

**Conceptualizing and treating chronic depression: A naturalistic study of  
psychotherapy and combination treatment.**

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## Abbreviations

ACT	Acceptance and Commitment Therapy
ADM	Antidepressant medication
APA	American psychological association
AUDIT	Alcohol use disorders identification test
BDI-II	Beck depression inventory-II
BDNF	Brain-derived neurotropic factor
CBASP	Cognitive-behavioral analysis system of psychotherapy
CD	Chronic depression
CFA	Confirmatory factor analysis
DSM-5	Diagnostic and statistical manual of mental disorders, fifth edition
EDT	Experiential dynamic therapy
EFA	Exploratory factor analysis
ESEM	Exploratory structural equation modeling
FML	Full maximum likelihood
GAF-F	Global assessment of function-function
GAF-S	Global assessment of function-symptom
GSI	Global Severity Index
HPA	Hypothalamic pituitary adrenal
ICD-10	International classification of disease, 10 <sup>th</sup> edition
ICM	Independent cluster model
IIP-64	Inventory of interpersonal problems-64
IPT	Interpersonal therapy
MAOI	Monoamine oxidase inhibitor
MBT	Mentalization Based Therapy

MCT	Meta Cognitive Therapy
MDD	Major depressive disorder
M.I.N.I	Mini-International Neuropsychiatric Interview
ML	Maximum likelihood
MLM	Multi-level modeling
NDRI	Norepinephrine-dopamine reuptake inhibitor
PDD	Persistent depressive disorder
PSM	Propensity score matching
PTSD	Post-Traumatic Stress Disorder
RCT	Randomized controlled trial
RIMA	Reversible inhibitor monoamine oxidase A
rMDD	Recurrent major depressive disorder
RML	Restricted maximum likelihood
SCID-2	Structured Clinical Interview for DSM-IV Axis II Personality Disorders
SCL-90-R	Symptom check list-90-revised
SD	Standard Deviation
SEM	Structural equation modeling
SMS	Serotonin modulator and stimulator
SNRI	Serotonin-norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic Antidepressant
TeCA	Tetracyclic antidepressant
UN	Unstructured covariance
WHO	World Health Organization



## Summary

Psychotherapy and antidepressant medication (ADM) are very different treatments that presumably work through different mechanisms of change. Still, research indicates they are both effective treatments and work equally well to treat chronic depression. An explanation for this may be that depression consists of different subgroups of affective, cognitive and somatic symptoms and that psychotherapy are effective for some of these, while ADMs are effective for others. Thus, these treatments may be hypothesized to treat limited and different parts of the symptoms that make up the total distress of patients with chronic depression. This is further supported by research findings indicating a combination of psychotherapy and ADM provides better outcomes compared to either monotherapy. However, the nature of the specific symptoms of depression and the mechanisms through which various treatments – alone or in combination – may affect them, remain largely unknown. Establishing how treatments may act differently on specific symptom groupings could assist therapists in assigning patients to treatments that better fit their needs, and thus improve remission rates.

The overarching aim of this thesis was to explore how different treatment conditions might affect specific symptoms of chronic depression and discuss possible mechanisms underlying these effects. To address this we conducted three studies. The first aim was to explore the assumption that combination treatment provides an accumulated effect resulting in better outcomes than either monotherapy. This was done by comparing outcomes of patients using antidepressant medication while in psychotherapy to patients only receiving psychotherapy. The second aim was to explore whether it was possible to identify specific symptoms that constituted meaningful subgroups within chronic depression. The third aim was to examine whether patients in the two treatment conditions had different outcomes on these symptoms.

The first aim was explored in papers 1 and 3. In paper 1, our sample consisted of patients who were all using ADM at the start of treatment, and we examined whether patients quitting ADM during psychotherapy had worse outcomes on overall depression compared to keeping their medication. We hypothesized that patients using medication and then discontinued would have worse outcomes than patients continuing ADM, since they would lose the accumulated benefits of two treatments (paper 1). In paper 3 our sample consisted of patients using ADM throughout psychotherapy and patients who were unmedicated prior to and throughout psychotherapy. We explored whether patients using ADM had better outcomes on overall depression compared to patients with no medication. Using the same reasoning of accumulated effect of two treatments, we hypothesized patients using ADM would have better outcomes than patients who did not use any medication (paper 3). There was no difference in outcome between continuers and discontinuers of ADM (paper 1), or between non-medicated patients and patients using ADM throughout psychotherapy (paper 3). The results thus indicated that patients with chronic depression using ADM did not experience the hypothesized accumulated effect of two treatments that could have provided better outcomes than patients with only psychotherapy, possibly because oppositional tolerance may have caused a lack of beneficial effects of ADM. This could also indicate that psychotherapy in some cases may be a viable alternative to combination treatment. In addition, since patients discontinuing did not have worsening of symptoms compared to patients keeping medication the treatment offered in the study may have provided a secure context that helped patients prevent relapse of depressive symptoms when discontinuing ADM.

