence.

The similarities in underlying principles of management of chronic recurring somatic conditions, such as diabetes, were noticed. An essential element in learning to live with a chronic physical illness is self-care. Treatment effects for many of these illnesses partly rely on self care skills and the motivation to collaborate with health care providers , including the PCP. Active participation in one's healthcare can improve health (Holman & Lorig 2000; Lorig 2003). Von Korff and coworkers (1997) identified the following elements of healthcare that could enhance collaborative management of chronic illness and patient outcomes:

1: collaborative problem definition, in which the perspectives of patient and provider on the problem are discussed and harmonized;

2: targeting, goal setting and planning , in which patients and providers focus on a specific problem, set realistic goals and develop an action plan for attaining these objectives in the context of patients preferences and readiness;

3: creation of a continuum of self-management training and support services, in which patients have access to services that teach them skills needed to carry out medical regimens, guide health care behavior changes and provide emotional support;

4: active and sustained follow-up, in which patients are contacted at specified intervals to monitor their health status, identify possible complications and check and reinforce progress in implementing the care plan.

One of the aims of the research described in this thesis was to find out whether this model could be successfully applied to the treatment of depression in primary care. At the time of developing the Seattle intervention from which our DRP-Program was derived, no such comprehensive management program existed.

Design and format of the DRP-Program

The main intervention was designed as a primary care based psycho-educational self-management intervention in which acute treatment and the prevention of depression relapse and recurrences were integrated. Core elements included patient education, three 1,5 hour face to face visits with a prevention specialist and active, provider-initiated regular follow-up care, consisting of systematic monitoring of depressive symptoms and treatment adherence by 12 telephone and mail contacts over the ensuing 3 years. All enhanced care patients received this structured form of follow-up care, in which monitoring took place on the basis of the patients' personal prevention plans that contained specific information on symptoms and warning signs that might identify relapse or recurrence in an early stage; a variety of coping and self management strategies in dealing with depression, including (social) reactivation; an emergency plan (what to do when depression returns); if applicable, a medication plan was also included. In each follow-up contact , prevention specialist and patients discussed the present state on the basis of patient's self-registration, and decided whether the preventative measures in the plan needed to be actualized or revised. An important goal of these regular continuation contacts was to reinforce the motivation of patients to comply with their prevention plan. In addition, regular contacts with the PCPs and care was taken to communicate with the patients own PCP whenever deemed necessary, emphasizing potential benefits from our approach for routine depression management in primary care.

This enhanced care program was tested in a randomized controlled trial, contrasting four treatment conditions including usual care.

The trial

Over a period of almost five years , fifty-five PCPs referred patients who they considered to be depressed. A total of 267 patients (67% of those referred) were included and randomly assigned to care as usual (CAU; n = 72) or to enhanced care (n = 195), which consisted of the DRP-Program either by itself (n= 112) or in combination with a psychiatric consultation (n = 39) or brief cognitive behavioral therapy (n = 44).

The included group of patients was diverse, both socio-economically and clinical. Randomization was successful; there were no significant differences between patients in the four conditions. Overall, 67% of participants suffered from recurrent major depression and 36% had had more than three previous episodes. The mean age of first onset was early thirties.

Response to the three-monthly study assessments ranged from 75% to almost 90%; on average, non-response per follow-up assessment was around 20% . The large majority (85%) participated at the final assessment 3 years after study inclusion. Loss to follow-up was not associated with baseline clinical or socio-demographic characteristics.

Summary of main findings as presented in this thesis

The DRP-program was well received by the large majority of patients assigned to this treatment. Adherence to all scheduled sessions and follow-up telephone contacts was high for DRP and PC+DRP patients, although significantly lower in CBT+DRP patients. Patient evaluations of enhanced care were generally positive. The conclusion is that the DRP-program proved to be both feasible and appreciated by most patients.

However, clinical effects were disappointing. Short term outcomes showed that 67% of all patients had recovered after six months, irrespective of treatment condition. On the longer run, nearly all patients remitted from the index-episode at some point, but only one-third did not relapse or suffer from a recurrence during the 3-year follow-up. Depression outcomes were largely similar for all patients, with no statistically significant differences on most outcome measures between patients in the four conditions. The only exception was the

BDI severity measure, that showed that over time enhanced care patients assigned to the combinations with PC and CBT fared slightly better than those receiving the basic DRP or CAU.

