Learning to swim the endless waves: examining self-management and risk factors for (chronic) depression

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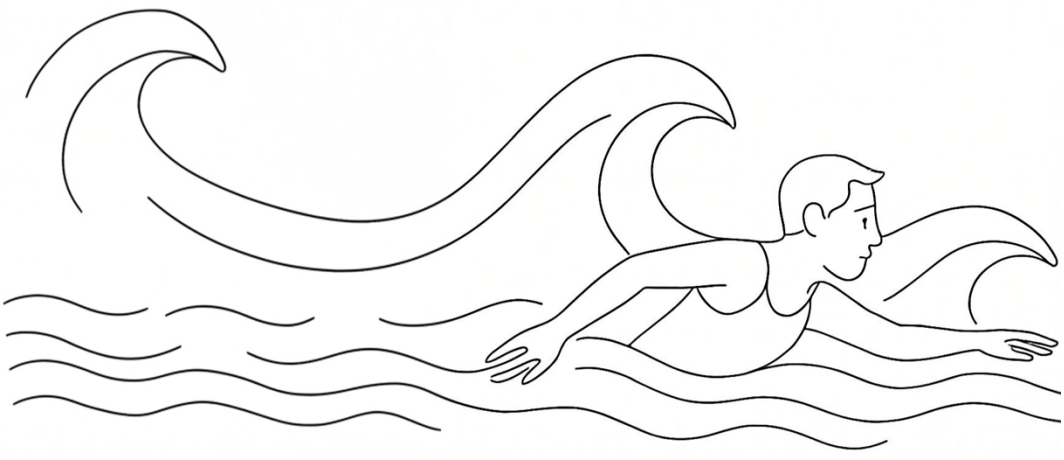

CHAPTER 9

Summary and General Discussion

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The primary focus of this dissertation was the evaluation of a self-management program as psychiatric rehabilitation in patients with (difficult-to-treat) persistent depressive disorder (PDD) and their informal caregivers. The secondary focus of this dissertation was to expand our understanding of the long-term course and risk factors of depression to improve future prognoses when treating depression. For these secondary aims, we also considered acute- and recurrent major depressive disorder (MDD).

9.1 SUMMARY

In specialized mental healthcare, there are 30-50% of patients with persistent depressive disorder (PDD) who do not sufficiently recover despite receiving several evidence-based short-term depression treatments (1-4). This group is often burdened by various psychosocial issues, which are presumed to underlie the persistence of their depressive symptoms. For this reason, multidisciplinary guidelines for depression have recommended psychiatric rehabilitation through self-management (i.e., self-management rehabilitation) (5, 6). However, prior to the start of this PhD-project in 2016, a self-management rehabilitation protocol for patients with PDD was not available in specialized mental healthcare and thus, urgently needed. In this PhD-project, we proposed using the nine-session *"Patient and Partner Education Program for All Chronic Diseases - Persistent Depressive Disorder" (PPEP4All-PDD)* as a possible solution. To evaluate this self-management program against current specialized mental healthcare for (difficult-to-treat) PDD, a mixed-methods pragmatic randomized controlled trial (RCT) was designed. The detailed *protocol and methodology of this PPEP4All study* was described in **CHAPTER 2** (7). The cost-effectiveness of PPEP4All-PDD was the primary outcome of this study, while

the clinical effectiveness and qualitative evaluation of PPEP4All-PDD were the secondary outcomes.

PDD is associated with high healthcare resource utilization (8-10) and high societal costs. This includes costs for treatment, medications, production loss, absence/sick leave, and early retirement (11-14). Thus, in **CHAPTER 3** (15), we evaluated the *cost-effectiveness of PPEP4All-PDD* compared to standard care. We found that the mean costs of PPEP4All-PDD were €232 with the patient's caregiver included, or €166 without the caregiver. There was no statistical difference in mean costs per patient for (mental) healthcare, non-healthcare, and societal costs, nor in quality-adjusted life years (QALYs), between PPEP4All-PDD and standard care. Looking at all acceptable values of willingness-to-pay for a QALY, PPEP4All-PDD was not expected to be more cost-effective than standard care. While our results are in line with previous relevant self-management/rehabilitation studies, the impact of the COVID-19 pandemic needs to be considered. The loneliness and anxiety experienced by patients, or possibly other factors, during the pandemic may have impacted our results (16). The pandemic may have also changed typical standard care and made it more difficult to end treatment or refer to primary mental healthcare, which was one important strategy in cost-savings.

In **CHAPTER 4** (17), we examined the *clinical-effectiveness of the PPEP4All-PDD* program for patients with PDD compared to standard mental healthcare. We also investigated *PPEP4All-PDD satisfaction* among patients, caregivers, and clinicians. Regarding the clinical effectiveness, we found no statistically significant difference in any clinical outcome between PPEP4All-PDD and standard care, even after adjusting for medication changes. Subgroup analysis for depressive symptoms did not show any interaction effect. Regarding

satisfaction, 78% of participants recommended PPEP4All-PDD. However, there was no difference in treatment satisfaction score between PPEP4All-PDD and standard care. Considering that PPEP4All-PDD did not result in improved clinical outcomes in relation to standard care, our qualitative feedback offered insight into how PPEP4All-PDD could be further optimized for patients with PDD. In this context, it was suggested to also offer PPEP4All-PDD earlier in depression treatment, provide biweekly sessions instead of weekly sessions, and extend the treatment period of PPEP4All. We believe that patients with PDD may require a longer duration to learn and integrate self-management practices into their daily life. In turn, it may take more time to see changes in quality of life and (mental) healthcare utilization. This may require a longer self-management treatment period.

