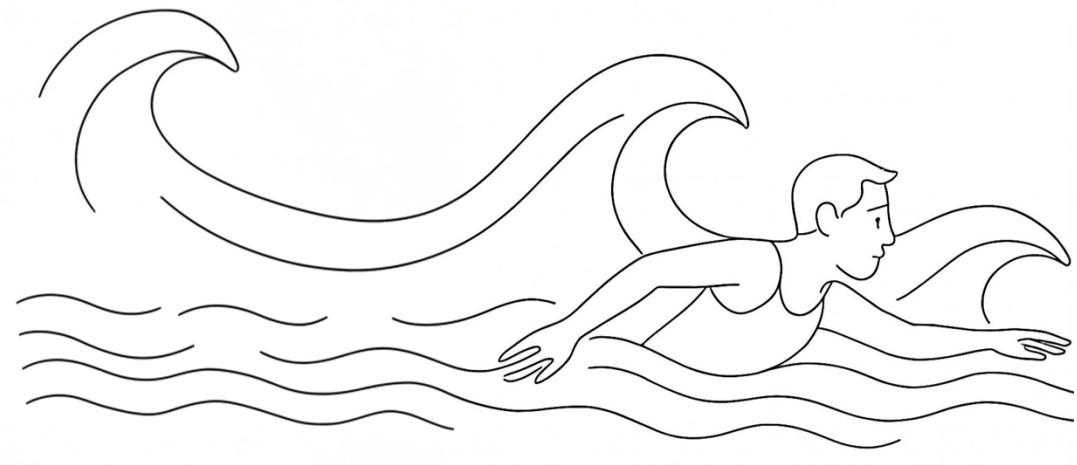
# Learning to swim the endless waves: examining self-management and risk factors for (chronic) depression

Solis, E.C.

*"It is not enough to promote health by avoiding stress or by building bridges to keep people from falling into the river. Instead, people have to learn to swim."*

Aaron Antonovsky (1987), an American-Israeli medical sociologist.



# CHAPTER 1

## General Introduction

Ericka C. Solis

*Mr. G is a 45-year-old client with a history of alcohol abuse. He suffers from severe depression, thoughts of death, anxiety, low self-esteem, and fatigue. He avoids social interactions. He recounts that his depression began long ago when he was fired, and he has been unable to work since. He was diagnosed with persistent depressive disorder, coupled with alcohol abuse and an unspecified personality disorder. Mr. G is single and lives alone but receives significant support from his parents, particularly his mother, who is concerned about him and wants to aid in his recovery and suicide prevention. Despite undergoing various treatments for his persistent depressive disorder—such as cognitive behavioral therapy, mindfulness therapy, and psychotropic medications (according to treatment guidelines)—the results have been insufficient. Now, he has reached a 'ceiling effect': he is 'tired of therapy' and feels lost in life. He primarily faces psychosocial problems that contribute to the persistence of his depressive symptoms. According to his caregiver, he could possibly benefit from a self-management/psychiatric rehabilitation program that focuses on quality of life and self-leadership instead of focusing on symptom recovery.*

## 1.1. PREFACE

### 1.1.1. History of the depression diagnosis

Beyond just "ordinary sadness," the phenomenon of depression has been contemplated and studied by physicians, theologians, and philosophers for centuries. As they began formulating the concept of depression, potential causes have been linked to spiritual, biological, and psychological factors. Looking at

