SUMMARY AND GENERAL DISCUSSION
Depression is common in MS patients and has a considerable impact on quality of life. However, it often remains undiagnosed and undertreated. Early recognition should be improved, and optimal treatment approaches further investigated. The general aims of this thesis were therefore to gain more insight in MS-related depression and its treatment in order to improve quality of care for depressed MS patients. More specifically, we aimed to calculate the prevalence rate of depression in MS, and to investigate the clinical symptom profile of MS-related major depressive disorder (MDD). Further, computer-based screening and treatment possibilities were examined, which mainly concerned investigation of the feasibility and effectiveness of an Internet-based CBT intervention for MS patients suffering from clinically relevant depressive symptoms.

Here, results from the previous chapters will be summarized. In addition, main findings are discussed in relation to the existing literature, and clinical implications and future perspectives will be addressed.

**SUMMARY OF THE MAIN FINDINGS**

In Chapter 2, a systematic review and meta-analysis with a targeted analysis of studies on the prevalence of depression and anxiety in MS was presented. In total, 58 articles with a total sample size of 87,756 MS patients were selected. Pooled mean prevalence was 30.5% (95%CI=26.3%–35.1%) for depression and 22.1% (95%CI=15.2%–31.0%) for anxiety. The weighted prevalence of self-reported clinically significant depressive or anxiety symptoms was higher (35% and 34%) compared with disorders (21%, \( p=.001 \) and 10%, \( p<.001 \)). Prevalence rate of a depressive disorder was relatively lower in studies from Europe compared with studies performed in Northern America, or in other continents. Anxiety disorder was more prevalent in community-based samples compared with samples from clinical settings. No differences in prevalence estimate were observed as a function of study quality, assessment method and prevalence period. However, despite our efforts to adequately enhance quality and decrease study differences, heterogeneity remained considerably high and subgroup analyses did not reveal the sources of heterogeneity making it difficult to predict which study results in which prevalence. Results emphasize the importance to agree on how to define depression and anxiety and how to recruit patients in order to improve prevalence estimates and to clarify their relation to specific patient related factors.

In Chapter 3 we aimed to investigate the clinical profile of MS-related depression. Results showed only subtle differences in the symptom profile of moderate to severe MDD in MS patients compared with the profile of MDD in patients without MS. The symptom ‘future pessimism’ was more common in MS patients (OR=1.62, 95%CI=1.02–2.59). ‘Diminished capacity for pleasure/enjoyment’ (OR=0.44, 95%CI=0.24–0.78), ‘increased appetite’ (OR=0.40, 95%CI=0.19–0.85), ‘arousal symptoms’ (OR=0.49, 95%CI=0.28–0.84) and ‘panic/phobic symptoms’ (OR=0.49, 95%CI=0.29–0.84) were less common in MS patients. Twenty-five symptoms (83%) out of 30, including depression’s core symptoms (sadness and loss of interest), were not differentially associated with MS and no differences existed for the symptom clusters (cognitive, somatic, melancholic,
atypical). MDD in MS was characterized by older age of onset ($p<.001$), and fewer comorbid anxiety disorders (37% versus 72%, $p<.001$).

In Chapter 4, it was shown that a computer-based screening is a feasible way to detect psychological distress in MS-patients in clinical care, and could support MS nurses in their work. Results demonstrated that most patients considered the screening meaningful ($n=35/40, 88\%$) and the system easily usable ($n=37/40, 93\%$). Average completion time of the screening was below 8 minutes. Many patients ($n=35/40, 88\%$) had elevated distress levels, of whom the majority was referred to psychosocial care or rehabilitation. The MS nurse was satisfied with the quality and content of the screening. The screening facilitated her work and helped her to more specifically focus on actual problems to be addressed, including unmentioned problems that could be overlooked easily. A randomized controlled trial with longer follow-up should test whether routine screening, in comparison to routine care, is effective in detecting distress (as depression), and results in appropriate referrals, adequate treatments, and improved outcomes.