To further understand the needs of patients with PDD and their caregivers, the results of our *qualitative interviews* were reported in **CHAPTER 5** (18). Here, patients and caregivers described their lived experience with (the patient's) chronic depression, self-management strategies, and current care needs. We conducted and analyzed individual semi-structured interviews of 28 PDD patients and 9 caregivers using Grounded Theory. Patients had 9 main themes and caregivers had 11 main themes. They shared 9 main themes, pertaining to powerlessness, patients' identity changes, shame/stigma, relationship dissatisfaction, family suffering, self-management attitudes, self-management strategies, coping support, and coping complications. In terms of lived experience, our results emphasized the profound burden of PDD on both patients and their caregivers. In terms of self-management, self-management attitudes of patients were mixed positive and negative and those of caregivers were positive. Patients who were negative either did not believe in their self-

management ability, did not know how to use self-management, or did not believe it had any positive impact. Utilized self-management strategies were generally similar for patients and caregivers. However, patients may focus more on simple, solitary activities (e.g., going for a walk) while caregivers may focus on meaningful and joyful activities to recharge energy (i.e., spending time with grandchildren). Finally, care needs of patients and caregivers focused primarily on psychoeducation and building communication skills. Caregivers also reported urgently needing support in dealing with patients' suicidal behavior. We strongly recommend that healthcare professionals encourage and facilitate the development of self-management in depressed patients early in the treatment process and involve informal caregivers, especially in the management of suicidal thoughts and plans.

Considering the high burden of disease for PDD, it is reasonable to consider the *long-term outcome of depression with comorbid anxiety*. In **CHAPTER 6** (19), we examined the 9-year course of depression with comorbid anxiety. Specifically, we looked at the disorders as syndromes (i.e., categories), in line with DSM-criteria, or overlapping symptom-trajectories (i.e., dimensions). For the syndrome/categorical approach, we used DSM depressive and anxiety diagnoses at the two-, four-, six-, and nine-year follow-up assessments of the Netherlands Study of Depression and Anxiety (NESDA) and described patient course as 'consistently recovered', 'intermittently recovered', 'intermittently recurrent', and 'consistently chronic'. For the symptom-trajectory/dimensional approach, we identified distinct classes using depressive, anxiety, fear, and worry symptom severity scores and latent class growth analysis (LCGA). Using the categorical approach, 8.5% were chronic, 32.9% were intermittently recurrent, 37.6% were intermittently recovered, and 21.0%

remained consistently recovered from any affective disorder at nine-year follow-up. Using the dimensional approach, 66.6% were chronic, 25.9% showed partial recovery, and only 7.6% had recovered. Our results show that using diagnoses alone as discrete categories to describe clinical course fails to fully capture the persistence of affective symptoms that were observed when using a dimensional approach. The enduring, fluctuating presence of subthreshold affective symptoms likely predisposes patients to relapse. The commonness of subthreshold symptoms and their adverse impact on long-term prognoses deserve continuous clinical attention in mental health care as well as further research.

Considering the high rate of relapse, we were interested in specific vulnerability factors for (recurrent) depressive episodes. In this context, we considered "cognitive reactivity" (CR), which is the (re-)activation of negative cognitive schemas during sad mood states that may trigger further depressive symptoms. In **CHAPTER 7** (20), we first investigated the *factor structure and validity of the Leiden Index of Depression Sensitivity-revised (LEIDS-R)* (21), a questionnaire that measures CR (NESDA). We conducted confirmatory factor analysis (CFA) to assess the theory-driven 34-item, 6-factor structure of the LEIDS-R. We then explored other data-driven factor structures of the LEIDS-R. The analysis showed a satisfactory model fit for the 34-item, 6-factor structure of the LEIDS-R, and the LEIDS-R showed good psychometric properties. However, due to the high inter-factor correlations, a 30-item, 5-factor model, the LEIDS-RR, was evaluated and showed better psychometric properties than the LEIDS-R. Higher scores were associated with a history of depression, especially in participants with a history of comorbid anxiety. The modified

version of the questionnaire, the LEIDS-RR, is recommended for future research.

Finally, in **CHAPTER 8** (22), we investigated the *potential of baseline CR, based on the LEIDS-RR, to predict depressive episodes* (i.e., onset or relapse) later on. Using Cox survival analysis, we examined whether CR predicts depressive episodes across a long follow-up period of nine-years, beyond subclinical depressive symptoms (SDS), neuroticism, past depressive episodes (PDE), age, sex, and education years. Next, using logistic regression, we explored the strength of CR compared to other factors, when predicting depressive episodes after two years or nine years. Our results showed that CR was a statistically significant predictor of depressive episodes after two years, with an odds-ratio of 1.04, 95% CI [1.02-1.06], and over nine years, with a multivariate-adjusted hazard ratio of 1.01, 95% CI [1.01-1.02]. However, the presence of PDE, especially ≥ 3, reduced the predictive potential of CR and SDS on relapse. In general, risk estimates for two-year and nine-year depressive relapse were high (at least 70% risk), with higher risk estimates for women than men. We concluded that CR is a moderate predictor of depressive episodes, which might be especially relevant in the prediction of first depression onset and potentially second depressive episode. For the prediction of depression relapse in patients with ≥ 3 PDE, however, depression history alone is sufficient for future prediction. Thus, relapse prevention and early treatment is crucial in the prevention of highly-recurrent/chronic depression.

9.2 GENERAL DISCUSSION

9.2.1 PPEP4All-PDD: self-management as psychiatric rehabilitation

In line with the General Introduction in Chapter 1, we now provide the answers to the main questions of our pragmatic randomized controlled study (PPEP4All-Study; Chapters 2, 3, 4, 5):

Is PPEP4All-PDD more cost-effective (i.e., lower costs in relation to improved quality of life) than standard care in secondary/specialized mental healthcare for patients with PDD and their partners/informal caregivers (i.e., caregivers)? (Chapter 3)

We expected PPEP4All-PDD to be cost-effective compared to standard care. This is because PPEP4All-PDD is brief, structured, (primarily) group-oriented, and administered by a less costly discipline: psychiatric nurses instead of psychiatrists/psychotherapists. Also, it may improve quality of life and shorten treatment duration due to its focus on functional recovery. However, despite our expectations, PPEP4All-PDD for patients with PDD and their caregivers was not cost-effective as psychiatric rehabilitation in specialized mental healthcare. While *health-care costs* appeared lower for PPEP4All-PDD than CAU, the difference between conditions was not statistically significant, p = .45. *Non-healthcare costs* appeared higher for PPEP4All-PDD than CAU, but this difference between conditions was also not statistically significant, p = .68. Total costs, thus, evened out and were similar between conditions after one year.