To study cost effectiveness, an economic evaluation from a societal perspective was performed, for which costs and health outcomes were registered during the full 36 months period. Proportion of depression-free time was used as the primary outcome measure in the cost-effectiveness analysis. Main analyses showed that the DRP-intervention was not cost-effective in comparison with CAU. For the combinations with PC and CBT , health outcomes were slightly better than for DRP alone, but differences with CAU were only modest while costs were higher.

Conclusion

Enhancement of PCP treatment for depression with the DRP-Program had no excess benefit over usual care. Thus , findings provide no support for the implementation of this form of enhanced care with a continuation phase in the current healthcare system.

Results in the light of evidence from other studies

The DRP–Program was developed as a primary care based psycho-educational intervention, characterized by active and sustained support of patients in their self-management of depression. Relapse and recurrence prevention strategies were integrated into treatment of the acute phase from the start, which is a new strategy for primary care and that has hardly been tested. Another key feature is that the format of the DRP was the same for each patient and independent of the present state of depression, although its contents were tailored to the individual patient and his or her depression history. Also, care was delivered in a collaboration between the patients' PCP and a specially trained prevention specialist who was responsible for disease management tasks such as monitoring of patients‘ progress. From the patient perspective, the intervention probably also improved access to specialist care, although this was not explicitly intended.

Interestingly, results of the in many respects comparable Relapse Prevention Program developed in Seattle by Katon and associates (2001; Ludman *et al.* 2000, 2003) were largely the same : no evidence was found for additional protective effects of this intervention over usual care. The main difference with our study concerns the target group, which in the Seattle-trial consisted of patients who had recently recovered from MD but were considered to be at high risk for relapse because of their depression history (recurrent episodes or dysthymia). In addition, their intervention included a much stronger focus on the continued use of antidepressants and the continuation phase was of shorter duration. Twelve month FU findings showed that , although intervention patients experienced less depressive symptoms across FU, they did not experience fewer episodes of depression. Overall relapse rates over 1 year were 35% and similar between intervention and usual care control patients.

In a related trial, Katon and coworkers (1999, 2002) evaluated an intervention targeted at patients with persistent symptoms of depression, despite being treated with antidepressants for about 2 months. Patients in the intervention group received psycho-education and 2 or 3 extra visits by a psychiatrist collaborating with the PCP. Although after six months more intervention than usual care patients had recovered, only patients with moderate symptom severity at study entry were found to benefit from this shared care and sustained benefit during the next 2 years was also found only in these relatively mild cases. Unfortunately, no data on relapse or recurrence has been published as yet.

Another study into the effects of an intervention targeted at specific high-risk patients was carried out by Rost and associates (2002). Key element was continued care management by practice nurses for patients who continued to report high numbers of depressive symptoms after six months of treatment. Thus, the intervention was matched to the level of symptom persistence. Nurse care managers provided an average of 7 telephone contacts per patient during the continuing intervention. This strategy was more effective than usual care since after 2 years, significantly higher remission rates were shown for the intervention patients.

Relapse and recurrence prevention strategies in other care settings

Although in the outpatient setting issues concerning the bleak long-term prognosis of major depression and what this entails for treatment have already been evident longer, targeted psychological interventions have only been studied fairly recently. Traditionally, much research in this setting concerns pharmacological treatment , from which there is evidence that continued AD use in high risk patients is effective in reducing relapse/recurrence rates (Melfi et al. 1998; Geddes et al. 2003) . However, information on necessary length of treatment is still needed and compliance with the prescribed medication remains an issue. Moreover, beneficial effects of antidepressants disappear once the medication is discontinued. Available studies show that many patients prefer psychotherapy over AD, not only because they fear that ADs are addictive but moreover, that medication will not be helpful in addressing the underlying problems of their depression (Schaik et al. 2004).

The dominant psychotherapy that is investigated in trials for it's protective effects, is CBT - either targeted at persistent symptoms after AD treatment or at patients with recurrent depression. Also, new therapies have been developed that often integrate elements of several other therapies , such as the cognitive behavioral-analysis system of psychotherapy (CBASP; McCullough 2000) and mindfulness-based cognitive therapy (MBCT; Segal *et al.* 2002).

