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Towards Personalized Medicine for Persistent Depressive Disorder: Moving from "one size fits all" to "what works for whom?"

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Dedication

~ For my beloved parents ~

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Abstract

Persistent Depressive Disorder (PDD) is, by definition, a chronic mental disorder that severely affects the quality of life of those affected. Despite numerous available treatment options, response and remission rates are generally scarce in patients with PDD, with effectiveness of different treatments varying between individual patients. However, empirical evidence predicting and understanding the individual treatment benefit is largely lacking. Personalized medicine aims to match patients with the most promising treatment on an individual basis by identifying pre-treatment characteristics that predict the outcome of a particular treatment for an individual patient. While other medical disciplines have achieved great progress in the field of personalized medicine, psychiatry still lags far behind, holding on to the 'one size fits all' concept, which assumes that a certain treatment will work equally well for all patients diagnosed with a particular disorder. This is also broadly applicable to the research field on PDD.

The overarching aim of this publication-based dissertation is to advance the field of personalized medicine for PDD by providing evidence for the effectiveness of certain psychotherapeutic and pharmacological treatments for specific subgroups of patients with PDD based on their multivariable pre-treatment profile. Beginning with an introduction, this thesis will first provide a theoretical framework for the two main thematical concepts of this work, namely PDD and personalized medicine, as well as an overview of previous evidence on treatment prediction in patients with PDD. Afterwards, the main objectives and research questions of this thesis are presented with respect to two specific clinical decision-making scenarios that have been studied in the three scientific papers presented thereafter, namely the selection of and between two psychotherapies (Paper 1 and Paper 2) and the choice between psychotherapy and antidepressant medication (Paper 3). Paper 1 identified and combined pre-treatment characteristics of patients with early-onset PDD that moderate their benefit from disorder-specific Cognitive Behavioral Analysis System of Psychotherapy (CBASP) versus non-specific Supportive Psychotherapy (SP), thereby detecting two subgroups with differential treatment benefits. Paper 2 investigated treatment predictors and identified several subgroups

of patients experiencing a comparable treatment effectiveness of CBASP and SP. Finally, following the same question and methodology as Paper 1 for the comparison of CBASP and pharmacotherapy with Escitalopram plus Clinical Management (ESC/CM), Paper 3 identified two subgroups of patients with differential benefit from these two treatment options.

Altogether, the main findings of the three papers extend the body of evidence for treatment prediction in patients with PDD in several aspects: first, they show that behind the general cross-sample effects reported in the main studies, there exist underlying subgroup effects, suggesting that the effectiveness of the investigated treatments varies greatly depending on the patient's pre-treatment profile. Second, they present novel methodological approaches together with advantages of a multivariable consideration of the pre-treatment profile and its prediction of treatment response. Third and lastly, they provide new evidence for whom the treatments studied are more or less likely to work, possible underlying reasons, and other research questions that arise and need to be investigated by future research.

List of Abbreviations

ADM	Antidepressant medication
APA	American Psychiatric Association
CBASP	Cognitive Behavioral Analysis System of Psychotherapy
CBT	Cognitive-Behavioural Therapy
CDRS	Cornell Dysthymia Rating Scale
CTQ	Childhood Trauma Questionnaire
DSM	Diagnostic and Statistical Manual of Mental Disorders, respective edition indicated by following number
EPA	European Psychiatric Association
ESC/CM	Escitalopram plus Clinical Management
ETI	Early Trauma Inventory
HRSD	Hamilton Rating Scale for Depression
ICD	International Classification of Diseases, respective edition indicated by following number
IIP	Inventory of Interpersonal Problems
IPD-NMA	Individual Participant Data Network Meta-Regression
IPT	Interpersonal Therapy
Lasso	Least Absolute Shrinkage and Selection Operator (regression)
M*	Combined moderator (after H. C. Kraemer)
MADRS	Montgomery-Asberg Depression Rating Scale
MBCT	Mindfulness-Based Cognitive Therapy
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
PAI	Personalized Advantage Index
PDD	Persistent Depressive Disorder
RCT	Randomized Controlled Trial
SCID-5-CV	Structured Clinical Interview for DSM-5, Clinician Version
SP	Supportive Psychotherapy
SSRI	Selective Serotonin Reuptake Inhibitor
TAU	Treatment as usual
WHO	World Health Organization

List of Scientific Publications

This publication-based dissertation incorporates the following three scientific papers. Their corresponding full texts are included in the appendices.

Paper 1 | Appendix 1

Serbanescu, I., Walter, H., Schnell, K., Kessler, H., Weber, B., Drost, S., Groß, M., Neudeck, P., Klein, J. P., Assmann, N., Zobel, I., Backenstrass, M., Hautzinger, M., Meister, R., Härter, M., Schramm, E., & Schoepf, D. (2020). Combining baseline characteristics to disentangle response differences to disorder-specific versus supportive psychotherapy in patients with persistent depressive disorder. *Behaviour Research and Therapy, 124,* 103512. https://doi.org/10.1016/j.brat.2019.103512

Paper 2 | Appendix 2

Serbanescu, I., Backenstrass, M., Drost, S., Weber, B., Walter, H., Klein, J. P., Zobel, I., Hautzinger, M., Meister, R., Härter, M., Schramm, E., & Schoepf, D. (2020). Impact of Baseline Characteristics on the Effectiveness of Disorder-Specific Cognitive Behavioral Analysis System of Psychotherapy (CBASP) and Supportive Psychotherapy in Outpatient Treatment for Persistent Depressive Disorder. *Frontiers in Psychiatry, 11*, 607300. https://doi.org/10.3389/fpsyt.2020.607300

Paper 3 | Appendix 3

Serbanescu, I., Schramm, E., Walter, H., Schnell, K., Zobel, I., Drost, S., Fangmeier, T., Normann, C., & Schoepf, D. (2022). Identifying subgroups with differential response to CBASP versus Escitalopram during the first eight weeks of treatment in outpatients with persistent depressive disorder. *Behaviour Research and Therapy*. (Revised and Resubmitted)

1. Introduction

"In all its complexity, the question towards which all outcome research should ultimately be directed is the following: What treatment, by whom, is most effective for this individual with that specific problem, and under which set of circumstances?"

(Paul, 1967, p. 111)

"An important diagnostic question to be asked at screening when seeing a depressed psychotherapy patient is, "Is the patient chronically depressed?" If the answer is "yes," CBASP combined with an antidepressant medication is an appropriate treatment […]."

(McCullough, 2003, p. 244)

Worldwide, it is estimated that over 320 million people, representing 4.4% of the world's population, suffer from major depression, which is a global leading cause of disability (World Health Organization [WHO], 2017). Roughly 20-30% of the patients diagnosed with major depression develop a chronic course lasting two years or longer (Arnow & Constantino, 2003; Murphy & Byrne, 2012), while in clinical settings, up to 50% of the patients with depression are affected by a chronic course (Schramm et al., 2020). The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) introduced this condition as a distinct clinical category for the first time around a decade ago and labelled it "Persistent Depressive Disorder" (PDD) (American Psychiatric Association [APA], 2013). The performed differentiation was mainly due to the many observed clinical differences between episodic and chronic courses, with the latter being associated with more severe symptom profiles, more negative health consequences and poorer outcomes to various treatment approaches (Arnow & Constantino, 2003; Satyanarayana et al., 2009; Schramm et al., 2020).

Psychotherapies and antidepressant medication (ADM), delivered alone or in combination, are so far the two main pillars of treatment for PDD. Research undertaken for over more than two decades has shown that the treatment success of various investigated

psychotherapeutic and pharmacotherapeutic interventions is however limited for patients with PDD, particularly when compared to those with non-chronic depressive disorders (Cuijpers et al., 2010; Cuijpers et al., 2011; Thase, 2006). Numerous factors such as treatment commencement delays, low motivational attitudes of patients as well as insufficient treatment durations have been discussed as factors contributing to the scarcity of the treatment success in patients with PDD (Cuijpers, 2018; Schramm et al., 2020). Among them is also the mismatch of patients and treatments or the failure to assign the most beneficial available treatment to an individual patient, which is in turn the main driving aspiration and effort of the approach of personalized or precision medicine (Hamburg & Collins, 2010; Simon & Perlis, 2010). The core assumption of personalized medicine is that no single treatment works best for everyone, and that individual, pre-treatment (baseline) characteristics of patients must be considered when selecting the most appropriate type, form, duration, or path of administration of certain treatments in order to achieve maximum benefit and safety for the treated individual. In line with this view, the "European Psychiatric Association (EPA) Guidance Group on psychotherapy in chronic depression" has recommended clinicians to choose the type of psychotherapeutic treatment by considering individual baseline characteristics such as early versus late illness onset, type of PDD, number of episodes, childhood trauma, symptom severity, patient treatment preference or comorbidity of personality disorders (Jobst et al., 2016). Despite the evident plausibility of this meaningful recommendation, efforts to generate evidence for guiding personalized treatment selection and thereby improving treatment responses in patients with PDD are limited (Cuijpers et al., 2017; Schramm et al., 2020), which is largely due to the complexity of the topic and the associated challenges for both research and clinical practice (Cohen & DeRubeis, 2018). Therefore, it is of considerable scientific interest and urgent clinical need to expand the body of evidence towards personalized treatment selection for patients with PDD. With the aim of contributing new empirical findings to address this need, the three studies of this publication-based dissertation investigate the extent to which patients' baseline profiles predict or moderate their individual response to certain widely used psychotherapeutic and pharmacotherapeutic treatments. For this purpose, data

from a randomized controlled trial (RCT) comparing two psychotherapies for patients with PDD and another RCT comparing psychotherapy with pharmacotherapy are reanalysed.

The following Chapter 2 provides a theoretical framework including an overview on PDD (sub-chapter 2.1) and the academic field of personalized medicine (sub-chapter 2.2). This is complemented by the current state of research on personalized medicine for PDD provided in sub-chapter 2.3. Thereafter, Chapter 3 presents the motivation, aims and research questions of this dissertation, followed by a summary of the three scientific papers in Chapter 4 (see also Appendixes 1, 2, and 3 for full texts of all papers). Finally, Chapter 5 discusses the main empirical findings of the three papers in context of the available evidence, outlines their strengths and limitations, and reflects on future directions, hopes and pitfalls of personalized medicine for PDD with regard to research and clinical practice, before a general conclusion is drawn.

2. Theoretical Framework

2.1 Persistent Depressive Disorder

2.1.1 Nosology, assessment, and epidemiology of PDD

Nosology of PDD. The concept of chronic or persistent depression has been subject to considerable changes and controversies regarding its classification and diagnosis over the past few decades and up to date. To account for the large proportion of patients with a chronic course of depression, dysthymic disorder was first introduced in the DSM-III (APA, 1980) and later also in the tenth edition of the International Classification of Diseases (ICD-10; WHO, 1993) as a diagnosis for milder states of unipolar depression not fully meeting criteria for Major Depressive Disorder (MDD) but lasting for two years or more, warranting clinical attention due to the cumulative burden of the persistent symptoms. More precisely, dysthymia resulted as a consolidation of various older clinical constructs such as neurotic depression as well as depressive personality disorder (Klein et al., 1993; Schramm et al., 2020; Victor et al., 2006). In addition, chronic forms of depression with a more severe symptomatology found their classification by specifiers under the category of MDD. Up to the DSM-IV-TR (APA, 2000), they included chronic MDD (i.e., MDD lasting for at least two years), recurrent major depression without complete remission between the episodes, or double depression (i.e., a major depressive episode (MDE) superimposed on a pre-existing dysthymic disorder). The DSM-III and subsequent editions further classified dysthymia and the mentioned forms of chronic major depression into those with an early onset (i.e., younger than 21 years at onset) or late onset (i.e., 21 years or older at onset).

Simultaneously, over the years, a considerable number of studies emerged indicating several differences between chronic and episodic forms of depression. For instance, chronic forms of depression have been associated with greater childhood adversity (Angst et al., 2009; Lizardi et al., 1995; Rhebergen et al., 2009; Wiersma et al., 2009). Moreover, compared to episodic depression, chronic depression is marked by a longer illness duration, a lower life quality, higher rates of comorbid psychiatric and personality disorders, more suicide attempts,

pronounced dysfunctional interpersonal behaviour as well as poorer responses to various treatments (Arnow & Constantino, 2003; Berndt et al., 2000; Jobst et al., 2016). At the same time, the at that time differentially classified dysthymia, double depression, and chronic major depression appeared to strongly similarize in terms of their association with comorbid anxiety, personality disorders, maladaptive coping styles, childhood trauma and poor chances of treatment response (e.g., Blanco et al., 2010; Klein et al., 1995; Lizardi et al., 1995; McCullough et al., 2000; McCullough et al., 2003; Pepper et al., 1995). Taken together, this accumulating evidence questioned the meaningfulness of the distinctions between the various forms of chronic depression presented in the DSM version of that time, and chronic, or as a newer term, *persistent* depressive disorder was proposed as a distinct clinical category in advance of the development of the fifth version of the DSM in response to the growing body of research emphasizing the homogeneity of different types of chronic depression (Schramm et al., 2020). With the DSM-5 (APA, 2013), PDD was thus introduced for the first time as a unique diagnostic category, encompassing the DSM-IV-TR defined category of dysthymic disorder as well as those forms of MDD with chronic specification. This new classification has again encountered scientific debate (e.g., Parker & Malhi, 2019), and implies caution when transferring older scientific results to patients diagnosed with PDD according to the DSM-5. Among others, there has been a proposal for an alternative, more unifying model that conceptualizes PDD along the two dimensions of severity and longitudinal course (Schramm et al., 2020), as the DSM-5 classification places more relevance to the duration of illness rather than its severity. Furthermore, classifying chronic or persistent depression also remains a question of the applied diagnostic system nowadays: the eleventh edition of the ICD (ICD-11; WHO, 2019) contains a category for dysthymic disorder (code: 6A72) and persistent MDE (code: 6A80.2), but not the PDD concept according to the DSM-5 as such.

Assessment of PDD. Table 1 displays the diagnostic criteria and specifications of PDD according to the DSM-5 (APA, 2013). Briefly, for being diagnosed with PDD, a patient must experience depressed mood for most of the day, for most of the days, as indicated by either subjective account or observation by others, for at least two consecutive years, with the

modification of one year in children and adolescents (Criterion A). Moreover, the persistent depressed mood must be accompanied by at least two of the following six symptoms: poor appetite or overeating, insomnia or hypersomnia, low energy or fatigue, low self-esteem, poor concentration, difficulties in making decisions, or feelings of hopelessness (Criterion B). Furthermore, to be diagnosed with PDD, the person must never have been without symptoms of criteria A and B for more than two months at a time during the two-year period of the disorder (Criterion C). Importantly, the symptomatology must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning (Criterion H) and must not be attributable to the physiological effects of a substance or another medical condition or psychiatric disorder (Criterions F and G). During this two-year period, the criteria for MDD can (but must not) be continuously present (Criterion D).

The DSM-5 (APA, 2013) further provides specifiers that define possible combinations between dysthymia and MDD, including: 1) PDD of pure dysthymic syndrome with no MDE occurring during the two-year period; 2) Persistent MDD, whereby the full criteria for a MDE have been met throughout the two-year period; 3) PDD with intermittent MDE, with current episode, whereby full criteria for a MDE are currently met, but there have been periods of at least eight weeks in at least the preceding two years with symptoms below the threshold for a full MDE; and 4) PDD with an intermittent MDE, without current episode, whereby full criteria for a MDE are not currently met, but there has been one or more MDEs in at least the preceding two years. Moreover, the clinician can specify the current illness severity (mild, moderate, or severe), the type of illness onset (an early onset before age 21 years or a late onset at age 21 years or older), or the presence of specific features (e.g., melancholic, or atypical). The status can be further classified as in partial or full remission.

To diagnose PDD, clinicians must thus not only check for the current presence of symptoms of Criteria A and B, but also assess their presence over the last two years and examine the patient´s life history for ruling out a history of mania, hypomania, or cyclothymic disorder. This can be challenging, as many patients with depression present autobiographical memory deficits (Dalgleish & Werner-Seidler, 2014; C. Köhler et al., 2015).

Table 1

Diagnosis criteria for Persistent Depressive Disorder according to DSM-5 (code 300.4)

Criteria	Specifiers
A. Depressed mood for most of the day, for most of the days, as indicated by either subjective account or observation by others, for at least two consecutive years (or one year in children and adolescents). B. Depressed mood is accompanied by at least two of the following six symptoms: 1. Poor appetite or overeating 2. Insomnia or hypersomnia 3. Low energy or fatigue 4. Low self-esteem 5. Poor concentration or difficulty making decisions 6. Feelings of hopelessness C. During the 2-year period of the disturbance, the individual has never been without the symptoms in Criteria A and B for more than two months at a time. D. The criteria for MDD may be continuously present for two years. E. There has never been a manic episode or a hypomanic episode, or a cyclothymic disorder. F. The disturbance is not better explained by a persistent schizoaffective disorder, schizophrenia, delusional disorder, or another specified or unspecified schizophrenia spectrum or other psychotic disorder. G. The symptoms in Criteria A and B are not attributable to the physiological effects of a substance or another medical condition. H. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.	Specify if (for most recent two years of PDD) with: • Pure dysthymic syndrome (full criteria for a MDE have not been met in at least the preceding two years) • Persistent MDE (full criteria for a MDE have been met throughout the preceding 2-year period) • Intermittent MDEs, with current episode (full criteria for a MDE are currently met, but there have been periods of at least eight weeks in at least the preceding two years with symptoms below the threshold for a full MDE) • Intermittent MDEs, without current episode (full criteria for a MDE are not currently met, but there has been one or more MDEs in at least the preceding two years) Specify if with: • Anxious distress • Mixed features • Melancholic features • Atypical features • Mood-congruent psychotic features • Mood-incongruent psychotic features • Peripartum onset Specify current severity: • Mild • Moderate • Severe Specify if: • In partial remission • In full remission Specify if with: • Early onset (illness onset was before age 21 years) • Late onset (illness onset was at age 21 years or older)

Note. Presented diagnostic criteria are based on the DSM-5, code 300.4 (APA, 2013).

In addition to standardized manuals, a life chart constructed together with the patient can be useful to track the level of depression over time (McCullough et al., 2016).

For diagnosing PDD according to DSM-5, trained clinicians can use the Module A "Mood Episodes and Persistent Depressive Disorder" of the semi-structured Structured Clinical Interview for DSM-5, Clinician Version (SCID-5-CV; First et al., 2016). To help clinicians rate criteria as present or absent, interview questions are assigned to each DSM-5 criterion. Notably, the professional background of raters (psychiatrists versus psychologists) was associated with significant disagreements in rating PDD by the SCID-5-CV, leading to its potential underestimation (Osório et al., 2019). The majority of other, older fully structured and semi-structured diagnostic interviews contain a section for assessing dysthymic disorder, with some instructing raters to skip the dysthymia section when a recent or recurrent MDE is present, which is why diagnoses of double depression have been often overlooked (Schramm et al., 2020).

When it comes to clinician-rated scales, it is important to check whether the symptoms that are classified under PDD are actually captured or not by the respective scale (Schramm et al., 2020), which is the case for the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1967), but nor for other scales. Notably, Mason and colleagues developed the clinician-rated 20-item Cornell Dysthymia Rating Scale (CDRS) especially for diagnosing dysthymia (Mason et al., 1995). The CDRS was found to have greater severity range scores and a better content validity than the 21-item version of the HRSD with regard to dysthymic patients (Hellerstein et al., 2002).

As for self-report inventories, the General Behaviour Inventory (Depue et al., 1989) is so far the only self-report based questionnaire especially developed to assess chronic mood disorders including dysthymia (Schramm et al., 2020), having good psychometric properties and significantly discriminating patients with dysthymia from patients with non-chronic major depression and nonaffective disorders (Mallon et al., 1986).

Despite these available older and newer tools for its assessment, PDD often remains unrecognized and undiagnosed in clinical practice (Schramm et al., 2020). This may be due in

part to the fact that many patients with early-onset PDD consider symptoms as part of their personality, thereby not reporting them in clinical interviews (Akiskal, 1983), with many diagnostic instruments defining and assessing patients' symptoms as deviations from their usual state (Schramm et al., 2020). Together with the different terms used to define chronic depression over the decades and the existing current controversies around its appropriate classification, these aspects pose challenges for the diagnosis of PDD in clinical practice and for comparing studies conducted across various clinical populations diagnosed with PDD following different criteria.

Epidemiology of PDD. The lifetime prevalence of dysthymia and chronic major depression has been estimated to range between 1% and 6% (Blanco et al., 2010; Kessler et al., 1994; Kessler et al., 2005; Markkula et al., 2015; Rubio et al., 2011). Concerning the newer diagnostic construct of PDD, the 12-month prevalence in the United States has been estimated at 0.5% by the DSM-5 (APA, 2013). This number is somewhat lower than the lifetime prevalence of 4.6% found by Murphy and Byrne (2012) in a nationally representative Australian study. Moreover, in a study conducted in Swiss adults, Vandeleur and colleagues (2017) reported a lifetime prevalence for any DSM-5 subtype of PDD of 18.0%. National differences between the assessed populations, the assessed PDD subtypes, together with the variability in applied diagnostic criteria may likely cause the variation in these numbers. For instance, lifetime prevalence varied considerably between the different DSM-5 PDD subtypes in the study by Vandeleur and colleagues (2017), with a rate of 15.2% for PDD with a persistent MDE, 2.5% for PDD with pure dysthymic syndrome, and 0.4% for PDD with an intermittent MDE.

Roughly 20-30% of patients with diagnosed major depression develop a chronic course lasting two years or longer (Arnow & Constantino, 2003; Murphy & Byrne, 2012), while in clinical settings, 33% to 50% of patients with depressive disorders present with a chronic course (Benazzi, 1998; Ildirli et al., 2015; Markowitz et al., 1992). Furthermore, the prevalence of PDD is nearly double as high for women as for men (Blanco et al., 2010; Garcia-Toro et al.,

2013; Vandeleur et al., 2017), which needs to be further elaborated with regard to possible causal factors.

2.1.2 Aetiology and risk factors of PDD

While extensive neurobiological research has been conducted to understand the risk factors and aetiology of non-chronic depression, comparative little attention has been paid to investigate similar questions for dysthymia and other forms of chronic depression (Schramm et al., 2020). In addition, the variety in the classification of PDD over decades makes it challenging to review literature on its aetiology and risk factors, given the heterogeneity of the assessed populations across different studies.

In general terms, the development and maintenance of PDD is most likely multifactorial and highly complex. Besides a certain role of genetic heritability, the DSM-5 briefly further lists early parental loss or separation as well as a negative affective temperament as risk factors for PDD (APA, 2013). Although there is no clearly confirmed cause or pathophysiology of PDD, its development seems to be particularly linked to increased levels of childhood adversity and trauma, certain unfavourable personality traits and personality disorders, lengthy environmental stress as well as a heightened stress reactivity (Riso et al., 2002). With PDD often having an early onset, the roles of adverse childhood experiences and the childhood home environment have been often subject to investigation and found to be one of the most replicable risk factors in the development of PDD. Numerous studies have linked the development and persistence of chronic forms of depression to childhood adversity. For instance, in a multi-center trial conducted in Germany, Schramm and colleagues (2017) found 74.2% of the outpatients with early-onset PDD to report childhood trauma experiences, with childhood emotional abuse and neglect being the most commonly reported forms (59.0% and 65.5%, respectively). Similar, in another German study, Negele and colleagues (2015) found 75.6% of the chronically depressed patients to report at least one form of childhood trauma, while 37.0% reported at least three forms of childhood trauma, which was associated with significantly more severe depressive symptoms later in life. Additionally, in contrast to non-

chronic courses, PDD has been associated more often with experiences of childhood emotional neglect, psychological abuse, physical abuse, and sexual abuse in a study by Wiersma and colleagues (2009). Moreover, patients with PDD reported a significantly poorer parental care during their childhood compared to patients with episodic depression (Lizardi et al., 1995). Finally, a meta-analysis by Nelson et al. (2017) found that depressive disorders are twice as likely to take a chronic course in individuals with a history of childhood maltreatment.

These various findings regarding adverse events in the childhood history of patients with PDD have been postulated to derail their social-emotional maturational development and entrap them until adulthood in a preoperational state of psycho-emotional development often reported in PDD patients with an early illness onset (McCullough, 2021). Pronounced interpersonal fear, avoidance behaviour, insecure attachment styles and the perceptual disconnection from one's social-interpersonal environment are further consequences causing persistent interpersonal problems for patients with PDD, which are particularly addressed by the CBASP (McCullough, 2000; McCullough, 2021).

Moreover, several studies have investigated the association between personality, personality disorders and PDD. For instance, neuroticism has been revealed to be the strongest predictor for dysthymia in a four-year follow-up study of patients with major depression (Weissman et al., 1988). Moreover, patients with dysthymia showed higher levels of neuroticism and introversion compared with nondepressed individuals in another study (McCullough et al., 1994). Interestingly, both personality traits remained elevated after recovery from dysthymia in a follow-up study (Hirschfeld, 1990), suggesting their possible role as contributing factors in the development of the disorder. Furthermore, comorbidity with various personality disorders is generally high in PDD: patients with PDD have higher rates of avoidant personality disorder, borderline personality disorder and antisocial personality disorder compared to patients with episodic depression (e.g., Klein et al., 2015; Rothschild & Zimmerman, 2002). Possible, childhood adversities and certain personality traits or disorders may interact with each other in causing PDD, as avoidant personality disorder was found to interact with the effects of childhood trauma in the development of PDD in a retrospective

analysis by Klein and colleagues (2015). Further studies are needed to investigate the multifactorial relationship between different risk factors of PDD.

With regard to genetic risk factors, a review by Schramm and colleagues (2020) on dysthymia and PDD underlined the scarcity and low quality of most conducted behavioural, genetic, and molecular genetic studies conducted on dysthymia and chronic depression and refrains therefore from any conclusions about the influence of genetic factors in the development of PDD, warranting further research on this topic. The same was concluded for literature on altered brain structure and function in patients with PDD. Prospective studies, larger sample sizes, replication trials in independent samples and genome-wide approaches should be an integral part of future neurobiological research aimed at revealing neurobiological and genetic risk factors of PDD. In addition, future research may adopt a more personalized approach by considering the clinical heterogeneity of the disease phenotype (Schramm et al., 2020).

2.1.3 Treatment of PDD

Psychotherapy and pharmacotherapy, delivered as monotherapy or in combination, are so far the two main pillars of treatment for PDD. A large body of research suggests that pharmacotherapeutic and psychotherapeutic interventions are generally less effective for chronic forms of depression, particularly dysthymia, than for episodic depressive disorders (Cuijpers et al., 2010; Cuijpers et al., 2011; Thase, 2006). More precisely, patients with PDD are more likely to have a higher frequency of underwent treatments as well as a longer average treatment duration compared to those with a non-chronic course (S. Köhler et al., 2018). In a study by Angst and colleagues (2009), the lifetime prevalence of treatment for depression was 81.8% for patients with PDD in contrast to 60.7% for patients with non-chronic MDD. Regarding inpatient treatment, patients with PDD showed a lifetime prevalence of 24.1% for hospitalizations due to mental health problems in contrast to 12.1% in patients without chronic depression (Satyanarayana et al., 2009). Furthermore, inpatients with PDD were reported to

have a longer average duration of inpatient treatments, as well as lower response and remission rates in a study by S. Köhler and colleagues (2015).

On the other hand, it is not uncommon for patients with PDD to seek their first treatment only several years after the onset of the disorder, which may result in a less positive outcome even when the appropriate treatment is provided (Schramm et al., 2020). Moreover, a positive treatment outcome is often impeded by an insufficient dose or duration of the administered treatment (Kocsis et al., 2008), with many patients showing a relatively low treatment compliance (Gopinath et al., 2007). The scarcity of treatment responses may explain why approximately 40% of patients with PDD are considered treatment-resistant in terms of their symptomatology (Schramm et al., 2020), although there is no consensus on the definition of treatment-resistant depressive symptoms in either research or clinical practice (Brown et al., 2019). In the following, previous evidence on the general effectiveness of various forms of psychotherapy, pharmacotherapy, and their combination will be reviewed. The suitability of specific therapies for individual subgroups of PDD patients will be further addressed in sub-chapter 2.3. Moreover, the German health care guideline for the treatment of unipolar depression will be briefly presented with regard to its current recommendations for the treatment of PDD within the German health care system.

Psychotherapy. Psychotherapy, along with pharmacotherapy, is one of the two central components in the treatment of PDD. A meta-analysis based on 16 RCTs conducted in patients with chronic major depression and dysthymia by Cuijpers and colleagues (2010) revealed that in general, psychotherapy has a small yet significant effect (d = 0.23; 95% CI: 0.06 to 0.41) on PDD compared with various control groups such as treatment as usual (TAU), nonspecific control groups, placebo, or wait-list. This meta-analysis further found that the size of the effect was related to the number of psychotherapy sessions, with a minimum of 18 sessions being necessary for psychotherapy to achieve an optimal effect in patients with PDD. The fact that all investigated single studies contained psychotherapeutic interventions with fewer than 18 sessions could be one explanation for the relatively general low effect of psychotherapy in PDD, particularly in patients with dysthymia (Cuijpers et al., 2010). This

conclusion is supported by other findings, which suggest that a longer duration of psychotherapy and a higher number of sessions results in better outcomes for PDD patients (Schramm et al., 2015; Schramm et al., 2017; Wiersma et al., 2014).