The feasibility pilot described in Chapter 5 showed that an adjusted version of guided Internet-based CBT is a feasible treatment for depressive symptoms in MS patients. Forty-four MS patients with mild to severe depressive symptoms followed an Internet-based problem-solving treatment (IPST). More than half of the patients (52%) completed the intervention and the majority (85%) reported satisfaction with the intervention, which is comparable with similar studies [1],[2]. After the intervention, depressive symptoms had significantly decreased (BDI-II change: mean=-3.9, $p=.01$, $d=0.51$ in intention-to-treat analysis; BDI-II change: mean=-9.0, $p<.001$, $d=1.50$ in completers analysis). Preliminary findings indicate that guided IPST can reduce depressive symptoms in MS patients, especially in those who report more depressive symptoms at baseline and those who complete the intervention. The results of this pilot study are encouraging and supported the initiation of a randomized controlled trial to investigate the effectiveness of IPST for depressed MS patients.

In Chapter 6, the study protocol of the intended randomized controlled trial (RCT) to investigate effectiveness of IPST for depressive symptoms in MS was described.

Finally, results of the RCT on effectiveness of a guided IPST for depressive symptoms in MS patients were presented in Chapter 7. In total, 171 patients were randomized to IPST ($n=85$) or a wait list control ($n=86$). Early follow-up (T1: within a week after the intervention) was completed by 152 (89%) MS patients, and 4-months follow-up (T2) by 131 (77%) patients. The IPST group and wait list control both showed a large significant improvement in depressive symptoms but no significant difference between groups was found at T1 ($d=0.23$, 95%CI=−0.17–0.63, $p=.259$) or at T2 ($d=0.01$, 95%CI=−0.44–0.46, $p=.953$). Also no significant difference was found when comparing IPST completers ($n=57, 3$ or more modules completed) with the wait list control at T1 ($d=0.33$, 95%CI=−0.11–0.77, $p=.136$) or at T2 ($d=0.05$, 95%CI=−0.43–0.53, $p=.828$).

Additional telephone support (text messages) did not increase compliance rate of the intervention (3 or more modules completed), compared with no telephone support (65% versus 69%, $p=.703$). There was a significant improvement in depressive symptoms of 66% ($n=49/74$) in the IPST group and 53% ($n=41/78$) in the wait list control at T1 ($p=.087$) and 63% ($n=40/64$) versus
60% \( (n=40/67) \) at T2 \( (p=.743) \). In the IPST group 24% \( (n=18/74) \) was recovered from depressive symptoms at T1 versus 18% \( (n=14/78) \) in the wait list control which did not significantly differed \( (p=.335) \). At T2, 28% of patients \( (n=18/64) \) was recovered in the IPST group versus 26% \( (n=17/67) \) in the wait list control \( (p=.722) \). Results showed there is no indication that IPST for MS patients with moderate or severe depressive symptoms is more effective in reducing depressive symptoms compared to a waiting list.

**DISCUSSION OF THE MAIN FINDINGS**

**Prevalence of depression in MS**
In this thesis we showed a 31% prevalence of depression in MS. In line with what one would expect \[3\], we found that the prevalence of clinically significant depressive symptoms was elevated (35%) compared with the prevalence of depressive disorder (21%). These results add to previously performed reviews reporting high depression rates in MS \[4\]–\[6\] and suggest depression percentages are elevated in MS compared with rates in the general population \[7\]–\[11\]. This is supported by the first population-based study comparing depressed MS patients with concurrent controls that was recently published \[12\]. Our results also correspond with the general finding of increased risk of depression when a chronic (neurological) illness is present \[3\],\[13\] and approach prevalence estimates of reviews on depression in other chronic medical illnesses like Parkinson’s disease and Diabetes \[14\],\[15\]. Seemingly, the presence of a disease somehow results in elevated depression comorbidity. However, there is considerable spread in all these estimates due to different study designs which leads to uncertainty about the actual prevalence of depression.