recorded history, the first notion of "depression" was found in Mesopotamian texts as early as the second century B.C. (1). At that time, as was prevalent in ancient Greek, Roman, Babylonian, Chinese, and Egyptian cultures, depression was viewed primarily as a spiritual condition, caused by divine punishment, evil curses, or demonic possession (1). Depression would be further contemplated by theologians, such as Saint Augustine (354 A.D.), who himself suffered from severe depression. He would describe depression as "a state of despair that is inherent to the human condition and is allowed by God through free will" (2). Early writings by Hippocrates (460-375 B.C.) and Aelius Galenus (129-216 A.D.), Greek physicians and philosophers, however, shared a different view on depression: they described depression (initially called "melancholia"; from Greek, *mêlas* = black, and *chole* = bile) as a biological, rather than spiritual, condition that affected one's mood (3). These prominent physicians at the time, believed that illness was a result of an imbalance in body fluids called humors (i.e., black bile, yellow bile, blood, phlegm), and as such, depression was a consequence of an excess in "black bile" in the spleen, which makes one sorrowful (4). For this reason, depression was sometimes also referred to as "spleen" or "vapors" (5). These views became particularly prominent in our world from the 15$^{th}$ century onwards, after the rediscovery of the extensive medical writings of Galenus that had been preserved in the Arabic world. On the other hand, Marcus Tullius Cicero (106-43 B.C.), a Roman philosopher and statesman, believed that melancholia had psychological causes such as rage, fear, and grief. Similar to Saint Augustine, he had personal experience with severe depression and suicidal ideations, following his divorce and the death of his daughter (6). Despite the personal and professional experience of these learned men with the concept of depression, it was not until the nineteenth

century that the term "depression" appeared, as did the concept of affective disorders, with the work of the German psychiatrist, Emil Kraepelin (1856-1926) (7). Kraepelin began classifying "depressive states" based on the alternation or the permanence of episodes and their duration (3, 4). In modern times, the concept of depression has been further formulated into a "medical illness" that affects how one feels, thinks, and acts, and we recognize the complexity of factors (i.e., biological, physical, emotional, cognitive, social, cultural, etc.) associated with depression.

### 1.1.2. Identifying and diagnosing depression

In current mental healthcare, depression is categorized using the Diagnostic and Statistical Manual of Mental Disorders (DSM), which is currently in its fifth revision (DSM-5-TR) (8). Depression can be episodic, or it can persist over long periods, often with changing severity. In the DSM, acute episodic depression is called *major depressive disorder* (**MDD**). To diagnose MDD, at least five out of nine symptoms must be present (see Table 1), and depressed mood or diminished interest or pleasure (anhedonia) must also be present for at least two weeks. Persistent depression is called *persistent depressive disorder* (**PDD**), which is a chronic mood disorder that is often more disabling than episodic MDD. In the DSM-5(-TR), PDD subsumes several chronic depressive diagnoses, such as dysthymia with or without superimposed MDD episodes, chronic MDD, and recurrent MDD without recovery between episodes. PDD is diagnosed when at least two out of six symptoms are present for at least two years (see Table 2). If criteria for both MDD and PDD are met, both can be diagnosed.

**Table 1: DSM-5(-TR) criteria – major depressive disorder (MDD)**

**A.** At least five of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure:

- Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g. feels sad, empty, hopeless) or observations made by others (e.g., appears tearful).
- Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
- Significant weight loss when not dieting or weight gain (e.g., change of more than 5% of body weight in a month), or decrease in appetite nearly every day.
- Insomnia or hypersomnia nearly every day.
- Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
- Fatigue or loss of energy nearly every day.
- Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
- Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by their subjective account or as observed by others).
- Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

**B.** The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

**C.** The episode is not attributable to the direct physiological effects of a substance or to another medical condition.

**D.** The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.

**E.** There has never been a manic or hypomanic episode.

***Specify if with:***

| | | |
|---|---|---|
| anxious distress | mixed features | atypical features |
| psychotic features | catatonia | peripartum onset |
| seasonal pattern | | |

**Table 2: DSM-5(-TR) criteria - persistent depressive disorder (PDD)**

**A.** Depressed mood most of the day, for more days than not, as indicated by either subjective report or observations made by others, for at least 2 years.

**B.** Presence, while depressed, of least two of the following six symptoms:

- Poor appetite or overeating.
- Insomnia or hypersomnia.
- Low energy or fatigue.
- Low self-esteem.
- Poor concentration or difficulty making decisions.
- Feelings of hopelessness.