Regarding single psychotherapies, most research has been conducted on the effectiveness of CBASP as the only psychotherapy model specially designed to meet the needs of patients with PDD (McCullough, 2000). CBASP operates on different techniques including situation analysis, interpersonal discrimination exercises, and behavioural skills training by using the patient-therapist relationship as a central therapeutic tool of interpersonal fear reduction (McCullough, 2000; McCullough, 2003). In a systematic review and meta-analysis by Negt and colleagues (2016) based on six RCTs comprising a total of N = 1510 patients with PDD, the authors reported a significant posttreatment effect size of small magnitude (g = 0.34; 95% CI: 0.09 to 0.59; p = 0.007), indicating a small general superiority of CBASP over the compared conditions including TAU, Brief Supportive Psychotherapy, ADM, Interpersonal Therapy (IPT) or Mindfulness-Based Cognitive Therapy (MBCT). More precisely, CBASP had a general superiority when compared to other psychotherapies such as IPT (Schramm et al., 2011), SP (Schramm et al., 2017), or TAU consisting of psychotherapy treatments generally offered to PDD patients in Dutch study centres (Wiersma et al., 2014). In another RCT included in this meta-analysis, Michalak and colleagues (2015) compared TAU to a 8-week group version of CBASP plus TAU as well as MBCT plus TAU in a sample of patients with PDD and could not detect a significant difference between the effects of these two latter treatment groups, but a non-significant trend favouring CBASP over MBCT in reducing depression severity. Furthermore, the CBASP plus TAU group was significantly more effective in reducing depressive symptoms than TAU.

Notably, a recent paper by Habtewold and colleagues (2022) addressed several methodological limitations in relation to the meta-analysis by Negt and colleagues (2016) and presented the results of an updated version of this meta-analysis including a further RCT by Rief and colleagues (2018) in the study database. Their reported findings from both a conventional meta-analysis and an additional Bayesian meta-analysis suggested that CBASP

was not significantly superior to other treatments overall, which is in contrast to the earlier findings of Negt and colleagues (2016). This main finding was further confirmed in a leave-one-out sensitivity analysis excluding single studies. A further meta-regression including the number of sessions as a potential moderator showed that additional treatment sessions, however, significantly increased the effect size. However, as expressed in a comment by Elsaesser and colleagues (2022), the meta-analysis by Habtewold and colleagues (2022) merits critical evaluation itself due to several reasons: the authors did not base their analysis on a systematic review, omitted one large RCT conducted in outpatients with PDD (Schramm et al., 2017), and instead included the additional RCT (Rief et al., 2018) that comprised mostly patients with episodic depression. Given these and other methodological weaknesses of this newer meta-analysis, its results remain questionable.

While most RCTs conducted on PDD mainly involved outpatient samples, there are also some studies that have examined CBASP in an inpatient setting. For instance, Brakemeier and colleagues (2011) investigated the acceptance and effect of CBASP in a sample of N = 10 inpatients with DSM-IV (APA, 1994) defined severe chronic depression. Patients rated their satisfaction with CBASP as high and improved significantly in terms of depression severity. These promising results could be confirmed by a larger study conducted by Sabaß and colleagues (2018), who investigated the feasibility of 10 sessions of CBASP delivered as group therapy in a naturalistic multi-center trial conducted in N = 116 inpatients with PDD. Overall, the results indicated that CBASP was well accepted by both patients and therapists. It was further associated with significant improvements in both depression and quality of life. Moreover, in a pilot study by Brakemeier and colleagues (2015), CBASP appeared to be feasible as a 12-week treatment delivered for N = 70 treatment-resistant inpatients with PDD, leading to a clinically relevant effect size, a response rate of 75.7% and a remission rate of 40.0%. However, the findings of these studies should be interpreted with caution given the lack of a control group and their small samples sizes.

Further advocacy for the use of CBASP for PDD was provided by the expert panel review of the “EPA Guidance Group on Psychotherapy in chronic depression”, which concluded that

psychotherapeutic treatment specifically targeting patients' common characteristics should be a clinician's first choice, which is why CBASP has been recommended as first-line treatment for PDD (Jobst et al., 2016). This recommendation was based on the comprehensive evaluation of numerous systematic reviews, meta-analyses, RCTs, as well as cohort studies, case series, and open studies conducted to examine the effectiveness of CBASP for PDD.

As a further result, given the rather limited evidence of its effectiveness for PDD, Cognitive-Behavioural Therapy (CBT) has been recommended as a third-line treatment for PDD. Further, due to the limited available empirical support as well as the clinical experiences of experts, the same recommendation was provided for psychodynamic and psychoanalytic treatments, as well as for Problem-Solving Therapy, Schema Therapy, Radically Open Dialectic Behavioural Therapy and MBCT (Jobst et al., 2016). The effectiveness of these approaches needs to be further examined in future trials, preferably by adopting a personalized, sample-stratifying approach. In line with this, the expert panel recommended clinicians to select the type of psychotherapy on an individual basis, taking into account patient personal characteristics such as early or late onset, type of depression, number of episodes, recall of childhood trauma, symptom severity, treatment preference, or comorbidity of personality disorders (Jobst et al., 2016). To date, however, there have been very few studies examining which psychotherapies work best for patients with these characteristics (see also sub-chapter 2.3). The overarching aim of Paper 1 (Serbanescu, Walter, et al., 2020) of this dissertation is to provide evidence to help understand which of two psychotherapies (i.e., disorder-specific CBASP versus non-specific SP) is likely to work better for certain subgroups of patients, while Paper 2 (Serbanescu, Backenstrass, et al., 2020) aims to provide evidence to help understand which subgroups of patients are likely to benefit more or less from both psychotherapies.

Pharmacotherapy. Several short- and long-term clinical trials have investigated the effect of several classes of ADM in patients with chronic depression and dysthymia. A review by Kocsis (2003) yielded that the effectiveness of antidepressants in dysthymia and double depression has been demonstrated reasonably conclusively in several six to 12-week short-term studies, although the average rate of complete remission has been well below 50%. Long-

term studies found maintenance therapy with Desipramine and Sertraline to be more effective than placebo in patients who respond to the acute and continuation phases of treatment. The need of studies with sequential algorithms of pharmacotherapy, of augmentation strategies for patients who are not fully responsive to the first treatment, and of psychotherapy as an alternative or adjunctive treatment was finally pointed out in this review. In addition, a newer network meta-analysis of pharmacological interventions for PDD revealed that selective serotonin reuptake inhibitors (SSRIs), Moclobemide, Imipramine, Ritanserin, and Amisulpride were in average more efficacious and at least as acceptable as placebo (Kriston et al., 2014). Moreover, the SSRI Fluoxetine proved to be less effective, and Imipramine less acceptable than other drugs in this study.

When compared to psychotherapy, pharmacotherapy, especially in the form of SSRIs, was more effective (d = -0.31; 95% CI: −0.53 to −0.0) in a meta-analysis by Cuijpers and colleagues (2010). However, this result was exclusively due to patients with dysthymia included in the analysed studies, leaving open the question of which type of treatment works likely better in other forms of PDD. In an Individual Participant Data Network Meta-Regression (IPD-NMA) by Furukawa and colleagues (2018) based on three RCTs with broader PDD populations, psychotherapy and ADM showed essentially similar results when delivered as monotherapies. However, this result was only valid for patients with characteristics near the population averages (e.g., low or moderate baseline depression and anxiety), with both monotherapies displaying different effects depending on the severity of baseline depression and anxiety, previous history of pharmacotherapy, age at baseline, and PDD subtypes. These important results suggest that for some subgroups of patients either CBASP or ADM alone is a likely more effective treatment option and highlight the need for more investigations. Paper 3 of this dissertation aims to provide further evidence on which subtypes of patients with DSM-IV defined chronic depression are likely to benefit more from monotherapy with Escitalopram in combination with Clinical Management than from CBASP and vice versa.

Combination treatment of psychotherapy and pharmacotherapy. Regarding the evaluation of combination treatments consisting of pharmacotherapy and psychotherapy

versus pharmacotherapy or psychotherapy delivered as monotherapy, a number of systematic reviews and meta-analyses consistently revealed that patients with PDD are likely to benefit more from a combined treatment (e.g., Cuijpers et al., 2010; Kriston et al., 2014; Spijker et al., 2013; von Wolff et al., 2012). In addition, a 12-week single-trial by Manber and colleagues (2008) revealed that the combination of ADM and psychotherapy led to full remission from PDD more rapidly than either of the two treatment options delivered as monotherapies, which did not differed from each other. Moreover, two extensive clinical trials conducted in patients with PDD revealed that the majority of patients preferred combination therapy over monotherapy (Kocsis, Leon, et al., 2009; Steidtmann et al., 2012). In line with this, the IPD-NMA by Furukawa and colleagues (2018) suggested that a combination of CBASP and ADM was significantly superior over both monotherapies in terms of efficacy and acceptability.

However, in a reanalysis of archival data, Stulz and colleagues (2010) identified three PDD patient subgroups based on their typical patterns of change in depression severity during a 12-week acute treatment phase. Differential treatment effects were found in these three subgroups, with combination treatment consisting of CBASP plus Nefazodone outperforming the two monotherapies with CBASP and Nefazodone in the largest patient subgroup, which was characterized by a moderate baseline depression severity, but not in the remaining two subgroups, which were characterized by low and severe depression severities at baseline. Consequently, these results suggest that it is not reasonable to generalize that a combination treatment of ADM and psychotherapy is likely to work better than monotherapy with either ADM or psychotherapy for any given patient. In line with this, several studies could not demonstrate a clear benefit for combination treatment versus ADM alone in patients with dysthymia (e.g., Browne et al., 2002; Markowitz et al., 2005). Taken together, and similar to other previously mentioned findings related to the effectiveness of monotherapies, these results suggest that interindividual differences exist between several PDD subgroups regarding their benefit from combination treatment over monotherapy. Once more, personalized medical research focusing on the differential effect of combination versus single treatments is required,

which will however not be addressed within the scope of this dissertation, which focuses on comparing the effects of various monotherapies.

Recommendations of the German Care Guideline for the Treatment of Unipolar Depression with regard to the treatment of PDD. The German Care Guideline for the Treatment of Unipolar Depression ("Nationale Versorgungsleitlinie – Unipolare Depression – Version 3.0"; Bundesärztekammer et al., 2022), which was released by several national committees at the end of September 2022 and will remain valid for the German health care system until its next revision in 2027, includes several recommendations for the management of PDD in a specific subchapter. According to this guideline, the recommendations are based on the extrapolation of scientific evidence as well as on the results of systematic searches and systematic reviews. Because of the low quality of evidence, recommendations regarding PDD are mainly consensus-based and rely on clinical considerations. More precisely, for previously untreated chronic depressive disorders, severity-specific recommendations for acute depressive episode should be followed. From the point of view of the expert panel, the choice of treatment should be based not only on the severity but also on the type of symptoms and other individual factors, however without specifying these further. An initial treatment attempt with monotherapy, preferably psychotherapy, appears to be reasonable in terms of a stepped-care approach, considering chronification as a risk factor for non-response. Additionally, appropriate supportive services such as exercise or light therapy as well as peer support can be offered to the PDD patient. Furthermore, for moderate and severe forms of PDD, combination treatment of psychotherapy and pharmacotherapy may be considered according to the national guideline. Low-intensity or internet- and mobile-based interventions, on the other hand, do not represent adequate options for therapy-naive PDD in the view of the expert panel of the guideline. Moreover, according to the panel, CBASP is particularly suitable for patients with an early illness onset and/or a trauma history. However, due to the lack of widespread availability and because CBASP elements are also used by other cognitive-behavioural therapy interventions, the expert panel sees no need for a specific recommendation of CBASP for PDD. As for dysthymia, the

panel recommends the same clinical management approach as for other PDD forms given the high burden of suffering. Further, the national guideline does not recommend favouring psychotherapy over pharmacotherapy and vice versa. In the case of non-response to monotherapy, the panel recommends combination treatment of psychotherapy and pharmacotherapy. As for double depression, combination therapy is considered appropriate. Finally, according to the expert panel, when depressive disorders become chronic despite an applied treatment, the type of previous treatment is decisive for the choice of further therapy. Consequently, depressive disorders that have become chronic despite an applied treatment should be treated according to the guideline recommendations for action in the event of non-response or resistance to a treatment. These include evaluating the cause of non-response or resistance to a previously applied treatment, modifying specific elements of the applied therapy, selecting a different therapy, adding another therapy, or using measures to improve the therapy adherence (Bundesärztekammer et al., 2022).

2.2 Personalized Medicine – moving beyond "one size fits all"

2.2.1 Definition of Personalized Medicine

As stated by Kraemer & Gibbons (2009), from a statistical perspective, an effect size comparing two different treatments tested in an RCT represents merely an average effect over multiple individual patients included in the analysis; however, *"It is seldom, if ever, true that "one size fits all", that the effect size in a population, particularly a heterogeneous one, applies to every individual patient within that population."* (Kraemer & Gibbons, 2009, p. 739). In conclusion, the fact that many treatments showing statistically significant effects in RCTs turned out to be of poor effect when used for individual patients in mental health care has necessitated a more personalized approach to both research and treatment (Kraemer, 2016). The resulting development of personalized treatment approaches, or, more briefly, of *personalized medicine*, is widely considered to be one of the most promising but also greatest challenges for health research in the coming decades (Hamburg & Collins, 2010; Topol & Lauer, 2003).

In the last decades, the term "personalized medicine" has been widely used across different spheres of the healthcare system such as patient care and research, while lacking a clear definition and thus remaining open to interpretation at the same time (Schleidgen et al., 2013). Nonetheless, there is largely consensus across literature in that compared to population-based research models, personalized medicine relies on using a patient's individual socio-demographic, clinical, (neuro-)biological, genetic or environmental characteristics as basis for making predictions regarding illness prevention, diagnosis as well as treatment effects and selection (Simon & Perlis, 2010; Wium-Andersen et al., 2016). More precisely, the main three goals of personalized medicine are to predict the individual's susceptibility to a certain disease or disorder, to achieve an accurate individual diagnosis, and to provide an efficient and favourable treatment (Ozomaro et al., 2013). Thus, instead of focusing on general treatment effects or illness trajectories in a clinical population, research embracing the philosophy of personalized medicine seeks to understand how certain preselected pre-treatment or pre-illness characteristics influence the treatment outcome, or, respectively, the illness trajectories.

Other synonyms frequently used are "individualized medicine" or "precision medicine", the latter of which was introduced by the US National Research Council as a more appropriate substitute for "individualized medicine", which was thought to be misinterpreted as implying that individualized treatments are provided for individuals (National Research Council (US) Committee on A Framework for Developing a New Taxonomy of Disease, 2011). The term personalized medicine is also to differentiate from the one of "stratified medicine", which is often used as a synonym, but which is rather aiming at identifying biomarkers or psychological tests in order to stratify patients in subgroups relevant to treatment instead of matching treatments to individual patients based on their promising effectiveness (Wium-Andersen et al., 2016).

As proposed by Schleidgen and colleagues (2013), the methodology of research based on personalized medicine can be basically divided into its ends (*what does it want to optimize/improve?*) and means (*by what means does it achieve this?)*. In terms of ends,

personalized medicine may aim at improving or optimizing the outcome of treatments regarding different dimensions such as effectiveness (e.g., reducing illness severity or certain symptoms), safety (e.g., reducing side effects), or cost-efficiency. This is strongly related to the aim of personalizing treatment selection, i.e., the expertise to match patients with what is likely to be the most effective, and/or safe, and/or cost-efficient treatment. Moreover, personalized medicine can aim to improve the accuracy of diagnostics and the prediction of illness trajectories (Wium-Andersen et al., 2016). In terms of its means, in order to successfully reach these overarching aims, personalized medicine research relies on pre-treatment or baseline characteristics such as biomarkers, clinical factors, or phenomenology (Cuijpers et al., 2012; Schleidgen et al., 2013; Wium-Andersen et al., 2016), which are used to predict the selected ends as accurate as possible. Most research literature based on personalized medicine and related terms has focused on genetic and molecular predictors of treatment response, as shown by a comprehensive review including 683 papers using the term of personalized medicine by Schleidgen and colleagues (2013). However, this represents an existing research bias, as in mental health research (and not only there), predictors and moderators of treatment response may also origin from other categories relevant for treatment outcome.

Moreover, personalized medicine may focus on predicting post-treatment ends with regard to single treatments, or on predicting the differences in these ends (e.g., effectiveness) between two or more treatments which are directly compared, as for instance in an RCT. This is investigated at the level of patient subgroups, rather than the entire sample (Cohen & DeRubeis, 2018; Kraemer et al., 2006), and requires specific statistical methods in order to achieve predictive accuracy. The following sub-chapter 2.2.2 provides an overview of older and newer statistical methods used in personalized medical research.

2.2.2 Statistical Approaches in Personalized Medicine

For investigating the question of "*what works for whom*?" in depression research, most studies to date have relied on single variables prediction models, thereby identifying isolated predictors or moderators of treatment outcome (Cohen & DeRubeis, 2018). However, due to

several reasons, multivariable prediction methods that use data from RCTs to build statistical models linking several patient characteristics to the outcome have been also developed and applied over time. The main methodological definitions and used statistical single- and multivariable approaches are presented and discussed in the following section.

Predictor variables. Let´s assume one wants to learn whether a particular baseline variable (e.g., age at baseline) can predict the treatment outcome (e.g., post-treatment depression severity) of one or two treatments compared in an RCT (e.g., CBASP versus ADM). In an RCT, for a variable to be a predictor of an outcome, it must first timely precede both the treatment and the outcome (i.e., be measured before the treatment start or at randomisation/ baseline) and, second, be statistically correlated with the outcome variable obtained after the treatment or intervention (Kraemer, 2013). Theoretically, in an RCT comparing two treatments, a baseline variable can be a predictor of the treatment outcome in 1. the treatment group, 2. the control or comparison group, 3. both, or 4. neither (Kraemer, 2013). For instance, a higher age may predict a higher mean post-treatment depression severity in both the CBASP and ADM group, or only in one of the two groups. The strength of prediction can vary and is usually conveyed by a correlation coefficient between the baseline variable and the outcome variable (Kraemer, 2013). Importantly, with regard to the interpretation of results, the correlation between predictor and outcome variables implies no direct causality between them.

Moderator variables. A researcher may next want to learn whether a particular baseline variable (e.g., gender) can predict the difference in outcome (e.g., post-treatment depression severity) between two treatments directly compared in an RCT (e.g., CBASP versus ADM). In our example, we may want to explore the question of whether women do likely benefit more from CBASP than from ADM compared to men, and vice versa (i.e., do men likely benefit more from ADM than from CBASP compared to women). In an RCT, for being a moderator of the treatment effect on the outcome, a variable must fulfil three conditions: first, the moderator variable must timely precede the treatment (i.e., be measured before the treatment start or at randomisation/baseline) which, in turn, must timely precede the outcome. Second, the moderator variable and treatment allocation must be statistically

independent form each other, which can be assured by randomisation (Kraemer, 2013). In our example with gender as potential moderator, statistically equal proportions of men and women would have to be distributed across the two treatment groups at baseline. Third, if the study sample is stratified by the moderator variable (e.g., men versus women), the treatment effect size (e.g., of CBASP versus ADM) is different in the stratified subgroups (Kraemer, 2013). In our example, CBASP might be associated with a lower post-treatment mean depression severity than ADM in women, whereas in men, ADM might be associated with a lower post-treatment mean depression severity than CBASP. In summary, a moderator of treatment effect is a baseline variable that identifies subgroups of patients within the study sample who have different treatment effect sizes (Kraemer et al., 2006).

Importantly, the term "moderator" must be differentiated from the term "mediator", given that both terms have been used inconsistently and often idiosyncratically by researchers in the last 60 years (Kraemer & Gibbons, 2009). In contrast to a moderator, a mediator is a variable that is measured *after* the treatment start or randomisation, thus occurring during, and not before, the treatment or intervention, being correlated with the treatment assignment, and explaining the relationship between treatment and outcome, thereby revealing possible causal mechanisms through which a treatment might achieve its effects (Kraemer et al., 2002). For instance, the quality of the therapeutic alliance between patient and therapist established within the treatment phase was found to mediate the effects of CBASP and Brief Supportive Therapy (Arnow et al., 2013). A moderator analysis may be thus meaningfully followed by a mediator analysis examining possible causal mechanisms in each identified subgroup (Kraemer, 2013).

Finally, both predictors and moderators can be of categorical as well as of metric nature, the latter stratifying the population to a higher degree (Kraemer, 2013). Baseline variables analysed as potential predictors or moderators might include gender, ethnicity, socioeconomic class, initial severity, certain biomarkers, or the subtype of the disorder. Moreover, because from a clinical perspective, one is usually interested in selecting the likely most beneficial treatment from a variety of available options for a given patient, moderators play a more

important role for research that aims to inform clinical practice than predictors (Kraemer et al., 2006; Kraemer, 2013).

Multivariable prediction models. As pointed out by DeRubeis (2019), findings of statistically significant individual predictors or moderators were never quite likely to inform clinical practice. Despite the large body of evidence reporting single characteristics that influence the response to treatments for depression, no single biomarker, demographic, personal, or clinical variable has yet been selected to support personalized treatment recommendations in real practice (Cohen & DeRubeis, 2018). This is primarily because individual moderators rarely account for enough variance in clinical populations to be replicated across multiple studies, especially since most RCTs are statistically underpowered and thereby fail to detect even modest interaction effects between moderator variables and the treatment group (Kraemer & Gibbons, 2009; Luedtke et al., 2019). Moreover, single moderator variables tend to have relatively small moderator effect sizes, which is further limiting their relevance for personalized treatment selection in clinical practice (Wallace & Smagula, 2018). Furthermore, different evidence-based recommendations, each based on different distinct moderator findings, may be contradictory for the same patient, whenever the case arises that moderator findings recommend different treatments for the same patient. To address these issues, researchers have developed multivariable prediction models, in which information from multiple baseline variables identified as moderators or predictors are combined in a way that captures a greater proportion of the variance in the population and simultaneously predict treatment outcome as a function of this variance (DeRubeis, 2019).

To start presenting one multivariable approach, about 20 years ago, Wolfgang Lutz and colleagues transferred a statistical method developed by avalanche researchers, also called the "nearest neighbour" method, to the question of clinical prediction (Lutz et al., 2005). Most of their work based on this method focused on predictors of treatment effectiveness, but they also described how it can be used to predict which of two treatments a particular person is more likely to benefit from (Lutz et al., 2006). Briefly, the nearest neighbour method examines the outcomes of several patients in a sample who are most similar to a fictitious target patient in

terms of baseline variables such as demographics, symptoms, and other measures. Predicting the outcomes of the target patient results from comparing the average outcomes of those nearest neighbours who received treatment X, to the average outcomes of those nearest neighbours who received treatment Y. However, the determination of the nearest neighbours depends on many factors and rather subjective decisions that the researcher must make in advance. These include choosing which baseline variables to use to determine the closeness, whether and how to weight the included baseline variables, and deciding how much of the neighbours' data to use to predict the outcome of the target patient (Cohen & DeRubeis, 2018).

Several years after the introduction of this method, DeRubeis and colleagues (2014) developed an alternative method for treatment outcome prediction called the Personalized Advantage Index (PAI). The goal here is to estimate the outcomes that each patient in a sample would experience under each of two compared treatments, and to yield the difference between these estimates to predict which treatment is likely more effective for a certain patient. More precisely, this method first implies that single baseline variables are individually examined for their roles as predictors or moderators of treatment success (Cohen & DeRubeis, 2018). This is usually done in the context of regression models in which the interaction term between the treatment condition and the baseline variable of interest is tested for statistical significance (see Fournier et al., 2009, for an application of this method). Next, from the set of baseline variables that have thus been identified as significant predictors or moderators of treatment effect, a multivariable statistical model is constructed, including the main terms of the treatment variable and the baseline variables as well as interaction terms between the treatment variable and moderators. To deliver a prediction for the outcomes of a given patient under treatment A or B, this researcher group has relied on the leave-one-out-technique, in which a patient's observed values for all independent variables and the value representing treatment A or B, respectively, are inserted into the prediction model which is estimated in the sample of all other patients. The PAI for a given patient is equivalent to the difference in the predicted outcomes for the two treatments (Cohen & DeRubeis, 2018).

While this method has found its application in various studies (e.g., DeRubeis et al., 2014; Huibers et al., 2015; van Bronswijk et al., 2019; Webb et al., 2018) and helped to achieve some progress for personalized medicine in mental health research, methodologically, it has some weaknesses. First, selecting individual variables based on their isolated statistical significance as predictors or moderators can be problematic in the context of small samples sizes, which are underpowered for detecting significant interaction effects (Kraemer, 2013). Second, the statistical significance of a moderator is not indicative of its moderator effect size (i.e., the degree to which it differentiates the outcome per treatment condition), which is however more relevant for clinical practice (Kraemer et al., 2006). Finally, examining numerous baseline variables by many performed statistical tests will likely lead to false positives results that may reduce the predictive accuracy of the PAI regression model.

Simultaneously with the development of the PAI method and during a time where statistical methods assessing the strength or impact of a moderator in a clinically and/or scientifically meaningful way were largely lacking, Helena Kraemer (2013) developed the "combined moderator" method, sometimes also referred to as the "optimal composite moderator". As suggested by its name, this method combines multiple individual baseline variables identified as moderators based on their moderator effect size to a combined moderator M^*, which is further used to identify and subsequently characterize patients who are likely to benefit more from one treatment than from another (Kraemer, 2013; Wallace et al., 2018). Importantly, baseline variables are defined as moderators based on their moderator effect sizes rather than the *p*-values of their interaction effects with the treatment variable - abstaining from including the statistical significance of interaction effects between treatment and moderator variables is thus in line with the exploratory character of most of moderator analyses (Kraemer, 2013; Wasserstein & Lazar, 2016). Moreover, moderator effect sizes obtained after this method are invariant over linear transformations of the baseline variable or the outcome, varying between –1 and +1, with higher magnitudes indicating a stronger moderation and zero indicating the absence of a moderation effect (Kraemer, 2013). Usually, an effect size $\geq|0.10|$ (i.e., at least small) is set to consider a variable as a moderator (see

Smagula et al., 2016 and Wallace et al., 2018, as examples of applications of this method). Next, in a dataset pairing each patient who received treatment A with each one who received treatment B, weights of the single moderators are estimated by a multivariable regression model, in which the between-patients difference in outcome is predicted by the averages of all preselected individual moderators for each patient pair. Afterwards, the thereby resulting regression weights of all preselected moderators are extracted to calculate the value of M^* for each patient. Finally, in the unpaired dataset, a regression analysis predicting the outcome from the combined moderator M^*, the treatment group, and their interaction is performed. Additionally, the combined moderator can be further used to subdivide the total sample into two subgroups each of which is likely to benefit more from one treatment than the other. By characterizing these subgroups based on their baseline profiles, one can gain an understanding of which treatment is likely more effective for which type of patients (Kraemer, 2013). Thus, compared to the PAI method, the combined moderator method does not imply to conduct numerous statistical tests to pre-select baseline variables, and considers effect sizes which are comparable across different studies rather than statistical significances, which are sample-dependent, when selecting moderators.

So far, the method of the combined moderator was applied in several secondary analyses of RCTs examining interventions for episodic depression (Wallace et al., 2013), late-life depression (Smagula et al., 2016), bipolar disorders (Frank et al., 2014) and anxiety disorders (Niles, Loerinc, et al., 2017; Niles, Wolitzky-Taylor, et al., 2017; Wallace et al., 2017). Based on the discussed methodological advantages over the other two multivariable methods presented in this sub-chapter, the combined moderator method was also applied in Paper 1 and Paper 3 of this dissertation, both of which focused on moderator effects, being thus used for the first time in two populations with PDD.

2.3 Personalized Medicine for PDD: State of the Art

In order to gain a better understanding regarding the effect of different psychotherapeutic and pharmacotherapeutic treatments for specific subgroups of patients

with PDD, several studies have examined the extent to which baseline characteristics predict or moderate the effectiveness of treatments for patients with PDD. In the following, the main findings of several secondary analyses are summarized grouped by examined baseline characteristics.

Baseline severity of depression and anxiety. In their IPD-NMA, Furukawa and colleagues (2018) analysed data from three RCTs (Keller et al., 2000; Kocsis, Gelenberg, et al., 2009; Schramm et al., 2015) aiming to understand for whom CBASP, ADM, or their combination work best. Primary outcomes were reduction in depression severity as well as dropout rates indicating treatment acceptability. Various baseline variables including baseline severity of depression and anxiety were examined as potential predictors and moderators of treatment effect. Results revealed that for patients with severe baseline depression and severe baseline anxiety, combination treatment was generally more effective than pharmacotherapy alone, which in turn was more effective than CBASP alone. In contrast, patients with moderate baseline depression and mild baseline anxiety benefited equally well from combination treatment and CBASP alone, but less from pharmacotherapy alone.

Age. So far, there exists only one finding examining age in its function for treatment outcome: in the IPD-NMA by Furukawa and colleagues (2018), pharmacotherapy alone was concluded to be likely more acceptable in younger patients with PDD, given the relatively high dropout rates in these patients for both combination therapy and CBASP alone.

Childhood trauma. Given the close association between PDD and childhood trauma (see also sub-chapter 2.1.2), several studies have focused on investigating the effect of childhood (sometimes also labelled as “early”) trauma on the differential effectiveness of various treatments. Nemeroff and colleagues (2003) were the first to publish an analysis of the influence of childhood trauma (defined in their study as loss of parents at an early age, physical or sexual abuse, or neglect) on the effect of psychotherapy versus ADM in a sample of $N = 681$ patients with DSM-IV defined chronic depression randomized to receive a 12-week treatment with either Nefazodone, CBASP, or their combination (Keller et al., 2000). Monotherapy with CBASP was superior to monotherapy with Nefazodone among those with a history of childhood

trauma. Moreover, the combination of CBASP and Nefazodone was only marginally superior to monotherapy with CBASP among the subgroup of patients with childhood abuse. These results thus suggested that CBASP is an effective, recommendable treatment for patients with PDD who report childhood trauma, and likely superior to ADM.