**Chapter 2 of this thesis** demonstrated that in spite of scrutiny of a number of subgroups, which seemed adequately selected and well-defined, heterogeneity persisted in the depression estimates hampering solid conclusions for the MS population. Explaining heterogeneity and improving prevalence estimates may help to better understand the prevalence of depression in MS and assist clinicians to identify MS patients who are at high risk for depression and require more extensive examination. Explanations for high heterogeneity could be related to methodological limitations of the studies in the existing literature and a number of (untested) factors that varied across these studies. In this context, one could think of differences in methods of depression assessment and of varying patient characteristics. These two issues will be discussed in more detail below.

**Assessment of depression**
High heterogeneity could be related to variation in depression definition and assessment across studies. MS researchers often do not make the distinction between depression as a symptom or depression as a syndrome. In addition, studies on comorbidity of depressive disorder use many different data sources as medical record review, self-report, interview and administration data.
Information on assessment method is frequently missing in studies, especially when data are extracted from medical records and insurance databases [16].

The most widely used approach by psychiatrists to establish a depressive disorder is the standardised interview which is based on the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) [17] and on the World Health Organization's International Statistical Classification of Diseases and Related Health Problems (ICD-10) [18]. The interviews are performed by trained interviewers. They are valid, use rigorously defined criteria for depressive disorders, and form the bulk of the clinical research on depressive disorders [19]. In our systematic review, only five studies of the included studies used (semi) structured interviews to establish DSM criteria, of which a mere two were rated with good quality. More high quality studies with large population-based samples using diagnostic interviews for the MS population are therefore encouraged [20]. As these studies may require considerable effort and time, it was recently suggested to consider administrative databases with ICD codes to assess depression in large population-based studies. However, clinical details are typically lacking in these databases that are mainly collected for health system management and also their validity for research must still be assessed [21],[22].

A self-report instrument is typically used to screen a large population of patients. It cannot be used to make a formal diagnosis of depression and tend to report higher rates compared with standardised interviews [3], which was also supported by our findings (Chapter 2). Still, self-report scales could be used to quickly capture a range of depressive symptoms in MS, or as the first stage of a two-phase survey which also includes a diagnostic interview to determine actual cases of depressive disorder in MS [3],[23]. Variation in and the appropriateness of self-report scales and cut-off scores to assess clinically significant symptoms may however have further contributed to high heterogeneity in prevalence rates presented in Chapter 2. Applied self-report scales were not always validated for the MS population and often contained a number of questions related to physical symptoms of MS such as fatigue, sleep problems, and pain. Including these items could increase the score simply because a physical illness is present [5].

The American Academy of Neurology Guidelines advised the Beck Depression Inventory (BDI) to detect depression in MS [24]. This self-report instrument is validated for the MS population and most widely used in MS research. Since sufficient evidence for other existing instruments to measure depression in MS was lacking [24], recent studies by Patten et al. (2015) [25] and Fischer et al. (2015) [26] validated various self-report depression scales against clinical diagnoses of MDD in MS patients and provided appropriate cut-offs. The Center for Epidemiologic Studies Depression scale (CES-D) [27], Hospital Anxiety and Depression Scale (HADS) [28], Patient Health Questionnaire (PHQ-9) [29], Inventory of Depressive Symptoms (IDS-SR) [30] and BDI-II [31],[32] demonstrated good accuracy, but all have their own advantages and disadvantages [25],[26]. The BDI is mostly used, but is copyrighted. The PHQ and IDS-SR are widely used instruments, freely available and translated in many languages, making them particular interesting to screen and quantify depression in MS. Brevity of the PHQ is suggested to enhance the feasibility of its use [25]. The IDS-SR covers all DSM-IV criteria, and offers a self-rated validated 16-item short version. The
IDS-SR is increasingly used, and applied in large longitudinal (no MS) cohort studies [33]. Subscales for cognitive and somatic symptoms can be constructed [34] and algorithms for identification of melancholic [35], or atypical depression [36] are available. Atypical and melancholic subtypes of MS-related depression were lately suggested to be relevant to elucidate biological substrates of depression in MS [26],[37].