Although psychotherapy and medication seem to be equally efficacious on overall depression they may act differently upon specific symptoms. An implication of this could be that treatment may be more effective if patients receive treatment that fit their specific

symptom profile. Hence, the second aim of the present thesis was to explore the structure of depressive symptoms in chronic depression by way of factor analysis (Paper 2). The results indicated a bi-factor model provided the best fit, where the structure of depression symptoms corresponded to one global depression factor and two sub-factors. One sub-factor consisted of self-critical cognitions, and the other consisted of somatic items related to sleep, appetite, and fatigue. Also, depressive symptoms typically labelled as affective loaded on the general factor but did not form a separate factor independent from the general factor. These findings indicated chronic depression may be understood as characterized by a state of negative emotionality (i.e., affective symptoms) that influence all depressive symptoms, while at the same time specific independent sub-factors cause expressions of self-criticism and somatic symptoms which could be regarded as relevant treatment targets for this patient group.

There may be several explanations as to why combination treatment seems to provide better outcomes than monotherapies. One explanation could be that ADM and psychotherapy act on different symptoms providing independent and accumulative effect on overall improvement. Another explanation may be that the accumulated effects of psychotherapy and medication provide superior improvement on each symptom, thus producing better overall outcomes. The third aim of the thesis was to explore potential differences in treatment outcomes between ADM users and non-medicated patients on specific symptom clusters identified in Paper 2. Thus, we explored whether patients using ADM while in psychotherapy had different outcomes than non-medicated patients on the sub-factors “self-criticism” and “somatic symptoms” (Paper 3). We hypothesized that the combination of ADM and psychotherapy provided accumulative effect on a symptom level, and that ADM-users would have better outcomes on both sub-factors compared to patients only receiving psychotherapy. The results showed chronically depressed patients not using

medication while in psychotherapy reduced self-criticism more than patients using ADM, while there was no difference between groups on the somatic factor. This indicated that rather than providing an added effect, the use of ADM in addition to psychotherapy may have had a negative effect on self-critical schemas. We speculated that effects of ADM, especially for long term users where the risk of oppositional tolerance increases, could interfere with psychotherapeutic interventions that target self-criticism, and thus make application of new problem-solving strategies harder.

In sum, the results of the present thesis indicate patients with chronic depression may experience oppositional tolerance to ADM and not benefit from continued use, and that psychotherapy in some cases may be a viable alternative to combination treatment. Furthermore, self-criticism may be a key factor in maintaining chronic depression, and ADM may have negative effects on psychotherapeutic interventions that target self-criticism. The results of the thesis thus challenge the assertion that combination treatment is better than monotherapy for patients with chronic depression.

The empirical analyses were based on naturalistic data from the Depression Forefront study conducted at Modum Bad hospital, in which 437 patients with chronic depression underwent a 12-week inpatient treatment program.

## Introduction

*“The tower of Babel never yielded such confusion of tongues, as the chaos of melancholy doth variety of symptoms.”* (Burton, 1893, p. 325).

This thesis aims to describe key features of chronic depression, discuss different perspectives on etiology, and present findings on the effectiveness of different treatments. It also discusses potential mechanisms of change and how one might understand the effects of different treatments on specific symptoms of chronic depression. The overarching goal is to contribute to the understanding of how to conceptualize the complex phenomenon of chronic depression and how to treat it.

### What is depression?

From the 5<sup>th</sup> century B.C. writings of Hippocrates, later expanded upon by the 2<sup>nd</sup> century scholars Rufus of Ephesus and Galen, melancholia was recognized by the cardinal (affective) symptoms of sadness and fear (Jackson, 2008). Somatic symptoms pertaining to disturbances in sleep, appetite, weakness and tiredness, and cognitive symptoms such as fearing punishment, hopelessness, and guilt, were also prevalent in early descriptions and became common in definitions of melancholia during the 16<sup>th</sup> century (Jackson, 2008). In textbooks of psychiatry between 1880-1900, and from 1900-1960 melancholia/depression more consistently became described as a negative *affective* state (i.e., sadness, “soul-pain”, misery, woe) accompanied by *cognitive* changes (i.e., resignation, hopelessness, helplessness, pessimism, self-accusation, guilt), and *somatic* and psychomotor symptoms (i.e., loss of appetite, sleep disturbance, fatigue, slowing of speech and movement; Kendler, 2016, 2017). Different treatment models have also incorporated the assumption of three types of symptoms in depression. For instance, within Sigmund Freud’s psychoanalytic framework melancholia has been described as a state of painful sadness due to an experience of loss. Furthermore, loss of energy and harsh self-critical thoughts follow

through a process in which aggression against the lost object is turned upon the self (Freud, 1953). In Aaron Beck's cognitive model of depression, patients think of themselves as defective and worthless. This assumption along with pessimistic thoughts about the future cause affective symptoms such as sadness and somatic symptoms such as fatigue and low energy (Beck et al., 1979). Thus, different treatment models generally agree with the 2500-year-old idea that affective, cognitive, and somatic symptoms in some way co-occur and interact to form the syndrome of "depression" although they often differ in defining what constitutes the "core" mechanisms (Katz et al., 1996/1997).