Comparing to past research, albeit limited, it generally showed mostly poor results for self-management rehabilitation programs in psychiatry. Two

studies using the Wellness Recovery Action Plan (WRAP), a self-management tool found positive results in adults with SMI, reflecting enhanced quality of life, as assessed with the World Health Organization Quality of Life-BREF (WHO-QoL-BREF) environment subscale (23). The smartphone-delivered mobile health version of WRAP, compared to the face-to-face WRAP intervention, demonstrated similar clinical outcomes, at half the price, in patients with severe mental illness (SMI) (24). On the other hand, in line with our results, the Boston University Approach to Psychiatric Rehabilitation (BRP) program did not result in statistically-significant differences in costs, social participation, nor QALYs, compared to an active control condition at 12-month follow-up for patients with severe mental illness (SMI) (25). Also, Interpersonal Community Psychiatric Treatment (ICPT), compared to usual care, for patients with SMI in the Netherlands, found no difference in societal and medical costs, in QALYs, nor in patient-perceived quality of life at 18-month follow-up (26). Pertaining to PDD, one Dutch study examining an individual self-management program for treatment-resistant chronic depression and anxiety ("Self-management for Chronic Anxiety and Depression", SemCAD) found no improvement in quality of life at 18-month follow-up (27). In sum, the few available studies on self-management/psychiatric rehabilitation interventions regarding chronic depression to date mostly found no lower costs nor improved quality of life, which is consistent with our results.

*Is PPEP4All-PDD more **clinically effective** than standard care in secondary/specialized mental healthcare for patients with PDD?* (Chapter 4)

PPEP4All-PDD was also not superior to standard care in terms of clinical effectiveness: PPEP4All-PDD did not reduce depressive symptoms, and it also did not improve any functional-recovery-related outcomes such as psychosocial burden, happiness/wellness, or mental resilience. The results of our qualitative study revealed that patients with PDD were generally satisfied with PPEP4All-PDD, although not significantly more than CAU patients. Patients rated the program with an acceptable score of 6.6, and the majority of patients (78%) recommended the program. Our results indicate there is room for improvement. The program can be optimized for PDD and their caregivers based on qualitative feedback (see Chapter 5 for more details).

Results have been inconsistent across RCT studies investigating therapist-assisted self-management programs for depression. Some programs resulted in improved depression severity and quality-of-life/self-efficacy outcomes for persons with mild depression (e.g., *COPERS, Pacifica, iFightDepression)* (28-30), with moderate-to-severe depression (e.g., *eCare for Moods*) (31, 32), or with SMI (e.g., *Wellness Recovery Action Planning (WRAP*)) (23). On the other hand, other self-management programs (e.g., the web-based *Big White Wall*) for persons with mild-to-moderate depression (33), or for treatment-resistant moderate-to-severe depression (e.g., *Self-management for Chronic Anxiety and Depression (SemCAD)*) (27) failed to improve depression severity compared to the control group. The SemCAD program did, however, improve self-empowerment in patients with treatment-resistant depression (27). All the aforementioned studies (except for Zoun et al., 2019) (27) differed from our study in terms of settings, depression severity, and treatment resistance. Similarly, while there was evidence for the clinical effectiveness of the original,

generic PPEP4All program for patients with chronic somatic diseases (34-38), our trial differed in terms of patient population, research/treatment design (e.g., PPEP4All-PDD adaptations), and outcome measures, which may explain the difference in results. It may also be possible that treatment needs and expectations of patients with PDD as the primary diagnosis may be different than patients with chronic somatic diseases as the primary diagnosis, with comorbid chronic depression.

*Does PPEP4All-PDD improve **psychosocial burden** in partners/informal caregivers of patients with PDD in secondary/specialized mental healthcare?* (Chapter 4)

Our main partner/caregiver outcome (psychosocial burden) did not sufficiently improve after PPEP4All-PDD. We present several explanations for this result. First, our qualitative data indicated that many participating PPEP4All-PDD partners already had basic knowledge of chronic depression, and our quantitative data showed that several partners/caregivers had very mild psychosocial burden prior to PPEP4All-PDD, resulting in a floor effect and thus, no room for improvement. Second, despite our expectations based on the generic PPEP4All protocol for chronic somatic diseases with comorbid chronic depression (38, 39), partners/caregivers of patients with PDD may be different than those of partners/caregivers of patients with other chronic somatic illness. This could be due to the level of prior knowledge regarding the disease and long-term experience with the patient's depression. Finally, our results indicated that approximately two-thirds of PPEP4All-PDD patients did not have a

participating partner/caregiver. This was due to a lack of a life partner in general, or their life partner/informal caregiver was not available due to other activities (e.g., work, childcare, etcetera).

In previous research pertaining to the generic PPEP4All, the program led to reductions in psychosocial burden in partners/caregivers of patients with Parkinson's disease and patients with symptom-manifested Huntington's disease (32, 35). Partners of patients with a chronic pituitary disorder showed improved and sustained vitality and delayed lower anxiety and depression. However, past research on treatment modifiers found no effect of patient participation with or without a partner/caregiver in patients with Parkinson's disease (40). Other programs such as the "Relatives' Education And Coping Toolkit" (REACT) intervention are available for caregivers of patients with recent-onset psychosis. This program was shown to reduce distress and increase perceived support and coping ability (41). Another program called the "Caregiver Suicide Education Program" may help caregivers cope with patient suicidality, with higher active support seeking and perceived caring ability for once-suicidal patients (42). We did not find other programs that focused specifically on partners/caregivers of patients with PDD. Therefore, we cannot provide evidence regarding other caregiver programs relating to PDD.