In addition to the studies above, findings from Chapter 3 support the idea that different instruments to identify depression that are used in depressed patients without MS could be used to assess depression in MS, as the depressive symptom profile does not seem to differ substantially between depressed patients with and without MS. It may be time to move towards a consistent approach to identify and measure psychiatric comorbidity in MS to improve comparability of prevalence rates [4],[24].

**Patient characteristics**

Heterogeneity may be also hidden in specific patient related factors such as age, gender, MS course, duration, and severity. However, studies often lack adequate information about these factors and/or are mixed in their conclusions regarding presence of depression and these clinical and disease characteristics [5],[38]. For example, there is evidence suggesting prevalence of depression to be higher among patients with progressive forms of MS compared with those with relapsing remitting MS (RRMS) independently of disease duration and physical disability [39]. Primary progressive (PP) MS is possibly more distressing for patients, also because it is considered a primary neurodegenerative disease with a different pathogenesis. On the contrary, other studies found that patients with PPMS had lower life time risk of MDD compared with RRMS patients, suggesting the inflammatory component of RRMS course may be associated with elevated depression [40], or found no association with disease course at all [41],[42]. Some studies found younger age, or greater extent of functional limitation to be predictive of more depressive symptoms [41],[43]. Longer [43] but also shorter [41] duration of MS were found to increase the risk for depressive symptoms. Other studies found no difference in MS duration, age or disease severity for patients with or without depression [42],[44]. Some studies indicated different prevalence rates for women and men [12],[45], but other suggested that depression is equally prevalent in both [43].

These findings may be inconsistent due to diversity of MS itself. MS is not a homogeneous and constant disease thus resulting in large variability between patients. Patients with similar MS durations could have very different disease courses, relapse rates, and cerebral and spinal involvement, each having a potentially different effect on mood. In addition, the important determinant of depression may be just as well related to the way MS patients adjust to adversity [38]. Furthermore, heterogeneity in prevalence rates of depression may be partly explained by depression-related variables that were not assessed, such as number of depressive episodes, onset, and duration. In addition, there may be MS or depression related factors we are not aware of. All these differences in case mix between studies may cause unexplained variability, and make it difficult to predict, rate and explain depression in MS. This case mix factor is however difficult to control and more extensive disease information of individual patients is required.
For now, although this may seem trivial, the first step to further clarify variation in prevalence of depression in MS would be to conduct more high quality studies with sound designs. These studies should include representative study populations and report patient related variables like age, sex, and disease-specific estimates for different geographical regions, and use common and validated methods such as the BDI, PHQ-9 or IDS-SR to assess depression in MS. In addition, measurement of key data elements such as sex, race/ethnicity, clinical course, comorbidity and MS diagnostic criteria and outcome measures must be harmonized to facilitate pooling and comparison of study findings [21]. Next to consistent subgroup analyses, analyses with a more multivariate approach could then be used to examine (more) sources of heterogeneity in the prevalence of depression in MS taking into account different patient (MS) related factors [46]. As lack of access to individual patient data is a common limitation, researchers may consider proceeding to individual patient meta-analyses.

The concept of depression in MS
Research on the clinical profile of depression in MS is still scarce. Earlier publications have been inconsistent, and were generally based on small samples and self-reported depression [47],[48]. In Chapter 3 of this thesis we therefore compared the depressive symptom profile of moderate to severe MDD in patients with MS with moderate to severe MDD in patients without MS. It appeared that MDD in the context of MS has a similar symptom presentation and refers to the same concept as MDD where no underlying medical illness is present. MDD in MS patients was, however, characterised by later onset and less comorbidity and anxiety distress which may suggest a purer form of MDD. Our results replicate recent findings of a similar clinical phenotype of depression in patients with and without MS [47] and are in line with literature that showed similar symptom profiles in other depressed groups consisting of immigrants [49] or diabetes patients [50]. Apparently, a clinical depression is phenomenologically robust and remains diagnostically valid among psychiatric as well as medical samples.