Current diagnostic guidelines also reflect the notion that different type of symptoms (i.e., affective, cognitive, somatic) co-occur to form depression, but do not precisely specify which symptoms need to be present. Rather, depression is defined as the simultaneous presence of five or more (DSM-5; American Psychiatric Association, 2013) or four or more (ICD-10; WHO, 1993) of the following symptoms: 1) depressed mood, 2) loss of interest and pleasure, 3) decreased energy or increased fatigability, 4) decrease or increase of appetite, 5) sleep disturbance, 6) feelings of worthlessness, guilt, or reduced self-confidence 7) diminished ability to think or concentrate, 8) recurrent thoughts of death or suicide or suicidal behavior, and 9) psychomotor agitation. Depression is highly prevalent in the adult population with a past-year prevalence of 16.3% (Moffitt et al., 2010). About half of those experiencing symptoms which qualify for a depressive disorder, is unlikely to experience it again (Monroe et al., 2019). In diagnostic terms these patients meet the criteria for Major Depressive Disorder (MDD; American Psychiatric Association, 2013). For the other half depression is unremitting in 15% of the cases and recurrent in 35% (Eaton et al., 2008). For diagnostic purposes these conditions are classified either as Persistent Depressive Disorder (PDD) or recurrent Major Depressive Disorder (rMDD; American Psychiatric Association, 2013). The symptoms required to diagnose either rMDD or PDD are overall identical with

MDD. Thus, the key distinction between MDD, PDD and rMDD is based on duration or recurrence of symptoms. The key feature for PDD is *persistence of symptoms for at least two years*, and recurrence is defined as *re-emergence of symptoms after at least two months without symptoms* (American Psychiatric Association, 2013). Furthermore, diagnostic criteria for both PDD and rMDD allow for periods without depressive symptoms. According to criteria set forth by Frank et al. (1991) which have become standard in the literature (Burcusa & Iacono, 2007), re-emergence of symptoms within two months is assumed to constitute relapse of the same episode (i.e., PDD), while return of symptoms after two months have passed is considered a new episode (i.e., rMDD). Thus, the distinction between PDD and rMDD for patients with a long history of depressive symptoms will often depend on the duration of symptom free periods between symptoms (Høstmælingen et al., 2021a, 2021c). However, differentiating between *persistence* and *recurrence* based on duration criteria, lacks empirical support (de Zwart et al., 2019). There is also significant overlap between PDD and rMDD on diagnostic validation criteria (Rhebergen & Graham, 2014). Furthermore, it is difficult to confirm whether patients' past symptoms constitute persistence or recurrence as they often have trouble recalling the precise nature, severity, and timing of their symptoms (Harris et al., 2020). Additionally, similar risk factors such as severity of general dysfunction, depressive symptoms at baseline, severity of comorbidities, failure to seek treatment at baseline (Hoertel et al., 2017; ten Have et al., 2018), childhood maltreatment (Buckman et al., 2018; Nanni et al., 2012), post-treatment residual symptoms of depression, and history of recurrence (Buckman et al., 2018) are shared between PDD and rMDD. These findings suggest that both PDD and rMDD should be categorized as chronic and contrasted to non-chronic single episodes of depression, and several studies thus define chronic depression (CD) by including both rMDD and PPD (e.g., Barnhofer et al., 2009; Bockting et al., 2005;

DeRubeis et al., 2020; Hollon et al., 2014; Humer et al., 2020; Ma & Teasdale, 2004).

Informed by the reviewed research, the studies conducted in this thesis include both rMDD and PDD in the term chronic depression.