How do patients with PDD and their partners/informal caregivers ***experience and cope with PDD*** *and can we identify their* ***healthcare needs*** *and any potential challenges to meeting them?* (Chapter 5)

The burden of PDD is immense for both patients and their partners/caregivers. Both patients and caregivers feel a sense of powerlessness, shame, and stigma. The effects of PDD on the patient are pervasive: PDD affects relationships with friends, family, and even neighbors. It also affects the ability of the patient to hold employment, creating a limited social network. As the caregiver picks up more daily tasks and care for the patient, the patient and his/her caregiver often form an interdependent relationship. This effect appears stronger for caregivers living with the patient. Our results emphasize the importance of the role of the caregiver. Although desired by the caregiver, the care needs of the caregiver may be overlooked in the patient's care. In terms of care needs, both patients and caregivers desire psychoeducation and assistance in improving communication skills. Patients need support in understanding the benefits of self-management and incorporating self-management strategies in their daily lives. Caregivers specifically desire more involvement in understanding treatment decisions and support in dealing with the patient's relapse and suicidality. Challenges for patients include pharmacological and psychological treatment dissatisfaction, partner aggression, cognitive blocks, and physical and psychological comorbidities. Challenges for partners/caregivers include dealing with frustration with the patient's treatment, partner aggression, and fear of the patient committing suicide.

Regarding the lived experience with PDD, our results were in line with previous research. De Smet & Meganck (43) previously described identity-related changes in personality, interests, and will to live; they called this new identity the "depressed self." The "depressed self" is reinforced by the shame and stigma surrounding PDD and the resulting social withdrawal. This finding

has been previously documented in research in depressed adults in primary care (44, 45). Our finding that caregivers feel overwhelmed, frustrated, isolated and experience aggression by the patient was corroborated by a study in female caregivers of males with (acute) depression (46). Moreover, the interdependence of the patient-caregiver relationship was also previously described (47, 48). This interdependence should be considered in specialized mental healthcare in PDD-treatment.

Regarding self-management, patients had positive and negative attitudes towards self-management, suggesting varying levels of insight, knowledge, and self-efficacy. Negative attitudes towards self-management might be due to the substantial effort demanded from the patient (49, 50). Patients require intrinsic motivation, insight, self-efficacy (i.e., confidence in their ability), and emotion management to effectively utilize self-management strategies, and this process takes time and effort (51-53). Caregivers, on the other hand, readily recognized the benefits of self-management strategies and consistently employ them for self-care and self-preservation, especially for female caregivers, which was suggested in previous research (46).

The reported care needs of PDD patients align with those of individuals with depression in online forums, which included medication advice, professional treatment, understanding depression, disclosure and stigma, and help with comorbid mental health problems (49). Both patients and partners/caregivers desire psychoeducation and improved communication skills. Psychoeducation has been shown to be a consistent unmet need in managing chronic depression and should be more widely implemented for patients and caregivers (54).

9.2.2 Course of (chronic) depression

What is the long-term course of depression when we consider concurrent and switching comorbid anxiety symptoms and using a categorical and dimensional approach? (NESDA; Chapter 6)

Examining the course of depression and co-occurring anxiety can help mental health professionals tailor long-term treatment plans for optimal effectiveness and efficiency in mental health care. Thus, we explored the course of depression and anxiety while focusing on concrete diagnoses (i.e., categorical approach) versus symptoms (i.e., dimensional approach). When using the diagnoses/categorical approach, we found that, when considering comorbidity and diagnostic switching (i.e., depression to anxiety and vice-versa), remission is less likely, and approximately three-quarters (78.5%) of participants experience at least one relapse over a nine-year follow-up period. When using the dimensional approach, the number and severity of symptoms vary over time, showing symptom fluctuation, yet depressive or anxiety symptoms were always present, even if an individual no longer met full criteria for a mood disorder.

Examining previous literature, we found that, compared to those without symptoms, individuals with subthreshold depression or anxiety symptoms relapsed sooner (55-58) and suffered more frequent chronic episodes and fewer symptom-free weeks (59, 60), in line with our results. Other studies have also found a recurrent course with (non)chronic episodes in at least 50% of participants (61-66) and up to 80% (67). Furthermore, when using the categorical approach, as expected, those with comorbid depressive and anxiety diagnoses had a relatively poorer long-term course when compared to those

baseline depressive diagnoses only. This finding is in line with previous research examining anxiety and (comorbid) depressive disorders (62, 68-70).

9.2.3 Predicting (chronic) depression using cognitive reactivity

Can we predict future MDD risk using cognitive reactivity (cognitive vulnerability factor), neuroticism (personality vulnerability factor), and depression history? (NESDA; Chapters 7-8)

Considering the high rate of relapse of depression (19), we examined vulnerability factors, such as cognitive reactivity (CR), neuroticism, subclinical depressive symptoms, and past depressive episodes, that could help mental health professionals identify individuals at high risk and offer treatment to prevent relapse (71). Our study found that CR is a moderate, independent predictor of depressive disorders early in the course of the disorder. After three or more past depressive episodes, the effect of CR on depression relapse disappeared. The presence of any prior depressive episodes is the strongest predictor of future relapse. Overall, the risk of relapse within nine years is at least 70%, with higher risk observed in women than in men. Comparing two-year and nine-year risk, the contribution of CR weakened progressively due to the strong effect of depression history.