MS-related pathways
Although the symptom profile of MDD patients with MS is similar to MDD patients without MS, it is unknown whether underlying similar aetiological mechanism are involved. Knowledge on the aetiology of MDD is limited and complex, but diverse gene-environment interactions, endocrine, immunologic and metabolic mediators, and cellular, molecular and epigenetic forms of plasticity are suggested to play a role [51]. In MS, MDD pathophysiology might be overlapping with that of many psychiatric patients, as damage to the hippocampus, HPA-hyperactivity and chronic neuroinflammation are present in both groups [51]–[54]. Since most of these studies are cross-sectional, more longitudinal research on the behavioural, genetic and biological (e.g. neurodegeneration, enhanced peripheral immune activation) factors influencing MS and depression could improve our understanding of the pathways involved. New technologies such as magnetic resonance imaging may help to explain neuroanatomic links between depression and changes in the central nervous system due to MS [21]. Results from Chapter 3 suggest MDD in MS may be a purer form of MDD which might be due to the presence of a brain disease with
specific MS-related brain abnormalities related to MDD. In that case, examining neurobiological correlates of MS-related MDD and other disease-related factors perhaps contributes to an increased understanding of the pathogenesis of MDD in general.

**Course of depression**

Although the symptom profile of MDD patients with MS is similar to MDD patients without MS, MS-related MDD may display a different course. MDD in patients without MS is considered an episodic disease where depressive episodes can come and go over time [55]. Although longitudinal research on depression in MS has only been performed to a limited extent, findings point towards depressive symptom rates that remain high, static and chronic over time and do not remit spontaneously [42],[56]–[58]. Clinically relevant depressive symptoms at baseline was strongly related to the risk of depression at follow-up [42] and around 2/3 of MS patients with substantial depressive symptoms at baseline were depressed at 10 year [58]. When depression in MS is more chronic, this could implicate that it is not simply a reaction to the diagnose of MS or reaction to worsening of MS as one would expect improvement over time [42]. Absence of fluctuations in depressive symptoms could reflect inflammatory dysregulations and/or damage to the central nervous system that are characteristic for MS [5],[42]. This suggestion is supported by studies on depression in the general population that found certain inflammatory dysregulations among those with more chronic forms of depression [59].

**Symptom profile and MS characteristics**

As the MS-related MDD profile is similar compared with MDD patients without MS, one may be tempted to think that MS characteristics do not have any effect on the presentation of depression in MS. However, the relation between disease characteristics and differences in symptom profile were not explicitly assessed. As a result we do not know whether the MDD symptom profile itself is influenced by MS characteristics and it may still differ within the MS group. Depression characteristics and phenomenology at MS onset may be different compared with characteristics later in the disease, during relapses and different cerebral involvement, or at particular stages (e.g. when RRMS changes into SPMS and MS is definitely becoming progressive). For example, SPMS patients tend to demonstrate more depressive thought such as hopelessness than RRMS patients [60]. A review revealed a more specific association between MS lesion location and affective symptoms and somatic complaints, but not with cognitive distortions [5],[61]. And abnormalities in both the limbic and endocrine system may be more closely related to affective and cognitive depressive symptoms in MS [52],[62], whereas MS-inflammatory markers showed stronger correlations with somatic symptoms [54],[62]. Various mood-related symptoms (sadness, irritability) in MS are suggested to fluctuate more over time than somatic symptoms (sleep, appetite) and evaluative symptoms (feelings of guilt and worthlessness) [63]. However, there is inconsistent evidence whether depressive symptom fluctuations correlate with disease relapse, course and physical disability [42],[57]. Replication of our findings on the MS-related symptom profile is therefore required in different MS samples (inpatients, nursery homes, clinics, general population) that vary in onset, course, and MS-disability and at different moments in time (longitudinal).
Summary and general discussion