Chronic depression is ranked among the top 20 leading causes of years lost to disability (Vos et al., 2013), and is associated with severe impairment of daily functioning (Arnow & Constantino, 2003). Still, the nature of depression and its underlying mechanisms are not well understood (Cuijpers, Stringaris, et al., 2020), and the reason why 50% of those experiencing the disorder have a chronic course, remains unknown. One theory is that in the event of severe life stressors, depression may be a typical human response, but for those prone to recurrence or persistence there may exist some underlying vulnerability that is periodically expressed through symptoms crossing the diagnostic threshold (Bockting et al., 2015; Hollon, 2020). For instance, many patients with CD have experienced childhood maltreatment (Buckman et al., 2018; Nanni et al., 2012), and exhibit severe interpersonal problems that may originate from disturbed attachment, invalidating parenting, and interpersonal trauma during childhood (Jobst et al., 2016). Another theory is that hidden within the overall diagnosis of depression, there may be specific patterns of symptoms that may differentiate people with a chronic course from those experiencing single episodes. Using the criteria in DSM-5, there are 227 possible unique symptom profiles that all would qualify for the diagnosis of depression (Fried & Nesse, 2015a), and there is considerable heterogeneity when it comes to differences in symptom profiles between patients with depression (Fried & Nesse, 2015a, 2015b; Simmonds-Buckley et al., 2021; van Loo et al., 2012). Thus, there may be meaningful sub-groups of symptoms of depression that are particularly prevalent for different groups of depressed patients (Simmonds-Buckley et al., 2021). For instance, previous research indicates that self-critical cognitions may play a central role in maintaining chronic depression (Blatt et al., 1982;



Dent & Teasdale, 1988; Hawley et al., 2014; Luyten et al., 2007; Mongrain & Leather, 2006; Zeeck et al., 2020) and should be specifically targeted in treatment (Werner et al., 2019). Inspired by the reviewed research this thesis aims to explore whether patients with CD experience specific symptoms that might cause or maintain a chronic course of depression.

## **Different Etiological Models of Depression**

### ***The Medical Disease Model***

The idea that all depression has a single cause stemming from some form of brain dysfunction, remains deeply entrenched in the field of psychiatry (Fried & Nesse, 2015a). This reflects a medical disease model in which observable or self-reported problems are symptoms of an underlying disorder, and that this disorder is the actual cause of the symptoms (Hyland, 2011). Within such a model, the symptoms of depression (e.g., reduced quality of sleep, crying and self-criticism) are connected because they are caused by “depression” in the same way the symptoms of headaches and foggy eyesight are connected if they are caused by a tumor (Borsboom & Cramer, 2013). Emil Kraepelin’s major task in the works he published from 1887 to 1926 was to organize all mental disorders within this framework (Bentall, 2004). He assumed mental and physical disorders were not fundamentally different, and that psychiatric disorders could be distinguished from one another, had different causes (etiology), and associated pathology in the brain. Following this logic, a disorder is *essentialist* in nature; it exists whether we recognize it or not (i.e., a tumor might be present before someone experiences the symptoms), it has a single well-defined etiological agent, and symptoms of the disorder are direct consequences of this *essence* (Kendler et al., 2011).

One reason why depression (along with most common mental disorders) is poorly understood may stem from the fact that it breaks with central premises of an essentialist

disease model. For almost all mental disorders, symptoms are the only identifiable sources of distress, while the proposed cause – the disorder itself – cannot be identified and is virtually impossible to conceptually separate or diagnose independently from their symptoms (Borsboom & Cramer, 2013; Kendler et al., 2011). Thus, essentialist models are poorly suited to classify mental disorders as the symptoms they consist of are probabilistically linked to several possible causes, rather than one identifiable common cause (Kendler et al., 2011). This idea of multiple causes is further supported by the fact that on average, antidepressant medication (ADM) and a range of psychotherapies work equally well for depression, but only 30-40% will achieve remission (Craighead & Dunlop, 2014). The fact that many patients will not respond to presumably efficacious treatments, supports the hypothesis that depressed patients may suffer from several syndromes that differ in etiology, symptom presentation and biological dispositions (Fried & Nesse, 2015a), and that the current diagnostic systems of DSM-5 and ICD-10 have failed to identify the key phenomena that make up and differentiate these problems from one another.

### ***The Transdiagnostic Approach to Classification***

In recent years there has been increasing interest in *transdiagnostic classification* as an alternative to current diagnostic taxonomies. This approach focuses on different psychological processes that contribute to the etiology and/or maintenance of many mental disorders (Frank & Davidson, 2014). Rumination, experiential avoidance, self-attacking, emotion dysregulation and cognitive fusion are examples of proposed mechanisms that cause symptoms and maladaptive functioning across a wide range of diagnoses (Frank & Davidson, 2014). For instance, rumination (i.e., thoughts focusing on own symptoms and causes, which leads to increased experience of these symptoms) can be found in patients with depression, anxiety, eating disorders and substance abuse (Johnson et al., 2016).