Promising findings from these studies demonstrate that a targeted strategy is effective on the longer run with outpatients. For example, Paykel and Scott (Paykel et al. 1999; Scott et al. 2000) found lower relapse rates in outpatients who had previously recovered with AD but continued to suffer from residual symptoms, for which they then received CBT. Included patients were randomized to either standard clinical management alone (regular meetings with a psychiatrist) or in combination with CBT. During a period of 17 months , fewer CBT than usual care patients suffered a relapse . Recently, results of an extended follow-up of this patient sample were published (Paykel et al. 2005) showing that CBT had delayed recurrences over a 6 year-period. Nonetheless, no significant differences in total recurrence rates were found : 60 to 65% of all patients had experienced one or more

recurrence. Another example of a targeted outpatient study, in this case focusing on maintenance treatment, is reported by Klein and co-workers (2004). Remitted outpatients with various chronic forms of depression were assigned to (monthly) maintenance CBASP-sessions or to assessment only, without any formal treatment. Over one year, recurrence rates were significantly lower for the intervention patients.

Effectiveness of relapse and recurrence prevention strategies have in recent years also been studied in convenience samples, often consisting of a mix of individuals recruited through media advertisements, in primary care practices and / or outpatient psychiatric centers. Again, CBT is often the treatment of choice. A recent example is the RCT conducted by Ma and Teasdale (2004), which examined 1-year protective effects of a novel form of group CT called mindfulness-based cognitive therapy (MBCT) in individuals with a history of recurrent MD. MBCT is described as a skills-training program that integrates components of traditional CBT and a stress reduction program. Over a period of 14 months this resulted in lower relapse/recurrence rates for the intervention patients, with the strongest effects found in those with three or more previous episodes. A similar link with depression history was found in a recent study in the Netherlands by Bockting and coworkers (2005) . Patients in this study, who were in remission at study entry, were assigned to either group CT or assessment only and followed up for 2 years. Main findings show that the intervention was effective in reducing relapse/recurrence, but only in patients with five or more previous episodes. One should also keep in mind that for the control group, treatment as usual in this trial could also mean no treatment.

Thus, putting the main findings of our trial in a broader context, the conclusion is that there is a lack of primary care studies evaluating not only which treatment alleviates the current episode of major depression but also protects best against relapse and recurrence. The few studies that have been performed, including the research that is the subject of this thesis, provide indications that a more pro-active risk-reduction approach either focusing on specific factors (such as residual symptoms) or at enhancing protective aspects (such as

self-care skills) results in more favorable course and long-term outcome of depression for high risk patients. However, at present evidence for this is still limited.

Studies involving targeted approaches in outpatient or convenience samples show that (individual and group) psychotherapy can have protective effects on the longer run. These results challenge the assumption that continued AD use is the only tool to achieve better long-term outcome. Depression history and especially the number of previous episodes emerge as predictors of treatment effects. These could be used to guide decisions about the patients for whom such a targeted risk-prevention strategy is indicated, and about the treatment setting that is most suitable for providing such care.

Finally, findings underscore the variation that exists in course patterns and depression outcome. Not all depressions are recurrent or persistent in nature but those that are, have proven to be difficult to modify. Thus, for a substantial subgroup of patients recurrence may continue to be the rule, rather than the exception.

Explanation and implications of findings

The ineffectiveness of the DRP-program might be due to a number of facts and circumstances. Several explanations will be considered.

1: The dynamics and quality of usual care practice

There was a long time lag between the design of the study (with the grant application) and the end of data collection. Primary care practice in the Netherlands changed in the meantime. Our findings demonstrate that ‘usual’ primary care practice for identified patients with major depression now generally includes the prescription of antidepressants (on average, participants used an AD during 44% of the total follow-up time), regular follow-up visits with the PCP (most kept in touch) and frequent referral to specialized mental health agencies (around 38% received additional mental healthcare at some point during the study period). Consequently, there was less contrast than expected between the care provided in

the experimental interventions and the usual care from the involved PCPs.