Treatment for depression in MS

Internet-based treatment

Depression in MS is often not adequately treated. Research on mental health interventions for depressed MS patients is still in its infancy, and treatment guidelines for depression in MS do not yet exist [24], [64]. A standard easily accessible and low-intensity Internet-based problem-solving intervention (IPST) was expected to be a suitable candidate for the MS population to overcome treatment barriers. Results of the pilot study presented in Chapter 5 provided evidence for the feasibility of IPST for depressed MS patients (BDI-II ≥ 16) and a significant reduction of depressive symptoms after the intervention. Subsequently, a high-quality trial was designed (Chapter 6) and performed to investigate the effectiveness of IPST for moderate or severe depressive symptoms in MS. Results described in Chapter 7 demonstrated that MS patients treated with guided IPST showed a large decrease in depressive symptoms that sustained over four months follow-up. However, a similar improvement was observed in the wait list control, and it was concluded that a 5-week self-help IPST has no additional value to a waiting list.

The considerable decrease in depressive symptoms in the wait list control was unexpected and several explanations were suggested in Chapter 7. It was for example attributed to recruitment of highly motivated patients that are willing to address their complaints, resulting in improvement. A small degree of contact with a clinician (e.g. interview), inclusion and assessment of patients in our trial could have improved outcomes [65] and/or facilitated awareness of complaints leading to beneficial effects such as seeking help in different ways. Decreased depression symptomatology in the wait list control could also be a result of ‘regression to the mean’ as high scores are typically more likely to decrease.

There is no reason yet to conclude that ICBT cannot be a helpful (additional) intervention for the depressed MS population and overcome treatment barriers, particularly given findings of its effectiveness in two trials on ICBT for depression in MS [66], [67]. Results from these studies correspond to results found for non-Internet-based CBT for depression in MS [68], [69], and with literature on ICBT for depression in general [70]. However, as we found no indication that IPST is more effective than a waiting list, findings on ICBT for depression in MS should be considered inconsistent and more research is therefore needed. In addition, potential advantages of different or more extensive ICBT interventions should be investigated, as well as a combination of ICBT with face-to-face psychotherapy or other treatments [71]. Next to that, it should be further explored if and how this treatment should be adapted to this particular population [72], [73] and which MS patients could benefit from Internet-based intervention, in what form (guided, blended, automatic, personalized) and in what intensity. Finally, treatment adherence should have our attention as very little is still known about which patients stop treatment, at what moment in time, and under which circumstances (e.g. recovery, deterioration, not acceptable) [74].

In future research, we may need to temper our expectations of treatment outcomes, as it was recently suggested that effectiveness of psychotherapy or medication treatment for depression has been overestimated. High quality psychotherapy studies show smaller effects than was previously suggested and some reserve is therefore appropriate [75].
Chapter 8

Clinical improvement and recovery

The overall improvement in depressive symptoms in the study population of the RCT presented in Chapter 7 could have represented the natural course of depressive symptoms in MS patients. In the general population, half of depressed patients recover within three months [55]. More than half of the included MS patients demonstrated significant improvement in depressive symptoms at follow-up assessments and around 25% of this group fully recovered. This recovery percentage is relatively low and supports the aforementioned suggestion of a more chronic course of depression in MS. Still, a subgroup of depressed MS patients reached remission and many showed clinical significant improvement in depressive symptoms. It is known that people could profit from their own adequate emotional, social and medical support systems and react with resilience to major (disease) events, and show recovery after initial distress [76]. In MS, a period of grieving and depression could be considered normal given the accumulation of irreversible losses patients face [73],[77]. Accordingly, not all depressed MS patients that were included in our trial may have interpreted their depressive symptoms as a problem; meeting criteria for clinical relevant depression does not have to imply a need for formal mental health care [78]. Actively providing treatment to patients that are resilient or without a specific need for help will then lead to overtreatment and unnecessary medicalization, stressing the importance to distinguish between adaptive (negative) emotions that improve over time and persisting emotional disorders with a true need for formal mental health care.