Within a transdiagnostic framework, one assumes that it is possible to tailor treatments to specific problems, but that the current taxonomy used to conceptualize mental disorders (i.e., diagnostic manuals) does not identify the relevant problems. Furthermore, if efforts to uncover underlying mechanisms for mental disorders are successful (e.g., rumination or experiential avoidance rather than ‘depression’ or ‘anxiety’), this could be a starting point to identify treatments that specifically address these, and construct treatments that better fit patients’ needs (Barlow et al., 2004). The fact that between 73.8 and 98.2% of patients with a mental disorder also have at least one more disorder (Gadernann et al., 2012) also lends support to the transdiagnostic approach. These high rates of comorbidity indicate there may be transdiagnostic processes that make people vulnerable to experience a range of symptoms cutting across diagnostic thresholds (Hagen et al., 2012; Sauer-Zavala et al., 2016). There is a growing amount of proposed transdiagnostic mechanisms that underlie symptoms of depression such as attentional control (Hsu et al., 2015), perfectionism (Egan et al., 2011), intolerance of uncertainty (Rosser, 2019), hope (Gallagher et al., 2020), emotional awareness (Weissman et al., 2020), anger dysregulation (Kim, 2018), dysfunction in decision-making (Goschke, 2014), abnormal reward functioning (Basking-Sommers & Foti, 2015), and dysfunctional coping processes (Elhai et al., 2019). However, as the number of proposed transdiagnostic mechanisms becomes larger, so does the challenge of synthesizing these findings into a comprehensive classification system that is more valid than the diagnostic manuals it opposes. For instance, transdiagnostic treatment protocols have failed to establish superiority over diagnosis specific treatment (Pearl & Norton, 2017), and thus seem to have similar problems with matching treatment to transdiagnostic mechanisms. A recent review also concludes the transdiagnostic literature is heterogeneous and incoherent, transdiagnostic mechanisms are applied in a loose and unstandardized way, encompassing several different and conflicting conceptualizations, and

as such has been unable to develop and validate an alternative classification system (Fusar-Poli et al., 2019).

### ***The P-Factor Approach to Classification***

Another recent approach to understanding the structure of mental disorders assumes there may exist an underlying process that accounts for meaningful variance across clusters of psychiatric symptoms (Caspi & Moffit, 2018). Indeed, factor analytic research of mental health symptoms has found good model fit for a bi-factor model of mental disorders, in which one overall general factor accounts for most of the variance among patients, while some sub-factors independently account for subsets of symptoms (i.e., internalizing and externalizing symptoms) that do not overlap with the general factor (Caspi et al., 2014). A bifactor model assumes that a global construct exists as a unitary dimension underlying all symptoms, and at the same time coexists with specific factors explaining the residual variance not explained by the general factor (Morin et al., 2016). One example of such a global factor is the “p-factor” (the “p” represents a general psychopathology factor) identified by Caspi et al. (2014). The p-factor seems to represent a general propensity to develop mental disorders as such, while other subfactors, which do not overlap with the p-factor, may reflect different genetic and environmental risk factors influencing how this general vulnerability is expressed through different clusters of symptoms in different patient samples (Caspi et al., 2014; Caspi & Moffit, 2018). Caspi and Moffit (2018) hypothesize that a general cause for mental disorders could be phenomena that permeate most common mental disorders such as a diffuse unpleasant affective state (i.e., neuroticism or negative emotionality), poor impulse control over emotion, deficits in intellectual function, or disordered form and content of thought (Caspi & Moffit, 2018).

It is unlikely that the heterogeneity of depressive symptoms reflects one psychopathological process (Lichtenberg & Belmaker, 2010). A bifactor model of mental

disorders allows for an understanding of depression as caused by some shared general vulnerability such as negative emotionality or disordered thought, and at the same time may account for the large heterogeneity of symptom profiles evident among different subsamples of depressed patients (Fried & Nesse, 2015a; van Loo et al., 2012). Within the p-factor approach, symptoms clustered in different subfactors may represent personality or behavior styles and preferences that steer how an individual's tendency for general psychopathology will be expressed (Caspi et al., 2014). In line with this thinking, a possible general underlying vulnerability for depression may be expressed through different clusters of symptoms, where some psychopathological processes may lead to a chronic course while others do not. The p-factor model thus offers a possible alternative to current conceptualizations of depression, and in addition provides grounds for hypothesizing about the effect of different treatments that have inspired the studies in this thesis.