**C.** During the 2-year period of the disturbance, the person has never been without these symptoms in Criteria A or B for more than 2 months at a time.

**D.** Criteria for a major depressive disorder may be continuously present for 2 years.

**E.** No history of mania or hypomania.

**F.** The disturbance is not better explained by a persistent schizoaffective disorder, schizophrenia, delusional disorder, or other specified or unspecified schizophrenia spectrum and other psychotic disorder.

**G.** The symptoms are not attributable to the physiological effects of a substance or another medical condition (e.g., hypothyroidism).

**H.** The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

***Specify if:***

- with anxious distress - OR - with atypical features
- in partial remission - OR - in full remission
- Early onset (before age 21 years)
- Late onset (at age 21 years or older)

***Specify current severity:***

- Pure dysthymic syndrome
- Persistent major depressive disorder
- Intermittent major depressive disorder, with current episode
- Intermittent major depressive disorder, without current episode

***Specify current severity:***

- Mild. - Moderate. - Severe.

### 1.1.3. Epidemiology of depression

Depression is one of the most common mental healthcare concerns worldwide (9), and, especially chronic depression (i.e., PDD) (10), is associated with a high burden of disease for patients, (informal) caregivers, and society in general (11). For most people, depression concerns a single, time-constrained depressive episode (12, 13), which may be diagnosed as *major depressive disorder* (MDD). Approximately 19% of the Dutch population has had MDD before the age of 65 (14). Approximately 10-17% of those with MDD suffer a chronic course that persists for at least 2 years and may be diagnosed with *persistent depressive disorder* (PDD) (8). The lifetime prevalence of PDD is between 1 and 6% (10, 15-18), although other research has resulted in a higher lifetime prevalence of PDD up to 18% (19). It is estimated that at least 30% of patients treated in specialized/secondary mental healthcare already experience a persistent course of depression (20, 21). Depression, especially (treatment-resistant) PDD, is associated with impaired functioning in social and family relationships, reduced performance in work or school, and comorbid psychiatric and somatic problems (22-24). Compared to non-chronic MDD, PDD is associated with more severe health consequences, poorer clinical and treatment outcomes, and higher suicide risk (18).

In addition to personal burden, the societal and economic impact of PDD is immense (25, 26). Compared to those without MDD, individuals with MDD, especially (treatment-resistant) PDD, use more (mental) healthcare and social security (27-29). In the Netherlands, direct costs for MDD treatment were 660 million euros in 2008 (27). The indirect costs for depression in productivity loss due to absence from employment were 953 million euros (27). Since 2010, the

number of patients in specialized mental healthcare, which is more expensive than first-line care, was expected to grow by 10% each year (30).

At present, there is still an urgent challenge in mental healthcare in the Netherlands: healthcare expenditures continue to rise, with more patients seeking care, longer waiting times for new patients, fewer available resources, and an insufficient number of mental healthcare professionals (30-34). According to the Dutch National Healthcare Authority (*Nederlandse Zorgauthoriteit*, NZa), in 2023, 55,390 (56.8%) of new patients had waiting times beyond the accepted norms for registration/intakes (> 4 weeks) or treatment (> 10 weeks) for specialized mental healthcare, with an average total waiting time of 20.9 weeks (35-37). In 2023, the highest influx of new patients was in the depressive disorders department, in addition to higher numbers of those with trauma- and stress-related disorders, and a higher number of registrations to first-line/basic mental healthcare. Waiting time for depressive disorders in specialized mental healthcare ranged from 5.7 to 28.8 weeks in 2023 (35, 36, 38). The number of patients waiting for care has steadily increased since 2016 (the start year of this PhD-project), with 97,450 total patients waiting for specialized mental healthcare at the end of 2023 (36, 38, 39). For this reason, mental healthcare clinics have been looking for empirically-supported protocolized treatments that are effective, time-limited, and can reduce healthcare costs.