The majority of MS patients in our trial showed persistent residual depressive symptoms and did not recover which could increase the risk of relapse and poor functional and psychosocial outcomes [79]. Non-recovery could be due to high depression severity at baseline [42], to the low intensity e-health intervention, or might have to do with the MS-related depression itself that is suggested to be static and more difficult to treat [42],[80]. Mohr et al. (2001) found that the majority of MDD patients treated with 16-week CBT, group therapy or antidepressants remained refractory to treatment and continued to meet criteria for MDD after 16 weeks of treatment [80]. In another trial, 75% of MS patients with clinical significant depressive symptoms at baseline (BDI>13) did not show recovery after a 9-week ICBT [67] which is similar to recovery findings in our pilot study (70%) [81] and the treatment arm of our trial (76%) [82]. A single (e-health) intervention might than not be sufficient for this patient group and combined treatment options need to be considered. Also one may speculate that full recovery is not realistic for many MS patients due to the presence of a chronic progressive disease where symptoms overlap and biological and psychosocial changes are continuously involved. Poor treatment response may indicate evidence of an aetiologically different subtype of depression in which inflammatory dysregulation plays an important role. Research has shown that inflammation may be associated with poor response to pharmacotherapy for depression, which in turn may contribute to a more chronic course of depression [83]. As inflammatory dysregulations are characteristic for MS patients, this patients group may not fully benefit from regular treatments. It is suggested that alternative treatments as anti-inflammatory medication or exercise may be better able to improve depression when inflammatory dysregulations are present [84]. It is therefore essential to further identify and understand non-recovery of depressed MS patients and adjust treatment accordingly [55],[85],
as well as to provide an accurate and feasible method to distinguish them from depressed MS patients that do recover over time without treatment.

Clinical implications and future perspectives
Due to the highly variable, unpredictable and chronic course of MS, patients with MS will face different challenges to physical, social and psychological well-being resulting in various needs, frequently over a period of many years [86]. Integrated approaches of patients management and formation of multidisciplinary teams in many branches of medicine have improved access to psychological care for these kind of patients [19]. However, MS research is still not extensive enough to guide recommendations about how to assess and manage depression in MS [24].

Diagnostics
In order to provide effective treatment for depression, depressed MS patients should first be identified. As the clinical profile of depression remains valid among MS patients, the signs, symptoms and also the instruments to identify depression that have been developed in mental health care can be used among MS patients. In further clinical diagnostic assessment, the patient’s current circumstances and symptoms, and biographical and family history can be further assessed by a trained clinician or psychologist. MS itself should be included in the differential diagnosis, especially in patients with atypical features of depression, who lack response to regular psychological treatment [87].

This thesis does not resolve the challenges in diagnostic evaluation of individual patients posed by the overlap between psychiatric and neurological symptoms and their different causes. It is still unclear if and in what way depression is a reaction to MS and/or integral to inflammatory and degenerative brain changes associated with MS [5]. Ways to disentangle depression from somatic illness and disability is complicated and may even come at the cost of a comprehensive attitude towards the disease. Overlapping symptoms of depression that are related to MS symptoms and pathophysiology (neurodegeneration, inflammation) may be even of extra relevance to the syndrome of depression as it occurs in MS patients [88]. Overlapping psychiatric and neurological symptoms should then not be viewed as two different comorbid entities but as inseparable lying in the grey area between psychiatry and neurology. As psychiatry and neurology are separate medical specialties it is tempting to disentangle complex brain disorders as MS and depression into marked categorizations that are based on single symptoms. Instead, dual complexities of MS and depression may require more integral diagnostics and a closer collaboration between neurologists on the one hand and psychiatrist and psychologist on the other hand in order to offer adequate interpretation and treatment selection for the psychiatric aspects of MS [89],[90]. In doing so, clinicians should assess their patients carefully and differentiate those with MS or depression as their sole problem, while remembering that there will be those who seem to have both at the same time [91].
**Treatment**