### ***How Can the P-Factor Provide Grounds for Hypotheses about Treatment Effects?***

Medication, psychotherapy, or a combination of the two are commonly used treatments for chronic depression. They are different treatments that presumably work through different mechanisms of change, but one could still hypothesize that they would work equally well. Within a p-factor approach, one hypothesis could be that different treatments work to reduce an underlying general vulnerability through different pathways (i.e., an unpleasant affective state may be reduced by ADM increasing serotonin levels, but also by identifying problem solving strategies for addressing self-criticism). Another hypothesis could be that different treatments have differential effects if they are matched to the types of symptoms that constitute the subfactors of p. That is, if specific symptom clusters reflect different personality or behavior styles that steer how a general propensity for psychopathology is expressed, treatments that specifically target these symptoms may be more efficient in addressing the underlying vulnerability for that person. For instance, if

an underlying state of negative affectivity is expressed through behavioral patterns that lead to interpersonal problems, one could assume that therapeutic problem-solving strategies that improve interpersonal functioning also leads to an improved state of negative affectivity. Conversely, ADM may also offer improvement in negative affectivity through other pathways, but this improvement may be diminished or cancelled out if the behavioral pattern leading to interpersonal problems persists. On the other hand, if an underlying negative affectivity is expressed through somatic symptoms, ADMs may do a better job in addressing the underlying issue than therapy directed toward improving interpersonal relations. The finding that psychotherapy and ADM on average are equally efficacious but with low remission rates may support this hypothesis, and that targeting specific symptoms with different treatments could be a way to achieve better remission rates (Craighead & Dunlop, 2014). Analyzing specific symptoms could be an initial step towards personalized treatment of depression that recognizes the heterogeneity of the disorder (Fried & Nesse, 2015b), and could assist in developing models that provide decision support based on specific symptom profiles that respond differently to different treatment options (Cohen & DeRubeis, 2018; DeRubeis et al., 2014; Kessler et al., 2017; Simmonds-Buckley et al., 2021). Establishing the differential rates at which treatments act upon meaningful symptom groupings could thus assist therapists in assigning patients differentially to treatments most likely to be effective for their symptom profile (Stewart & Harkness, 2012). Inspired by the reviewed research this thesis explores possible symptom groupings in chronically depressed patients, and whether different treatment conditions may affect these differently.

### **Treatment effects for chronic depression**

Although they represent fundamentally different approaches to the same disorder, both psychotherapy (Munder et al., 2018) and antidepressant medication (Cipriani et al., 2018) are effective treatments for depression, and seem to work equally well (Cuijpers,

Noma, et al., 2020). Psychotherapy or pharmacotherapy alone has demonstrated efficacy for mild to moderate depression (Weitz et al., 2017), and for moderate to severe depression (DeRubeis et al., 2005). Investigations of chronic depression have found both pharmacotherapy and psychotherapy to be effective (Cuijpers et al., 2010; Imel et al., 2008; Komossa et al., 2010; Silva de Lima et al., 2005), and positive effects for pharmacotherapy, psychotherapy and their combination were found in a combined meta-analysis (Cuijpers et al., 2014), as well as a network meta-analysis (Kriston et al., 2014) for chronic depression. In addition, no significant difference has been found in treatment effects or remission rates between psychotherapy and pharmacotherapy (Cuijpers, Noma, et al., 2020; Kappelmann et al., 2020). Combination of psychotherapy and ADM has been found to have significantly larger effects on symptom reduction relative to either monotherapy in treating recurrent and chronic depression (Craighead & Dunlop, 2014; Cuijpers et al., 2011; Cuijpers, Dekker, et al., 2009; Cuijpers et al., 2014; Cuijpers, van Straten, et al., 2009; Forand et al., 2013), and may especially be preferable for moderate to severe depression (Weitz et al., 2017).

When it comes to long term effects, continued ADM after remission is found to reduce risk of relapse (Geddes et al., 2003; Glue et al., 2010; Hansen et al., 2008). On the other hand, several empirically supported psychotherapies demonstrate enduring relapse prevention, comparable to keeping patients on medication after remission (Cuijpers et al., 2013; Hollon, 2016; Hollon et al., 2005). Some evidence suggests patients who have received psychotherapy have lower relapse rates than patients who receive continued pharmacotherapy after remission (Cuijpers et al., 2013), but combination treatment seems to outperform either monotherapy in terms of preventing relapse (Bockting et al., 2018; Forand et al., 2013). Thus, both when it comes to acute phase treatment and prevention of relapse combination treatment outperforms both psychotherapy and ADM, and either monotherapy seems to perform equally well.

Making predictions of who are more likely to benefit from which monotherapy, is currently not possible (Cuijpers, Stringaris, et al., 2020). There is however some evidence to suggest that ADM and psychotherapy may have differential effects on specific symptoms of depression (Boschloo et al., 2019; Dunlop et al., 2018; Fournier et al., 2013; Stewart & Harkness, 2012), and thus work through different mechanisms of change (Fournier et al., 2013).