## 1.2 TREATMENT OF DEPRESSION

### 1.2.1. Treatment guidelines for depression

Treatment of depression follows stepped, evidence-based guidelines, which are the same for men and women (see "*Algorithms for the Treatment of*

*Depression*" on page 140 of the guidelines) (40-42). During the time of data collection for this dissertation, the 2013 guidelines (third revision) were relevant (41). However, treatment guidelines (fourth revision) were updated in 2024 (42). For patients suffering from moderate or severe MDD without psychotic symptoms, 2024 guidelines recommend offering a combination of psychotherapy and antidepressant medication (preferably cognitive behavioral therapy (CBT) and selective serotonin reuptake inhibitors (SSRIs)) as the first treatment step. Combination therapy has been shown to be more effective than psychological or pharmacological treatment alone (43-45). For mild to moderate MDD, however, psychotherapy and pharmacological treatment alone have been proven to be equally effective, although drop-out may be higher for pharmacotherapy due to side-effects (46, 47). Regarding psychotherapeutic treatment for MDD, CBT, behavioral therapy (BT) and interpersonal therapy (IPT) are recommended. These have been proven to be equally effective (43). Patients may also be offered short-term psychodynamic therapy, problem-solving therapy, acceptance and commitment therapy (ACT), mindfulness-based cognitive therapy (MBCT), cognitive behavioral analysis of system psychotherapy (CBASP), or schema therapy, depending on their complaints and needs (48-58). Therapies such as preventative cognitive therapy (PCT) can be offered as relapse prevention (52, 59, 60). Regarding pharmacotherapy, SSRIs (e.g., fluoxetine, sertraline, citalopram), serotonin and norepinephrine reuptake inhibitors (SNRIs) (e.g., duloxetine, venlafaxine), and atypical (tetracyclic) antidepressants (e.g., mirtazapine, bupropion) are effective options (61). There are also tricyclic antidepressants (TCAs) (e.g., imipramine) or monoamine oxidase inhibitors (MAOIs) (e.g., tranylcypromine) (28), although these may result in more side effects, and thus, lower tolerability (62). For this reason,

these latter are considered after SNRIs or atypical antidepressants (42). The optimal doses are also reported in the 2024 guidelines (see section "*General principles of treatment: Treatment plan for pharmacotherapy*," Table 5.1 on page 117 of the guidelines) (42).

Most patients with MDD recover within 6 to 12 months from pharmacological and/or psychological treatment, reflecting that, ideally, treatment should start early during the acute phase of depression (63). Research has shown that individuals who receive late or inadequate treatment may be resigned to suffering a chronic course (64). However, many individuals with a history of MDD episodes experience relapse or recurrence (65), and 30-50% of patients with PDD do not achieve adequate symptomatic reduction (i.e., no response or partial response, considered as a 50% reduction in depressive symptoms) (66-69). In other words, patients who received adequate treatment may still experience some level of treatment resistance (70). Thus, relapse prevention program and eventually psychiatric rehabilitation are crucial steps to depression treatment (70).

### 1.2.2. Standard treatment for persistent depressive disorder

According to the latest revision of the multidisciplinary depression guidelines (2024) (42), if a newly-registered patient presents with PDD and has not yet received any treatment, it is advised to start with treatment algorithms for moderate/severe depression, considering the long duration of symptoms (see treatments described in section "*Algorithms for treatment of depression*" on page 141 of the guidelines) (42). For patients with PDD and a history of past treatment, it is imperative to evaluate whether the treatment was optimally delivered (e.g., adequate dosage, frequency/intensity of psychotherapy) and if

treatment compliance was sufficient. Mental health professionals are advised to start with the treatment step that was not yet provided or not yet adequately administered, taking into account any possible treatment complications. For those with treatment-resistant chronic depression (see section "*Psychotherapy for therapy resistant depression*" on page 189 of the guidelines) (42), combination psychotherapy with pharmacotherapy is preferred (71, 72) and should be offered for a sufficient period of time, with a longer medication period of 10 weeks, instead of 4-6 weeks (73). Psychotherapy options include CBT, CBASP, and MCBT (42). Mental health professionals may consider offering more frequent sessions per week. If these options do not result in sufficient symptom reduction, patients may be referred to a specialized top-clinical center for further diagnostic evaluation (e.g., for co-morbid personality disorder), medication advice, or a second opinion (73).