In a later secondary analysis of a bi-centric RCT carried out in non-medicated adult outpatients meeting DSM-IV criteria for chronic depression (Schramm et al., 2015), Bausch and colleagues (2017) aimed to replicate these findings by analyzing the impact of childhood trauma as measured by the Childhood Trauma Questionnaire (CTQ; Bernstein et al., 2003) and the Early Trauma Inventory (ETI; Bremner et al., 2000) on the effectiveness of CBASP versus Escitalopram plus Clinical Management (ESC/CM). In the original RCT, $N = 60$ patients were randomized to an 8-week acute treatment with CBASP or ESC/CM, followed by further 20 weeks of extended treatment. Contrary to the hypotheses, the presence of childhood trauma was not found to be a significant moderator of differential treatment effect regarding any outcome measure after 28 weeks of treatment. However, after eight weeks of treatment, patients with a history of childhood trauma receiving CBASP had a significantly lower response rate compared to patients without childhood trauma and to those receiving ESC/CM. Overall, it was concluded that CBASP and ESC/CM are equally effective in treating patients with PDD and childhood trauma, although CBASP may have a longer treatment latency. The data of this RCT by Schramm and colleagues (2015) have also been subject of the analyses conducted in Paper 3, so it will be referred to again in sub-chapters 4.3 and 5.1.

In another secondary analysis, Klein and colleagues (2018) investigated the effect of childhood trauma on the differential effect of 20 weeks of treatment with CBASP versus SP based on the data from an evaluator-blinded multi-centric RCT (Schramm et al., 2017). A total of $N = 268$ non-medicated adult outpatients meeting DSM-IV criteria for chronic depression with early onset were randomized to receive a total of 48 weeks of CBASP or SP. In the secondary analysis by Klein and colleagues (2018), the presence of childhood trauma as well as various subtypes measured by the CTQ were tested as predictors and moderators. As expected, childhood trauma was found to moderate the effect of treatment in terms of

depression severity and chances of remission, but not of response, in favour of CBASP after the 20-week treatment phase. Among the subtypes, early emotional abuse was found to moderate the effect of treatment in favour of CBASP, while emotional neglect predicted a less favourable outcome independent of treatment allocation. However, in sensitivity analyses in which the clinician-rated ETI was used to divide patients into subgroups with and without childhood trauma, the interaction effects were not found to be statistically significant, which may have been due to the low statistical power (Klein et al., 2018). Overall, CBASP was concluded to be more beneficial than SP for PDD patients with childhood trauma.

Finally, in a secondary analysis of the RCT comparing eight weeks of TAU to CBASP and TAU as well as to MBCT and TAU (Michalak et al., 2015), Michalak and colleagues (2016) found childhood trauma as measured by the CTQ at baseline not to moderate the differential treatment effect between CBASP and MBCT, but between CBASP and TAU as well as MBCT and TAU between the end of treatment and a six-month follow-up in favour of CBASP and MBCT. This moderator role was however not found for the time between baseline and post-treatment.

Comorbid personality disorders. In another secondary analysis of the previously mentioned RCT comparing CBASP to SP in patients with early-onset chronic depression (Schramm et al., 2017), Erkens and colleagues (2018) examined the association between comorbidity of personality disorders and the outcome under both treatments. In total, 38.4% of the patients met criteria for at least one comorbid personality disorder. Nevertheless, the authors detected neither a significant main effect of comorbidity of personality disorders on treatment outcome at week 20, nor a significant interaction between comorbidity of personality disorders and treatment. The generalizability of these results is limited as patients with antisocial, schizotypal, and borderline personality disorders were not included in the study.

Treatment preference. The RCT comparing CBASP, Nefazodone and their combination (Keller et al., 2000) served for a further secondary analysis in which Kocsis, Leon, and colleagues (2009) examined the patients' treatment preference at baseline as a potential

moderator of treatment outcome. The performed analyses revealed an interactive effect of treatment preference and treatment group on post-treatment depression severity and remission rates. More precisely, among those patients who preferred CBASP, those receiving it had better outcomes than those receiving Nefazodone and vice versa - among patients preferring Nefazodone, those receiving it scored better than those who received CBASP. These results could however not be replicated in another moderator analysis by Steidtmann and colleagues (2012), who reported no association between the baseline treatment preference and symptom reduction or attrition in Phase II of the REVAMP trial (Kocsis, Gelenberg, et al., 2009). In this phase, patients who did not remitted in a previous 12-week treatment phase received further 12 weeks of either CBASP plus ADM, Brief Supportive Psychotherapy plus ADM, or ADM alone. Cell sizes were furthermore too small to conduct further analyses in this study.

Interpersonal problems. Interpersonal problems are an important feature in patients with PDD (S. Köhler et al., 2018) and were therefore investigated as moderator in the following secondary analysis by Probst and colleagues (2020). In the original RCT, patients meeting DSM-IV criteria for chronic depression were randomized to eight weeks of TAU, CBASP and TAU, or MBCT and TAU, both delivered in a group format (Michalak et al., 2015). Interpersonal problems assessed by the different scales of the 32-item version of the Inventory of Interpersonal Problems (IIP; Bailey et al., 2018) were examined as moderators of post-treatment depression severity measured by the 24-item version of the HRSD. Interestingly, in terms of post-treatment depression severity, patients with higher scores on the "vindictive/self-centered" subscale of the IIP had a better outcome with MBCT than with CBASP, while those with higher scores on the "non-assertive" subscale achieved better outcomes with CBASP than with MBCT.

Dysfunctional attitudes. As a further secondary analysis of the REVAMP trial (Kocsis, Gelenberg, et al., 2009), the study by Shankman and colleagues (2013) examined whether the pre-treatment levels of dysfunctional attitudes moderated the treatment response. In the second phase of this trial, the level of dysfunctional attitudes predicted a differential

response in the ADM group, but not in the two psychotherapy (CBASP and Brief Supportive Psychotherapy) plus ADM groups. Specifically, in the ADM group, patients with higher dysfunctional attitudes improved better than those with lower ones, indicating that greater pre-treatment dysfunctional attitudes in PDD may be associated with a better response to pharmacotherapy.

3. Motivation, Aims and Research Questions of this Dissertation

The review of secondary analyses summarized in the previous chapter shows that most previous studies focused on analysing the impact of a single baseline variable coming from a certain domain by following a sample stratifying statistical approach, which divided the sample in patients meeting the criteria for a categorical variable (e.g., childhood trauma) and those who don't, or, as for continuous variables, which differentiated the sample in patients with higher values of that variable and those with relatively lower ones (e.g., baseline depression). Therefore, the majority of available moderator and predictor studies in PDD can be categorized to follow the aims of stratified medicine, rather than personalized medicine (Wium-Andersen et al., 2016).

Although relevant for theory and novel treatment development, research emphasizing individual baseline variables has several limitations with consequences for both research and clinical practice: first, although investigated baseline variables such as baseline depression severity or dysfunctional attitudes are plausibly decisive for (differential) treatment success, they do not reflect the entire individuality of a patient with PDD, who will have many other treatment success determining variables that are left unconsidered when relying on stratifying statistical approaches focusing on single variables. Second, the composition of further unconsidered baseline variables in a clinical sample may likely influence the results of a stratifying predictor or moderator analysis, which may explain why previous research has repeatedly produced contradictory results or failed to replicate earlier findings. Third, with regard to clinical practice, the examination of single baseline variables can lead to contradictory treatment recommendations. For example, to a patient preferring ADM and recalling a history of childhood trauma, one would indicate ADM over CBASP based on its treatment preference as suggested by Kocsis, Leon, and colleagues (2009), and at the same time, CBASP over ADM with regard to its childhood trauma experiences according to the results by Nemeroff and colleagues (2003). Fourth, for clinicians, the evidence-based

treatment selection becomes increasingly complicated the more variables one wishes to simultaneously take into account when selecting between various treatment options. Taken together, these issues call for a new approach of personalized treatment prediction for patients with PDD that captures the heterogeneity of the disorder (Schramm et al., 2020) and yields findings that can be more easily translated into clinical practice. The three papers of this publication-based dissertation pursued the overarching goal of capturing the assessed baseline diversity of patients with PDD and using it to predict outcomes under different psychotherapeutic and pharmacological treatments, thereby increasing the evidence base needed to personalize treatment selection for patients with PDD. The resulting research questions are as follows:

I. **Which psychotherapeutic or pharmacotherapeutic treatment, among two options compared in an RCT, is more likely to lead to a comparable better response for certain subgroups of patients, depending on their multivariable baseline profile?**
    - For answering this research question, Paper 1 combines multiple moderators to detect subgroups of patients with likely differential treatment benefit from disorder-specific psychotherapy with CBASP versus non-specific psychotherapy with SP.
    - In addition, Paper 3 combines multiple moderators to detect subgroups of patients with likely differential treatment benefit from disorder-specific psychotherapy with CBASP versus ADM in the form of ESC/CM.

II. **Which patients are more likely than others to respond better to specific psychotherapeutic treatments, depending on their multivariable baseline profile?**
    - For answering this question, Paper 2 examines various baseline characteristics as predictors of treatment outcome for psychotherapy with CBASP and SP, thereby detecting subgroups of patients who are likely to benefit more or less from both treatments.

4. Synopsis of Empirical Findings

This chapter presents a synopsis of the three scientific papers of this dissertation focusing on the research objectives pursued, the scientific methodology applied, as well as the results obtained. Additionally, detailed information on each paper is provided in the corresponding full-text in the appendices.

4.1 Paper 1: Combining baseline characteristics to disentangle response differences to disorder-specific versus supportive psychotherapy in patients with persistent depressive disorder

by Serbanescu, Walter, and colleagues (2020) – for full-text, see Appendix 1

This paper examined whether the baseline profile of patients with PDD moderates their benefit from disorder-specific psychotherapy with CBASP versus disorder non-specific SP. For this purpose, data from a 48-week multi-center RCT conducted by Schramm and colleagues (2017) was reanalysed, in which the effectiveness of 48 weeks of CBASP was compared to SP. The sample consisted of $N = 237$ outpatients with DSM-IV defined chronic depression with an early-onset who were not taking ADM throughout the entire treatment period. By using the combined moderator methodology by Kraemer (2013), a combined moderator was developed as a weighted combination of 13 preselected baseline variables and used for identifying and characterizing subgroups for which CBASP was likely to result in a better response than SP and vice versa. Baseline variables examined as potential moderators came from domains including socio-demography, self-reported and clinician-rated aspects of the clinical status, childhood trauma, treatment history and treatment preference. Methodologically, the method of the combined moderator was used in combination with least absolute shrinkage and selection operator (lasso) regression to select only relevant moderators as well as *k*-fold cross-validation in order to build a multivariable model that is more likely to have a good predictive performance in future new data sets (for more details, see the full-text of Paper 1 in Appendix 1). The percentage change in scores of the 24-item version of the HRSD from baseline to week 48 was used as outcome.

As for the results, two distinct subgroups were identified: one including 58.65% of the patients for whom treatment with CBASP was likely to result in a greater improvement, and another comprising 41.35% of the patients, for whom treatment with SP was likely to result in a greater improvement. A between-subgroup analysis of the baseline profiles of the two subgroups revealed that patients likely responding more favourably to CBASP were initially more severely depressed and more likely affected by moderate-to-severe childhood trauma including early emotional, physical, or sexual abuse, as well as emotional or physical neglect. Patients likely responding more favourably to SP had a higher baseline global and social functioning level, a higher quality of life and more often a recurrent illness pattern without complete remission between the episodes.

Altogether, the findings of Paper 1 emphasize the relevance of considering the multiple pre-treatment characteristics identified as moderators when selecting between CBASP and SP for treating PDD. Once validated in an independent sample with more flexible inclusion criteria, these results could support mental health practitioners to select between CBASP, SP, or similar approaches such as Brief Supportive Psychotherapy for long-term psychotherapeutic treatment of patients with PDD and to enhance their individual response chances.

4.2 Paper 2: Impact of Baseline Characteristics on the Effectiveness of Disorder-Specific Cognitive Behavioral Analysis System of Psychotherapy (CBASP) and Supportive Psychotherapy in Outpatient Treatment for Persistent Depressive Disorder

by Serbanescu, Backenstrass, and colleagues (2020) – for full-text, see Appendix 2

The goal of this paper was to identify baseline characteristics that predict a comparable treatment effectiveness of CBASP and SP, thereby focusing on finding predictors of treatment success. Data from the same RCT by Schramm and colleagues (2017) presented in the summary of Paper 1 was analysed for this purpose. Baseline variables analysed as potential predictors of treatment effect came from domains including socio-demography, psychosocial and global functioning, life quality, interpersonal problems, childhood trauma, treatment

history, preference for psychotherapy, and treatment expectancy of patients measured at baseline. In order to rule out possible treatment effect moderator effects, these variables were also examined as potential moderators. For determining whether a variable was a predictor or moderator of treatment effect, linear regression models were constructed with post-treatment depression severity measured by the 24-item version of the HRSD as continuous dependent variable.

Results revealed that a poor response to both psychotherapies was predicted by higher baseline levels of clinician-rated depression, elevated suicidality, comorbid anxiety, lower social functioning, higher social inhibition, moderate-to-severe childhood emotional or sexual abuse, no preference for psychotherapy, and the history of at least one previous inpatient treatment. As for moderators, in line with results from Paper 1, patients with higher baseline levels of self-rated depression, comorbidity of at least one Axis-I disorder, self-reported moderate-to-severe childhood emotional or physical neglect, or at least one previous antidepressant treatment, had a significantly lower post-treatment depression severity with CBASP compared to SP.

In conclusion, these results suggest a complex multivariable baseline profile characterized by severe initial depression, suicidality, childhood abuse, social inhibition, and anxiety, that may impede response to both CBASP and SP in patients with early-onset chronic depression. Future research is needed to understand how to improve the effectiveness of these treatments or what other alternative treatments may be more appropriate for patients with this baseline profile.

4.3 Paper 3: Identifying subgroups with differential response to CBASP versus Escitalopram during the first eight weeks of treatment in outpatients with persistent depressive disorder

Serbanescu and colleagues (2022), revised and resubmitted – for full-text, see Appendix 3

The overarching aim of the third paper of this dissertation was to identify and characterize subgroups of patients with PDD who are likely to benefit more from an acute

treatment with CBASP than from ADM and vice versa. For this purpose, data from another RCT conducted by Schramm and colleagues (2015) was re-analyzed. In this bi-centric RCT, a total of N = 60 non-medicated outpatients with DSM-IV defined chronic depression were randomized to receive eight weeks of acute treatment with CBASP or Escitalopram, a well-tolerated standard SSRI, combined with clinical management (ESC/CM). Findings of the original analysis by Schramm and colleagues (2015) revealed that the clinician-rated Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979) scores decreased significantly after both eight and 28 weeks in both treatment groups, however without statistically significant differences between the two treatments at both time points. In case of non-improvement (defined in this study as < 20.0% reduction in depression severity) after the 8-week acute treatment phase, the other treatment condition was augmented for further 20 weeks of the extended treatment phase. The main analysis revealed that non-improvers to the initial treatment caught up with the initial improvers in terms of depression severity by the end of the extended treatment phase after being augmented with the respective other condition (Schramm et al., 2015).

The focus of the moderator analysis conducted in Paper 3 was to examine whether, despite the reported general equivalence of the two treatments, there were subgroups of patients who were likely to benefit more from CBASP than from ESC/CM and vice versa during the acute 8-week treatment phase. In addition, this secondary analysis investigated whether the initial lack of response in those patients augmented with the other treatment condition at week eight was because they did not receive their likely more effective treatment during the first eight weeks, and whether the observed improvement at week 28 was likely due to the augmentation with the treatment condition from which they would have likely benefitted more from the beginning of the trial. Similar to Paper 1, by using the combined moderator method by Kraemer together with lasso regression and k-fold cross-validation, several baseline variables were compiled into one combined moderator M^* that enabled to identify two subgroups of patients who were likely to benefit more from CBASP than from ESC/CM and vice versa. The baseline variables whose moderator effect sizes were large enough to be

included in the calculation of *M** were the following seven: the number of previous suicide attempts, the number of adverse life events, the presence of at least one form of moderate-to-severe childhood trauma, age, an early illness onset, female gender, and the number of previous treatments with antidepressants. The main outcome was the percentage change in depression severity measured by the MADRS from baseline to week eight.

Results revealed that for 56.0% of the patients, ESC/CM was likely associated with a greater reduction in depression severity than CBASP, while for the remaining 44.0% of patients, CBASP was likely associated with a greater reduction in depression severity than ESC/CM. Between-subgroup analyses showed that patients likely to benefit more from ESC/CM were more often female, had higher rates of moderate-to-severe childhood trauma, more adverse life events as well as more previous suicide attempts. Patients likely to benefit more from CBASP were older, had more often an early illness onset and more previous treatments with ADM. Overall, after the 8-week acute treatment phase, symptomatic response, remission, and reductions in symptom severity occurred more often in those patients treated with their likely more effective treatment condition. Moreover, 95.0% of the patients augmented with the other treatment condition after week eight received their likely less beneficial treatment during the acute treatment phase.

Overall, the findings of Paper 3 suggest that the multivariable baseline profile of patients with PDD moderates their benefit from acute treatment with CBASP relative to ESC/CM. Furthermore, according to these results, the improvement during the extended treatment phase in initial non-responders can be explained by the fact that after the eighth week, most of these patients received the treatment that was likely to be more effective for them personally, in addition to the initial, probably less effective treatment that led to their non-response. These findings are especially relevant for patients who experience side effects when receiving or discontinuing treatment with ADM or who cannot access or afford treatment with CBASP. After confirmation by an independent sample, these results could be used to guide the selection between acute psychotherapy with CBASP and pharmacotherapy with Escitalopram or comparable antidepressants in patients with PDD.

5. General Discussion

The overarching aim of the present dissertation was to advance the research field of prediction of treatment outcomes for the difficult-to-treat clinical population of patients with PDD, thereby paving the way for personalized medicine for PDD. Unlike population-based research, which provides general average treatment effects that are rarely indicative for individual patients, the pathway of personalized medicine moves beyond the "one size fits all" assumption and aims to answer the question of "*what works for whom?*" (Cohen & DeRubeis, 2018). Moreover, in contrast to the previous research on predictors and moderators of treatment outcomes in PDD, which mostly relied on the hypothesis-driven analysis of single, isolated baseline variables, the three papers of this dissertation captured a broader baseline diversity of the studied PDD populations and used it to predict outcomes of different psychotherapeutic and pharmacological treatments. In the following sub-chapter 5.1, the main empirical results of each paper are discussed and embedded in the framework of previous evidence summarized in sub-chapter 2.3. Finally, strengths and limitations of the three papers are discussed in sub-chapter 5.2, followed by a brief reflection on possible future directions in personalized medicine for PDD and their implications in sub-chapter 5.3, and a general conclusion provided in sub-chapter 5.4.

5.1 Discussion of Main Empirical Findings

The aim of the present thesis was to gain insight into which of the two treatments compared in an RCT is more likely to result in a better response for a particular subgroup of PDD patients (research question 1), and secondly, which PDD patients are more likely to respond to certain treatments compared to others (research question 2). The identified findings refer and are limited to the comparison of CBASP versus SP investigated in a multicentre RCT by Schramm and colleagues (2017) as well as to the comparison of CBASP versus ESC/CM analysed in a second, double-centre RCT by Schramm and colleagues (2015) in outpatients with PDD. Table 2 summarizes relevant aspects of the study design and the main empirical findings of the three papers of this publication-based dissertation.

Table 2

Overview of main features of the studies of the three papers included in this dissertation

Paper Nr.	Sample size	Compared treatments	Statistical methods	Main findings
1	*N* = 237	RCT comparing 48 weeks of CBASP versus SP	Combined moderator (*M**) by Kraemer, lasso regression, *k*-fold cross-validation	Baseline variables compiled to *M**, indicating that *CBASP is superior to SP:* · Being separated, divorced, or widowed · Higher depression severity (self- and clinician rated) · Longer illness duration · Subtype = chronic MDE · ≥ 1 comorbid Axis-I disorder · Childhood emotional or physical neglect · Lower quality of life *SP is superior to CBASP:* · Subtype = recurrent MDE without complete remission between episodes · ≥1 comorbid Axis-II disorder · Higher social and global functioning
2	*N* = 209	RCT comparing 48 weeks of CBASP versus SP	Multiple linear regression analyses	Baseline variables identified as predictors, indicating a lower response to both treatments: · Higher depression severity, clinician rated · Higher suicidality and general anxiety · Lower social functioning and higher social inhibition · Childhood emotional or sexual abuse · ≥1 previous inpatient treatment · No preference for psychotherapy
3	*N* = 53	RCT comparing 8 weeks of CBASP versus ESC/CM	Combined moderator (*M**) by Kraemer, lasso regression, *k*-fold cross-validation	Baseline variables compiled to *M**, indicating that *ESC/CM is superior to CBASP:* · Female gender · Higher number of previous suicide attempts and adverse life events · ≥1 form of childhood trauma *CBASP is superior to ESC/CM:* · Higher age · Early illness onset · Higher number of previous treatments with ADM

Note. ADM = Antidepressant medication; CBASP = Cognitive Behavioral Analysis System of Psychotherapy; MDE = major depressive episode; RCT = randomized controlled trial; SP = Supportive Psychotherapy; ESC/CM = Escitalopram plus with Clinical Management. The sample sizes indicate the numbers of patients included in the statistical analyses. Moderator findings from Paper 2 are not shown due to overlap with results from Paper 1.

To elaborate on research question 1, Paper 1 (Serbanescu, Walter, et al., 2020) re-analysed data from the RCT comparing 48 weeks of disorder-specific psychotherapy with CBASP versus disorder non-specific psychotherapy with SP (Schramm et al., 2017) and exploratively detected two subgroups of patients with differential treatment responses for CBASP versus SP. Briefly, this analysis revealed that CBASP was likely to result in better outcomes than SP for initially more severely depressed patients who had higher rates of childhood trauma in form of sexual, emotional or physical abuse, or emotional or physical neglect. These last two neglect-based trauma forms were further used to compile the composite moderator because of their relatively large moderator effect sizes and are thus particularly noteworthy. They suggest that long-term treatment with CBASP may be more beneficial than SP particularly for patients with neglect-based childhood trauma. These conclusions are plausible considering that CBASP was developed specifically to treat behavioural and cognitive deficits related to childhood traumatic experiences in patients with early-onset PDD (McCullough, 2000). In addition, the finding that CBASP is likely more beneficial than SP in patients with childhood trauma is consistent with an older secondary analysis by Klein and colleagues (2018) of the same RCT, which applied more traditional regression analyses and revealed that childhood trauma moderated the treatment effect in terms of both depression severity and chances of remission, but not of response, in favour of CBASP after the 20-week treatment phase (see also sub-chapter 2.3). However, in their analysis, after 20 weeks of treatment, CBASP proved to be more beneficial than SP for patients with childhood emotional abuse, whereas for patients with emotional neglect, both psychotherapies showed a less favourable outcome. These results are striking considering that Papers 1 and 2 of this dissertation found a reverse effect after 48 weeks of treatment, when CBASP likely performed better than SP for patients with childhood emotional and physical neglect (see Paper 1, Appendix 1, Table 1 and 2), while childhood emotional and sexual abuse predicted a lower treatment response for both CBASP and SP (see Paper 2, Appendix 2, Table 3). The comparison of these findings suggests that the superiority of CBASP over SP for patients with childhood neglect experiences may require some treatment time for being established, while effectiveness

is overall lower for those with childhood abuse experiences after a longer treatment period for both psychotherapies. Furthermore, in addition to the different treatment durations considered, methodological differences between the secondary analysis by Klein and colleagues (2018) and Papers 1 and 2 of this thesis may have contributed to the different findings, particularly given that the older moderator analysis relied its findings on statistical significances, whereas the moderator analysis in Paper 1 used an alternative statistical procedure based on moderator effect sizes (Kraemer, 2013).

In addition, Paper 1 found that patients who were more likely to benefit more from SP had higher baseline levels of life quality, social and global functioning, less childhood trauma, and a lower baseline depression severity. At its core, SP refrains from confronting biographical aspects such as childhood trauma and focuses instead on providing a liberal and supportive therapeutic framework that helps the patient to activate existing resources (Markowitz, 2014). Given its constellation of more favourable baseline characteristics, this subgroup may thus have benefited more from this resource-activating, supportive approach. The lower rates of childhood traumatic experiences and higher baseline social functioning level in this subgroup may also explain why the childhood trauma and interpersonal problem-solving focused approach of CBASP was likely less effective for these patients. The finding that patients with a higher baseline social functioning level likely benefitted more from SP than from CBASP further complements the moderators findings of Probst and colleagues (2020), who suggested that MBCT should be preferred to CBASP in PDD patients who are vindictive/self-centered, whereas CBASP should be preferred to MBCT in PDD who are non-assertive. The patients' pre-treatment social profile appears thus to play a critical moderating role in the effectiveness of different psychotherapies for patients with PDD.

Interestingly, Paper 1 further found that CBASP likely performed better for patients with a comorbid Axis-I disorder, while SP performed better for those with a comorbid Axis-II (personality) disorder. Case numbers were too small to conclude which comorbid disorders were driving these moderator trends. Part of these results contrast with those of Erkens and colleagues (2018), who performed another moderator analysis of the RCT by Schramm and

colleagues (2017) examining the impact of comorbid personality disorders on the treatment effect after 20 weeks. Contrary to their hypotheses, the authors did not find that the effect of CBASP compared to SP was moderated by the presence of comorbid personality disorders, nor did comorbidity of personality disorders statistically significantly predict treatment outcome across both treatment groups, which was likely due to the underpowered study (Erkens et al., 2018). Paper 1 of this thesis revealed that the exploratory identified subgroup more likely benefiting from SP had higher rates of comorbid Axis-II disorders (53.1% versus 26.6%; see Paper 1, Appendix 1, Table 2), and raises the possibility that SP may have exceeded CBASP in its effectiveness for these patients after 48 weeks of treatment, thereby appearing to be quite well suited for their needs. Further mediator analyses which go beyond the scope of this thesis are needed to understand which therapy-related processes were responsible for these effects during the treatment. Since most patients had an anxious-avoidant or obsessive-compulsive personality disorder (Erkens et al., 2018), it would be interesting to evaluate whether SP's supportive and resource-oriented approach also led to stronger improvements in the interpersonal problem domain.

Overall, the results of Paper 1 challenge the main conclusion of the principal statistical analysis of the RCT, which suggested that CBASP is more effective than disorder nonspecific SP in outpatients with early-onset chronic depression (Schramm et al., 2017). While this conclusion is entirely correct from a general, cross-sample perspective regarding the population in this trial, it remains however no longer valid as soon as one takes a more differentiated, subgroup-oriented view. The validity of results and conclusions thus becomes a matter of perspective, which can be more or less differentiated, depending on the research purpose. While providing general, population-wide evidence makes considerable sense from an epidemiological point of view, from a clinical perspective, the transfer of empirical evidence to the individual patient is much more relevant. Here, research for PDD has been strongly limited, with this paper being the first one to provide exploratorily identified multivariable baseline profiles of patient subgroups with differential treatment benefits. In the trial underlying this study, the number of patients likely benefiting more from CBASP than from SP

and vice versa was in a modest range; however, in real clinical practice, these numbers could represent several million people. Treating large numbers of patients with a psychotherapy that has been found to be general superior to another, but that is not appropriate for these patients themselves, can imply major negative direct and indirect consequences such as lack of responses, worsening of symptoms, increased hopelessness of the patient, as well as wasteful use of time and financial resources within the mental health care system (Furukawa et al., 2018). On the other hand, these patients would not get what they most benefit from. Considering the results suggesting that SP may also prove quite beneficial for the described subgroup of patients with PDD and given that SP is largely available in clinical practice (Markowitz, 2014), future research may further explore its potential to treat certain patients with PDD.

The second research question resulted in the predictor findings of Paper 2 (Serbanescu, Backenstrass, et al., 2020), in which several subgroups of patients likely benefiting more (or less) from both treatments were identified. Consistent with previous research, the predictor results of Paper 2 suggest that patients who were initially psychologically more stable (i.e., less depressed, less anxious, less suicidal), better socially functioning, and preferring psychotherapy, likely responded better to both psychotherapies when compared to patients on the other side of the respective characteristic. It is plausible that an initial higher functioning and overall better mental condition facilitated psychotherapeutic learning and thereby also the recovery process in both treatment groups. From the opposite perspective, patients who were initially more pathologic likely benefitted less from both psychotherapies. In conclusion, and as recommended by others (Cuijpers et al., 2012; Furukawa et al., 2018), for initially more severe pathological patients, psychotherapy alone may not be sufficient to achieve significant symptom reduction and may lead to better outcomes when combined with ADM. Moreover, considering the results of Paper 1, the predictor findings of Paper 2 somewhat limit the superiority of CBASP for initially more affected PDD patients: although CBASP performed better than SP for more pathological patients, it also seems to reach its limits for the most

pathological patients. For instance, although the subgroup of patients likely to benefit better from CBASP had all five trauma forms of the CTQ more frequently reported (see Paper 1, Appendix 1, Table 2), patients with experiences of childhood emotional and sexual abuse appeared to likely benefit more poorly from both psychotherapies than those without these trauma forms (see Paper 2, Appendix 2, Table 3).

Moreover, the finding that patients preferring psychotherapy responded better to both psychotherapies than those not preferring it sustains the results of the secondary analysis by Kocsis, Leon, and colleagues (2009), which revealed that patients preferring CBASP had better outcomes when receiving it compared with Nefazodone and vice versa. It however contrasts the secondary analysis by Steidtmann and colleagues (2012), who reported no association between the baseline patient treatment preference and symptom reduction or attrition in Phase II of the REVAMP trial (Kocsis, Gelenberg, et al., 2009). The fact that this study was based on patients who did not initially respond to treatment may explain the different results and warrants further investigation on the prediction of treatment effects in patients with PDD who did not initially respond to a particular treatment.