Our results confirm that the mood-activation of negative cognitions (i.e., CR) contribute to the first depressive episode (72). However, previous studies both confirmed (73-78) and did not confirm (79-84) that CR predicts relapse. This could be explained by the use of a different questionnaire to measure CR, namely the Dysfunctional Attitude Sale (DAS) (85) rather than the LEIDS-RR we

used (79). The DAS measures CR by using a change score, before and after inducing a sad mood, and it has certain limitations, which may explain the inconsistent results (20). Moreover, our risk estimates for depression relapse were in line with previous research (86, 87). It remains plausible that CR contributes to relapse risk in the case of 1 or 2 past episodes, but not after 3 episodes. However, it is also possible that, due to the high contribution of earlier episodes in persons with a history of three of more past depressive episodes, a ceiling effect occurred, and CR nor any other vulnerability factor could have improved the prediction model.

9.2.4 Clinical implications and future research recommendations

9.2.4.1 PPEP4All-PDD/Self-management for PDD-Patients

Prior to discussing the implications, there are key points of attention regarding the PPEP4All-Study. The first is that we examined a self-management program (PPEP4All-PDD) for adults and elderly (65+ years) with persistent depressive disorder (PDD) with a moderate-level of treatment resistance (i.e., at least one unsuccessful psychotherapy and two unsuccessful adequate trials of pharmacotherapy). This self-management program was offered at the end of the treatment process as psychiatric rehabilitation, with the option (i.e., not obligatory) to end current treatment and refer the client to the GP/POH-GGZ or other primary/first-line care. However, attitudes surrounding psychiatric rehabilitation were mixed. Focus on functional recovery rather than symptomatic recovery is still a relatively new concept in secondary/specialized mental healthcare. Despite the option to end treatment after completion of PPEP4All-PDD, based on shared decision making, both patients and therapists found it difficult to accept PPEP4All-PDD as the "final" treatment". Most patients returned

to their usual care therapist after PPEP4All-PDD. Therapists may have perceived referral or ending care as "failing" and "giving up on the patient" (32). Therefore, they often took the patient back and continued treatment as before. Moreover, first-line mental healthcare is also currently overwhelmed and under pressure (88), leading to long waiting times, which may have affected the decision to refer a patient to first-line care. Additionally, considering that our study partly took place during the COVID-19 pandemic, we cannot fully confirm whether COVID-19-related factors affected the decision to end treatment. During this period, standard care may have changed, or patient attitudes towards standard care may have changed.

While PPEP4All-PDD was not superior to standard care for PDD in terms of cost- and clinical-effectiveness, our qualitative results emphasize the need and desire for self-management. Despite our results, PPEP4All-PDD is still a promising, brief self-management program. PPEP4All-PDD, however, requires optimization for the PDD-population, which may possibly lead to improved outcomes in the future. Based on our qualitative data, we suggest the following improvements or optimizations of PPEP4All-PDD (see also Chapter 5): 1- schedule sessions at least every two-weeks rather than every week; 2- offer intermittent homework-discussion sessions; 3- use an online mobile phone app to measure progress; 4- communicate clearer rules regarding absence during group sessions; 5- use more examples to clarify the active material; 6- improve the workbook (e.g., shorter/more PDD-specific); 7- keep groups small (maximum 6 participants); 8- offer PPEP4All-PDD with two therapists instead of one; 9- offer PPEP4All-PDD (also) earlier in treatment; and 10- offer PPEP4All-PDD (partly) as digital e-health program (24, 29, 31, 89).

Considering mixed results from previous studies (27, 90) regarding the process of ending treatment, future researchers should include qualitative interviews to better understand the duration of treatment, the number of (adequate) treatments received, treatment expectations, and the factors related to the decision to (dis-)continue (supportive) treatment sessions. Future research on PPEP4All-PDD/self-management can also investigate the following questions: 1- Does PPEP4All-PDD (in-person or online) as a longer program (i.e., sessions offered every 2-3 weeks) result in improved clinical effectiveness in patients with PDD?; 2- Is PPEP4All-PDD more cost-effective than standard care when used as a digital program in specialized mental healthcare for patients with PDD, and is this mediated by the severity of (chronic) somatic disease?; 3- Is PPEP4All-PDD clinically effective in patients with acute/recurrent/chronic depression if PPEP4All-PDD is offered earlier?; 4- Which outcomes are more amenable to change when considering chronic depression/PDD? As demonstrated by Zoun et al. (27) and Tjaden et al. (91), increasing empowerment does not necessarily translate to a reduction of depression symptoms. However, increased empowerment/self-efficacy may lower experienced stigma (92), which may aid depression treatment. Moreover, other functional recovery-focused outcomes like "connectedness and meaning", "social contact", and "general functioning" (e.g., Global Assessment of Functioning; Social and Occupational Functioning Assessment Scale) can be considered (91, 93).

9.2.4.2 PPEP4All-PDD/Self-management for partners and caregivers

The *Alliance for quality in Dutch mental healthcare (*in Dutch: *Alliantie kwaliteit in de geestelijke gezondheidszorg*, Akwa-GGZ) posed the question

whether involving the life partner or informal caregiver (i.e., caregiver or PPEP4All-PDD partner) in patient treatment improves the patient's clinical outcomes (94). Based on our study, PPEP4All-PDD did not result in improved clinical outcomes for patients compared to standard care, suggesting that involvement of the caregiver may not result in any improvement of patient outcomes (35, 37, 39). However, our results are not conclusive considering that we did not include the caregivers of standard care-patients, and only one third of PPEP4All-PDD-patients had a participating caregiver. It was, thus, not possible to compare PPEP4All-PDD and standard care in terms of caregivers. Also, our qualitative results indicated that many participating PPEP4All-PDD partners already had a basic level of knowledge regarding chronic depression, suggesting they primarily sought connection and empathy during the program.