In addition to these aforementioned treatments, lithium-augmentation, repetitive transcranial magnetic stimulation (rTMS) (74, 75), or electroconvulsive therapy (ECT) (76-78) may be considered, in line with shared decision-making between the therapist, patient, and family relatives (42). If two antidepressant trials have not sufficiently reduced symptoms, lithium-augmentation or rTMS is advised as the third-step in treatment. The advantage of rTMS is that it can be offered together with pharmacotherapy, or alone, in the case that a patient experiences severe side-effects to medication. If SSRIs and SNRIs do not provide adequate results, and the mental health professional is considering irreversible MAOI medication, ECT is advised as an alternative to pharmacotherapy. ECT is advised in the case of severe suicidality, catatonic symptoms, psychotic depression, or older age. For patients who do not respond to any prior treatment, there is also the option to offer deep brain stimulation

(DBS) (79, 80). These treatments, however, are often not offered in specialized/secondary care. As such, patients may need to be referred to other clinics, such as specialized third-line hospital care. Potentially for this reason, in addition to patient choice/stigma, ECT has been reported to be insufficiently offered in specialized mental healthcare as part of standard care for treatment-resistant depression (20). In regards to the treatment algorithms, there is currently no strong scientific evidence for one specific, precise and fully-developed algorithm, although network meta-analyses have been performed for some possible components of treatment steps (81-83).

For the group of patients for whom these options do not result in sufficient symptom reduction, guidelines recommend *psychiatric rehabilitation through, for instance, self-management interventions* (41, 42). Prior to the start of this PhD-project in 2016, a standard self-management rehabilitation protocol was not available in specialized/ secondary mental healthcare. Bereft of a specific protocol, patients with PDD often received individual sessions focused on monitoring, support, and stabilization. This was provided by a psychiatric nurse, psychologist, or psychotherapist, with pharmacological maintenance therapy from a psychiatric nurse specialist or psychiatrist, in line with the continuance/maintenance phase of care (see section "*General principles of treatment: Continuation/Maintenance Phase*," page 120 of the guidelines) (42). These supportive sessions were standard care, at that time (i.e., in 2016), and could have a long-term duration of several years, making it very costly (29). In addition, standard care did not often include the partner/caregiver of the patient, thus, leaving the partner/caregiver/system as a whole unsupported (see the case study of patient with PDD, Mr. G, and his mother in the introduction) (84). Standard care could result in frustration, passiveness, and (emotional)

dependence from the patient. On the other hand, the therapist could experience frustration and demoralization due to the relapses and suicidality of his/her patient (84).

### 1.2.3. Psychiatric rehabilitation through self-management for persistent depressive disorder

Psychiatric rehabilitation focuses on functional recovery rather than symptomatic recovery and can be achieved by providing self-management interventions. It entails restoring (psycho-)social functioning, improving health-related quality of life, and enhancing patient autonomy (70, 85, 86). Rehabilitation through self-management (i.e., self-management rehabilitation) has already been established in care for chronic somatic diseases, such as Parkinson's disease, and for severe psychiatric illnesses, such as psychosis or schizophrenia (87-91). However, psychiatric rehabilitation for PDD is relatively new. For PDD, self-management rehabilitation focuses on symptom stabilization, enhancing autonomy, improving psychosocial functioning, boosting work/life functioning (e.g., participating in civic activities, going to school/ (volunteer)work) and the prevention of relapse and suicide (92).