Finally, for adding evidence to research question 1 for a psychotherapy-pharmacotherapy comparison, Paper 3 (Serbanescu et al., revised and resubmitted) applied a similar statistical method as Paper 1 in order to exploratorily detect subgroups of patients with differential treatment effects with regard to an acute 8-week treatment with CBASP versus ESC/CM. Findings revealed that below the lack of statistically significant differences between the effects of the two treatments observed in the main analysis (Schramm et al., 2015), there however exist subgroup effects that imply that certain patients did not benefit from their assigned condition within the first eight weeks of treatment. More precisely, patients who received the treatment that was likely less effective for them personally not only did not improve within the first eight weeks of treatment, but worsened, with depression severity increasing by an average of 5.8% from baseline to week eight. In contrast, patients who received their personally likely more effective treatment experienced a decrease in depression

severity by 42.9% and achieved more frequently response and remission after week eight. Taken together, these results speak out for the relevance of such moderator analyses for detecting "hidden" subgroup effects in RCTs after examining overall treatment effects. Similar to Paper 1, the results of the Paper 3 question the general conclusion of the main analysis (Schramm et al., 2015), which stated that CBASP and ESC/CM are equally effective treatment options for outpatients with PDD. This older conclusion may be still valid from a generalized perspective, but no longer from a more differentiated, subgroup-centered perspective.

In terms of the baseline profiles of the two identified subgroups, patients likely to benefit more from ESC/CM were more often female, had higher rates of moderate-to-severe childhood trauma, more adverse life events as well as more previous suicide attempts. Part of these trends are plausibly in line with an older, more traditional moderator analysis of this RCT by Bausch et al. (2017) who found that patients with moderate-to-severe childhood trauma were more likely to respond and remit to ESC/CM than to CBASP within the first eight weeks of treatment. They however contradict with the moderator analysis by Nemeroff et al. (2003), who found CBASP to be superior to antidepressant monotherapy with Nefazodone in patients with childhood trauma. However, this discrepancy could be caused by several differences between both studies: besides different applied statistical methods, Paper 3 investigated the comparison of CBASP with another antidepressant as well as a shorter treatment period (eight weeks versus 12 weeks in the original study by Keller et al., 2000). Moreover, in their study, Nemeroff et al. (2003) measured childhood trauma history by another scale which assessed parental loss - a trauma type not investigated in the analysis of Paper 3. Finally, the baseline profiles of the subgroups identified in Paper 3 were not only made up by the impact of childhood trauma, but also of several other baseline characteristics which went into the compilation of M^* (see Paper 3, Appendix 3, Table 2).

With regard to the interpretation of this childhood trauma related finding, as already suspected before (Bausch et al., 2017; Schramm et al., 2015), the recall of childhood traumatic memories through psychotherapy with CBASP may have led to an initial worsening of symptoms in patients with childhood trauma within the first eight weeks of treatment. In

consequence, when treated with CBASP, patients with PDD and childhood trauma may need a longer treatment time to restructure past traumatic memories and recover from PDD. This assumption is also consistent with the findings from the secondary analysis by Michalak and colleagues (2016), who found that CBASP performed better than TAU in patients with childhood trauma in terms of change in depression severity between the post-treatment time point and a six-month follow-up, but not between baseline and week eight, which corresponds to the duration of the acute treatment phase analyzed in Paper 3. During this acute treatment period, an augmentation of CBASP with ADM or another psychotherapy focusing on coping with traumatic memories might be more beneficial for patients with this baseline profile than CBASP alone. In addition, the baseline profile of this subgroup also included other distinct characteristics mentioned before (see sub-chapter 4.3). Taken together, they suggest an association between female gender, childhood trauma and possibly also later traumatic events, as well as suicide attempts, which has already been evidenced by others (e.g., Dias de Mattos Souza et al., 2016; Roy & Janal, 2005; Sarchiapone et al., 2007; Zatti et al., 2017). This association is further complemented by the results of Paper 3 in that PDD patients with this baseline profile may likely benefit more from medication with Escitalopram in the acute treatment phase than from CBASP.

Furthermore, the analyses of Paper 3 revealed that patients more likely to benefit from CBASP were older. This is consistent with the IPD-NMA of Furukawa et al. (2018) conducted on three RCTs including the trial by Schramm et al. (2015), which found that younger PDD patients were more likely to discontinue CBASP monotherapy, possibly because of lack of response to or acceptance of CBASP. In addition, analyses of Paper 3 revealed that patients more likely to benefit from CBASP had more often an early illness onset, which is reasonable in view of the fact that CBASP was especially developed to target PDD with an early onset (McCullough, 2003; McCullough, 2021). Furthermore, patients in this subgroup also reported more previous treatments with antidepressant medication. Their ongoing PDD at the time point of the trial leads to the conclusion that previous interventions with ADM were not

successful, at least not in the long-term, which may reflect their tendency to not respond to ADM or experience recurrent MDEs after treatment with ADM.

Finally, Paper 3 was able to replicate to some extent the findings of Furukawa et al.´s (2018) IPD-NMA suggesting that pharmacotherapy is likely more beneficial than CBASP for patients with a severe baseline depression severity, as higher baseline MADRS scores were associated with a greater reduction in depression severity with ESC/CM compared with CBASP in this moderator analysis (see Paper 3, Appendix 3, Table 2). However, due to an insufficiently large moderator effect size, the MADRS baseline score was not further selected for compilation of *M**. Also, both subgroups did not differ statistically significantly in terms of their MADRS baseline scores (see Paper 3, Appendix 3, Table 3), which could, however, be explained by the small sample size and insufficient statistical power of the study. In this context, larger studies are needed to derive more conclusive subgroup differences.

5.2 Strengths and Limitations of this Dissertation

Strengths. The findings of the three papers of this dissertation add to and extend the body of evidence for PDD in several ways: first, by employing novel statistical methods, they demonstrate that behind the general cross-sample effects reported in the two main studies (Schramm et al., 2015; Schramm et al., 2017), there exist underlying, clinically relevant subgroup effects, suggesting that the effectiveness of the investigated treatments varies greatly with regard to the patient multivariable baseline profile. The results are based on three widely used psychotherapeutic and pharmacological treatments for PDD (Schramm et al., 2020), and are further specifying their differential superiority. Future studies, and possibly also earlier RCTs, will hopefully be supplemented by similar secondary analyses yielding detailed subgroup findings. Second, they present novel methodological approaches and demonstrate the advantages of the consideration of the patient multivariable pre-treatment profile and its potential to predict treatment outcomes. Third and lastly, the three studies provide new, important evidence for whom the treatments studied are more or less likely to work, possible suggested underlying reasons, and other research questions that arise and are worthy to be

investigated by future research. Altogether, they achieve the overall goal of this thesis to advance personalized medicine for PDD.

Limitations. The findings of the three papers of this dissertation need to be also considered in the context of some limitations briefly discussed in the following. First, as for most studies, the transfer of the empirical findings into clinical practice is limited due to different factors: all three performed secondary analyses relied on RCTs with limiting inclusion and exclusion criteria (e.g., non-medicated outpatients, certain excluded comorbid disorders), rigorously predefined study protocols as well as relatively modest sample sizes. Overall, these factors are limiting the generalizability of the findings regarding clinical settings. Furthermore, the diagnosis of various subtypes of chronic depression was performed according to DSM-IV criteria (in the RCT comparing CBASP with ESC/CM by Schramm et al., 2015 even with a modification of one year of duration of symptoms). Thus, the transfer of these findings to patients diagnosed with PDD according to DSM-5 criteria is partially limited, since the DSM-5 includes pure dysthymia (which was not included in the two RCTs), but no longer the subtypes analysed as moderators and predictors in the papers of this thesis. Therefore, findings such as the predictive performance of the developed combined moderators in Paper 1 and Paper 3 must be externally validated in new PDD populations based on current diagnostical guidelines as well as real clinical settings.

Second, the treatments compared in the papers are just three out of many possibilities to treat PDD. Furthermore, the analyses were based on comparisons between two treatments at a time. In clinical practice, however, a choice must be usually made between several available psychotherapeutic and pharmacotherapeutic treatments. Future studies might therefore develop statistical approaches that rank the effectiveness of several treatments for various subgroups with PDD. Moreover, the secondary analyses performed in the three papers were based on a limited number of baseline variables assessed in the original RCTs. It is very likely that there were other not assessed baseline variables with a treatment outcome moderating or predicting role, such as biological characteristics or environmental factors. Finally, for the sake

of methodological complexity, interactions between individual baseline variables or nonlinear moderation effects were not examined.

Third, in terms of the analysed outcome variables, the three papers investigated post-treatment depression severity (Paper 2) as well as pre-post-treatment depression severity reductions (Paper 1 and Paper 3). Other clinically relevant outcomes such as improvement in secondary outcomes (e.g., social skills, life quality or working ability) or possible side effects of treatments have not been addressed for reasons of quantity of content, but merit further investigation.

Fourth and finally, the moderator analyses performed do not allow conclusions to be drawn about underlying causal mechanisms linking the baseline condition to the treatment outcome, leaving the interpretation of the results in a rather speculative realm. Further mediator analyses are necessary to identify causal mechanism for a deeper understanding of these results.

5.3 Future Directions and Implications for Research and Clinical Practice

The relatively new field of personalized medicine for PDD is an overall promising one. Future research will hopefully emphasize the integration of multiple baseline variables in treatment outcome prediction more than has been done before in order to deliver reproducible, personalized treatment recommendations. The predictive performance of the combined moderators developed in Papers 1 and 3 should ideally be validated in follow-up studies with new clinical samples. A study design suitable for this purpose could start by calculating the value of M^* for all patients at baseline by using the regression weights of the baseline variables included in the compilation of M^* as reported in Paper 1 and 3 and the patient's actual value for this baseline variable. Next, one would predict a patient's outcomes under each of both treatments. Thereafter, patients would be randomized to receive either the treatment that is likely to be more effective, or the one that is likely to be less effective for them personally. With two treatment conditions compared, this would result in four treatment groups. Finally, at the

end of the intervention phase, researchers would examine whether those patients who received the treatment that was predicted to be more effective for them actually improved more than those who received the treatment predicted to be likely less effective for them personally. The goodness of its predictive performance would provide an indication of the validity of the combined moderator. As for the predictors results of Paper 2, one could test these findings in single RCTs by stratifying samples according to the predictor variables. Especially, one could investigate whether combination treatments with ADM or other psychotherapeutic elements lead to better outcomes than monotherapy with CBASP or SP in those subgroups of patients who responded more poorly to both psychotherapies in Paper 2. Finally, to allow a good transfer of the results for clinical practice, replication studies would ideally be conducted in natural clinical populations.

In addition, effects of the duration of treatments, their structural organisation and long-term effects are further important factors to study (Schramm et al., 2020) in a more personalized manner. Data from older RCTs could be re-analysed cost-effectively and quickly using more advanced statistical approaches, such as those presented here, to exploratively detect previously hidden subgroups, while new RCTs could examine comparisons between available or newer treatment approaches such as modular psychotherapy.

Despite the many advantages and promises of personalized medicine for PDD and mental disorders in general, there also exist several implications and pitfalls that will arise in future research and clinical practice. Research based on the collection of multidimensional variables that are assessed by technologies at the interface of pharmacology, neuroimaging, and genetics, as well as clinical data, will be laborious and costly, requiring intensive interdisciplinary collaboration across various disciplines (Domschke et al., 2015). With regard to psychotherapy research, in addition to the comparison of different psychotherapies, the effects of other possible treatment effect-modulating factors such as the choice of therapists (e.g., in terms of gender, experience, or professional background), therapy formats (e.g., group versus individual therapy), therapy intensity, or even delivery form (e.g., online versus face-to-face) need to be examined to enable accurate predictions. At the same time, the complexity of

this field would increase together with the growing evidence base, and this could likely lead to professionals relying more on algorithm-based predictions than on their personal understanding and clinical experience, which could affect how they perceive their role and relationship with the patient. Furthermore, besides novel biostatistical approaches that can model the complex interplay of multiple variables, cost-utility analyses evaluating the socioeconomic benefit of personalized therapy approaches, data collection and protection as well as consensus guidelines to inform clinicians about the newest findings in this area will be necessary (Domschke et al., 2015). Moreover, given that mental disorder treatment guidelines in different countries are often based on generalized results obtained from RCTs, systematic reviews and meta-analyses, with the latter method generalising findings to an ever-higher degree, it will be essential to address the weight to be given to analyses from the field of personalized medicine in these guidelines.

Moreover, when research will reach the point that evidence is transferred into clinical practice and personalized treatment recommendations can be delivered to patients, it will be important to inform patients that there is no guarantee, but only a higher comparative probability that a recommended treatment will work (comparatively better) for them personally (Kalow, 2007). Finally, in those cases in which patients or practitioners will disagree with the treatment recommended by a personalized algorithm-based prediction and abstain from selecting it, further considerations must be encountered in how to choose the most appropriate treatment.

5.4 Conclusion

Altogether, this publication-based dissertation extends and complements previous research on treatment prediction for patients with PDD, thereby advancing the relatively young field of personalized medicine for PDD. As described in the previous chapters, the multivariable pre-treatment condition of patients with PDD seems to both predict a similar and moderate a differential response to various treatments. Although the trends of the identified subgroups need to be confirmed in further studies for being transferred into reliable

clinical recommendations, they caution against generalizing sample-crossed results from RCTs to the entire PDD population, which is highly heterogenous and thereby varying in its responses to various treatments.

Altogether, the more precise and individual-oriented approach of personalized medicine holds many hopes regarding better treatment chances for patients with PDD, as well as regarding the reduction of the personal, economic and societal consequences resulting from poor treatment responses and continuing chronification. Nevertheless, the required progress in this field will also create new challenges for research, clinical practice, technology, and the health care system, which, however, will be worth solving by joint interdisciplinary forces in view of the burden of those affected.

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Paper 1 | Appendix 1

This appendix includes the full text of the following paper published in *Behaviour Research and Therapy*:

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Contributions of doctoral candidate: Ilinca Serbanescu designed the concept of this secondary study, developed the applied combination of statistical methods, selected the software for processing and analysing the data, analysed the data, interpreted the findings, drafted the manuscript, revised the manuscript as part of the peer-review process, and coordinated the publication of the manuscript.

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Combining baseline characteristics to disentangle response differences to disorder-specific versus supportive psychotherapy in patients with persistent depressive disorder

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ABSTRACT

Does the pre-treatment profile of individuals with persistent depressive disorder (PDD) moderate their benefit from disorder-specific Cognitive Behavioral System of Psychotherapy (CBASP) versus supportive psychotherapy (SP)? We investigated this question by analyzing data from a multi-center randomized clinical trial comparing the effectiveness of 48 weeks of CBASP to SP in n = 237 patients with early-onset PDD who were not taking antidepressant medication. We statistically developed an optimal composite moderator as a weighted combination of 13 preselected baseline variables and used it for identifying and characterizing subgroups for which CABSP may be preferable to SP or vice versa. We identified two distinct subgroups: 58.65% of the patients had a better treatment outcome with CBASP, while the remaining 41.35% had a better outcome with SP. At baseline, patients responding more favorably to CBASP were more severely depressed and more likely affected by moderate-to-severe childhood trauma including early emotional, physical, or sexual abuse, as well as emotional or physical neglect. In contrast, patients responding more favorably to SP had a higher pre-treatment global and social functioning level, a higher life quality and more often a recurrent illness pattern without complete remission between the episodes. These findings emphasize the relevance of considering pre-treatment characteristics when selecting between disorder-specific CBASP and SP for treating PDD. The practical implementation of this approach would advance personalized medicine for PDD by supporting mental health practitioners in their selection of the most effective psychotherapy for an individual patient.

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1. Introduction

Approximately one-third of all individuals with a lifetime depressive disorder develop a chronic course that lasts two years or longer (Murphy & Byrne, 2012), also referred to as persistent depressive disorder (PDD). PDD often begins early in life (i.e., before the age of 21), and is commonly associated with childhood trauma, mental comorbidities, as well as a low interpersonal and occupational functioning level (Arnow & Constantino, 2003; Berndt et al., 2000; Klein et al., 1999). A large number of patients with PDD experience side effects, relapses or resistances when treated with antidepressant medication (Arnow & Constantino, 2003; Kocsis, Gelenberg, et al., 2009; Schramm et al., 2017) and many report a preference for psychological over pharmacological treatments (McHugh, Whitton, Peckham, Welge, & Otto, 2013). For these reasons, psychotherapy is an indispensable tool in the treatment of many patients with PDD.

So far, the Cognitive Behavioral Analysis System of Psychotherapy (CBASP; McCullough, 2003) is the only psychotherapy model specially designed for treating PDD. As a manualized cognitive-behavioral-oriented therapy, CBASP uses techniques including situation analysis, interpersonal discrimination exercises, and behavioral skills training to improve the patients' social functioning and recovering from PDD (McCullough, 2003; Neudeck, Walter, & Schoepf, 2012). There is strong empirical evidence of the effectiveness of CBASP for the treatment of PDD (e.g. Furukawa et al., 2018; Jobst et al., 2016; Schramm et al., 2011; Wiersma et al., 2014).

Due to the body of evidence that indicates its general superiority over alternative psychotherapeutic approaches, CBASP has been recommended as first-choice psychotherapy for treating PDD (Jobst et al., 2016). However, CBASP is poorly accessible in many communities where it is not routinely implemented in the mental health care system (Schramm et al., 2017).

Supportive psychotherapy (SP), which is more widely used, emphasizes non-specific, common core therapeutic factors like empathic listening, building a therapist-patient alliance, and therapeutic optimism (Markowitz, 2014). Unlike CBASP, SP does not use specific techniques like problem-solving or exposure exercises (Markowitz, 2014). In a meta-analysis, Cuijpers et al. (2012) found that SP has a considerable effect on mild to moderate depression in adult patients and is equally effective as cognitive-behavioral-oriented psychotherapies when controlling for investigator allegiance. Moreover, the authors concluded that non-specific factors account the most for the effectiveness of all investigated psychotherapies, while the contribution of specific techniques was limited at best. This may suggest that for some patients with PDD, SP might be equally or even more effective than CBASP. For others, disorder-specific CBASP might be more beneficial than a supportive approach. However, so far, little has been understood about which psychotherapeutic approach works for which patients with PDD (Cuijpers, Huibers, & Furukawa, 2017; Jobst et al., 2016).

In randomized clinical trials, an essential step in understanding who benefits from which treatment is to identify moderators of treatment response, i.e. pretreatment or baseline characteristics that are independent of the assigned treatment and show a different treatment effect depending on their value (Kraemer, 2013). For example, Nemeroff et al. (2003) found that for chronically depressed patients with a history of childhood trauma (i.e., early loss of parents, physical or sexual abuse, or neglect), CBASP was superior to monotherapy with nefazodone. Another analysis revealed that the effectiveness of CBASP and nefazodone varied depending on the patients' preference, in that they responded better to their preferred treatment (Kocsis, Leon, et al., 2009). The results of a meta-analysis of individual participant data (Furukawa et al., 2018) indicated that for PDD patients with severe depression and anxiety, the combination of CBASP and antidepressant medication was more effective than monotherapy with CBASP or antidepressant medication.

Although relevant for theory and treatment development, research emphasizing individual moderators often produces inconsistent results across different trials (Kraemer, 2013; Wallace & Smagula, 2018). For example, Bausch et al. (2017) failed to replicate the moderating role of childhood trauma (Nemeroff et al., 2003) in a comparison trial of CBASP and escitalopram in patients with PDD. Moreover, the isolated examination of individual moderators can lead to contradictory treatment recommendations. For instance, for a patient who prefers antidepressant medication and who has a history of early trauma, one might indicate medication over CBASP based on the treatment preference (Kocsis, Leon, et al., 2009), and at the same time, CBASP over medication with regard to the early trauma history (Nemeroff et al., 2003). Another issue with individual moderators is that they often have weak effects (Kraemer, 2013), and many studies do not report effect sizes that capture their moderation effect. To address these issues, Kraemer (2013) developed the optimal composite moderator approach, in which multiple individual moderators are combined to an optimal composite moderator 'M*', which is used to identify and subsequently characterize patients who benefit more from one treatment than from another. This approach was applied to a number of randomized clinical trials examining interventions for episodic depression (Wallace, Frank, & Kraemer, 2013), late-life depression (Smagula et al., 2016), bipolar disorders (Frank et al., 2014) and anxiety disorders (Niles, Loerinc, et al., 2017; Niles, Wolitzky-Taylor, Arch, & Craske, 2017; Wallace et al., 2017). In all of these studies, the effect size of M* was larger than any effect size of an individual moderator. So far, no previous work has applied this approach to a trial conducted in patients with PDD.

In a multi-center randomized clinical trial, Schramm et al. (2017) compared the effectiveness of 48 weeks of CBASP to SP in outpatients with early-onset PDD who were not taking antidepressant medication. The findings suggested that both interventions were associated with pre- to post-treatment reductions in depression severity, but that CBASP was modestly superior to SP. The present exploratory study used data from the trial conducted by Schramm et al. (2017) to identify and characterize subgroups of patients for whom CBASP was more likely to result in symptom reduction than SP, and vice versa. By addressing the question of what worked for whom, we aimed to generate findings that may be validated in future independent clinical populations, serve for developing treatment recommendations, and thus meet the need to advance personalized medicine for chronic forms of depression (Cuijpers et al., 2017).

2. Method

The data used had been collected as part of an evaluator-blinded, prospective, parallel-group randomized clinical trial conducted at eight university centers throughout Germany (ClinicalTrials.gov identifier NCT00970437). The trial was carried out following the latest version of the Declaration of Helsinki and was separately approved by the ethics committees of all study centers. Patients provided written informed consent after receiving explanations of all procedures. Detailed information on the study trial can be found in the published protocol (Schramm, Hautzinger, et al., 2011) and the published main results of the trial (Schramm et al., 2017).

2.1. Participants

Among 622 patients assessed for eligibility, 268 were randomized to either CBASP (n = 137) or SP (n = 131). Study participants were outpatients aged 18–65 years who met the DSM-IV (American Psychiatric Association, 1994) criteria for a current major depressive disorder (MDD) of at least two years duration (chronic MDD; 31.5%), MDD superimposed on a pre-existing dysthymic disorder (double depression; 45.8%), or recurrent MDD without complete remission between episodes (22.7%), all with an early illness onset (before age 21). At the screening, patients scored at least 20 points on the 24-item

Hamilton Rating Scale for Depression (HRSD-24; Hamilton, 1967). Exclusion criteria included: an acute risk of suicide; a primary diagnosis of another Axis I disorder; a lifetime history of psychotic symptoms; a diagnosis of bipolar disorder, antisocial, schizotypal, or borderline personality disorder; a severe medical condition; an organic brain disorder; severe cognitive impairment; no response to a previous trial with CBASP or SP; or an ongoing treatment with a psychotherapy or antidepressant medication. The intake of any antidepressant medication was prohibited during the entire trial.

2.2. Interventions

The CBASP is a highly structured, theory-driven psychotherapy from the third generation of behavioral therapy models specially designed to treat PDD. During the therapy, the patients are trained to develop a better understanding of the consequences of their behavior on others. The therapist uses techniques such as situation analysis, interpersonal discrimination exercises, and behavioral skill training to facilitate this (McCullough, 2003). Supportive psychotherapy is a disorder non-specific psychotherapy that emphasizes "common" factors that are supposed to be relevant tools across all psychotherapies including empathic listening and therapeutic optimism (Markowitz, 2014). In our trial, treatments were delivered by trained and experienced therapists who followed standardized CBASP and SP manuals. Sessions of CBASP and SP were held twice weekly for the first four weeks and weekly for the next 16 weeks in the acute treatment phase, followed by eight continuation sessions during the next 28 weeks, resuming to 32 sessions.

2.3. Baseline variables examined as potential individual moderators

Before treatment randomization, study participants completed several diagnostic interviews, psychological questionnaires, and rating scales related to socio-demography, clinical characteristics, and treatment history. In our exploratory analysis, we considered 36 baseline variables as potential individual moderators and calculated moderator effect sizes as developed by Kraemer (2013) for each of them. Details on the assessment of all analyzed baseline variables are provided in Supplemental Table 1 in the supplemental materials (SM).

Demographic characteristics: Gender, age at randomization (years), being single, married or cohabiting, separated, divorced, or widowed, having a high educational level (= at least 12 years), being employed and the presence of morbidities were each considered as a potential moderator.

Questionnaires administered at baseline: We considered the baseline sum scores of the following questionnaires: HRSD-24 (Hamilton, 1967), self-rated Inventory of Depressive Symptomatology (IDS-SR; Rush, Gullion, Basco, Jarrett, & Trivedi, 1996), the sum scores of the anxiety and phobic anxiety subscales of the Brief Symptom Inventory (BSI; Derogatis & Melisaratos, 1983), Generalized Anxiety Disorder Scale-7 (GAD-7; Spitzer, Kroenke, Williams, & Löwe, 2006), Beck Scale for Suicidal Ideation (BSSI; Beck, Kovasac, & Weissman, 1979), Inventory of Interpersonal Problems (IIP-64; Horowitz, Strauβ, & Kordy, 2000), Global Assessment Functioning Scale (GAF; Endicott, Spitzer, Fleiss, & Cohen, 1976), Quality of Life in Depression Scale (QLDS; Hunt & McKenna, 1992), and Social Adaptation Self-Evaluation Scale (SASS; Duschek, Schandry, & Hege, 2003).

Mental comorbidities: We examined the presence of any comorbid Axis I disorders (diagnosed by the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, SCID-I; First, Spitzer, Gibbon, & Williams, 2002) as well as the presence of any comorbid Axis II personality disorders (diagnosed by the Structured Clinical Interview for DSM-IV Axis II Personality Disorders, SCID-II; First, Gibbon, Spitzer, & Williams, 1997).

Illness characteristics and history: We examined the three subtypes (chronic MDD, double depression, and recurrent MDD without complete remission between episodes), the illness duration (in years), the age of illness onset (in years), and the history of at least one previous suicide attempt.

Early trauma: Early trauma was assessed using the Childhood Trauma Questionnaire (CTQ; Bernstein, Stein, & Newcomb, 2003). The CTQ assesses five types of early trauma that happened before the age of 18: emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect. In our analysis, the presence of each type was defined as at least moderate-to-severe, corresponding to a specific cut-off on the respective scale (for details, please refer to Supplemental Table 1 in the SM).

Treatment history and preference for psychotherapy: The examined variables included a history of at least one previous psychotherapy (with a duration of at least eight sessions) to treat depression, a history of at least one treatment with antidepressant medication (taken for at least four weeks), a history of combination treatment of psychotherapy with antidepressant medication, and a history of inpatient treatment for depression. Lastly, because we compared the effectiveness of two forms of psychotherapy, we analyzed the patients' preference for psychotherapy over other treatments for depression as a potential moderator.

2.4. Outcome

In the present analysis, we used the percentage change in HRSD-24 scores from baseline to week 48 as an outcome. Negative scores reflect a reduction in depression severity, a score of zero reflects no change and positive scores indicate an increase in depression severity from baseline to week 48. The HRSD-24 ratings were performed by trained and experienced evaluators who were blind to treatment assignment. The interrater reliability of the HRSD-24 ratings was calculated based on data from 21 evaluators' ratings of nine audio- or videotaped interviews and had an intra-class correlation coefficient of 0.973 (95% CI, 0.889–0.999). Missing HRSD-24 data at week 48 (n = 59; 22.0%) were replaced by the last observation carried forward method, as specified in the study protocol (Schramm, Hautzinger, et al., 2011).

2.5. Statistical analyses

Individual moderator effect sizes: First, we used the method described by Kraemer (2013) to examine moderator effect sizes for all 36 candidate variables. We started by pairing each patient assigned to CBASP to each patient assigned to SP. Next, for each pair in this dataset, we calculated the difference in the outcome (i.e., the percentage change in HRSD-24 scores) and the average value of each baseline variable. Next, to obtain the effect sizes, we computed non-parametric Spearman correlations between the difference in the outcome and each average, and estimated their 95% bootstrap confidence intervals (CI) based on 100 replications. Effect sizes obtained after this method are invariant over linear transformations of the baseline variable or the outcome, varying between -1 and $+1$, with higher magnitudes indicating a stronger moderation and 0 indicating the absence of a moderation effect (Kraemer, 2013). Variables were considered to be moderators if their effect size was $\geq |0.10|$ (i.e., at least small). This cutoff is similar to those used in previously published applications of Kraemer's composite moderator method (e.g., Smagula et al., 2016; Wallace et al., 2017). Given the exploratory character of this analysis, we abstained from including the statistical significance of interaction effects between the treatment and the moderator as a selection criterion (Wasserstein & Lazar, 2016).

Model selection of the composite moderator: Next, we wanted to identify which of the variables with effect sizes $\geq |0.10|$ to include in the composite moderator (M*) and to determine their weights contributing to M*. According to Kraemer (2013), in the paired dataset, the weights of the single moderators have to be estimated by a multivariable regression model, in which the difference in outcome is

predicted by the averages of all preselected individual moderators. Similar to previous applications of the composite moderator approach (e.g., Smagula et al., 2016; Wallace et al., 2017; Wallace et al., 2018), we chose to perform least absolute shrinkage and selection operator (lasso) regression (Tibshirani, 1996) in the multivariable model. In principle, lasso regression selects the most useful independent variables and shrinks the regression weights of the least useful variables (e.g., those with little predictive power or correlated with other predictors) to zero, thereby removing them from the model (Tibshirani, 1996). Moreover, to optimize the model's predictive performance and to avoid overfitting, we combined lasso regression with *k*-fold cross-validation (James, Witten, Hastie, & Tibshirani, 2013). Other recent applications of the composite moderator approach have discussed the advantages of combining *k*-fold cross-validation with Kraemer's method, and have successfully applied it to develop composite moderators of continuous and dichotomous outcomes (refer to Niles, Loerinc, et al., 2017; Niles, Wolitzky-Taylor et al., 2017). In *k*-fold cross-validation, the data is randomly sampled into *k* folds: (*k*-1) folds are used as the training dataset, and the *k*th fold constitutes the validation dataset. The model is estimated within the training dataset, and its predictive performance is assessed within the held-out validation dataset (James et al., 2013). The entire procedure is repeated *k* times so that each fold is used for validation once. When applied to lasso regression, *k*-fold cross-validation can be used to identify the value of the tuning parameter (λ) that minimizes the estimated mean-squared prediction error (MSPE) in the validation dataset. Thus, *k*-fold cross-validation enables to select a model that is more likely to have a good predictive performance in future new data, than a model that was trained *and* tested within the same data. In our analysis, for defining the tuning parameter that yields the smallest MSPE, we applied 10-folds cross-validation as described by Ahrens, Hansen, and Schaffer (2019) and implemented in their package *lassopack* developed for use in STATA. Within the paired dataset, we ran the 10-folds cross-validation by using the command "*cvlasso*", which internally repeats lasso regression and finally selects the model with the optimal tuning parameter (λ_{opt}) that yields the smallest MSPE.