## **Proposed Mechanisms of Change for Different Treatments**

### ***Proposed Mechanisms of Change for Psychotherapy***

Even if there is substantial evidence that psychotherapy for depression is effective (Munder et al., 2018), little evidence exists on which mechanisms are responsible for change (Kazdin, 2007). Most psychological treatments are developed as therapeutic strategies rooted in universal theoretical assumptions on what causes and maintains mental disorders (Alexander & Shelton, 2014; Sauer-Zavala et al., 2016). In psychology, such theories often provide exhaustive and incommensurable explanations of the same phenomena and attempts to unite them under a unifying meta-theory have failed (Alexander & Shelton, 2014; Hillix & L'Abate, 2012; Melchert, 2016). Thus, theories of *psychotherapy* are often top-down efforts to universally apply a therapeutic approach to all people experiencing psychological distress and stand in contrast to bottom-up efforts in which theoretical models of *psychopathology* are identified and then intervention strategies are crafted to target them (Sauer-Zavala et al., 2016). When adopting a treatment method – to some degree – one also adopts a theory on human psychology. By believing in one theory, one gives support to one perception of reality at the expense of another (Allport, 1961). Consequently, the divide between different theories of psychotherapy have sparked ‘culture wars’ within psychology’s ranks (Norcross et al., 2006), and empirical research does not seem to be able to broker between them. The verdict of the dodo-bird – “Everyone has won,



and everyone will get a price” (Carrol, 1996, p. 12) – is often used to describe the overall finding that research fails to identify differential effects between psychotherapies (Wampold & Imel, 2015). This also seems to be the case for depression. Currently there is strong to modest research support for 14 different psychological treatments for depression (Division 12 of the American Psychological Association, 2021), and different psychotherapies do not seem to differ notably in efficacy (Barth et al., 2013; Cuijpers et al., 2011).

One way to explain the dodo-verdict is that different types of psychotherapy offer common ingredients necessary to alleviate depression. To achieve change, regardless of specific symptoms, patients need a relationship with the therapist in which they feel less alienated, a chance to experience positive emotions, and hope that change is possible. They also need new experiences of learning and mastery that furthers a belief that change can be achieved, along with a safe arena to practice what needs to be changed (Frank & Frank, 1991). Thus, regardless of method and theoretical orientation, psychotherapy will likely be successful if it facilitates 1) an empathic, trusting relationship, 2) trust in and positive expectations that the treatment will be helpful, and 3) specific ingredients that induce the patient to engage in healthy actions (Wampold & Imel, 2015). The relationship and positive expectations are often described as “common factors” that among other things are dependent on general interpersonal skills in the therapist (Wampold & Imel, 2015). While these common factors generally will be the same across treatment models, the specific ingredients (i.e., therapeutic problem-solving strategies) differ according to the theoretical foundation of the treatment model. Furthermore, in this view, the specific ingredients of psychotherapy would not be regarded as something that mechanistically cures specific symptoms. Rather, different psychotherapies could be hypothesized to engage patients in healthy actions through the human capacity for a subjectively experienced “self” to

consciously recognize, understand, and manipulate other aspects of the self (i.e., in order to observe one's own thoughts or feelings humans also possess a sense of an irreducible self that does the observing; Skjervheim, 1976). A common denominator between many different psychotherapies is that they use different theoretically derived concepts to help patients separate dysfunctional thoughts, feelings, and behaviors from healthy ones, and in turn act upon them.

For instance, in this thesis, a form of short-term psychodynamic therapy was used to treat patients with CD. The theoretical framework is based on the work of Malan (1979), where the "triangle of conflict" and the "triangle of person" are central concepts, representing universal principles of psychodynamic psychotherapy (McCullough et al., 2003). The triangle of conflict refers to how mental disorders arise when healthy (activating) expressions of emotion (feelings), such as enjoyment, sadness, sexual desire, or anger, trigger inhibitory feelings (i.e., anxiety), such as shame or fear. Defenses such as rumination, avoidance, and self-criticism, are then developed to avoid internal conflict between feelings and anxiety, and the conflict triangle is created (McCullough et al., 2003). The triangle of person, on the other hand, illustrates how defenses are developed in response to *past persons* giving rise to the inhibitory feeling (i.e., father was critical when you cried as a child), and how this is maintained in relation to *current people* (i.e., does not express emotion with husband), and how these patterns are likely to be played out with the therapist (McCullough et al., 2003). Short term psychodynamic therapy has three broad treatment objectives: 1. Helping the patient identify and prevent defensive responses (defense restructuring), 2. Helping the patient to experience affect without excessive inhibition (affect restructuring), and 3. Helping the patient improve relationships and develop more positive feelings toward the self (self- and other restructuring; McCullough et al., 2003). Helping patients identify their defenses and in turn act upon them (i.e.,