Starting in 2016, our project examined a program that may be of benefit to patients with PDD as self-management rehabilitation: the "*Patient and Partner Education Program for All Chronic Diseases-Persistent Depressive Disorder*" (PPEP4All-PDD: 9 weekly group sessions for PDD-patients with separate partner/caregiver groups) (see Chapters 2 to 5 of this dissertation). As of 2024, there are few national and international psychiatric rehabilitation (PR) or self-management (SM) programs for chronic depression/PDD available. There is the web-based *eCare for Moods* (for recurrent/chronic depression) (93, 94)

and the in-person *Self-management for Chronic Anxiety and Depression* (SEMCAD) program (for chronic depression and anxiety) (95). Other programs, such as *iFightDepression* (96), *Pacifica* (97), or the web-based *Big White Wall* (98), have been developed for mild-to-moderate depression.

## 1.3 THEORETICAL BACKGROUND OF THIS DISSERTATION

This dissertation primarily examines PDD. Information regarding the causation of PDD, specifically, is scarce (68). However, depression in general is considered complex and multi-factorial, with biological, psychological, and social factors (99). ***Biological factors*** include genetics, physical health conditions, the microbiome, inflammatory markers (e.g., C-reactive protein (CRP), interleukin-6 (IL6), tumor necrosis factor alpha), metabolic factors (e.g., higher triglyceride levels, lower levels of vitamin D), stress and hypothalamic-pituitary adrenal (HPA) axis dysfunction (e.g., lower cortisone awakening response), and the kynurenine pathway (99, 100). Cognitive decline and cognitive deficits are also linked to increased depression risk. ***Psychological factors*** include sensitivity to rejection (i.e., interpersonal sensitivity), negative emotionality, neuroticism, lower extraversion, and cluster C personality features (68, 101-103). In addition, it includes cognitive processes such as negative self-concept, negative cognitive styles, dysfunctional attitudes, rumination, and *cognitive reactivity (this dissertation),* or the ease with which dysfunctional cognitions are (re-) activated by a mild sad mood (104, 105). The notion is that people's thoughts, inferences, attitudes, and interpretations, and how they focus on and recall information (i.e., biased information processing), can increase their risk for depression (106-108). ***Social factors*** include sociodemographic characteristics (e.g., lower income), poor social support, and greater childhood adversity and

maltreatment (e.g., emotional abuse and neglect) (99). In this dissertation, we examine psychological factors (see chapters 7 and 8).

The self-management program we evaluated in this dissertation – "*Patient and Partner Education Program for All Chronic Diseases for PDD*" (PPEP4All-PDD) - has an eclectic theoretical background (109). It includes theoretical influences of system theory ("patient system") (110-112), cognitive behavioral theory ("(dys)functional cognitions") (113), social cognitive theory ("self-efficacy") (114), the stress coping model ("coping strategies") (115, 116), transtheoretical model ("motivation to change") (117), biopsychosocial model (quality of life) (118-120), and general model of self-management, which relates to social factors (92). In regards to the bio-psychosocial model, patients are encouraged to continue to take medication and adjust their expectations, beliefs, and behaviors. During the PPEP4All program, PPEP4All-PDD therapists offer information on biological aspects of depression and advise on psychosocial aspects of disease management. This is achieved using a cognitive-behavioral approach based on the biopsychosocial model to influence health behaviors and outcomes. This allows patients to better manage the impact of symptoms and the (emotional) consequences of the disease.

## 1.4 DATA USED IN THIS DISSERTATION

This dissertation is based on collected data from the Self-management and Chronic Depression Study ("PPEP4All Study", funded by grants from both the ZonMw Doelmatigheidsonderzoek program and GGZ Rivierduinen Mental Health Care Provider) *(Chapters 2 to 5)* and on pre-existing data from the Netherlands Study of Depression and Anxiety (NESDA) *(Chapters 6 to 8)*.