Identification of subgroups: After selecting the optimal model based on the procedure described before, we extracted the weights from each of the moderators selected by this model and calculated the value of M* for each patient as described by Kraemer (2013). Finally, in the unpaired full dataset, we conducted a regression analysis predicting the outcome (i.e., percentage change in HRSD-24 scores) from the composite moderator M*, the treatment group, and their interaction, and computed the effect size of M* together with the 95% bootstrap CI. We calculated the value of M* at which the predicted outcomes for CBASP and SP group crossed one another. When they crossed, we divided the sample into two subgroups, one below and one above the cross-point, each with a different treatment associated with a more favorable outcome. Within both subgroups, we calculated Cohen's *d* treatment effect sizes with 95% CI. Finally, we characterized the baseline profiles of each subgroup. Analyses were conducted in STATA version 15.1 (StataCorp, 2017).

3. Results

Effect sizes of individual moderators: Table 1 displays effect sizes with 95% CI for each of the 36 baseline variables. Effect sizes ranged from −0.209 (IDS-SR; self-rated depression severity) to 0.084 (past psychotherapy). Negative values indicate a better outcome (i.e., a greater reduction in HRSD-24 scores from pre-to post-treatment) with CBASP than with SP for higher values of the moderator. Positive values indicate a better outcome with SP than with CBASP for higher values of the moderator. In total, we identified 13 baseline variables with an effect size ≥ |0.10|. These were self-rated depression severity (IDS-SR), clinician-rated depression severity (HRSD-24), having at least one comorbid Axis I disorder, early moderate-to-severe emotional neglect, early moderate-to-severe physical neglect, quality of life (QLDS, with higher values indicating lower quality of life), being divorced, separated, or widowed, illness duration (years), chronic MDD as subtype, recurrent MDD without complete remission between the episodes as subtype, having at least one comorbid Axis II disorder, social functioning (SASS), and global functioning (GAF).

Optimal composite moderator M*: By using 10-fold cross-validation as described in the methods, we selected an optimal model that contained all 13 moderators with an effect size ≥ |0.10|. Supplemental Fig. 1 of the SM provides a plot of the estimated MSPEs as a function of the tuning parameter resulting from the 10-fold cross-validation. The estimated weights for the composite moderator M* are provided in Table 1. They represent the extent to which each moderator distinguishes differences in the outcome between patients from CBASP and those from SP in the context of the other selected moderators. The effect size of the composite moderator M* was r = 0.34 (95% CI, 0.32; 0.36). In comparison, the effect size of the largest individual moderator, self-rated baseline depression severity (IDS-SR), was r = −0.209 (95% CI of −0.227 to −0.190).

Identified subgroups: Values of M* were calculated for n = 237 patients who had complete data on all 13 moderators. Next, in the unpaired dataset, we performed the regression analysis explained in the methods. Fig. 1 illustrates the predicted pre- to post-treatment percentage change in HRSD-24 scores for CBASP and SP across the range of M*. The lines cross at M* = 8.40. Below this cross-point (M* < 8.40), CBASP was moderately preferable to SP (Cohen's d = −0.57; 95% CI: 0.91; −0.23) for n = 139 (58.65%) patients. Above this cross-point (M* > 8.40), SP was little preferable to CBASP (Cohen's d = 0.29; 95% CI: 0.11; 0.68) for n = 98 (41.35%) patients.

Table 2 provides descriptive statistics to characterize patients in both subgroups. Patients responding more favorably to CBASP had a more prolonged illness duration, were more often divorced, separated, or widowed, and more likely diagnosed with chronic MDD. More often, they had at least one comorbid Axis I disorder as well as higher initial self- and clinician-rated depression severity. All five forms of moderate-to-severe childhood trauma (emotional abuse, emotional neglect, physical abuse, physical neglect, and sexual abuse) were more often reported by these patients. Conversely, patients responding more favorably to SP tended to have higher baseline general and social functioning levels. Their baseline quality of life was less affected by PDD. They were also more likely to have recurrent MDD without complete remission between the episodes as well as at least one Axis II disorder. Note that, because of the explorative character of this analysis, we abstained from testing any of these subgroup differences.

4. Discussion

The aim of this study was to identify and characterize subgroups of patients with early-onset PDD who responded more favorably to 48 weeks of CBASP versus SP and vice versa. By using the approach described by Kraemer (2013) and two statistical learning methods (lasso regression and *k*-fold cross-validation), we preselected and combined single baseline variables into an optimal composite moderator to predict whether a patient will be more likely to benefit from CBASP or SP. In line with previous applications of the composite moderator approach (e.g. Niles, Loerinc, et al., 2017; Niles, Wolitzky-Taylor et al., 2017; Smagula et al., 2016; Wallace et al., 2017), the effect size of M* was larger than the effect size of any individual moderator. We found two subgroups: one comprising approximately 59% of patients for whom CBASP was preferable to SP, and another comprising 41% of patients for whom SP was preferable to CBASP. We finally characterized and compared both subgroups in terms of their pre-treatment profiles.

The CBASP was associated with a better outcome than SP for more severely depressed patients who had higher rates of early trauma in the form of sexual, emotional or physical abuse, or emotional or physical neglect. Importantly, CBASP was specially developed to treat early-trauma-driven behavioral and cognitive deficits in chronically

Table 1
Moderator effect sizes for analyzed baseline variables and weights for the composite moderator.

Baseline variable	Moderator effect size (95% CI)	Weight in the final model
Included in the final model		
IDS-SR	−0.209 (−0.227; −0.190)	−1.610
HRSD-24	−0.162 (−0.180; −0.144)	0.124
At least one comorbid Axis-I disorder	−0.141 (−0.155; −0.127)	−18.821
Early emotional neglect	−0.121 (−0.136; −0.106)	−6.326
QLDS	−0.118 (−0.132; −0.103)	0.674
Separated, divorced or widowed	−0.114 (−0.128; −0.100)	−15.680
Illness duration	−0.108 (−0.121; −0.095)	−0.034
Chronic major depression	−0.108 (−0.122; −0.094)	−9.941
Early physical neglect	−0.102 (−0.116; −0.089)	−6.518
Recurrent major depression without complete remission between episodes	0.100 (0.084; 0.117)	20.919
At least one comorbid Axis-II disorder	0.106 (0.092; 0.119)	30.943
SASS	0.113 (0.098; 0.127)	0.456
GAF	0.144 (0.126; 0.163)	0.744
Not included in the final model		
GAD-7	−0.098 (−0.115; −0.081)	
Age at randomization	−0.095 (−0.108; −0.081)	
At least one lifetime suicide attempt	−0.086 (−0.102; −0.071)	
At least 12 years of education	−0.075 (−0.089; −0.061)	
Early physical abuse	−0.069 (−0.084; −0.055)	
BSI, subscale anxiety	−0.064 (−0.080; −0.047)	
Past treatment with antidepressant medication	−0.060 (−0.074; −0.046)	
Having at least one morbidity	−0.047 (−0.062; −0.032)	
IIP-64	−0.042 (−0.058; −0.027)	
Gender (= female)	−0.027 (−0.042; −0.011)	
Early emotional abuse	−0.026 (−0.040; −0.011)	
Past inpatient treatment	−0.009 (−0.023; 0.005)	
BSSI	−0.003 (−0.018; 0.013)	
BSI, subscale phobia	−0.001 (−0.014; 0.013)	
Past combination treatment	0.003 (−0.012; 0.019)	
Early sexual abuse	0.013 (−0.005; 0.031)	
Double depression	0.017 (0.002; 0.032)	
Preference for psychotherapy	0.029 (0.015; 0.043)	
Being single	0.034 (0.020; 0.049)	
Married or cohabiting	0.052 (0.037; 0.068)	
Employed	0.061 (0.050; 0.073)	
Age at illness onset	0.072 (0.056; 0.087)	
Past psychotherapy	0.084 (0.068; 0.100)	

Abbreviations: BSI = Brief Symptom Inventory; BSSI = Beck Scale for Suicidal Ideation; CI = confidence interval; GAD-7 = Generalized Anxiety Disorder Scale-7; GAF = Global Assessment Functioning Scale; HRSD-24 = 24-Item Hamilton Rating Scale for Depression; IDS-SR = Inventory of Depressive Symptomatology, self-rated; IIP-64 = Inventory of Interpersonal Problems; QLDS = Quality of Life in Depression Scale; SASS = Social Adaptation Self-Evaluation Scale.
Notes: Negative values indicate a better outcome with CBASP than with SP for higher values of the moderator. Positive values indicate a better outcome with SP than with CBASP for higher values of the moderator.

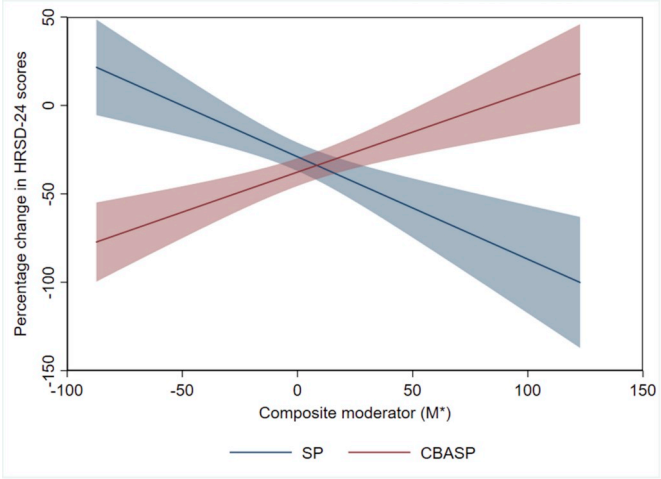

Fig. 1. Predicted percentage change in HRSD-24 scores with 95% confidence intervals for CBASP and SP across the observed range of the composite moderator M*.
Abbreviations: CBASP, Cognitive Behavioral Analysis System of Psychotherapy; HRSD-24, 24-Item Hamilton Rating Scale for Depression; SP, supportive psychotherapy.

depressed patients (McCullough, 2003). The CBASP therapist seeks to help his clients to recognize the negative consequences of their dysfunctional behavior on others, as well as to improve their stress management skills and emotional control over depression by applying bottom-up and top-down techniques to encourage formal operative thinking and behavior (McCullough, 2003; Neudeck et al., 2012; Schramm et al., 2017). Thus, it is plausible that this approach was more useful than non-structured SP for those patients with a lower social and global functioning level at baseline, who were also more early traumatized and who had a higher initial depression severity. Their baseline profile corresponds more to the picture of the chronically depressed patient portrayed by McCullough in the early years of the development of CBASP (McCullough, 2003) than the pre-treatment characteristics dominating in the subgroup benefiting more from SP. Patients who responded more favorably to SP had a higher initial social and global functioning level, less early trauma, and a lower baseline depression severity. According to Markowitz (2014), SP bypasses the confrontation with biographical aspects while offering a more liberal and supportive therapeutic setting that focuses on activating available resources. Given the constellation of more beneficial baseline features, this subgroup might have benefited from the resources that were activated through the approach of SP. The lower rates of early traumatic experiences in this subgroup might also explain why the early-trauma emphasizing approach of CBASP was less beneficial for these patients. Given the

Table 2
Baseline profiles of patients within the two subgroups above and below M* = 8.40

Baseline characteristics	CBASP is preferable to SP (M* < 8.40; n = 139)	SP is preferable to CBASP (M* > 8.40; n = 98)
Illness duration, y, mean (SD)	34.1 (13.2)	28.7 (13.4)
Separated, divorced or widowed (%)	25.2	8.2
Chronic major depression (%)	46.8	12.2
Recurrent major depression without complete remission between episodes (%)	10.1	39.8
Any Axis I disorder (%)	53.2	23.5
Any Axis II disorder (%)	26.6	53.1
CTQ emotional neglect (%)	74.8	52.0
CTQ emotional abuse (%)	66.9	48.0
CTQ physical neglect (%)	41.7	15.3
CTQ sexual abuse (%)	29.0	15.5
CTQ physical abuse (%)	28.8	10.2
Self-rated depression severity, IDS-SR, mean (SD)	43.1 (8.4)	33.3 (8.1)
Clinician-rated depression severity, HRSD-24, mean (SD)	27.0 (6.7)	21.7 (6.3)
Quality of life, QLDS, mean (SD)	20.7 (7.1)	16.6 (7.8)
Social functioning, SASS, mean (SD)	28.6 (6.5)	32.0 (5.9)
Global functioning, GAF, mean (SD)	51.1 (8.1)	58.5 (8.5)

Abbreviations: CBASP, Cognitive Behavioral Analysis System of Psychotherapy; CTQ, Childhood Trauma Questionnaire; GAF, Global Assessment Functioning Scale; HRSD-24, 24-Item Hamilton Rating Scale for Depression; IDS-SR, self-rated Inventory of Depressive Symptomatology; QLDS, Quality of Life in Depression Scale; SASS, Social Adaptation Self-Evaluation Scale; SD, standard deviation; SP, supportive psychotherapy; y, years.
Notes: Higher values of the QLDS indicate a lower quality of life due to depressive disorder.

greater availability of SP in clinical practice (Markowitz, 2014), future research should investigate its potential to treat PDD in patients with such pre-treatment characteristics.

Importantly, we want to emphasize that these subgroup effects apply, so far, only to the here investigated population of outpatients with PDD who were not taking antidepressant medication. Although we performed cross-validation, the replicability of the model generated to calculate M*, as well as the effect size of M*, have to be tested in a rigorous external validation before these findings can be generalized and applied to clinical practice. Besides the validation of the model provided in this work, one might also select prominent baseline differences that differed (e.g., early trauma, PDD subtype) between both subgroups and stratify new populations according to them in order to test specific hypotheses or new treatment combinations. For the prediction of treatment response, models based on integrating several multi-domain characteristics might, however, be more realistic and useful than the traditional approach of examining one moderator per model (for a discussion, refer to Cohen & DeRubeis, 2018 and Wallace & Smagula, 2018).

4.1. Limitations and outlook

Our findings should be considered in the context of some limitations. First, we want to emphasize that our study was a hypothesis-generating one. As already mentioned, the predictive performance of the developed composite moderator must be externally validated in a new population. Also, mediator analyses are further necessary to identify the factors that have influenced the process between randomization and post-treatment within each subgroup. Second, the psychotherapies compared here (i.e., CBASP and SP) are two out of many possibilities to treat PDD. Future studies might develop composite moderator approaches that rank the effectiveness of several treatments. Another necessity is to develop more sophisticated models that consider the benefits and the side effects of treatments. Third, we only had a limited number of variables, with which to develop the composite moderator. It is likely that other moderators, which were not assessed, would have enhanced the effect size of M* if included. Forth, in order to restrict the model's complexity, we did not examine interactions between single variables or non-linear moderator effects. Due to the many possible models, sophisticated machine learning methods might represent a more useful alternative for testing this diversity. Finally, further analyses should be performed to determine whether the composite moderator is also reflective of outcomes at a given follow-up time point.

5. Conclusion

By using the composite moderator methodology, we have identified two subgroups with differential benefits from disorder-specific CBASP compared to SP. These results emphasize the relevance of detecting subgroups with differential treatment benefits in randomized clinical trials by methods such as the one applied here. After validation in an independent sample, algorithms based on this method could help mental health practitioners select the most promising psychotherapy for patients in the community. Further progress in this research field is urgently needed to personalize treatment selection for patients suffering from PDD.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brat.2019.103512.

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Paper 2 | Appendix 2

This appendix includes the full text of the following paper published in *Frontiers in Psychiatry*:

Serbanescu, I., Backenstrass, M., Drost, S., Weber, B., Walter, H., Klein, J. P., Zobel, I., Hautzinger, M., Meister, R., Härter, M., Schramm, E., & Schoepf, D. (2020). Impact of Baseline Characteristics on the Effectiveness of Disorder-Specific Cognitive Behavioral Analysis System of Psychotherapy (CBASP) and Supportive Psychotherapy in Outpatient Treatment for Persistent Depressive Disorder. *Frontiers in Psychiatry, 11,* 607300. https://doi.org/10.3389/fpsyt.2020.607300

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Contributions of doctoral candidate: Ilinca Serbanescu designed the concept of this secondary study, developed the applied combination of statistical methods, selected the software for processing and analysing the data, analysed the data, interpreted the findings, drafted the manuscript, revised the manuscript as part of the peer-review process, and coordinated the publication of the manuscript.

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Impact of Baseline Characteristics on the Effectiveness of Disorder-Specific Cognitive Behavioral Analysis System of Psychotherapy (CBASP) and Supportive Psychotherapy in Outpatient Treatment for Persistent Depressive Disorder

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Importance: In the treatment of persistent depressive disorder (PDD), disorder-specific Cognitive Behavioral Analysis System of Psychotherapy (CBASP) has been shown to be superior to Supportive Psychotherapy (SP) in outpatients. It remains to clear which subgroups of patients benefit equally and differentially from both psychotherapies.

Objective: To identify those patient-level baseline characteristics that predict a comparable treatment effectiveness of CBASP and SP and those that moderate the differential effectiveness of CBASP compared to SP.

Design, setting and participants: In this analysis of a 48-week multicenter randomized clinical trial comparing CBASP to SP in adult antidepressant-free outpatients with early-onset PDD, we evaluated baseline variables from the following domains as potential predictors and moderators of treatment effectiveness: socio-demography, clinical status, psychosocial and global functioning, life quality, interpersonal problems, childhood trauma, treatment history, preference for psychotherapy, and treatment expectancy.

Interventions: A 48-week treatment program with 32 sessions of either CBASP or SP.

Main outcomes and measures: Depression severity measured by the 24-item Hamilton Rating Scale for Depression (HRSD-24) at week 48.

Results: From $N = 268$ randomized outpatients, $N = 209$ completed the 48-week treatment program. CBASP completers had significantly lower post-treatment HRSD-24 scores than SP completers ($mean_{CBASP}$ =13.96, $sd_{CBASP} = 9.56$; $mean_{SP} = 16.69$, $sd_{SP} = 9.87$; $p = 0.04$). A poor response to both therapies was predicted by higher baseline levels of clinician-rated depression, elevated suicidality, comorbid anxiety, lower social functioning, higher social inhibition, moderate-to-severe early emotional or sexual abuse, no preference for psychotherapy, and the history of at least one previous inpatient treatment. Moderator analyses revealed that patients with higher baseline levels of self-rated depression, comorbidity of at least one Axis-I disorder, self-reported moderate-to-severe early emotional or physical neglect, or at least one previous antidepressant treatment, had a significantly lower post-treatment depression severity with CBASP compared to SP (all $p < 0.05$).

Conclusions and relevance: A complex multifactorial interaction between severe symptoms of depression, suicidality, and traumatic childhood experiences characterized by abuse, social inhibition, and anxiety may represent the basis of non-response to psychotherapy in patients with early onset PDD. Specific psychotherapy with CBASP might, however, be more effective and recommendable for a variety of particularly burdened patients compared to SP.

Keywords: persistent depressive disorder, CBASP, supportive psychotherapy, moderator analysis, predictor analysis, childhood trauma, personalized medicine

INTRODUCTION

Over 20% of the patients with major depressive disorder (MDD) develop a chronic course lasting two years or longer (1), called Persistent Depressive Disorder (PDD) (2, 3). Compared to single major depressive episodes, PDD is characterized by a longer illness duration with a more complicated treatment course, lower quality of life, concurrent generalized anxiety disorder, more frequent suicide attempts, comorbid psychiatric and personality disorders, dysfunctional interpersonal behavior and more complicated treatment courses (1, 4, 5). More than two-thirds of all patients with PDD report an early illness onset (before age 21) often associated with severe experiences of childhood maltreatment characterized by emotional, physical, and sexual abuse or by deprivation in form of emotional or physical neglect (1, 4, 6, 7). Importantly, a large majority of patients with PDD experience side effects, relapses or resistances in the treatment with antidepressant medication (1, 7, 8) and report to prefer psychological over pharmacological treatment (9). Thereby, psychotherapy is an indispensable tool in the treatment of PDD.

So far, the Cognitive Behavioral Analysis System of Psychotherapy (CBASP) (10) is the only psychotherapy-model especially designed to address the specific needs of patients with early-onset PDD. Its principle lies on treating early trauma related dysfunctionalities by focusing on the patient's interpersonal problems through systematic social problem solving and discriminative interpersonal learning (10, 11). Its effectiveness has been evidenced in a number of clinical trials that compared CBASP to other psychotherapies (7), antidepressant medication (12, 13), or to combined treatments (8, 12). The European Psychiatric Association has recommended CBASP as the first-line psychotherapy for PDD, which is largely justified by its superiority over alternative, non-specific psychotherapies (5).

Nevertheless, little progress has been achieved in understanding which PDD subpopulations may or may not profit from psychotherapy in general and which benefit from CBASP in particular, leaving the questions for whom and when exactly CBASP should be recommended largely unanswered (5, 14).

This is particularly problematic, as PDD is a heterogeneous disorder, and different PDD subpopulations may benefit to varying degrees from CBASP (15). Gaining evidence is crucial not only for further explaining its general effectiveness, but also for detecting specific subpopulations for which CBASP can be recommended as first-choice psychotherapy.

One possibility to examine its disorder-specific effectiveness is by comparing it to alternative forms of psychotherapy. In a multicenter randomized clinical trial, Schramm and colleagues (7) evaluated the effectiveness of CBASP by comparing it with non-specific supportive psychotherapy (SP) in $N = 268$ antidepressant-free, adult outpatients with early-onset PDD (ClinicalTrials.gov identifier NCT00970437). Overall, CBASP was found to be more effective and acceptable than SP. Patients treated with CBASP showed small, but significant advantages in most primary and secondary outcomes, as well as in response and remission rates.

So far, a number of secondary analyses of this trial have been performed in order to analyze if CBASP outperformed SP for patients with early trauma (16), comorbid personality

disorders (17), comorbid anxiety disorders (18), as well as various baseline characteristics combined to one single moderator (19). With regard to early trauma, only those patients reporting early severe-to-moderate emotional abuse seemed to benefit significantly more from CBASP than from SP at week 20 (16). The presence of comorbid personality disorders was neither a predictor nor a moderator of depression severity at week 20 (17). However, the CBASP was significantly more effective than SP in patients with comorbid anxiety disorders compared to those without anxiety disorders in terms of both depression severity and interpersonal problems as outcomes (18). In a more recent secondary analysis (19), the data of this trial was analyzed with a modern moderator approach combined with two machine learning algorithms. An optimal composite moderator (M*) was developed as a weighted combination of 13 preselected baseline variables and used for identifying and characterizing subgroups for which CABSP was more beneficial to SP and vice versa, focusing on the change in depression severity from baseline to week 48. Of the analyzed sample of patients, 58.65% experienced a better treatment outcome with CBASP, while 41.35% showed a better outcome with SP. In terms of baseline characteristics, patients responding more favorably to CBASP were more severely depressed, had more often a comorbid Axis-I disorder, were more often previously hospitalized, and were more likely affected by moderate-to-severe early emotional or physical neglect. In contrast, patients responding more favorably to SP had a higher pre-treatment global and social functioning level, a higher quality of life, and more often a recurrent MDD without complete remission between the episodes.

An important outstanding question which remains to be clarified is which subgroups of patients respond to both therapies. The main goal of this analysis will therefore be to identify *predictors*, i.e. baseline variables which predict treatment success regardless of treatment assignment. Discovering predictors is especially helpful for understanding which factors contribute to non-response to psychotherapy and consequently to the persistent course in chronically depressed patients. In contrast to the common practice of limiting analyses to a few characteristics and in order to gain a complex understanding, we investigated a large span of baseline characteristics including socio-demography, clinical status, psychosocial and global functioning, quality of life, interpersonal problems, childhood trauma, treatment history, preference for psychotherapy, and treatment expectancy.

Baseline characteristics which have been previously associated with a better treatment response for psychotherapy in patients with PDD and thus plausible to have contributed to a greater alleviation of depression severity in both arms are: lower baseline levels of depression and anxiety (20), having a preference for psychotherapy at the baseline (21, 22), as well as a positive treatment expectancy at baseline (23). We therefore expected an equally high effectiveness of both therapies in patients characterized by these features at baseline.

In addition, the present analysis will also examine the same baseline variables as moderators of differential treatment effectiveness of CBASP vs. SP at week 48. This will be done for statistical reasons (for determining if a variable is a predictor, one has to examine its interaction effect with the group variable), as well as for reasons of comparability with the previous moderator analysis (19) which was based on a more modern approach. Statistical models such as the one applied in the previous analysis (19), which are based on integrating several multi-domain baseline variables into one moderator to identify subpopulations with different treatment responses, are particularly useful for the prediction of treatment response in samples which are sufficiently statistically powered, and can be further validated as a prediction algorithm in new clinical populations. In comparison, the more classical approach of selecting and testing one baseline variable as predictor and moderator per model, which will be used in the analysis presented here, provides evidence about the individual impact of single baseline characteristics on the treatment outcome. These findings can further be used for selecting those clinical subpopulations which seem to respond particularly poorly to one or both therapies for testing new treatments or combination of treatments, which can be especially developed to target their needs (for instance, patients with childhood trauma, or comorbid anxiety). As for moderators, in view of its emphasis in treating cognitive-behavioral consequences of childhood trauma and previous moderator findings (19), we expected CBASP to outperform SP in reducing depression severity in patients marked by an elevated baseline depression severity, at least one comorbid Axis-I disorder, experiences of early emotional or physical neglect, lower quality of life, a longer illness duration, and those which were separated, divorced or widowed. Conversely, we expected to replicate those moderators of a higher effectiveness of SP vs. CBASP, which were: a recurrent MDD without remission between the episodes, having at least one comorbid Axis-II disorder, and a higher social and global functioning at baseline. Although these variables were not defined as moderators by testing for statistical significance in the previous approach (19), but by their moderator effect size, we expect many of them to significantly interact with the group variable in the present analysis.

METHODS

Participants

As described in (7), eligible outpatients were fluent in the German language, 18–65 years old and met *DSM-IV* criteria for a current episode of chronic major depressive disorder (MDD) with a total duration of at least two years, MDD superimposed on a preexisting dysthymic disorder ("double depression"), or a recurrent MDD with incomplete remission between two major depressive episodes (MDEs) with a current MDD and a total duration of at least 2 years. In addition, an early illness onset (i.e. before the age of 21) and a score of at least 20 on the 24-item version of the Hamilton Rating Scale for Depression (HRSD-24) (24) at screening as well as a 2-week medication-free period at baseline were required for inclusion. Patients were excluded from study participation if they had an acute risk for suicide and/or the need for hospitalization; a primary diagnosis of another Axis I disorder; a diagnosis of antisocial, schizotypal, or borderline personality disorder; a serious medical condition; severe cognitive impairment; a history of psychotic

symptoms, bipolar or organic brain disorder; an absence of a response to a previous adequate trial with CBASP and/or SP; or an ongoing psychotherapy or antidepressant medication. Intake of antidepressant medication during the trial was forbidden.

From the $N = 622$ patients assessed for eligibility, $N = 268$ met inclusion criteria and were randomized to receive CBASP ($N = 137$) or SP ($N = 131$). For further details on the inclusion process, refer to the chart flow of the main publication (7). The study was approved by the Ethics Committee of the following participating institutions: University of Freiburg, University of Bonn, University of Heidelberg, University of Tübingen, University Medical Center Hamburg-Eppendorf, University of Marburg, and University of Lübeck. Written informed consent was obtained from all participants.

Interventions

During the entire duration of the study, both CBASP and SP were each applied following a standardized treatment manual: The CBASP was applied based on a manual developed by James P McCullough (10), while SP was applied by a revised manual developed by John C Markowitz, which was translated into German by the trial coordinators. Eligible participants were allocated to one of the intervention groups by a 1:1 treatment ratio drawing on a computer-generated block randomization sequence with randomly varying block size, stratified for trial site.

The CBASP is a highly structured psychotherapy especially developed for treating patients with chronic depression. It builds on techniques such as situation analysis, interpersonal discrimination exercises, and behavioral skill training/rehearsal (25). It was designed to address the typical preoperational cognitive-emotive functioning of patients with chronic depression by demonstrating to patients that their behavior has (negative) consequences on their environment, leading to interpersonal difficulties. Predominantly relying on the administration of negative reinforcement, CBASP supports the patient in the process of recognizing and understanding the consequences of one's behavior on their environment, which, in turn, leads to a modification of one's behavior and, consequently, to an alleviation of chronic depression. In comparison to the widely used Cognitive Behavioral Therapy (CBT), the CBASP focuses primarily on the person's behavior and interaction with its environment, and not on the pure cognitive content, which is the case for CBT (26). There is strong evidence supporting the effectiveness of CBASP with or without antidepressant medication in early-onset chronic depression: For instance, one large study (27) demonstrated that CBASP was particularly effective for the subgroup of chronically depressed patients marked by early trauma when compared to Nefazodone as antidepressant medication (remission rates: 33% with Nefazodone, 48% with CBASP, and 54% with a combination of both). Moreover, in a trial (11) conducted in $N = 30$ chronically depressed outpatients with early onset, statistically significant differences were found between CBASP and Interpersonal Therapy (IPT) regarding remission rates (57% in CBASP vs. 20% in IPT) and the decrease of self-rated depressive symptoms in favor of CBASP.