In depressed MS patients with adequate emotional, social and medical support systems, and with a lack of significant suffering or a need for treatment, depression may recover due to patients' self-reliance. For these patients, a proper balance between support in their self-reliance and their need for professional care is advised [78]. When depressive complaints are not present for long, patients may benefit from a period of watchful waiting. For the group of MS patients that experiences significant impact from their depression, and experience no improvement after a waiting period, formal care should be available. Given the proposed complexity of MS-related depression, this patient subgroup may need a more intensive multimodal treatment approach with adaptations to specific needs and characteristics of MS patients [5] to maximize effectiveness. However, we still do not know which patients will receive the greatest benefit from this approach. Standard depression guidelines should therefore be followed until more specific guidelines for depression in MS are provided taking into account MS specific conditions (inflammatory component, physical problems, cognitive impairment) and specific needs of MS patients. In addition, research should focus on interactions between patient variables, treatment modalities, and their outcomes [21].

**Individual patient monitoring**

More individual discrimination between (depressed) MS patients could provide clues for underlying mechanisms, phenomenology, prognosis, diagnosis and (tailored) treatment of depression in MS and could improve outcomes for the individual patient. It is still unknown which MS patients with a particular combination of characteristics (course, severity, duration) are at risk to develop depressive symptoms or MDD, at what moment in time and under which circumstances. When depressed, information is lacking on how the depressive symptom profile develops over time and how it is related to the disease process. Which of these patients will recover spontaneously or remain depressed, and what specific treatment should be selected?

Ecological momentary assessment (EMA) is a frequent sampling method of patients’ behaviour and subjective experience in real-word contexts [92]. EMA research may provide more information about depression determinants, individual variation over time and interplay with the environment and MS-related factors. Although practical, statistical and technical shortcomings need to be considered, this technique promises that patients can be profiled, and that subtypes of patients groups can be distinguished based on a combination of variables such as gender, age, and disease characteristics [92],[93]. The resulting, specific risk profiles could help clinicians to decide when they should be extra alert and/or intervene in particular stages of the disease process. When extended with biological information, such a method may facilitate better understanding of the interplay between depression and MS, and improve diagnostics, monitoring and enhanced (tailored) treatment selection. However, this technology is not yet widespread available, is rapidly developing and will pose new challenges and obstacles.

**Homo digitalis**

Technological developments in for example EMA, virtual reality, mobile applications (e.g. smartphones, smartwatches, Google glass), avatars, serious gaming, automatic emotion recognition
and various Internet-interventions, will have a major and probable lasting impact on the field of mental health care [94]. These technological innovations arise extremely rapidly and are often warmly welcomed due to expected financial gains. They allow the relatively easy collection of more and new data regarding patient characteristics and mental health using GPS data, social media and the registration of social, physical and online activity. This may however come at the cost of proper reflection on the ethical consequences and of a (political) debate on our relationship with technology. We risk to blindly apply and use these innovations simply because they are available. However, governments and commercial parties have access to many of these data and borders of personal and public domain will fade jeopardising privacy and personal integrity [95],[96]. Although these innovations can be of great help in detecting psychological complaints and provide (tailored) support to the patients’ needs, we should also ask ourselves to what extent we want to move towards a world in which all behaviour will be controlled by technology. When we can predict, prevent and control all our emotions and dysfunctional behaviour, depression will not necessarily be eradicated; it will then become nothing more than a bug in the technological system. We should therefore not lose sight of the aims, reasons and consequences of technology that is applied to our patients and keep on reflecting on the advantages and disadvantages of the new technological possibilities offered to us.

**Closing remarks**

The research field of comorbid depression in MS has evolved greatly in the recent years making it a very interesting and dynamic research area. This thesis contributed to the improvement of recognition and treatment of depression in MS against the background of recent technological developments. There are still many challenges ahead as comorbidity of depression and MS is complex and interacts on different levels. If research is to progress, we should expand our understanding of specific characteristics of MS-related depression, interactions between patient variables and indications for psychological interventions. This will further increase our ability to effectively improve the quality of life for patients with MS making the future at least a bit more hopeful for those affected by a somatic disease for which there is currently no cure.
REFERENCES


Summary and general discussion