Our quantitative and qualitative results have important implications for the future involvement of caregivers in PPEP4All-PDD and secondary mental healthcare. First, based on the qualitative results, PPEP4All-PDD may be best suited for caregivers who require additional knowledge and support regarding caregiver issues. Second, a group format is advised over an individual format for caregivers in the future because caregivers reported the desire for empathy, connection, and shared learning with other caregivers. Third, involving the caregiver early in treatment may empower the patient and caregiver as a system and may, in turn, reduce dependence on the mental healthcare system. We recommend that mental health professionals perform an inventory of caregiver's questions or needs when starting treatment with the patient. Fourth, mental health professionals may consider providing system therapy or (online) psychoeducation programs that focus on the course of PDD, dealing with suicidality, and effective communication. In addition to PPEP4All-PDD, there is a

caregiver-specific '*caregiver suicide education program*' that may be beneficial in helping caregivers cope with patient suicidality and involve them in developing/understanding the patient's suicide prevention plan (42). This may reduce the burden of PDD for caregivers and improve patient outcomes.

Finally, more research is required to evaluate whether or including the caregiver in the patient's PPEP4All-PDD program is meaningful in terms of either patient or caregiver outcomes. Future research could explore further the effects of PPEP4All-PDD on quality of life and clinical outcomes in caregivers, in comparison to usual care, which could guide future policy on whether to continue to include caregivers in PPEP4All-PDD. The level of knowledge of the caregiver prior to PPEP4All-PDD should be assessed, and results should be tested for any modifying effect of prior level of knowledge. Also, attention needs to be placed on arranging evening sessions to accommodate caregiver work schedules.

9.2.4.3 Treatment Guidelines for Patients With PDD

The PPEP4All-Study is based on the third revision (2013) of the multidisciplinary treatment guidelines (2013) (6). In this version (third revision, 2013) (6), the following treatment strategy was considered: after a limited number of treatments that indicated certain treatment resistance, patients would be offered psychiatric rehabilitation, to learn to accept and cope with chronic subclinical/subthreshold symptoms. Considering that treatment resistance can be defined using stages, we considered the staging method by Thase and Rush. Here, five levels of therapy resistance, based on the number and classes of pharmacological treatment trials, are defined (95). Based on this staging method, in the PPEP4All-Study, patients were eligible if they had

inadequate response to at least two antidepressant trials and one psychological treatment, reflecting difficult-to-treat PDD. Considering that treatment guidelines were updated in 2024 (5), in this section, we discuss implications of our results and whether recent guidelines sufficiently address self-management and psychiatric rehabilitation for patients with PDD in secondary/specialized mental healthcare.

First, self-management can also be promoted in primary/basic mental healthcare or in secondary/specialized mental healthcare during an acute phase of depression (i.e., non-chronic depression). This may help to enhance autonomy and reduce chronic dependency. Fortunately, the most recent treatment guidelines (2024) now specify offering self-management early (see "Self-management/autonomy & Family/Relatives" in the chapter "General Principles for the Treatment of Depression", page 114-115) (5). Self-management is also promoted in secondary/specialized mental healthcare (see page 85, "Interventions focused on integrating the condition into daily life and learning to cope with temporary or permanent limitations" regarding "Specialized mental healthcare, acute, policlinic care") (5). New guidelines recommend involving the caregivers of the patient from the beginning of care (see page 105, "Relatives and Experience-experts") and involving them in making and implementing a prevention plan (page 99, "Continuity of care") (5). This is in line with our results.

Second, psychiatric rehabilitation should remain a crucial step in treatment. If treatment no longer helps the patient in terms of symptom reduction, functional recovery or psychiatric rehabilitation should be discussed with patients with difficult-to-treat PDD. Caregivers can be included as the first line of support. However, psychiatric rehabilitation is not explicitly described in

the recent depression guidelines (fourth revision) (5). In the these guidelines (5), "psychiatric rehabilitation" is mentioned mainly in Figure 3.2 "Organization of care combined with disease stages for depression" (see pages 69-70, in section 3 regarding the "Course markers and categorization of depression") (5). Also, additional treatments are promoted in the treatment guidelines (i.e., beyond two antidepressant and one psychological treatment), implicitly suggesting that psychiatric rehabilitation will be delayed in treatment plans. Therefore, it is not sufficiently clear in the text that psychiatric rehabilitation remains an option for patients in secondary/specialized mental healthcare in the case of insufficient response or remission. Also, it is not sufficiently clear at which point of treatment psychiatric rehabilitation should be offered. This should be considered in future revision of the current depression treatment guidelines.

To touch further on the last point: the question of *when* to offer psychiatric rehabilitation for PDD is complex, and this requires further research. For this, we need to examine the number of interventions received and the percentage of those achieving recovery or remaining depressed (i.e., increased treatment resistance), when following the new treatment algorithms (fourth revision, 2024). Currently, we have evidence based on the STAR*D Study. This study showed that the percentage of patients that achieves remission after antidepressant treatment drops dramatically - from 35% for the first two trials to 13% for the third or fourth trial. Also, the number of side effects and treatment termination increases as the number of treatment trials increases (2). After four treatment steps, the cumulative remission rate was less than 70% and relapse rates were higher (96). Therefore, there was an association between more treatment steps and lower response/remission rate. Even after first line treatment (e.g., cognitive behavioral therapy combined with

antidepressant), one-third suffered from difficult-to-treat depression (2, 96). This shows the challenge of finding the optimal number and types of treatment to offer patients with depression. In addition, the persistence of subclinical symptoms (96, 97) emphasizes the need to offer psychiatric rehabilitation during a reasonable number of treatment steps.

The recent 2024 treatment guidelines emphasize the need to use available treatment options to focus on reducing residual/subclinical symptoms, which may be cost-effective over a longer period of time (97). Clinicians may consider the adoption of longer-term psychotherapeutic strategies (98) or neuromodulation/biological treatments. Longer-term psychotherapy treatments include Cognitive Behavioral Analysis System of Psychotherapy (CBASP) (3, 99) or Long-Term Psychoanalytic Therapy (LTPP) (100-102), with intensive sessions across 1-5 years and combined with pharmacotherapy. Other effective treatments for PDD include Mindfulness-based Cognitive Therapy (MBCT) and Interpersonal Therapy (IPT) combined with pharmacotherapy (103). Moreover, neuromodulation/biological treatments, such as electroconvulsive therapy (ECT) or repetitive Transcranial Magnetic Stimulation (rTMS), are endorsed in the recent guidelines (5, 104). rTMS has been shown to be effective in reducing depressive symptoms and increasing remission/recovery rates, when compared to switching antidepressant medication, in patients with treatment-resistant depression (105). In addition, new treatments, such as psilocybin and (intranasal) ketamine, may reduce depressive symptoms and suicidality (104, 106). These treatments often carry stigma, which may make them underutilized. Therefore, patients and mental professionals may require information and education to promote use of these treatments.