In contrast, SP is a disorder non-specific, non-confrontational psychotherapy. The supportive therapist builds an emotional connection to the patient, follows his affect, encourages catharsis, inspires hopes, and emphasizes patient's strengths (28). The main effect of this approach is the enforcement of the patient's awareness of its self-efficacy in changing its own circumstances. In a 16-week study conducted in $N = 94$ patients with dysthymia, which is a milder form of PDD, SP equaled IPT in treatment effect (29).

In an earlier trial (8), CBASP did not prove to be superior to SP when applied as a short-term (12 sessions) augmentation strategy in chronically depressed patients who showed partial or non-response to a pharmacotherapy algorithm. The present study comparing CBASP to SP was designed in order to meet the need for more and larger trials in patients with early-onset PDD, controlling for medication, and including CBASP as a disorder-specific intervention with a more intensive (larger number of sessions) and a longer course of treatment to unfold beneficial and lasting effects in PDD. In this trial, during the acute treatment phase, patients received bi-weekly sessions of CBASP or SP in the first four weeks and weekly sessions for the next 16 weeks. For the following 28 weeks, eight further continuation sessions were delivered, resuming in a total of 32 sessions extended over 48 weeks.

Both the CBASP ($N = 42$ study therapists) and SP ($N = 39$ study therapists) sessions were conducted by psychotherapists or psychiatrists with experience in the treatment of depression (mean of 5.45 years for CBASP; mean of 4.00 years for SP). Age, gender, and experience of the therapists were similar in both study conditions. All study therapists had completed a 3-year, post-graduate psychotherapy training program or were in an advanced stage of their training. In addition, both groups of study therapists were trained in CBASP or SP during a 2-day training workshop. Before treatment start, study therapists' mastery of CBASP or SP methods was assessed by specific rating scales during two videotaped pilot cases (7).

The fidelity of the therapists to the therapy manuals was measured by adherence scales including standardized scales for disciplined personal involvement and situation analysis for the CBASP. Therapy sessions of both interventions were videotaped and reviewed by site supervisors regularly on a random basis to assess psychotherapists' fidelity to the treatment procedures. In addition, an independent team of trained expert raters randomly evaluated one video-taped session of each therapy. The evaluations revealed that of $N = 244$ evaluable sessions ($N = 123$ in CBASP and $N = 121$ in SP), $N = 227$ (93.0%; with $N = 112$ in CBASP and $N = 115$ in SP) met criteria for fidelity.

In order to ensure compliance with ethical principles and the study protocol, as well as to check data quality and accuracy, monthly telephone conferences, semi-annual Data and Safety Monitoring Board conferences, and annual monitoring visits at trial sites were conducted by the Principal Investigator in cooperation with all trial site coordinators (7).

Measurements

All ratings were performed by trained and experienced raters. Raters were furthermore blinded to patients' treatment allocation

in order to avoid their possible subjective influence on the rating. For ensuring the blinding of raters, they were separately located from the therapists. In addition, patients were instructed not to mention any information that could reveal their intervention to their rater. Furthermore, back-up raters were provided in case of unintentional unblinding (7).

The HRSD-24 was used to screen for participants' eligibility before randomization (approx. two weeks before treatment start), as a main outcome after 12 and 20 weeks of acute treatment, as well as at the end of the extended treatment phase, which was 48 weeks after randomization. The interrater reliability for the HRSD-24 scores was measured based on data from 21 evaluators who rated nine audio- or video-taped interviews (intra-class correlation coefficient, 0.973; 95% CI, 0.889–0.999). Further baseline variables which were rated and subject to the present secondary analysis are described in the following section.

Analyzed Baseline Characteristics

In the present secondary analysis of the trail by Schramm et al. (7), we tested the following baseline characteristics as potential predictors and moderators of depression severity measured by the HRSD-24 at week 48.

Socio-Demographic Characteristics

Gender (female/ male), age at the time point of randomization (years), marital status (single/ married or cohabiting/ separated, divorced or widowed), high educational level (corresponding to at least 12 years of education in the German school system with the possibility of university studies), employment status (employed/unemployed), working hours per week, and the presence of at least one physical illness (yes/no).

Clinical Characteristics

Illness subtype (chronic MDD, "double depression," or recurrent MDD with incomplete remission between episodes), age at illness onset (years), illness duration (years), baseline severity of depression by patients' self-rating using the Inventory of Depressive Symptomatology (IDS-SR) (30) and by clinicians' rating through the HRSD-24 (24), acute suicidality assessed by the Beck Scale for Suicide Ideation (BSSI) (31), a history of previous suicidal attempts (yes/no), generalized and phobic anxiety measured by the Brief Symptom Inventory (BSI) (32) and the Generalized Anxiety Disorder Scale (GAD-7) (33), as well as comorbidity of any Axis I or II disorder diagnosed by the Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders (SCID-I) (34) and the Structured Clinical Interview for *DSM-IV* Axis II Personality Disorders (SCID-II) (35). For examining comorbid anxiety as a predictor and moderator, we decided to only use the BSI and GAD-7 as self-report questionnaires for several reasons: First, they are continuous scales representing the current expression of anxiety, thereby providing more variance for the statistical analyses compared to diagnoses made by the SCID-I, which are of binary character, thus containing less variance. Second, we assessed all forms of anxiety disorders by the SCID-I (both lifetime and current diagnoses), and to test all these variables as predictors and moderators would needlessly increase the number of statistical tests.Third, we have less missing cases for the BSI and GAD-7 compared to the SCID-I.

Global, Psycho-Social Functioning, and Quality of Life

Baseline degree of global functioning and overall psychiatric burden assessed by the Global Assessment Functioning Scale (GAF) (36), dysfunctional social attitudes assessed by the Social Adaptation Self-Evaluation Scale (SASS) (37) and impairment of life quality through depression assessed by the Quality of Life in Depression Scale (QLDS) (38).

Interpersonal Problems

Self-reported, repeatedly occurring difficulties in interpersonal relationships assessed on the eight scales of the Inventory of Interpersonal Problems (IIP-64) (39); these are: domineering, suspicious/ distrustful, cold, socially inhibited, non-assertive, overly accommodating, self-sacrificing, and intrusive.

Childhood Trauma

Retrospective, self-reported forms of childhood trauma before the age of 18 assessed on the five scales of the Childhood Trauma Questionnaire (CTQ) (40). In this analysis, we defined the presence of the different types of childhood maltreatment as at least moderate-to-severe, corresponding to a pre-defined, specific cut-off of the respective scale set by Bernstein and Fink (41): emotional abuse ($\geq$ 13 points), emotional neglect ($\geq$ 15 points), physical abuse ($\geq$ 10 points), physical neglect ($\geq$ 10 points), and sexual abuse ($\geq$ 8 points).

Treatment History

Previous underwent antidepressant medication received for a minimum of 4 weeks, psychotherapy underwent for at least eight sessions, a combination of both, as well as any form of previous inpatient treatment (yes/no).

Treatment Preference for Psychotherapy

All patients were asked to indicate which treatment option they generally prefer: antidepressant medication alone; psychotherapy alone; combined treatment of antidepressant medication and psychotherapy; or no preference. In the present analysis, we classified the answers in preferring psychotherapy (=1) or not (=0; all other options).

Treatment Expectancy

Self-ratings of the expected depression severity at week 48 assessed by the e-IDS-SR, which is an unpublished adaptation of the IDS-SR, used in this trial.

There is a large overlap with those baseline variables tested in the previous analysis relying on the combined moderator (19); however, due to an insufficient moderator effect size, not all tested baseline variables were entered as moderators into the final regression analysis there. In this analysis, we tested all enumerated variables as both individual predictor *and* moderator, enabling to discuss the roles of each one of these variables in conclusion.

Treatment Outcome

The main outcome variable for all predictor/ moderator analyses was the HRSD-24 total score at week 48. Both groups did not differ in their baseline HRSD-24 scores (CBASP: mean=24.50, sd=7.60; SP: mean=25.18, sd=6.63; p=0.50).

Statistical Analyses

All statistical analyses were performed on treatment completers, i.e patients who completed the whole therapy program of 32 sessions of CBASP or SP and presented valid HRSD-24 ratings at week 48. Between-group analyses were conducted to compare general differences in post-treatment scores (*Student's t*-test). We tested differences in demographic variables between patients allocated to CBASP and those allocated to SP, as well as between completers and non-completers (i.e., patients who dropped out from the trial before week 48).

With regard to the predictor and moderator analyses, linear regression models were built as depression severity was a continuous outcome. By following the recommendations of Kraemer et al. (42), we first z-standardized all continuous baseline variables in order to facilitate the interpretation of their effects. Predictors were defined as those baseline variables that showed a significant main effect in predicting the outcome without demonstrating an interaction with the treatment group variable, while moderators were defined as baseline variables that interacted with the treatment group variable in predicting the outcome, independently of the significance of the main effect (42). Models were built for each candidate baseline variable separately and were adjusted for study site and baseline depression severity, which were implemented as covariates into the models. Models testing predictors thus contained the main effects of study site, standardized baseline HRSD-24 scores, treatment group and the respective candidate baseline variable. For identifying moderators, separate models were built by adding the interaction term of the candidate variable and the treatment assignment to the main effects of the predictor model accordingly. Results are presented by regression coefficients and reported as significant at the conventional threshold of $p < 0.05$, two-sided. Analyses were performed with STATA 15.1 (Stata Corp, College Station, Texas).

RESULTS

From the $N = 268$ randomized outpatients, $N = 209$ completed the 48-week treatment program with 32 sessions of either CBASP ($N = 113$) or SP ($N = 96$). For a detailed description of the completer population, see **Table 1**. At baseline, the only significant difference between CBASP and SP completers was a higher percentage of employment in the group treated with CBASP. We found no significant differences in baseline variables between completers and non-completers (see **Table 2** for descriptive statistics).

The between-group comparisons at week 48 revealed that CBASP completers had significantly lower HRSD-24 scores (CBASP: mean = 13.96, sd = 9.56; SP: mean = 16.69, sd = 9.87; $p = 0.044$).

TABLE 1 | Sociodemographic and clinical characteristics of the completers subdivided by treatment arm.

Variable	CBASP	SP
	(*N* = 113)	(*N* = 96)
Age at randomization, mean (SD), y	45.20 (11.98)	45.78 (11.98)
Female sex, No. (%)	81 (71.7)	57 (59.4)
Single, No. (%)	47 (41.6)	43 (44.8)
Married or cohabiting, No. (%)	45 (39.8)	40 (41.7)
Separated, divorced or widowed, No. (%)	21 (18.6)	13 (13.5)
High level of education, No. (%)	73 (64.6)	56 (58.3)
Employed, No. (%)*	90 (79.6)	59 (61.5)
Working hours per week, mean (SD), h	24.46 (16.51)	21.36 (20.13)
Presence of at least one physical illness, No. (%)	8 (7.3)	5 (5.4)
Subtype, No. (%)		
Double depression	47 (42.3)	43 (46.7)
Chronic MDD	35 (31.5)	31 (33.7)
Recurrent MDD with incomplete remission between episodes	29 (26.1)	18 (19.6)
Age at illness onset, mean (SD), y	13.01 (4.41)	13.02 (4.49)
Illness duration, mean (SD), y	32.19 (13.80)	32.77 (13.18)
HRSD-24 baseline score, mean (SD)	24.50 (7.60)	25.18 (6.63)
Remitters, No. (%)	41 (36.3)	24 (25.0)

HRSD-24, 24-Item Hamilton Rating Scale for Depression; MDD, major depressive disorder; SD, standard deviation; y, years.
**Significant between-group difference at p = 0.004.*

Predictors of Depression Severity at Week 48

In total, our analyses identified 10 predictors (all main effects with $p < 0.05$): Higher HRSD-24 scores at week 48 were predicted by higher baseline scores on the HRSD-24 scale, BSSI scale, BSI anxiety scale, GAD-7 scale, and IIP-64 social inhibition scale. In addition, higher HRSD-24 scores at week 48 were also predicted by the presence of early emotional or sexual abuse at baseline, as well as by the presence of at least one previous inpatient treatment. In contrast, lower HRSD-24 scores at week 48 were predicted by higher baseline scores on the SASS scale, as well as by the presence of preference for psychotherapy rated as baseline (for more details, please see **Table 3**).

Moderators of Depression Severity at Week 48

Baseline variables identified as moderators of lower post-treatment HRSD-24 scores for patients treated with CBASP were: Higher levels of self-rated depression severity (IDS-SR scores), comorbidity of at least one Axis I disorder, a history of childhood moderate-to-severe emotional or physical neglect (CTQ scales), and a history of at least one previous treatment with antidepressant medication. This means that CBASP patients showing these features at baseline had lower post-treatment scores at week 48 than those with similar features treated with SP. Concerning the PDD subtype, we found a crossover-effect in that patients with chronic MDD and Double Depression treated

TABLE 2 | Differences in baseline variables between completers and non-completers.

Baseline variable	Completers	Non-completers	
Continous variables	**Mean (SD)**	**Mean (SD)**	***p***
Age at randomization	45.47 (11.96)	42.93 (11.18)	0.15
Age at illness onset	13.01 (4.44)	12.95 (4.36)	0.92
Illness duration (y)	32.45 (13.49)	29.98 (12.51)	0.21
IDS-SR score	38.90 (9.82)	38.83 (8.33)	0.96
HRSD-24 score	24.81 (7.16)	24.70 (6.41)	0.91
BSSI score	6.30 (7.19)	7.49 (7.95)	0.30
GAD-7 score	10.86 (4.65)	11.02 (4.20)	0.83
BSI anxiety score	6.14 (3.78)	6.58 (3.82)	0.45
BSI phobia score	2.62 (2.48)	3.17 (2.76)	0.16
GAF score	54.38 (9.25)	54.09 (8.87)	0.84
SASS score	30.22 (6.55)	29.39 (6.19)	0.41
QLDS score	18.91 (7.70)	19.98 (7.72)	0.37
IIP-64 total score	14.89 (3.63)	14.77 (3.83)	0.83
Binary variables	**N**	**N**	***p***
Female gender	138	39	0.99
Single	90	27	0.71
Married or cohabiting	85	21	0.48
Separated, divorced or widowed	34	11	0.67
High level of education	129	43	0.11
Employed	149	41	0.79
Presence of morbidities (≥1 physical illness)	13	2	0.37
Chronic MDD	66	16	0.52
Double depression	90	29	0.38
Recurrent MDD with incomplete remission between episodes	47	12	0.74
History of suicidal attempts	58	18	0.47
Any Axis I disorder[a]	87	26	0.74
Any Axis II disorder[a]	82	21	0.61
Early physical abuse[b]	42	13	0.55
Early physical neglect[b]	61	21	0.18
Early emotional abuse[b]	119	32	0.82
Early sexual abuse[b]	48	9	0.99
Early emotional neglect[b]	132	35	0.76
Prior medication[c]	117	31	0.64
Prior psychotherapy[d]	117	36	0.49
Prior combination therapy[e]	39	14	0.39
Prior inpatient treatment[f]	105	33	0.44
Preference for psychotherapy	157	41	0.47

BSI, Brief Symptom Inventory; BSSI, Beck Scale for Suicidal Ideation; CTQ, Childhood Trauma Questionnaire; GAD-7, Generalized Anxiety Disorder Scale-7; GAF, Global Assessment Functioning Scale; HRSD-24, 24-Item Hamilton Rating Scale for Depression; IDS-SR, self-rated Inventory of Depressive Symptomatology; IIP-64, Inventory of Interpersonal Problems; MDD, major depressive disorder; QLDS, Quality of Life in Depression Scale; SASS, Social Adaptation Self-Evaluation Scale; y, years.

[a] *Diagnosed by the SKID-I or SKID-II according to DSM-IV classification.*

[b] *Presence indicates a clinical severity of at least moderate to severe on the CTQ.*

[c] *History of ≥ 4 weeks of treatment with antidepressant medication.*

[d] *History of ≥ 8 sessions of psychotherapy.*

[e] *History of combination treatment with antidepressant medication (≥ 4 weeks) and psychotherapy (≥ 8 sessions).*

[f] *History of any kind of psychiatric inpatient treatment.*

with CBASP had lower post-treatment scores at week 48 than those with these features treated with SP. In line with this, those classified to have a recurrent MDE without complete remission between the episodes benefited more from SP than from CBASP (**Table 3**). **Figure 1** illustrates all six identified moderators by plots of their interaction effects with the treatment group. All other baseline variables lacked statistical significance for being declared as predictors or moderators (all $p > 0.05$).

DISCUSSION

In a large randomized clinical trial conducted in adult, antidepressant-free outpatients with early-onset PDD, CBASP has been shown to outperform SP with response rates of 38,7% compared to 24,3% at the end of the extended treatment phase after 48 weeks (7). In this secondary-analysis conducted in patients who completed the interventions of this randomized clinical trial, we examined the roles of a wide range of baseline variables as predictors and moderators of the effectiveness of CBASP and SP on depression severity at the end of the extended treatment phase at week 48.

In terms of predictors, we found that a poor response to both psychotherapies was predicted by a higher baseline severity of depression (higher HRSD-24 baseline scores), more pronounced suicidality (higher BSSI baseline scores), more intense anxiety (higher BSI anxiety and GAD-7 baseline scores), stronger social inhibition (higher IIP-64 baseline scores), a self-reported history of moderate-to-severe emotional or sexual abuse, as well as at least one inpatient treatment. Patients who had higher baseline levels of social functioning (higher SASS baseline scores) and a preference for psychotherapy had, contrarily, lower levels of depression severity at week 48 independent of the assigned treatment form.

The findings of the performed predictor analyses largely confirmed our hypotheses and are in line with previous research confirming that those patients who were initially more mentally stable (i.e less depressed, less anxious, less suicidal), higher socially functioning and preferring psychotherapy, responded better to both treatments when compared to patients on the other side of the respective continuum or category. It is reasonable that a less pathological and higher functioning baseline status has facilitated the psychotherapeutic learning and enabled a better recovery process in both groups. Moreover, the confirmed positive impact of having a preference for psychotherapy on the outcomes of both psychotherapies is in line with previous results (21, 22) and supports the conclusion that psychotherapy is more effective and recommendable than other treatments options for PDD patients who prefer psychotherapy over other alternative treatments for depression (9).

From the opposite perspective, we can also conclude that patients who were initially more pathologic benefitted less from both therapies. Thus, for more severely affected patients, both psychotherapies might be insufficient for achieving significant symptom reductions when delivered as monotherapies, as was the case in this trial. These subpopulations might respond better to a combined approach between antidepressant medication and

TABLE 3 | Predictors and moderators of depression severity at week 48.

Baseline variable	Variable main effect		Variable x Group		Role
	B (95% CI)	*p*	B (95% CI)	*p*	
SOCIO-DEMOGRAPHY					
Female gender[a]	0.50 (−2.14; 3.15)	0.71	−1.05 (−6.34; 4.23)	0.69	
Age at randomization[b]	0.72 (−0.53; 1.98)	0.26	−2.03 (−4.45; 0.39)	0.10	
Single[a]	0.44 (−2.11; 3.00)	0.73	1.91 (−3.12; 6.95)	0.45	
Married or cohabiting[a]	−1.07 (−3.61; 1.47)	0.41	0.97 (−4.17; 6.11)	0.71	
Separated, divorced or widowed[a]	1.11 (−2.28; 4.51)	0.52	−5.61 (−2.42; 1.20)	0.17	
High level of education[a]	−0.11 (−2.70; 2.48)	0.93	−0.83 (−5.94; 4.29)	0.75	
Employed[a]	−1.65 (−4.47; 1.17)	0.25	2.68 (−2.90; 8.27)	0.34	
Working hours per week[b]	−0.27 (−1.64; 1.09)	0.69	−0.75 (−3.57; 2.07)	0.60	
Presence of morbidities (≥1 physical illness)[a]	1.53 (−3.57; 6.63)	0.55	−2.50 (−12.97; 7.97)	0.64	
CLINICAL CHARACTERISTICS					
Double depression[a]	0.11 (−2.53; 2.76)	0.93	−1.09 (−6.25; 4.07)	0.68	
Chronic MDD[a]	0.94 (−1.92; 3.81)	0.52	−3.51 (−8.98; 2.96)	0.21	
Recurrent MDD with incomplete remission between episodes[a]	−1.32 (−4.49; 1.84)	0.41	6.18 (0.16; 12.20)	0.044*	M
Age at illness onset[b]	0.36 (−0.91; 1.63)	0.57	1.55 (−0.92; 4.03)	0.22	
Illness duration[b]	0.53 (−0.73; 1.79)	0.41	−2.39 (−4.82; 0.04)	0.054	
HRSD-24 score[b]	2.43 (1.17; 3.70)	<0.001*	−1.10 (−3.62; 1.41)	0.39	P
IDS-SR score[b]	1.50 (−0.11; 3.11)	0.069	−3.68 (−6.14; −1.21)	0.004*	M
BSSI score[b]	2.32 (0.93; 3.71)	0.001*	1.13 (−1.45; 3.72)	0.39	P
History of suicidal attempts[a]	0.28 (−2.58; 3.14)	0.85	−4.33 (−10.00; 1.33)	0.13	
BSI anxiety score[b]	1.80 (0.38; 3.23)	0.014*	−1.83 (−4.31; 0.66)	0.15	P
BSI phobia score[b]	1.10 (−0.36; 2.56)	0.14	−0.35 (−2.96; 2.27)	0.79	
GAD-7 score[b]	1.57 (0.14; 2.99)	0.031*	−2.13 (−4.59; 0.32)	0.09	P
Any Axis I disorder[a,c]	1.43 (−1.21; 4.08)	0.29	−6.02 (−11.04; −0.99)	0.019*	M
Any Axis II disorder[a,c]	2.25 (−0.51; 5.01)	0.11	0.03 (−5.14; 5.21)	0.99	
FUNCTIONALITY AND QUALITY OF LIFE[b]					
GAF score	0.25 (−1.49; 1.99)	0.78	2.12 (−0.45; 4.70)	0.11	
SASS score	−2.05 (−3.39; −0.72)	0.003*	1.06 (−1.42; 3.54)	0.40	P
QLDS score	0.85 (−0.63; 2.33)	0.26	−1.19 (−3.80; 1.41)	0.37	
INTERPERSONAL PROBLEMS[b,d]					
Domineering	−0.46 (−1.80; 0.88)	0.50	−2.33 (−4.93; 0.28)	0.08	
Suspicious/distrustful	0.92 (−0.42; 2.26)	0.18	−1.31 (−3.99; 1.38)	0.34	
Cold	1.06 (−0.24; 2.37)	0.11	−1.32 (−3.91; 1.27)	0.32	
Socially inhibited	2.34 (1.04; 3.65)	0.001*	−1.35 (−3.86; 1.15)	0.29	P
Non-assertive	1.04 (−0.29; 2.38)	0.13	−1.14 (−3.70; 1.41)	0.38	
Overly accommodating	1.00 (−0.33; 2.33)	0.14	−1.45 (−3.95; 1.06)	0.26	
Self-sacrificing	0.76 (−0.56; 2.07)	0.26	−2.02 (−4.52; 0.48)	0.11	
Intrusive	−0.15 (−1.43; 1.13)	0.82	−0.67 (−3.24; 1.89)	0.60	
EARLY TRAUMA[a,e]					
Emotional abuse	3.40 (0.79; 6.01)	0.011*	−3.93 (−9.00; 1.14)	0.13	P
Emotional neglect	2.81 (0.08; 5.53)	0.043*	−6.72 (−12.04; −1.41)	0.013*	M
Physical abuse	−0.91 (−4.14; 2.33)	0.58	−4.09 (−10.39; 2.20)	0.20	
Physical neglect	1.44 (−1.37; 4.26)	0.31	−7.06 (−12.51; −1.61)	0.011*	M
Sexual abuse	6.03 (3.17; 8.88)	<0.001*	0.81 (−4.89; 6.52)	0.78	P
PREVIOUS TREATMENTS[a]					
Medication[f]	1.27 (−1.33; 3.87)	0.34	−5.58 (−10.50; −0.65)	0.027*	M
Psychotherapy[g]	1.80 (−0.71; 4.30)	0.16	0.95 (−4.11; 6.02)	0.71	
Combination[h]	1.94 (−1.26; 5.14)	0.23	−2.79 (−9.14; 3.55)	0.39	
Inpatient[i]	4.52 (2.00; 7.04)	0.001*	−4.41 (−9.24; 0.40)	0.07	P

(Continued)

TABLE 3 | Continued

Baseline variable	Variable main effect		Variable x Group		Role
	B (95% CI)	*p*	B (95% CI)	*p*	
Preference for psychotherapy[a]	−3.01 (−6.00; −0.01)	0.049*	−2.64 (−8.56; 3.28)	0.38	P
Therapy expectancy[b]	0.64 (−0.60; 1.88)	0.31	−2.08 (−4.53; 0.36)	0.09	

BSI, Brief Symptom Inventory; BSSI, Beck Scale for Suicidal Ideation; CI, confidence interval; CTQ, Childhood Trauma Questionnaire; GAD-7, Generalized Anxiety Disorder Scale-7; GAF, Global Assessment Functioning Scale; HRSD-24, 24-Item Hamilton Rating Scale for Depression; IDS-SR, self-rated Inventory of Depressive Symptomatology; IIP-64, Inventory of Interpersonal Problems; M, moderator; MDD, major depressive disorder; P, predictor; QLDS, Quality of Life in Depression Scale; SASS, Social Adaptation Self-Evaluation Scale.

[a] *Categorical variable (0=no; 1=yes).*

[b] *Z-standardized continuous variable (0=mean; 1=mean + 1SD).*

[c] *Diagnosed by the SKID-I or SKID-II according to DSM-IV classification.*

[d] *As assessed by the IIP-64.*

[e] *Presence indicates a clinical severity of at least moderate to severe on the CTQ.*

[f] *History of ≥ 4 weeks of treatment with antidepressant medication.*

[g] *History of ≥ 8 sessions of psychotherapy.*

[h] *History of combination treatment with antidepressant medication (≥ 4 weeks) and psychotherapy (≥ 8 sessions).*

[i] *History of any kind of psychiatric inpatient treatment.*

**significant at $p < 0.05$.*

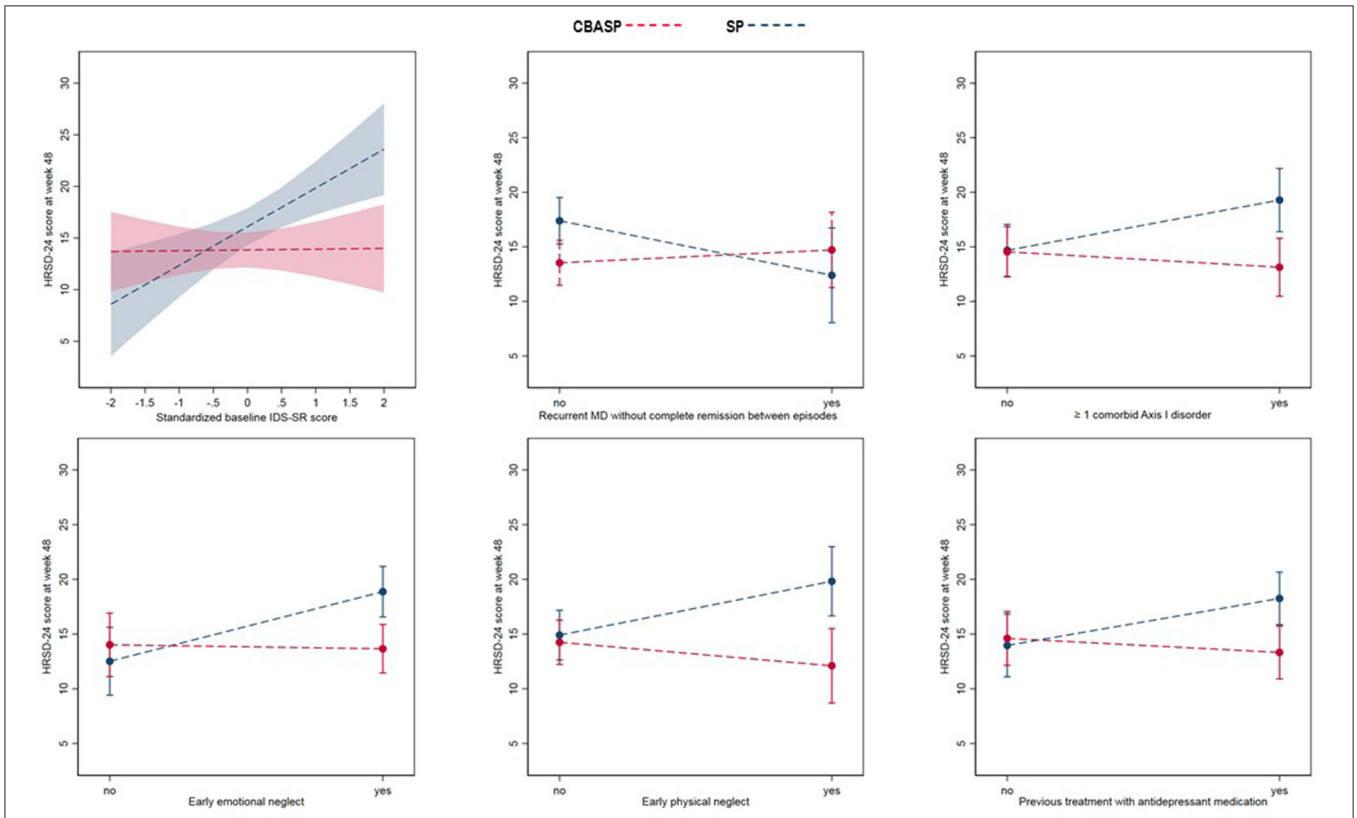

FIGURE 1 | Moderators of depression severity at week 48. IDS, self-rated Inventory of Depressive Symptomatology; HRSD-24, 24-Item Hamilton Rating Scale for Depression; MDD, major depressive disorder.

person-centered psychotherapy which flexibly and adaptively combines unspecific, transdiagnostic, and disorder-specific interventions. For example, it has been shown that the combination of CBASP and an antidepressant medication was more effective for PDD patients with a higher baseline symptom severity and pronounced anxiety (43, 44) than monotherapy with CBASP, indicating that an augmentation with pharmacotherapy is more recommendable for these patients than treatment with CBASP alone (7). This conclusion has also been supported in a participant data network meta-analysis which compared the effectiveness of CBASP as monotherapy to that of antidepressant medication and their combination (20). In a 2-year follow-up study of this trial, Schramm et al. (45) evaluated the effects of CBASP and SP one and two years after treatment termination.