Data from national studies show that PCPs are now responsible for the majority of AD prescriptions and also that the number of these prescriptions has increased substantially year by year (Marwijk *et al.* 2001, CVZ 2003). Previous fears about possible pharmacological under treatment of MD in primary care now seem outdated. Furthermore, despite specific efforts to support and strengthen the role of PCPs in the treatment of depression (by training, consultation, shared or collaborative care initiatives et cetera; Meijer *et al.* 2003 ; Laurant *et al.* 2004) , referral rates to private practice psychologists and specialized outpatient settings have continued to rise so that the de facto effect of these efforts seems to be a shift away from primary care. Given that Dutch general practice used to be characterized by it's generalist and contextual approach (Weel 2001; De Maeseneer *et al*. 2003, 2004) which was also applied in treating common mental disorders, this movement towards specialized mental healthcare may point at a certain erosion of the traditional gatekeeper role of PCPs in the Dutch healthcare system (Hutschemaekers *et al.* 2006).

2: Factors related to the enhanced care program

The DRP-program and its combinations with either a psychiatric consultation or brief CBT may simply not have been powerful enough to add to the effects already achieved by usual care, as discussed in the previous section. Also, the combination of low intensity and extended duration, in addition to a possibility to sensitize vulnerable patients (with the majority of study participants suffering from recurrent depression) may be of relevance. We found hardly any effects of treatment on self-efficacy beliefs, that is the perceived self-confidence in own abilities to effectively recognize and manage depressive symptoms and future episodes.

There is also a possibility that for some patients the continued focus on (recurrence of) depression may even have had a negative impact on their feelings of self efficacy. Not all patients may respond well to the prolonged and systematic monitoring of (residual) depressive symptoms that was a core element of the enhanced care. There are indications

that low-intensity long-lasting monitoring contacts may have sensitising effects on patients (Frasure-Smith *et al.* 1997; Kaasenbrood *et al.* 2004). It is conceivable that for some patients this may have increased awareness of their vulnerability and their feelings of incompetence in dealing with this susceptibility.

In addition, the monitoring aspect may inadvertively have contributed to a response style that negatively interfered with the patients' appraisal of their self-efficacy. Nolen-Hoeksema (1987) was the first to suggest that a ruminative coping style, involving a strong focus on self-awareness and a tendency to over-analyze problem situations and emotions, might intensify selective negative thinking to the relative neglect of active problem solving. The continued emphasis on the necessity to monitor depressive symptomatology may for some have triggered an inward focus that magnified their self-criticism and a passive response.

In the same line of reasoning, one might argue that an inherent contradiction was introduced in the DRP. While on the one hand the importance of self management as a crucial element in (re)gaining control over depression was continuously stressed, on the other hand all enhanced care patients were at the same time provided no less than three years of regular, provider-initiated contacts with depression specialists, which was offered irrespective of their depression status and expressed need. We can only speculate about the way these longitudinal contacts were perceived, but the possibility that for some this in fact undermined their coping style and self-efficacy beliefs cannot be ruled out.

3: Factors related to the study design

By leaving initial patient selection entirely in the hands of the participating PCPs and conducting this trial in the real world of general practice, we may have reduced the DRP-intervention's potential for success. Patient inclusion criteria were relatively broad, permitting most patients referred by their PCP to enter the trial. Unlike many other studies, we did not exclude depressed patients on the basis of their depression history, use of antidepressants, co morbid psychopathology or problematic alcohol use. Moreover, we choose not to target

the intervention to a specific subgroup of depressed patients but instead to provide the DRP to all those assigned to enhanced care, irrespective of their personal depression history, severity and phase of the present episode at study entry. The fact that almost two-third of included patients were found to suffer from recurrent major depression, with 37% of them having experienced even more than three previous major episodes at study-entry, suggests that PCPs mainly referred the more vulnerable or difficult to treat patients.