In general, more research for PDD treatment is needed. Treatment guidelines assert that current evidence about treatment options for PDD and treatment resistance is still very limited (5). Also, results on long-term therapy have been mixed, showing no clinical or cost improvements compared to short-term treatment or usual care (107, 108). While it is a valid approach to utilize all therapeutic options to try to achieve recovery in patients with PDD, more research is needed to confirm the long-term (cost-)effectiveness of using long-term therapy and/or neuromodulation as additional treatment steps for PDD (106). This is in light of a real and practical challenge in mental healthcare, namely increasing healthcare expenditures, limited time resources, limited therapist availability (109, 110), and the number of individuals waiting to start treatment (111). We also recommend that researchers investigate the optimal number of pharmacological and psychological trials needed for recovery. In this way, researchers could examine the number of unsuccessful and adequate trials prior to offering psychiatric rehabilitation, which is a crucial step in care.

9.2.4.4 Course and diagnosis of depression

We confirmed that diagnostic recovery is not equivalent to symptomatic recovery: patients who no longer meet the criteria for the diagnosis of depression often continue to experience depressive- and/or anxiety symptoms. This is clinically relevant as patients with subclinical symptoms experience relapse more often than patients without such symptoms (55-58). Vegetative symptoms often persist longer than mood symptoms (112), suggesting that treatment needs to continue focusing on these symptoms, even after mood begins to improve. Moreover, considering that patients with (chronic) depression often suffer from comorbid psychiatric/somatic disorders and various

psychosocial issues, treatment may need to be extended to reach full recovery. More research is required to confirm whether full recovery is possible.

Regardless, our results question our process of diagnosing patients: should we view individuals with depression and other comorbidity as having two or more distinct DSM disorders or as having a single dimensional disorder (i.e., symptoms on a continuum)? Previous studies (113-116) have identified risk factors, such as neuroticism, that affected individual depressive symptoms to varying degrees, suggesting that depression is not one unified latent construct. This pleads for the use of dimensional-based model for diagnosing. However, the DSM currently provides mental healthcare with a common, understandable language (117, 118). Until a better dimensional model is proposed, we suggest the integrative use of diagnostic classification using the DSM and a descriptive diagnosis, which includes symptom severity, symptom duration, and levels of impairment (68, 118, 119). In the future, improving our ability to accurately diagnosis an individual may help us tailor treatment to individuals and improve treatment results. *Future options to improve diagnosing include the following:*

(1) **Activity, Cognition, and Emotion (ACE) model** that groups symptoms commonly present in mood disorders like depression and bipolar disorder according to functional domains (120).

(2) Another option is the **dimensional symptom-based framework** which looks at individual symptoms and how they influence each other (121). One can use multiple measurements for each participant to examine how symptoms for each person changes, then aggregate these on group level. Data can be analyzed using Dynamic Time Wrap (DTW) analysis, which is a computational algorithm that could be used to process individual symptom data and takes account of potential non-linear dynamics among symptoms

and focuses on change profiles rather than absolute levels of symptom scores (122). However, more research is needed to confirm whether a dimensional symptom-oriented tool will lead to more accurate symptom-specific tailored treatment plans and better outcomes (123).

(3) Another tool, **Polly**, was developed within the Patterns of Life (www.patternsoflife.nl) study to improve the way that mental health professionals conduct the anamnesis/intake so that patients receive a more accurate diagnosis. This tool focuses on the idea that mental disorders are the result of a complex interaction between factors inside and outside of an individual: biological and body, psychological and mental, social, demographical, cultural, and societal. The diagnosis, thus, considers these distinct factors, which are discussed during three sessions. Patients and therapists together create links between these factors, to see which patterns maintain the problems experienced by the patient and the way ways that these patterns can be changed. Artificial intelligence will be used to analyze the database of collected data of each patient, to eventually aggregate the results on group level. Finally, a recovery plan is discussed with the patient and his or her relatives/caregivers.

9.2.4.5 Cognitive reactivity predicting future depression relapse

Finally, we also examined negative cognitions as a risk/vulnerability factor for (recurrent) depression episodes. Patients may be more likely to experience negative cognitions when feeling sad, a concept known as cognitive reactivity (CR). This involves biased information processing. After successive depressive episodes, CR, or the mood-activation of negative cognitions, appears to play a smaller role in the development of future depression. Alternatively, after successive depressive episodes, negative cognitions may become more

ingrained into a person's personality with each episode, and the threshold to triggering negative cognitions may become so low that an individual becomes sensitive to any stressor or negative mood. This makes it difficult to measure any change in negative cognitions and in research, this may be reflected in a person as mood-reactivity, or neuroticism, rather than cognitive reactivity. Indeed, previous research demonstrated that recurrently-depressed patients had higher levels of mood reactivity, rather than cognitive reactivity (77), and mood-reactivity predicted future recurrence/relapse (74, 124-126). Our results are not conclusive on CR, however, considering patients with three or more past depressive episodes. After stratifying our sample for past depressive episodes at baseline, our confidence intervals reflected an elevated level of uncertainty, due to a smaller sample size for participants with three or more past depressive episodes. More research is required to confirm whether the effect of CR, as measured with the LEIDS-RR, disappears with increasing number of past depressive episodes.