CBASP outperformed SP in the number of well weeks with no/minimal symptoms, self-rated depressive symptoms, and depression-related quality of life one year after treatment termination, but not after two years. This result could be strongly attributed to a worsening of symptoms in the subgroups marked by baseline characteristics here identified as predictors, who benefitted less favorable from both interventions, and indicates the necessity of maintenance treatment for PDD patients.

Interestingly, we detected a lower effectiveness of both interventions for patients reporting a history of moderate-to-severe early emotional or sexual abuse, while CBASP was found to be more effective than SP for patients reporting early emotional or physical neglect. These results suggest that early-life trauma in form of abuse might be an important factor that contributes to non-response to psychotherapy in chronically depressed patients, while cognitive-behavioral consequences of early neglect might be modifiable by disorder-specific psychotherapy with CBASP. If different types of early trauma are associated with different responses to psychotherapy, then this information may prove crucial in designing and selecting optimal treatments for chronically depressed patients.

Finally, treatment expectancy had no influence on the post-treatment depression severity in our trial. We did not identify predictors or moderators from the socio-demographic domain, which could be attributable to the relatively homogeneous population of this trial (7).

In terms of moderators, CBASP displayed a multifaceted superiority over SP, meaning that patients with an elevated self-perceived depression severity (higher IDS-SR baseline scores), no recurrent MDE without complete remission between the episodes, comorbidity of Axis-I disorders, a history of at least one previous antidepressant treatment, and, as mentioned before, early trauma in form of moderate-to-severe emotional or physical neglect, had a lower depression severity at week 48 when treated with CBASP than those who were treated with SP. These results are in line with the previous moderator analysis (19) based on the data of this trial, which applied a modern machine learning method in order to identify subgroups of patients who respond better to CBASP than to SP and vice versa. With except of previous antidepressant medication, all here identified moderators had a moderator effect size large enough to be entered into the final regression model used in the analysis by Serbanescu et al. (19) to combine the most relevant moderators in order to exploratory identify the subgroups. The fact that the moderating role of these variables could be replicated in this more classical analysis underlines its robustness and validity in this trial. A more detailed interpretation of the moderating role of these variables is provided in the previous article (19). As emphasized there, these promising findings are in need of additional detailed investigations in order to be understood, as well as replication in future trials for enabling reliable treatment choice recommendations for the clinical practice.

This study has a number of important strengths: First, the antidepressant-free status of the patients allows ascribing the findings to the two tested psychotherapies alone. Second, we tested a relatively wide range of baseline characteristics. Third, the here performed analysis provides evidence for predictors as well as for moderators of two widely used therapies. We tested a relatively high number of variables, yielding many interesting results that open new questions which remain to be further investigated. However, some limitations must be also considered: Possible undesired, side-effects including transient worsening of symptoms and transient risk of suicidality at the beginning of therapy or in the context of unexpected psychosocial stress might have occurred in both treatment groups, and were not subject of this analysis. As a further limitation, our sample included only medication-free patients who were evaluated as enough mentally stable to be able to participate in the study. It can be assumed that the effectiveness of both therapies would have been smaller in more severely depressed patients. The exclusion criteria of the trial therefore may limit the generalizability of the findings to the general PDD population. Furthermore, the therapy duration of 48 weeks has revealed numerous clinically relevant predictors and moderators, but may be very resource-intensive for implementation in clinical practice. Finally, given the exploratory approach and large number of performed tests, the possibility of false positive findings has to be taken into account when considering the results. Thereby, our results need replication in future trials in order to permit valid treatment choice recommendations.

CONCLUSION

A multifactorial combination between elevated depression severity, suicidality, traumatic childhood experiences characterized by abuse, social inhibition and anxiety may represent the basis of non-response to psychotherapy in patients with PDD and consequently contribute to the persistence of the illness and its refractoriness. Nevertheless, disorder-specific psychotherapy with CBASP might be more effective and recommendable for a variety of particularly burdened patients with PDD than Supportive Psychotherapy. Further personalized clinical research is needed in order to understand and develop the (combination of) treatments that meet the needs of the most affected patients with PDD.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: The dataset of the initial clinical randomized trial is not available to the public. Requests to access these datasets should be directed to elisabeth.schramm@uniklinik-freiburg.de.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the University of Freiburg, University of Bonn, University of Heidelberg, University of Tübingen, University Medical Center Hamburg-Eppendorf, University of Marburg, and University of Lübeck. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

IS and DS: had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis and drafting of the manuscript. IS: was responsible for statistical data analysis. IS, HW, SD, and DS: study concept and design. IS, HW, SD, JK, IZ, MB, MHa, RM, MHä, ES, and DS: acquisition, analysis, or interpretation of data. IS, BW, IZ, RM, MHa, MHä, DS, and ES: administrative, technical, or material support. All authors gave critical revision of the manuscript for important intellectual content.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Paper 3 | Appendix 3

This is the revised version of the following paper which was resubmitted to *Behaviour Research and Therapy*:

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Contributions of doctoral candidate: Ilinca Serbanescu designed the concept of this secondary study, developed the applied combination of statistical methods, selected the software for processing and analysing the data, analysed the data, interpreted the findings, drafted the manuscript, revised the manuscript as part of the peer-review process, and resubmitted the manuscript to the journal.

Identifying subgroups with differential response to CBASP versus Escitalopram during the first eight weeks of treatment in outpatients with persistent depressive disorder

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Abstract

Objective. So far, there is little empirical evidence helping clinicians to select the most effective treatment for an individual patient with persistent depressive disorder (PDD). The current study identifies and characterizes subgroups of patients with PDD who are likely to benefit more from an acute treatment with specific psychotherapy than from pharmacotherapy with escitalopram and vice versa.

Methods. Sixty non-medicated outpatients with PDD were randomized to eight weeks of acute treatment with the Cognitive Behavioral Analysis System of Psychotherapy (CBASP; n = 29) or escitalopram plus clinical management (ESC/CM; n = 31). We combined several baseline variables to one composite moderator (*M**) in order to identify subgroups of patients who are likely to benefit more from CBASP than from ESC/CM and vice versa.

Results. In total, n = 53 patients completed the acute treatment phase (n = 27 CBASP; n = 26 ESC/CM) and were included in the moderator analysis. The composite moderator *M** had a larger effect size than any individual moderator (r = 0.67). The interaction effect between *M** and the treatment variable was statistically significant ($p < 0.001$, $R^2 = 0.48$). For 56.0% of patients, ESC/CM was associated with a greater reduction in depression severity than CBASP, for the remaining 44.0% of patients it was the other way around. Patients likely to benefit more from ESC/CM were more often female, had higher rates of moderate-to-severe childhood trauma, more adverse life events as well as more previous suicide attempts. Patients likely to benefit more from CBASP were older, had more often an early illness onset and more previous treatments with antidepressant medication. Overall, symptomatic response, remission, and reductions in symptom severity occurred more often in those patients treated with the likely more effective treatment condition.

Conclusions. The present findings suggest that the baseline phenotype of patients with PDD moderates their benefit from acute treatment with CBASP relative to ESC/CM. Once confirmed in an independent sample, these results could serve to guide the choice between psychotherapeutic or pharmacological treatments for patients with PDD.

Keywords: persistent depressive disorder; personalized medicine; escitalopram; CBASP; moderator; randomized clinical trial

Introduction

Roughly 20-30% of patients with major depression develop a chronic course lasting two years or longer (Arnow & Constantino, 2003; Murphy & Byrne, 2012). In clinical settings, the prevalence increases up to 50% of the patients with depressive disorders presenting a chronic course (Schramm et al., 2020). In the fifth edition of the Diagnostic and Statistical Manual (DSM-5), this condition was first introduced as a distinct clinical category labelled as Persistent Depressive Disorder (PDD) (American Psychiatric Association, 2013). Based on the DSM-5, PDD should be diagnosed when symptoms have been present for at least two years and symptom-free intervals have never lasted longer than eight weeks at a time (American Psychiatric Association, 2013). The prevalence of PDD is estimated between 5% (Murphy & Byrne, 2012) and 18% (Vandeleur et al., 2017) in the general population, and is nearly double as high for women as for men (Blanco et al., 2010; Garcia-Toro et al., 2013; Vandeleur et al., 2017).

In comparison to episodic depression, PDD has been associated with higher rates of childhood trauma (Gopinath et al., 2007; Wiersma et al., 2009), medical and psychiatric comorbidity (Angst et al., 2009; Gilmer et al., 2005; Murphy & Byrne 2012; Satyanarayana et al., 2009), greater suicidal ideation (Angst et al., 2009; Satyanarayana et al., 2009) and a lower socio-economic status (Angst et al., 2009; Gilmer et al., 2005). In addition, patients affected by a chronic course improve more slowly and respond less well to various pharmacological and psychological treatments (Arnow & Constantino 2003; Cuijpers et al., 2011; Cuijpers et al., 2017; Klein et al., 2006). The lack of tailored treatment strategies can be counted as a key reason for the low treatment success in PDD (Schramm et al., 2020). So far, little empirical evidence exists to guide clinicians to select the most effective treatment for an individual patient with PDD (Cohen & DeRubeis 2018; Cuijpers et al., 2017). Treatments are commonly selected in an unsystematic matter, often based on subjective clinical experience, treatment-preference of patients or trial-and-error approaches (Cohen & DeRubeis 2018; Simon & Perlis 2010; Wallace et al., 2013). Therefore, further scientific evidence is urgently needed for personalizing treatment selection for PDD (Cuijpers et al., 2017).

Currently, there exists only one psychotherapy model that was specifically designed to meet the needs of patients with PDD – the Cognitive Behavioral Analysis System of Psychotherapy (CBASP) developed by James P. McCullough (McCullough, 2000). As a manualized cognitive-behavioural-oriented therapy, CBASP operates on various techniques including situation analysis, interpersonal discrimination exercises, and behavioural skills training by using the patient-therapist relationship as a central therapeutic tool of interpersonal fear reduction (McCullough, 2000; McCullough, 2003; McCullough 2021; Neudeck et al., 2012). By helping patients to acquire interpersonal empathy, social problem-solving skills, and more adaptive interpersonal behavior patterns, CBASP targets a substantial improvement of patient´s social behaviour, quality of interpersonal relationships, and thereby recovery from PDD (McCullough, 2000; McCullough, 2003; McCullough, 2021). CBASP has proven to be overall effective in treating chronically depressed patients and has been thus recommended as first line psychotherapeutic treatment for PDD by various national and international treatment guidelines (Jobst et al., 2016). Nevertheless, various findings have shown that CBASP may not be the most effective treatment for all patients with PDD: in a cross-over trial conducted in patients with PDD, Schatzberg et al. (2005) compared the outcome of non-responders to an initial monotherapy with CBASP or nefazodone to a successive 12-week cross-over treatment with CBASP or nefazodone, respectively. This study found that switching from CBASP to nefazodone and vice versa resulted in clinical and statistical improvements in symptoms but not in response and remission rates, yet left open the question of which type of patients benefited from the switch and why. A later moderator analysis by Kocsis, Leon, et al. (2009) comparing CBASP with nefazodone found treatment preference to be a significant treatment moderator in that patients who preferred medication at baseline had higher remission rates and lower depression scores at the end of the study if they received medication than if they received CBASP, and vice versa. Furthermore, in a more recent individual participant data network meta-regression based on three trials comparing CBASP to pharmacotherapy and/ or their combination, Furukawa et al. (2018) found that for the subgroup of patients with severe baseline depression and severe baseline anxiety, combination treatment was more effective than pharmacotherapy alone, which in turn was

more effective than CBASP alone. In addition, pharmacotherapy alone was found to be more beneficial for younger patients with PDD, given their relatively high dropout rates for combination therapy and CBASP (Furukawa et al., 2018). Finally, a more recent moderator analysis by Serbanescu et al. (2020) showed that CBASP was inferior to disorder-nonspecific Supportive Psychotherapy in its effectiveness for patients with a higher baseline global and social functioning level, a higher baseline life quality and a recurrent illness pattern without complete remission between the episodes. However, CBASP outperformed Supportive Psychotherapy in patients who were initially more severely depressed and who reported higher rates of moderate-to-severe childhood trauma at baseline. Given the diversity of these varied findings, it remains to be further clarified which subtypes of patients with PDD are likely to benefit more from CBASP than from other psychotherapies or pharmacological treatments, and vice versa.

In a bi-centric randomized controlled trial (RCT), Schramm et al. (2015) compared the effectiveness of CBASP versus escitalopram, a well-tolerated standard selective serotonin reuptake inhibitor, combined with clinical management (ESC/CM) over 28 weeks in a sample of outpatients with PDD. In case of non-improvement (defined in this study as < 20.0% reduction in depression severity) after the 8-week acute treatment phase, the other treatment condition was augmented for the following 20 weeks of the extended treatment phase. Results showed that the clinician-rated depression scores decreased significantly after both eight and 28 weeks, however with no significant differences between the two treatment groups. Non-improvers to the initial treatment caught up with the initial improvers in terms of depression severity by the end of the extended treatment phase after being augmented with the respective other condition (Schramm et al., 2015). In conclusion, CBASP and ESC/CM appeared to be equally effective treatment options for chronically depressed outpatients in both the acute and extended treatment phase, whereas for patients who did not respond to their first treatment in the acute phase, augmentation with the other condition during the extended phase appeared to be effective in reducing depression severity.

In this work, we will present a secondary analysis of the RCT by Schramm et al. (2015) conducted to revisit this conclusion by examining whether, despite the reported general equivalence of the two treatments, there were in fact 'hidden' subgroups of patients who were likely to benefit more from CBASP than from ESC/CM and vice versa during the acute 8-week treatment phase. In addition, we investigated whether the initial lack of response in those patients augmented with the other treatment condition at week eight was because they did not receive their likely more effective treatment during the first eight weeks, and whether the observed improvement at week 28 was likely due to the augmentation with the treatment condition from which they would have likely benefitted more from the beginning of the treatment. For identifying possible subgroups effects, we applied the composite moderator developed by Kraemer (2013). This modern statistical approach yields the advantage to combine multiple individual baseline characteristics, which are usually tested individually as single moderators, into one personal index, the composite moderator, that is further used to detect subgroups of patients who are likely to benefit more from one treatment than from another (Kraemer, 2013). The composite moderator method has served in a number of studies comparing treatments for episodic (Wallace et al., 2013), persistent (Serbanescu et al., 2020) and late-life depressive disorder (Smagula et al., 2016) as well as anxiety disorder (Niles, Loerinc, et al., 2017), providing valuable results and expanding the evidence base in favor of personalized treatment selection in psychiatry. By addressing the question of *"what works for whom"* in the context of a clinically relevant comparison between an internationally recognized disorder-specific psychotherapy and a widely used antidepressant, we aim to add further evidence that can guide clinicians in choosing between available psychotherapeutic and pharmacological treatments, thus addressing the urgent need to advance personalized medicine for PDD (Cuijpers et al., 2017).

Materials and methods

The mentioned study by Schramm et al. (2015) was an evaluator-blind, parallel-design, 2-armed RCT conducted between 2008 and 2013 at two university medical centers

(Department of Psychiatry and Psychotherapy of the University Medical Center Freiburg; University Medical Center Bonn) in Germany. The study was approved by the institutional review boards and ethics committees at each site. Written informed consent was obtained from all participants before study enrollment. Study registration was performed at the University Register of Clinical Studies (No. 2007-006914-41) and at www.clinicaltrials.gov (No. NCT00837564). Detailed study methods were published previously (see Schramm et al., 2015 for further details).

Participants and eligibility

For study inclusion, participants had to be 18 to 65 years old, fluent German speaking, and to meet DSM-IV criteria for a current episode of chronic major depressive disorder (MDD; with the modification of at least one year of depressive symptomatology) or a recurrent major depressive episode (≥ 3 episodes with the preceding episode being no more than 2.5 years before the onset of the present episode). Additionally, at screening, participants had to score at least 18 points on the Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery & Asberg 1979) and to be free from antidepressant medication minimum two weeks before baseline assessments. The exclusion criteria further comprised: an acute risk of suicide, a history of psychotic symptoms, bipolar disorder or dementia, a severe substance-related abuse or dependence disorder, a schizotypal, antisocial or borderline personality disorder, a serious medical condition or illness, severe cognitive impairment, hypersensitivity to escitalopram, absence of a response to a previous adequate trial with CBASP or escitalopram, or a treatment with a MAO-inhibitor within one week before the initiation of the study treatment (Schramm et al., 2015).

Interventions

Sixty patients (n = 45 in Freiburg; n = 15 in Bonn) including one non-starter who was excluded from the analyses were randomly assigned to receive treatment with CBASP (n = 29) or ESC/CM (n = 31) over a total period of 28 weeks, including an acute treatment phase within the first eight weeks. Of the n = 59 patients who began treatment, n = 6 discontinued it before

the end of the acute treatment phase, resulting in n = 53 completers (n = 27 CBASP; n = 26 ESC/CM), who were included in the present moderator analysis.

In the acute treatment phase of eight weeks, therapy sessions with CBASP were conducted twice weekly during the first four weeks and weekly during the next four weeks by trained and experienced psychotherapists. All CBASP sessions were videotaped and reviewed by experienced study supervisors. As a well-tolerated standard selective serotonin reuptake inhibitor with an excellent benefit-to-side effect (Cipriani et al., 2009), escitalopram was administered in an initial dose of 10 mg/day in the first week and was further enhanced to 20 mg/day throughout the following weeks. In case of adverse side effects, the dosage was adjusted individually. In addition to escitalopram, patients randomized to this condition received weekly 20 min-sessions of clinical management as a psychoeducative and supportive intervention. Its elements included symptom management, monitoring of the medication and its side effects, as well as simple expert advices. Patients whose MADRS scores failed to improve by at least 20.0% at the end of the eighth week were additionally provided with the other treatment condition (i.e., either ESC/CM or 12 CBASP sessions) during the following 20 weeks of extended treatment. The addition of the other condition to the initial treatment (rather than switching) intended a prolongation of the effects of the initial treatment.

Analyzed baseline variables

The utilized statistical procedure (Kraemer, 2013) preselects and combines multiple individual baseline variables into one optimal composite moderator (M^*) to detect possible subgroup effects. For being preselected for the compilation of M^*, a baseline variable had to fulfill the following criteria: 1. being of clinical-scientific interest for the research question; 2. being easy to assess for comparison and replication purposes; 3. containing at least n = 50 valid cases or no more than three missing cases so as not to reduce the sample size relevant for the final regression analysis. Our set of preselected initial baseline variables thus comprised 11 baseline variables from a wide range of domains including socio-demography, clinical characteristics, childhood trauma as well as the history of previous treatments (for more details on the variables and their measurement, see Table 1).

Table 1

List of initially considered baseline variables

Baseline variable	Type	Definition/ assessment
Socio-demographic characteristics		
1. Female gender	nominal	yes/ no
2. Age	metric	years
Clinical characteristics		
3. Early illness onset	nominal	defined as an onset of PDD before the age of 21; yes/ no
4. Depression severity	metric	clinician-rated MADRS total score at baseline
5. History of suicidality	metric	self-reported number of previous suicide attempts
6. Comorbidity of ≥ 1 Axis-I disorder	nominal	yes/no; diagnosed with the SCID-I by clinician
7. Comorbidity of ≥ 1 Axis-II disorder	nominal	yes/no; diagnosed with the SCID-II by clinician
Childhood and life trauma		
8. Childhood trauma	nominal	self-reported moderate-to-severe childhood trauma that occurred before the age of 18 in at least one of the five dimensions of the CTQ; yes/ no
9. Adverse life events	metric	item assessing the number of self-reported major psychosocial stressors over the lifetime
Previous treatments		
10. Previous psychotherapies	ordinal	self-reported number of previous psychotherapies, provided in categories (0 = none, 1 = 1, 2 = 2, 3 = 3, 4 = 4, 5 = more than 5)
11. Previous medication	ordinal	self-reported number of previous treatments with antidepressants, provided in categories (0 = none, 1 = 1, 2 = 2, 3 = 3, 4 = 4, 5 = more than 5)

Note. CTQ = Childhood Trauma Questionnaire (Bernstein et al., 2003); MADRS = Montgomery-Asberg Depression Rating Scale (Montgomery & Asberg, 1979); PDD = persistent depressive disorder; SCID-I = Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 2002); SCID-II = Structured Clinical Interview for DSM-IV Axis II Personality Disorders (First et al., 1997).

Main outcome

The main outcome in this secondary analysis was the percentage change in MADRS scores from baseline to week eight (corresponding to the end of the acute treatment phase) calculated according to the following equation:

$$percentchange_{MADRS} = \frac{MADRS_{week\ 8} - MADRS_{baseline}}{MADRS_{baseline}} * 100\%$$

Based on this equation, negative values of this outcome reflect a reduction in depression severity, a score of zero reflects no change and positive scores indicate an increase in depression severity from baseline to week eight. The MADRS ratings were performed by trained and experienced evaluators. All n = 53 completers had valid MADRS scores at week eight.

Statistical analyses

All analyses described in the following were performed in the sample of treatment completers (n = 53) at week eight using STATA version 15.1 (StataCorp, 2017). To ensure that the results of the analyses were nor driven by possible outliers, both the outcome variable as well as all analyzed baseline variables were tested for outliers and skewness before calculating the moderator effect sizes. We detected no outliers.

Calculating individual moderator effect sizes: By using the method described by Kraemer (2013), we first computed moderator effect sizes for the 11 preselected baseline variables. For this, we paired each patient assigned to CBASP to each patient assigned to ESC/CM. Next, for each pair of this dataset, we calculated the difference in outcome (i.e., the percentage change in MADRS scores) and the average value of each of the 11 baseline variables. Next, for obtaining moderator effect sizes, non-parametric Spearman correlations between the difference in outcome and each average were calculated together with their 95% bootstrap confidence intervals based on 100 replications. In principle, moderator effect sizes based on this method are invariant over linear transformations of the baseline variable or the outcome, and vary between -1 and +1, with higher magnitudes indicating a stronger moderation and zero

indicating the absence of a moderation effect (Kraemer, 2013). Baseline variables were preselected to be included in the model for complying M^* when their effect size was ≥ |.20|. This cutoff is more rigorous than others used in previously published applications of Kraemer's composite moderator method (e.g., Serbanescu et al., 2020; Smagula et al., 2016; Wallace et al., 2017), and was chosen as such in order to select as few meaningful moderator variables as possible to account for the modest sample size. Due to the exploratory character of our analysis and the modest sample size, we abstained from calculating and including statistical significance of interaction effects between the treatment variable and the baseline variables as a further selection criterion for a baseline variable to be used for the compilation of M^* (Wasserstein & Lazar, 2016).

Model selection of the composite moderator: Next, we determined the statistical weights of those baseline variables with effect sizes ≥|.20| for inclusion in the composite moderator. For this, in the paired dataset, the weights of the single moderators were estimated by a multivariable regression model, in which the difference in outcome was predicted by the averages of all preselected variables. Analogous to previous applications of the composite moderator approach (e.g., Serbanescu et al., 2020; Wallace et al., 2017; Wallace et al., 2018), we performed a least absolute shrinkage and selection operator (lasso) regression (Tibshirani, 1996) for the multivariable model. Lasso regression selects the most useful independent variables and shrinks the regression weights of variables with little predictive power or correlated with other predictors to zero, thereby removing them from the model (Tibshirani, 1996). In addition and in line with previous applications of the composite moderator method (Niles, Loerinc, et al., 2017; Niles, Wolitzky-Taylor, et al., 2017; Serbanescu et al., 2020), for optimizing the model's predictive performance and avoiding overfitting, we combined lasso regression with *k*-fold cross-validation (James et al., 2013). The methodological advantages of combining lasso regression with *k*-fold cross-validation have been explained before (e.g., Serbanescu et al., 2020). Briefly, due to its principle of training and validating regression models in different data folds of the same data set, *k*-fold cross-validation enables researchers to detect a model that is more likely to have a good predictive performance in future new data samples. Within the paired dataset, we ran 10-folds cross-validation by using the command

'*cvlasso*' from the STATA package '*lassopack*' developed by Ahrens et al. (2019), which internally repeats lasso regression and displays the model obtained by an optimal tuning parameter λ_{opt} which is associated with the smallest mean-squared prediction error.

Identification and characterization of subgroups: After selecting the optimal model based on the procedure described before, weights from each of the moderators selected by this model were extracted in order to calculate the value of *M** for each patient as described by Kraemer (2013). Thereafter, in the unpaired dataset, we performed a regression analysis predicting the outcome (i.e., percentage change in MADRS scores) from the composite moderator *M**, the treatment group, and their interaction. We furthermore computed the moderator effect size of the composite moderator *M** together with its 95% bootstrap confidence interval. We then calculated the value of *M** at which the predicted outcomes for the CBASP and ESC/CM group intersected and divided the sample into two subgroups, one below and one above this cross-point. Each of these subgroups is consequently associated with a likely more beneficial outcome for one of the two treatments compared to the other. For characterizing and comparing the two identified subgroups, we analyzed and compared relevant baseline characteristics and calculated between-group treatment effect sizes (Cohen's *d*).

Subgroup and treatment interaction effects: We next analyzed whether those patients who received the likely more beneficial treatment condition had higher response and remission rates than those who received the likely less beneficial condition. For this, we stratified the sample of completers in four clusters: 1. Patients randomized to CBASP and likely to respond better to CBASP; 2. Patients randomized to CBASP and likely to respond better to ESC/CM; 3. Patients randomized to ESC/CM and likely to respond better to ESC/CM; 4. Patients randomized to ESC/CM and likely to respond better to CBASP. In these four clusters, we compared rates of response (defined as ≥ 50.0% reduction in MADRS scores from baseline to week eight) and remission (defined as a MADRS score of ≤ 9 at week eight). We also analyzed between-cluster differences in MADRS scores at week eight as well as values of the percentage change of the MADRS scores from baseline to week eight. Finally, we examined whether those patients who did not experience a change of at least 20.0% after the acute treatment phase and

who received augmentation with the other treatment condition were, in majority, those who did not receive the likely more beneficial treatment condition during the acute treatment phase.

Results

Effect sizes of individual moderators

Among the 11 tested baseline variables, we identified six with an effect size < 0 and five with an effect size > 0. Negative values indicate a better outcome (i.e., a greater percentage reduction in MADRS scores from baseline to week eight) with ESC/CM than with CBASP for higher values or the presence of that moderator. Positive values indicate a better outcome with CBASP than with ESC/CM for higher values or the presence of that moderator. Individual moderator effect sizes, 95% confidence intervals and lasso regression coefficients derived from the lasso regression model are displayed in Table 2.

Table 2

Moderator effect sizes, 95% confidence intervals and lasso regression coefficients for selected and deselected baseline variables

Baseline variables	Effect size	95% CI	Lasso coefficient[a]
Indicating a superiority of ESC/CM			
Selected:			
Number of previous suicide attempts	-0.363	(-0.429; -0.297)	-8.806
Adverse life events	-0.288	(-0.354; -0.222)	-9.782
Childhood trauma[b]	-0.251	(-0.326; -0.175)	-65.803
Female gender	-0.213	(-0.280; -0.146)	-31.344
Not selected:			
MADRS (baseline) score	-0.117	(-0.188; -0.047)	
Comorbidity with ≥ 1 Axis-II disorder	-0.063	(-0.144; 0.018)	
Indicating a superiority of CBASP			
Selected:			
Age	0.238	(0.166; 0.309)	2.817
Early illness onset	0.215	(0.146; 0.285)	56.434
Number of previous treatments with AD	0.212	(0.155; 0.269)	12.629
Not selected:			
Number of previous psychotherapies	0.085	(0.025; 0.145)	
Comorbidity with ≥ 1 Axis-I disorder	0.042	(-0.016; 0.100)	

Note. AD = antidepressants; CI = confidence interval; CTQ = Childhood Trauma Questionnaire (Bernstein et al., 2003); MADRS = Montgomery-Asberg Depression Rating Scale (Montgomery & Asberg, 1979); [a] displayed only for those variables selected by the final lasso regression model; coefficients indicate the weight in the composition of M^* as derived from the lasso regression model; [b] presence indicates a clinical severity of at least moderate-to-severe on at least one of the five dimensions of the CTQ.