As to PCPs, the selection of participating PCP's was primarily guided by pragmatic principles and circumstances, such as the location of the practice, the number of physicians sharing a (group) practice and participation in earlier studies by the department. Initially, based on prevalence figures and prior research, we had calculated that 35 PCPs over a period of about 15 months would be sufficient for the recruitment of the required number of patients. However, although we made every effort to minimize the tasks involved in the study for the PCP's and tried to assure that participation would require minimal effort from them, *"(participation) inevitably demands a degree of commitment from GPs, both intellectually, to the premise that the clinical effectiveness (of the intervention) is unproven, and, practically, to recruiting patients and providing 'normal GP care' to those allocated to that group'* (Fairhurst & Dowrick 1996; p. 77). There were certainly periods where the slow recruitment process endangered the study's progress and as a consequence, recruitment not only took longer but also required the participation of more PCPs than had been foreseen. This may in turn also have influenced one of the core elements of the DRP-program, i.e. the collaboration between prevention specialists and PCPs. The possibility of building up such a relationship may have been negatively affected by the long inclusion period and the variation in actual patient numbers per PCP.

As far as we know, this is the first pragmatic type randomised trial targeting improvement of long-term depression outcome in primary care patients by focusing on enhancing self management and support of self-care skills taking place in the primary care setting in the Netherlands. Although these types of trials are needed to measure the effects

that treatment produces in routine practice and to enhance the empirical credibility of outcome research and evidence-based treatment, they are not easy to implement. Other researchers have also reported difficulties performing RCTs on effectiveness of treatments for common mental disorders in a primary care context, especially regarding patient enrollment. Unease with the process of randomization, experienced by the referring care providers as compromising the more traditional doctor-patient relationship, has been identified as one of the underlying problems (Hunt *et al.* 2001). Although implementation of the RCT was complicated, it nevertheless resulted in a wealth of data on the effects of the studied interventions in primary care settings and with patients that closely resemble 'real life practice'.

Future research

Ultimately, the goal of the interventions evaluated in this study was to improve long-term depression outcome in primary care patients. Given the findings, there is hardly a reason to argue that a Depression Recurrence Prevention Program such as this should be implemented. Nevertheless, we should also be careful not to throw the baby out with the bathwater. Several issues deserve special attention.

First, in our view it is too early to give up on the concept of self management in depression care. The DRP comprised an approach in which acquisition of coping skills and self-efficacy were considered crucial elements in (re)gaining control over depression and the prevention of future episodes. The importance of self management was stressed in the DRP-materials and in all contacts with the prevention specialists, and there was a strong emphasis on the patient's own responsibility and on the necessity of taking an active role. However, we may have introduced an inherent contradiction in the way the enhanced care was executed, which also neglected diversity between individual patients ('one size fits all' approach). Future interventions should take this diversity into account and bring the emphasis on the patient's own responsibility and the necessity of taking an active role a step further, for

example by leaving the initiative for continued contacts in the hands of the patient instead of the provider.

Second, we are not unique in finding treatment by the PCP to be equally or even more effective than the experimental interventions. On the contrary, all recent studies that have been conducted on this subject in the Netherlands have more or less come to the same conclusion (see Bosmans 2006). Given that treatment effects are always the result of several ingredients, both specific and non-specific, more interest should be invested in answering the question which elements of usual care for depression contribute to it's effectiveness. What are the strengths of the approach used by primary care physicians?

Finally, major depression is a common disorder with a clinical picture characterised by different course patterns and a variety of subtypes. In order for treatment to be more successful on the longer run, more differentiation is required between categories of depression and between the ways in which patients experience and deal with their distress. The current notion of MD may have become too much of a container concept, obscuring the reality instead of offering clarification. Parker (2005) has argued that the present concept of major depression had led to sterility in depression research and clinical practice. According to Fava (2006) "*we seem to be very concerned as to whether a treatment is effective, but we do not seem to care much as to whom "(p. 203)*. It has become the convention to neglect the heterogeneity that exists among patients. However, the reviewed outcome findings show that often different results are found for different subgroups of depressed patients, particularly in terms of severity and duration, that have meaning for treatment. For example, although the rate of AD prescriptions continues to rise, recent reviews show that there is insufficient evidence for the effectiveness of antidepressants in the treatment of mild to moderate depression (Ackermann *et al.* 2002), for which "watchful waiting" is recommended as the initial treatment choice (Hermens *et al.* 2005). To achieve a real improvement in long-term outcome of depression in primary care, future research should search for new directions that include a comprehensive view on the generalist and contextual approach that characterizes this treatment setting.