Moreover, the concepts of chronicity, neuroticism, and CR are difficult to unravel. Considering that neuroticism may be used as a proxy for chronic depression (116, 127), some participants may have already experienced chronic depressive episodes at baseline (116). In addition, the moderate correlation of neuroticism with CR in our study (r = .63), may have resulted in a weaker association of CR with relapse. Considering this conceptual overlap, future studies may decide to utilize baseline chronicity and CR, rather than only neuroticism.

Finally, our high risk estimates for depression relapse (>70%) suggest a severe risk for future chronicity of depression. We advise early treatment and relapse prevention in clinical treatment for patients with a depression history.

Treatments that focus on cognitive reprogramming, such as Preventive Cognitive Therapy (PCC) (84), may be beneficial in delaying future relapse/recurrence.

9.2.5 Strengths and Limitations

The PPEP4All-Study was the primary study of this dissertation, and thus, we focus on the strengths of this particular study. The PPEP4All-Study was the first mixed-methods, pragmatic randomized controlled trial to investigate the clinical- and cost-effectiveness of PPEP4All-PDD, in a complex population of patients with moderate treatment-resistant PDD – a population associated with a high burden of disease and high healthcare utilization. In addition, we included elderly patients (age > 65 years) and partners/caregivers – two groups of often not included participants in depression research. Starting in December 2016, this trial sought to provide an evidence-based, cost-effective self-management psychiatric rehabilitation protocol for use in specialized outpatient mental healthcare, for which there was an urgent need. PPEP4All-PDD is a structured, brief, generic self-management program that was adjusted for persistent depressive disorder. It can be offered as a group or individual treatment. Regarding cost-effectiveness, we measured and analyzed costs from a societal perspective, thus including the costs of non-healthcare costs from productivity loss. Regarding clinical-effectiveness, we collected both quantitative and qualitative data from various perspectives (PPEP4All-PDD/CAU patients, PPEP4All-PDD partners/caregivers, and PPEP4All-PDD therapists), in line with the mixed method. In addition, treatment was provided in a naturalistic setting, reflecting day-to-day clinical practice, thus, increasing external validity. Finally, our study included qualitative in-depth interviews to further understand self-

management attitudes/strategies and care needs of patients with PDD and their partners/caregivers.

There are also limitations pertaining to the PPEP4All-Study. First, the potential of PPEP4All-PDD as a self-management program may not have been fully captured due to the small sample size in our study. Accounting for 10% attrition, our aim was to recruit a total sample of 178 participants, or 89 per group. However, this was impacted by various factors, including the therapist/patient decision to end treatment without research participation (due to uncertainty of randomization), the patient's treatment preference (either PPEP4All only or standard care only), the patient's higher treatment resistance and disease severity, and the patient's anxiety during COVID-19 pandemic. Second, our sample included mainly Dutch and highly-educated patients, limiting the generalizability of the results to lower-educated patients or patients of other countries. Second, we included fewer partners/informal caregivers of PPEP4All-patients than expected in the study. Many patients did not have a partner/informal caregiver, or their partner/informal caregiver was not available due to, for instance, illness or work obligations. However, this did not appear to be a problem for the qualitative study, as most of the caregivers reported largely the same experiences or themes (i.e., saturation was reached). Third, we did not recruit the partners/informal caregivers of the control group in the PPEP4All-Study. This was in line with the pragmatic nature of our study, where standard care does not often include the partner/caregiver. However, it is a noteworthy disadvantage that we cannot compare the results of our PPEP4All-PDD partners to control group partners. Fourth, we did not formally collect data on comorbid personality disorders, (number of) past treatments, neuromodulation/ biological treatment trials, whether patients actually ended

treatment after completion of PPEP4All-PDD, or whether patients were referred to other care. We advise collecting this data in future research. Fifth, our study took place during the COVID-19 pandemic, which negatively affected mental health of many individuals (16). This may have resulted in patients continuing to see their mental health professional after completion of PPEP4All-PDD, which may have affected cost-effectiveness results. Also, the content or delivery of standard care may have changed during the COVID-19 pandemic, which may reduce the generalizability to the non-pandemic situation. Also, due to COVID-19 prevention regulations, we then offered PPEP4All-PDD sessions via online video-calls. While a few patients mentioned that they would have preferred face-to-face sessions, possibly due to the experience of loneliness (128), this was not possible for safety and health reasons.

9.2.6 General Conclusions

The present dissertation examined a brief self-management program as psychiatric rehabilitation for patients with difficult-to-treat PDD and their informal caregivers. Our primary questions centered on whether PPEP4All-PDD is more cost-effective and more clinically effective than standard care for patients with PDD and whether PPEP4All-PDD improves psychosocial burden in informal caregivers of patients with PDD. Considering our research findings, our answer is *No* - at least not in the current form that PPEP4All-PDD is offered. For future use, the PPEP4All-PDD program requires further optimization for patients with PDD, according to the recommendations outlined in this dissertation (see Chapter 5). As secondary questions, we asked: what is the long-term course of depression when considering concurrent and switching anxiety? – and can we predict future depression risk using cognitive reactivity, even when considering

other relevant vulnerability factors? Pertaining to our secondary questions, our results demonstrated the stubborn persistence and fluctuation of subclinical depression and/or anxiety symptoms as well as the strong impact of past depression history on predicting future relapse, beyond cognitive reactivity.

In light of real, practical problems in mental healthcare, the crucial question remains: when in the treatment process should mental health professionals offer psychiatric rehabilitation to depressive patients? While more research is required to answer this question, we stress that psychiatric rehabilitation should remain a crucial aspect of treatment for PDD. It promotes patient self-leadership and empowerment, and the patient learns to accept that the waves of depression are persistent. This means they must adjust their expectations about how to swim through life, while the informal caregiver helps them stay afloat. Currently, there is a need for clarity in the treatment of depression regarding the optimal number of treatments prior to psychiatric rehabilitation, which potentially include neuromodulation and long-term psychological treatments. Future research should examine whether longer-term active treatment, according to the recent treatment guidelines, may result in further symptom recovery and long-term cost-effectiveness.

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