The strongest moderator indicating a superiority of ESC/CM was a higher number of previous suicide attempts (effect size = -0.36); the strongest moderator indicating a superiority of CBASP was a higher age (effect size = 0.24). In total, we identified seven baseline variables with an effect size ≥ |0.20|. These were: number of previous suicide attempts, number of adverse life events, the presence of at least one form of moderate-to-severe childhood trauma,

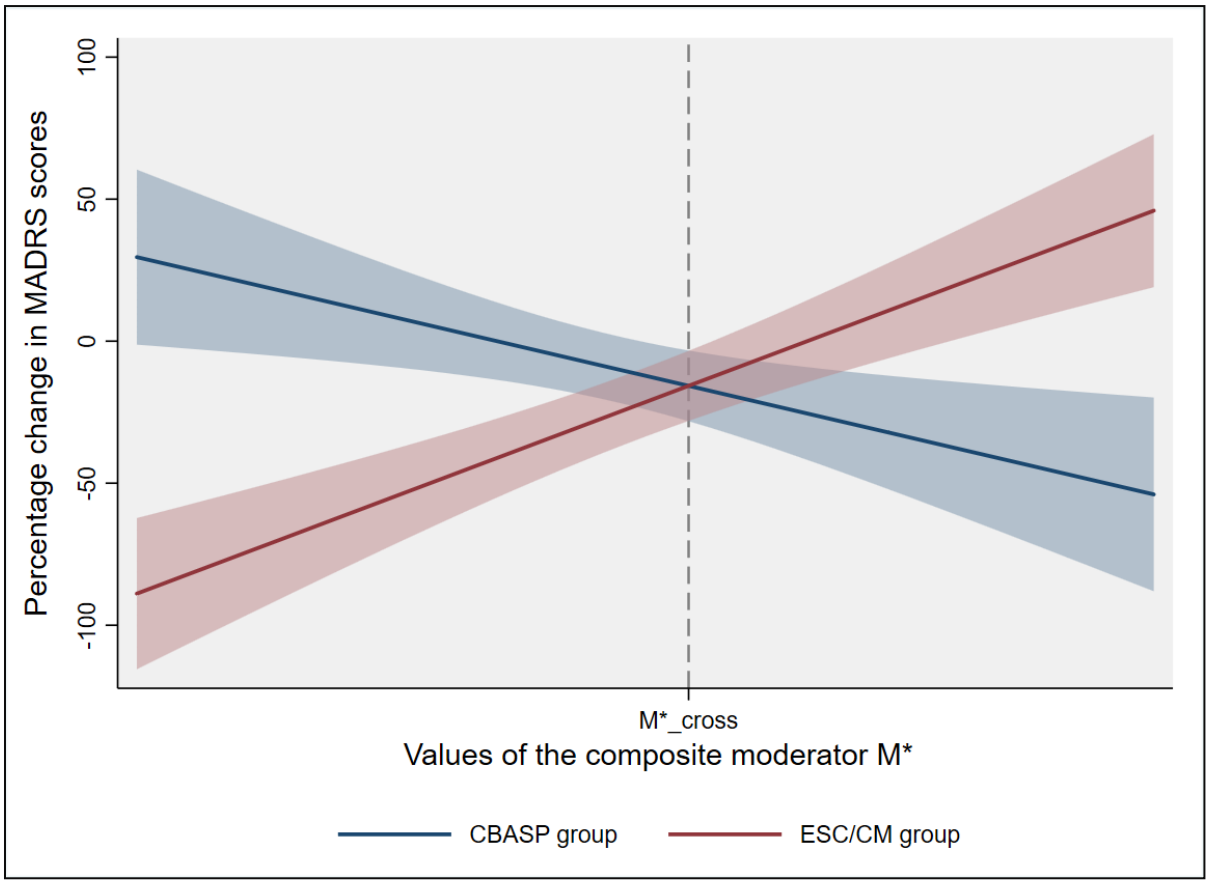
age, an early illness onset, female gender, and the number of previous treatments with antidepressants (for effect sizes, see Table 2). These seven variables were further used to calculate the composite moderator *M**. Other analyzed baseline variables whose moderator effect sizes were below the selected threshold ($r < |0.20|$) and which were therefore not included in the calculation of the composite moderator were baseline depression severity, comorbidity with at least one Axis-I or Axis-II disorder, and the number of previous psychotherapies (see Table 2).

Composite moderator

The lasso regression yielded lasso coefficients for all seven selected baseline variables (see Table 2, right column), which were all further combined to develop the composite moderator *M**. The lasso coefficients represent the extent to which each baseline variable distinguishes differences in the outcome between patients treated with ESC/CM and those treated with CBASP in the context of the other selected variables. The composite moderator *M** was calculable for n = 50 patients who had complete data on all seven variables. With r = 0.67 (95% CI: 0.63; 0.71), the effect size of *M** was larger than any effect size of the individual baseline variables. In the unpaired dataset, we next performed a simple regression analysis as explained in the methods. The final regression model revealed a statistically significant interaction effect between the treatment variable and *M** in predicting the individual-participant MADRS percentage change values (interaction term $\beta = 0.95$, S.E. = 0.17, $p < 0.001$, $R^2 = 0.48$). Figure 1 illustrates the predicted percentage change in MADRS scores from baseline to week eight for the CBASP and ESC/CM treatment groups across the observed range of *M** with 95% confidence intervals. The lines cross at *M** = 46.94. For n = 28 (56.0%) of the n = 50 patients who scored below this cross-point (*M** < 46.94), treatment with ESC/CM was associated with a likely better outcome (i.e., greater percentage reduction in MADRS scores) compared to treatment with CBASP (Cohen's *d* = -1.76; 95% CI: -2.64; -0.86). For n = 22 (44.0%) of the n = 50 patients who scored above this cross-point (*M** > 46.94), treatment with CBASP was associated with a likely better outcome compared to treatment with ESC/CM (Cohen's *d* = 1.28; 95% CI: 0.33; 2.19).

Figure 1

*Predicted percentage reduction in MADRS scores with 95% confidence intervals for CBASP and ESC/CM across the range of the composite moderator M**



Note. CBASP = Cognitive Behavioral Analysis System of Psychotherapy; ESC/CM = escitalopram plus clinical management; *M** = composite moderator; MADRS = Montgomery-Asberg Depression Rating Scale; negative values of the y-axis reflect a desired reduction in depression severity from baseline to week eight, a score of zero reflects no change, and positive scores indicate an increase in depression severity from baseline to week eight.

Baseline profiles of identified subgroups

We next compared the baseline profiles of the two identified subgroups. Table 3 presents descriptive statistics for all seven baseline variables used to create the composite moderator *M** per subgroup. To provide an even more comprehensive picture of the profiles of the two subgroups, Table 3 also shows descriptive statistics for additional baseline variables that were not included in the calculation of *M**, as well as for response and remission rates at week eight. To provide guidance on which differences between the subgroups are significant, differences in means or percentages are reported along with the corresponding 95% confidence

intervals and *p*-value determined by statistical significance testing. Importantly, due to the modest sample size and exploratory nature of this analysis, reported differences between the subgroups will be discussed with caution. We will next describe the differences between both subgroups with regard to the baseline variables which were used to compile the composite moderator.

Table 3

Descriptive statistics for the identified subgroups

Variables	Subgroup likely to benefit more from ESC/CM than from CBASP (n = 28)	Subgroup likely to benefit more from CBASP than from ESC/CM (n = 22)	Difference between subgroups with 95% CI and *p*-value
*Baseline variables which were included in the compilation of M**			
Female gender (%)	60.7	36.4	24.4 (-2.7; 51.4); $p = 0.2$
Age in years (mean (SD))	40.2 (10.8)	46.4 (9.9)	-6.2 (-12.2; -0.2); $p = 0.04$
Early illness onset (%)	42.9	77.3	-34.4 (-59.8; -9.1); $p = 0.02$
Number of previous suicide attempts (mean (SD))	0.50 (0.8)	0.1 (0.4)	0.4 (0.03; 0.8); $p = 0.03$
Childhood trauma (%)[a]	82.1	54.5	27.6 (2.4; 52.8); $p = 0.06$
Number of adverse life events (mean (SD))	2.1 (1.2)	1.4 (0.8)	0.7 (0.1; 1.4); $p = 0.02$
Proportion of patients with following number of previous treatments with AD (%)			Difference in chances of having ≥ 1 previous treatment with AD:
none	46.4	40.9	
≥ 1	53.6	59.1	-5.5 (-33.1; 22.1); $p = 0.8$
> 5	0.0	13.6	
*Further variables which were not included in the compilation of M**			
MADRS baseline score (mean (SD))	28.4 (8.1)	24.4 (8.8)	4.1 (-0.8; 8.9); $p = 0.10$
Diagnosis of ≥ 1 comorbid Axis-I disorder (%)	57.1	36.4	20.8 (-6.4; 48.0); $p = 0.2$
Diagnosis of ≥ 1 comorbid Axis-II disorder (%)	39.3	36.4	2.9 (-24.1; 30.0); $p = 1.00$
History of ≥ 1 suicide attempt (%)	35.7	4.5	31.2 (11.4; 50.9); $p = 0.01$
Emotional abuse (%)[b]	39.3	36.4	2.9 (-24.1; 30.0); $p = 1.00$
Physical abuse (%)[b]	14.3	9.1	5.2 (-12.5; 22.9); $p = 0.7$
Sexual abuse (%)[b]	14.3	4.5	9.7 (-5.9; 25.3); $p = 0.4$
Emotional neglect (%)[b]	57.1	54.5	2.6 (-25.1; 30.0); $p = 1.00$
Physical neglect (%)[b]	35.7	31.8	3.9 (-22.4; 30.2); $p = 1.00$
Proportion of patients with following number of previous psychotherapies (%)			Difference in chances of having ≥ 1 previous psychotherapy:
none	32.1	27.3	
≥ 1	67.9	72.7	-4.9 (-30.3; 20.5); $p = 0.8$
> 5	3.6	13.6	
Response at week eight (%)	25.0	13.6	11.4 (-10.2; 32.9); $p = 0.5$
Remission at week eight (%)	14.3	9.1	5.2 (-12.5; 22.9); $p = 0.7$

Note. AD = antidepressants; CBASP = Cognitive Behavioral Analysis System of Psychotherapy; CI = confidence interval; CTQ = Childhood Trauma Questionnaire (Bernstein et al., 2003);

ESC/CM = escitalopram plus clinical management; MADRS = Montgomery-Asberg Depression Rating Scale (Montgomery & Asberg, 1979); SD = standard deviation; [a] presence indicates a clinical severity of at least moderate-to-severe on at least one dimension of the CTQ; [b] presence indicates a clinical severity of at least moderate-to-severe on the respective dimension of the CTQ; for nominal and ordinal variables, *p*-values and 95% CIs from the Fisher´s exact tests are reported; for metric variables, *p*-values and 95% CIs from independent sample t-tests are reported.

Description of the subgroup likely to benefit more from ESC/CM: In comparison with the subgroup likely to benefit more from CBASP, patients in the subgroup likely to benefit more from ESC/CM were more often female (60.7% versus 36.4%) and had a higher average number of previous suicide attempts (average number of 0.5 versus 0.1). This goes in line with this subgroup reporting more often at least one previous suicide attempt (35.7% versus 4.5%). Moreover, patients in this subgroup reported more often at least one form of moderate-to-severe childhood trauma (82.1% versus 54.5%) as well as more adverse life events (average number of 2.1 versus 1.4).

Description of the subgroup likely to benefit more from CBASP: In comparison to the subgroup of patients likely to benefit more from ESC/CM, those likely to benefit more from CBASP tended to be slightly older (mean age of 46.4 years versus 40.2 years) and had more often an early illness onset (i.e., before the age of 21; 77.3% versus 42.9%). The previous usage of antidepressant medication was slightly higher in this subgroup: 59.1% (versus 53.6% in the other subgroup) of the patients in this subgroup had taken antidepressant medication at least once, and 13.6% (versus 0% in the other subgroup) reported more than five previous treatments with antidepressants.

As displayed in Table 3, we did not detect statistically significant differences between the two subgroups with respect to the rates of female gender, childhood trauma and previous treatments with antidepressant medication (all $p > 0.05$). Further, except for the history of at least one suicide attempt, which was not selected for the compilation of M* because of the intercorrelation with the mean number of suicide attempts, none of the baseline variables deselected for the compilation of M* showed significant differences between the subgroups. Consequently, the two subgroups were relatively similar with respect to the MADRS mean

baseline scores, rates of comorbid Axis-I and Axis-II diagnoses, various subtypes of childhood trauma assessed by the CTQ (i.e., emotional abuse, sexual abuse, physical abuse, emotional neglect, and physical neglect), and previous numbers of underwent psychotherapies. The same was true for both response and remission rates at week eight.

Differences in outcomes for each subgroup by treatment

In the subgroup likely to benefit more from ESC/CM, n = 12 patients underwent treatment with ESC/CM, while n = 16 received treatment with CBASP, which was likely less effective for them. In the subgroup likely to benefit more from CBASP, n = 10 patients underwent treatment with CBASP, while n = 12 received treatment with ESC/CM, which was likely less effective for them. Table 4 shows MADRS mean values at baseline and at week eight, as well as the mean percentage change and rates of response and remission at week eight for each of the four subgroups by randomized treatment condition. It also shows the same outcomes for those patients who received their likely more beneficial treatment and for those who received their likely less beneficial treatment. Briefly, we can conclude that patients likely to benefit more from ESC/CM and treated with ESC/CM had the largest percentage decrease (-50.9%) in depression severity from baseline to week eight, as well as the highest response (58.3%) and remission rates (33.3%) at week eight. They are followed by patients likely to benefit more from CBASP and treated with CBASP, which show more modest values in terms of percentage decrease (-33.3%) in depression severity as well as response (20.0%) and remission (10.0%) rates. Patients likely to benefit more from CBASP and treated with ESC/CM had, in average, an increase in depression severity (6.9%) from baseline to week eight and relatively low response and remission rates (both 8.3%) at week eight. Depression severity increased on average (5.0%) also among patients likely to benefit more from ESC/CM and treated with CBASP; additionally, there were no remitters or responders in this subgroup. The average percent change in depression severity from baseline to week eight is illustrated in Figure 2 for each subgroup by treatment interaction.

When pooling those patients who received their likely more beneficial treatment, the average decrease in depression severity reached up 42.9%, while response and remission rates

were 40.9% and 22.7%, respectively. These numbers stand in contrast to the pool of patients who received their likely less beneficial treatment, having an average increase in depression severity of 5.8% and smaller remission and response rates of 3.6%.

Table 4

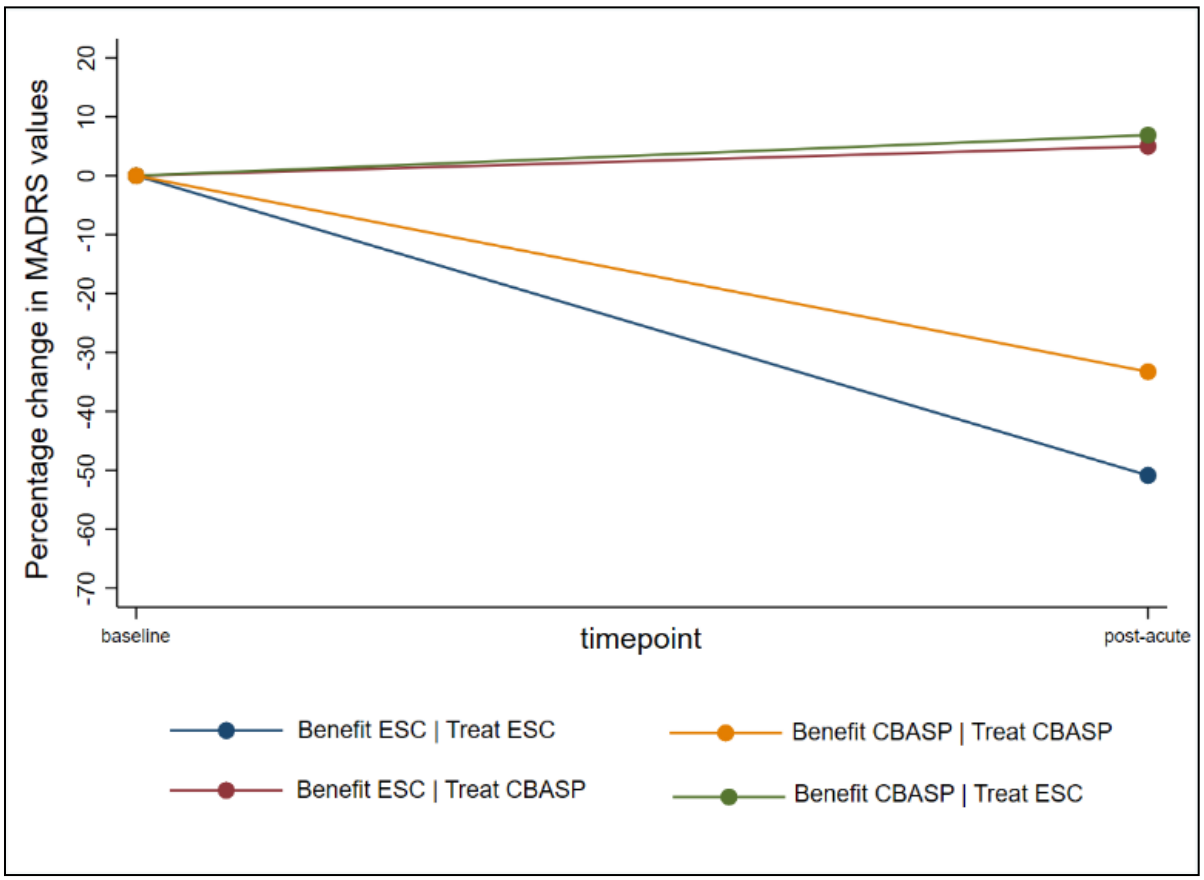
Comparison of different outcomes for each subgroup by assigned treatment

Subgroup x treatment	MADRS at baseline, mean (SD)	MADRS at week 8, mean (SD)	Percentage change (%), mean (SD)	Response at week 8, %	Remission at week 8, %
Be ESC/CM | Tr ESC/CM; n = 12	30.1 (6.9)	15.1 (11.2)	-50.9 (35.4)	58.3	33.3
Be CBASP | Tr CBASP; n = 10	26.8 (8.5)	17.5 (6.9)	-33.3 (22.3)	20.0	10.0
Be CBASP | Tr ESC/CM; n = 12	22.3 (8.9)	22.4 (9.4)	6.9 (37.3)	8.3	8.3
Be ESC/CM | Tr CBASP; n = 16	27.2 (9.0)	27.3 (8.4)	5.0 (28.7)	0.0	0.0
Be ESC/CM | Tr ESC/CM + Be CBASP | Tr CBASP; n = 22	28.6 (7.6)	16.2 (9.4)	-42.9 (30.8)	40.9	22.7
Be ESC/CM | Tr CBASP + Be CBASP | Tr ESC/CM; n = 28	25.1 (9.1)	25.2 (9.0)	5.8 (32.0)	3.6	3.6

Note. Be [treatment condition] = likely higher benefit from this treatment condition; CBASP = Cognitive Behavioral Analysis System of Psychotherapy; ESC/CM = escitalopram plus clinical management; MADRS = Montgomery-Asberg Depression Rating Scale (Montgomery & Asberg, 1979); SD = standard deviation; Tr [treatment condition] = treated with this treatment condition.

Figure 2

Percentage change in MADRS values for each subgroup by randomized treatment



Note. CBASP = Cognitive Behavioral Analysis System of Psychotherapy; ESC/CM = escitalopram plus clinical management; MADRS = Montgomery-Asberg Depression Rating Scale (Montgomery & Asberg, 1979).

Sub-analysis of patients augmented after week eight

As mentioned above, after completion of the 8-week acute treatment phase, a total of n = 20 patients whose depression severity had not decreased by at least 20.0% received the other treatment condition in addition to the initial treatment condition for the following 20 weeks. The main analysis showed that these patients eventually caught up with the initial improvers in terms of depression scores by the end of the extended treatment phase, reaching a remission rate of 30.0% and a response rate of 45.0% (Schramm et al., 2015). However, considering the present analyses enabling the stratification in subgroups based on the composite moderator, we can conclude that n = 19 (95.0%) of these n = 20 patients initially received the less beneficial treatment: 50.0% would likely have benefited more from ESC/CM and received CBASP and

45.0% vice versa. Only one patient who likely benefited more from ESC/CM and who received this treatment experienced no reduction of at least 20.0% and was supplemented with CBASP after week eight.

Discussion

The aim of our study was to identify and characterize subgroups of patients who were likely to benefit more from psychotherapy with CBASP than from medication with escitalopram combined with clinical management appointments or vice versa during an eight-week acute treatment phase. By using the composite moderator method, we uncovered two distinct subgroups with differential response to CBASP and ESC/CM. Our analyses revealed that those patients who received the likely less effective treatment not only did not improve within the first eight weeks of treatment, but worsened, with depression severity increasing on average by 5.8% from baseline to week eight. In contrast, depression severity decreased by an average of 42.9% from baseline to week eight for those patients in both subgroups who received the likely more effective treatment. Moreover, these patients also achieved response and remission more often than the others. In summary, we can conclude that below the general lack of statistically significant differences in the effectiveness of these two treatments observed in the main analysis (Schramm et al., 2015), there are however considerable subgroup effects implying that in terms of reduction in depression severity, certain patients did not benefit from their assigned condition within the first eight weeks.

In addition, we found that patients who did not achieve at least a 20.0% reduction in symptom severity after the acute treatment phase and who were subsequently supplemented with the other treatment condition were in the majority (95.0%) treated with the likely less effective treatment during the acute treatment phase. The main analyses by Schramm et al. (2015) found that these patients benefited substantially from the addition of the other treatment condition, resulting in response rates of 45.0% and remission rates of 30.0% at the end of the extended treatment phase. This subsequent improvement during the extended treatment phase can be plausibly explained by the fact that after week eight, these patients

received the treatment that was likely more effective for them personally in addition to the first, unsuccessful treatment, rather than that they received an additional treatment per se. This reasoning may also contribute to explain why there is no clear empirical evidence as to whether the combination of medication and psychotherapy always works better than monotherapy in patients with PDD, as shown by a review of Spijker et al. (2013).

Although the modest sample size of our study does not allow us to draw general conclusions about the pre-treatment profile of the identified subgroups, we can nevertheless summarize some interesting trends that have been uncovered: to sum up, the subgroup likely to benefit more from ESC/CM was more often female, reported more often at least one form of moderate-to-severe childhood trauma as well as more previous suicide attempts and more adverse life events. Similarly, a traditional moderator analysis of this trial by Bausch et al. (2017) found that patients with moderate-to-severe childhood trauma responded and remitted more often to ESC/CM than to CBASP within the first eight weeks of treatment. Further, patients reporting moderate-to-severe childhood trauma tended to have more previous suicide attempts in our sample (Bausch et al., 2017), which is in line with other findings: for instance, childhood trauma particularly in the form of physical abuse or sexual abuse has been reported to enhance the risk for suicidal attempts later in life in the general population (Zatti et al., 2017), while childhood emotional trauma was reported as a predictor for an elevated suicide risk in patients with major depression (Dias de Mattos Souza et al., 2016). Besides higher levels of childhood trauma, female gender was also found to be an independent risk factor for both an early onset of first attempting suicide and for a higher number of suicidal attempts (Roy & Janal, 2005). A study by Sarchiapone et al. (2007) conducted in patients with unipolar depression revealed that being female, having childhood trauma as well as a lifetime history of aggression significantly increased the risk of previous suicide attempts. Taken together, these previous findings suggest an association between female gender, childhood trauma and possibly also later traumatic events, as well as suicide attempts, which is complemented by the results of our analyses in that this phenotype may benefit better from medication with escitalopram in the acute treatment phase than from CBASP in the context of PDD. Notably, this interpretation is further supported by the fact that in our sample, patients reporting

moderate-to-severe childhood trauma reported significantly more often resistances to treatments with psychotherapy (defined as at least two self-reported nonresponses to psychotherapy of at least 10 sessions; Bausch et al., 2017), indicating that for some patients, psychotherapy has also failed to lead to a response in the past.

Furthermore, our finding that antidepressant medication may be more effective as an acute treatment for early traumatised patients contradicts an older moderator analysis by Nemeroff et al. (2003), who found CBASP to be superior to antidepressant monotherapy with nefazodone in patients with childhood trauma. However, this discrepancy could be due to various differences between both studies: first, besides different applied statistical methods, we investigated another antidepressant as well as a shorter treatment period (eight weeks versus 12 weeks in the original study by Keller et al. 2000). Second, Nemeroff et al. (2003) assessed childhood trauma history by a different scale which also assessed parental loss, a type of childhood trauma that affected approximately one-third of the patients in their study, and which was not investigated in our analysis.

Moreover, a possible explanation for the poorer response of early traumatized patients to CBASP in our trial could be that the invocation of memories of early traumatic experiences through CBASP may have led to an initial worsening of symptoms in these patients within the first eight weeks of treatment (Bausch et al. 2017). When treated with CBASP, PDD patients with moderate-to-severe childhood trauma may need a longer treatment time in order to cognitively restructure traumatic memories as well as to establish healthier interpersonal behavioural patterns and thereby recover from PDD (McCullough, 2000; McCullough, 2021; Schoepf, 2013). Combining CBASP from the beginning of treatment with escitalopram or a comparable antidepressant could help early traumatised patients to cope with the mental and emotional consequences of recalling and processing past traumatic experiences. The improvement observed in some of these patients after augmentation with ESC/CM in the extended treatment phase supports this assumption, which remains to be further investigated. In contrast, patients likely to benefit more from CBASP than from ESC/CM had more often an early illness onset. Given that CBASP was especially developed to meet the needs of patients with PDD with an early illness onset (McCullough, 2003), it is plausible that its specific

techniques to address early-onset based symptoms and illness-trajectories have led to a greater reduction in depression severity in these patients. The patients in this subgroup were also older, which is in line with a meta-regression by Furukawa et al. (2018) which revealed that younger PDD patients discontinued monotherapy with CBASP more often across three large studies including this RCT, possibly because of a lack of response or acceptance of CBASP. Furthermore, patients in this subgroup reported more previous treatments with antidepressant medication. The fact that they participated in our treatment trial suggests that previous medication therapies did not lead to long-term remission or prevention of relapses, which may be due to a reduced neurobiological and/ or metabolic responsiveness to antidepressants in these patients (Miller et al. 2013; Vadodaria et al. 2019; Willner et al. 2013) and could explain their likely poorer response to ESC/CM in our trial.

We did not detect statistically significant differences between the two subgroups with respect to rates of female gender, moderate-to-severe childhood trauma and previous treatments with antidepressant medication (all $p > 0.05$, see Table 3), although these baseline variables showed large moderator effect sizes (see Table 2). However, the lack of statistical significance can presumably be explained by the small sample size and highlights the importance of effect sizes for this type of exploratory analyses, particularly when being performed based on modest sample sizes. Finally, the two subgroups were relatively similar in terms of the baseline depression severity (MADRS mean score), rates of comorbid Axis-I and Axis-II diagnoses, all subtypes of childhood trauma, and the previous numbers of underwent psychotherapies. These baseline variables may or may not play a role as predictors of treatment efficacy, which warrants investigation in further analyses. Furthermore, response and remission rates at week eight were comparable in both subgroups, as both subgroups included patients treated with the likely less (or more) beneficial treatment condition.

Strengths and limitations

The results of our study should be viewed considering certain strengths and limitations. In terms of strengths, first, we compared two clinically highly relevant treatments in terms of their efficacy for specific subgroups of outpatients with PDD. Second, based on the composite

moderator method, we generated findings about the influence of numerous, for replication studies relatively easy to assess baseline variables, instead of examining the effect of only one potential moderator. Third, the design of the original study furthermore allowed us to examine the relationship between subgroup classification, initial treatment, and the effect of a combination treatment after the acute 8-week treatment phase. To our knowledge, this study is the first to date to examine the differential response of patients with PDD for the comparison of a psychotherapeutic and a pharmacotherapeutic treatment at this level of complexity in terms of the considered baseline characteristics.

Nevertheless, some important limitations should be considered as well: first, due to the initial sample size and the lack of baseline data in some patients, we had a relatively modest sample size at the basis of our analyses. This results in relatively small cell numbers when comparing both subgroups, which is why the comparison of the baseline profiles should be interpreted with caution. In this light, it is important to emphasize that the identified trends must be confirmed in further independent studies with larger populations and more participating centers before any treatment recommendations can be drawn. Second, the composite moderator was based on the set of available baseline variables and is thus one of many possible. Very likely, there were other not assessed relevant moderators such as genetic or neural biomarkers, that could have helped to further differentiate the subgroups. Moreover, the present analysis focused on moderator effects only, and did not consider other factors affecting treatment effectiveness such as predictors or mediators. For instance, in our sample, patients with higher baseline depression severity scores tended to have larger decreases in depression severity in both treatment groups. This and other possible predictors should be further explored in additional secondary analyses of this study. In addition, further secondary analyses of this trial could assess the impact of possible mediator variables such as the quality of the therapeutic relationship or changes in neurobiological parameters during the therapy process. Moreover, other outcomes relevant to treatment success in PDD such as improvements of life quality or interpersonal relationships could be analysed in further secondary analyses. Finally, our study had specific inclusion and exclusion criteria, so the generalizability of these results remains to be verified.

Conclusion

This study has highlighted the impact of several important features of the baseline profile of patients with PDD on their response to an acute psychotherapeutic versus pharmacological treatment. After being confirmed in independent studies, these findings could serve to inform clinical decision-making by helping clinicians to assign the most promising treatment to individual patients based on their baseline profile. The selection of non-effective treatments does not only result in non-responses, worsening of symptoms or side-effects, but also in misspend personal and economical costs of the health-care system. Expanding the body of evidence in favor of personalized treatment selection remains a crucial task in order to help clinicians to a priori identify the treatment with the greatest likelihood of response for an individual patient and thereby avoid these undesired consequences. The progress of personalized medicine could, together with the development of new therapies, substantially improve the life of individuals affected by PDD.

Statements and Declarations

Conflict of interest statements: We declare to take full responsibility for the integrity of the data and accuracy of the data analysis. All authors can provide full access to all the data in this study. Dr. Schoepf received honoraria for workshops and presentations relating to CBASP. Dr. Schramm received modest book royalties and honoraria for workshops and presentations relating to CBASP. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical standards statement: The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committee on human experimentation with the Helsinki Declaration of 1975, as revised in 2008.

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