## 1.5 AIMS AND RESEARCH QUESTIONS OF THIS DISSERTATION

### 1.5.1. Aims

The present dissertation aims to examine the cost- and clinical-effectiveness of a PDD- self-management rehabilitation program in patients with (difficult-to-treat) PDD and their partners/caregivers. In addition, we aimed to expand our understanding of the long-term course and psychological risk factors of chronic depression to improve future diagnoses and prognoses when treating chronic depression. While the primary focus of this dissertation is chronic depression (PDD), we also considered recurrent/acute MDD when examining course and risk factors. In addition, when examining the course of (chronic) depression, we also incorporated the presence of anxiety symptoms, due to the high prevalence of patients with depression and comorbid anxiety. In relation to long-term course, we considered vulnerability and risk factors for depression. In this dissertation (see Chapter 8), we examine cognitive vulnerability (i.e., cognitive reactivity), personality-related vulnerability (i.e., neuroticism), and past depression history as some of the possible risk factors for future depression. These all relate, however, to psychological factors of PDD (see 1.3).

### 1.5.2. Research questions

The research questions of this dissertation are as follows:

1. *Cost-effectiveness*. Is PPEP4All-PDD/ self-management rehabilitation more cost-effective (i.e., lower costs in relation to quality of life) than standard care in secondary/specialized mental healthcare in patients with persistent depressive disorder (PDD) and their partners/informal caregivers? (Chapter 3)

2. *Clinical-effectiveness in patients.* Is PPEP4All-PDD/ self-management rehabilitation clinically-effective in patients with PDD, compared to standard care in secondary/specialized mental healthcare? (Chapter 4)

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

4. *Qualitative investigation.* 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)

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

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

## 1.6 OUTLINE OF THIS DISSERTATION

In **CHAPTER 2**, we describe in detail the protocol and RCT-methodology of the primary study in this dissertation (PPEP4All Study).

In **CHAPTER 3**, we examined the cost-effectiveness of the PPEP4All-PDD program compared to standard care, using a net-benefit approach and willingness-to-pay threshold. Quality-adjusted life years (QALYs) and costs of PPEP4All-PDD, (mental) healthcare, and productivity loss after a 12-month period were evaluated (PPEP4All Study).

In **CHAPTER 4**, we examined the clinical-effectiveness of the PPEP4All-PDD program compared to standard care. Specifically, outcomes included depressive symptoms, psychopathology, mental resilience, happiness/well-being, psychosocial burden, and need for help at 0, 3, 6, and 12 months. We also investigated the satisfaction with and optimization of PPEP4All-PDD. For the latter, we elicited direct feedback about PPEP4All-PDD from patients, partners/ caregivers, and clinicians via individual semi-structured qualitative interviews (PPEP4All Study).

In **CHAPTER 5**, we investigated the lived experience of chronic depression, self-management strategies, and current care needs for patients with PDD and partners/caregivers by conducting individual in-depth qualitative interviews, using Grounded Theory (PPEP4All Study).

In **CHAPTER 6**, we examined the nine-year course of depression and anxiety as separate categories (i.e., syndromes), in line with DSM-criteria, or overlapping symptom-trajectories (i.e., dimensions). Specifically, we considered anxiety-depression comorbidity and anxiety-depression switching over time (NESDA).

In **CHAPTER 7**, we investigated the psychometric properties of the Leiden Index of Depression Sensitivity-Revised (LEIDS-R) questionnaire, which measures cognitive reactivity. We developed a shorter version of the questionnaire, resulting in the LEIDS-RR (NESDA).

In **CHAPTER 8**, we investigated whether we could predict depressive episodes at nine-year assessment using baseline cognitive reactivity (using the LEIDS-RR), neuroticism, and depression history as risk factors (NESDA).

In **CHAPTER 9**, we summarized and discussed our findings, alongside a number of implications for clinical practice and future research.

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