understand why they are self-critical, how it causes problems, and work to reduce it), could be hypothesized to increase the likelihood of engaging the patient in healthy actions regardless of whether the underlying theory of mental disorder is valid or not. This could also be the case for other treatments derived from other theories on how mental disorders are developed and maintained. For instance, in metacognitive therapy (MCT) patients are invited to use “metathoughts” to control and guide other dysfunctional thoughts (Nordahl, 2014). In acceptance and commitment therapy (ACT), a key challenge is addressing “cognitive fusion” and help the patient recognize the difference between experiencing an emotion and assessing its validity (Holden & Lenndin, 2014). In mentalization-based therapy (MBT), patients are invited to address “psychic equivalence” and critically assess whether the world actually operates in accordance with their own feelings (Skårderud & Sommerfeldt, 2014). Thus, although different in theoretical approach, these therapeutic models have in common that they engage the patient in healthy actions by helping them identify and address their own dysfunctional thoughts, feelings, or behaviors. This separates psychotherapy from pharmacotherapy in that it relies on conscious processing of experiences and analysis of the problem at hand. Accordingly, psychotherapy may provide lasting symptom relief through changes in dysfunctional attitudes, negative thoughts, rumination, worry (Lemmens et al., 2016) and affect regulation (Watson et al., 2011). This is further supported by a meta-analysis which found psychotherapy relies on distinctly different neural networks than pharmacotherapy. Psychotherapy was found to mainly target cortical brain networks involved in high-level cognitive processes such as processing self-relevant information and was thus hypothesized to produce a ‘top-down’ effect on symptom improvement (Boccia et al., 2016). Thus, in contrast to pharmacotherapy, psychotherapy may work through processes which changes conscious evaluation of emotional experience which in turn influences automatic patterns of processing (Harmer et al., 2009).

### ***Proposed Mechanisms of Change for ADM***

Almost every compound that has been synthesized for the purpose of inhibiting norepinephrine and serotonin reuptake have proved to be a clinically effective antidepressant, leading to the hypothesis that depression is caused by monoamine-deficiency in the brain (Belmaker & Agam, 2008). ADMs are assumed to treat depression by increasing the levels of the monoamines serotonin and norepinephrine in the synapse, either by blocking the reuptake of the monoamines in the pre-synaptic neuron (TCAs, SSRIs and SNRIs), or inhibiting the enzyme monoamine oxidase which catabolizes norepinephrine and serotonin in the presynaptic neuron (MAOIs, RIMAs; Belmaker & Agam, 2008). In addition, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis in response to stress and increased production of cortisol is one of the most replicable biological findings in depression (Burke et al., 2005; Pariante & Lightman, 2008). Furthermore, increased levels of circulating cortisol are thought to decrease the expression of brain-derived neurotrophic factor (BDNF) which is critical for axonal growth, neuronal survival, and synaptic plasticity, thus causing hippocampal atrophy (Belmaker & Agam, 2008; Duman et al., 2016). ADMs up-regulate BDNF (Belmaker & Agam, 2008; Duman et al., 2016) and is thus hypothesized to have a positive effect on depression by increasing synaptic plasticity including birth of new neurons in adult hippocampus, and regulation of synapse formation (Castrén & Hen, 2013; Duman & Aghajanian, 2012; Krishnan & Nestler, 2010).

The mechanisms by which the neurochemical and neural changes induced by antidepressant drugs are translated into clinically meaningful effects in depression are still broadly unknown (Harmer et al., 2009). Pharmacotherapy seems to affect neural activation in regions that influence how one perceives signals from one's own body (interoception) and processing of psychosomatic sensation (Boccia et al., 2016). Thus, ADMs may work by

remediating negative affective biases not directly accessible to conscious processing, and the effect of processing emotional and social stimuli in a more positive manner leads to gradual changes in social reinforcement, behavior and mood over time (Harmer et al., 2009). ADM is thus thought to provide a ‘bottom-up’ process by affecting automatic processing of stimuli which in turn modulates the conscious appraisal and experiencing of these stimuli (Boccia et al., 2016; Harmer et al., 2009; Rosier et al., 2012).

The placebo effect (i.e., patients responding to medication without acting agents) may indicate that common factors play a central role in pharmacotherapy as well as psychotherapy (Wampold, 2021). For instance, positive expectations for painkilling drugs will affect how much pain is experienced after the drug is administered (Bingel et al., 2011), and impact of expectations on allergic response is enhanced when the doctor or other health professional acts in a warm manner and is perceived to be more competent (Howe et al., 2017). Thus, exhibiting competence and warmth creates positive expectations, which in turn harness the underlying mechanism of the placebo effect and augments the effect of medication (Blasini et al., 2018; Howe et al., 2019). As ADMs seem to influence how signals from one’s own body are experienced (Boccia et al., 2016), therapists providing a warm relationship, creating positive expectations, and assisting in regulating emotions may provide a healing context helping patients interpret and respond to the changes ADM provides in a positive manner and thus augment their effect (Howe et al., 2017; Howe et al., 2019; Wampold, 2021). Hence, it seems common factors play a key role along with the specific ingredients of medication also for pharmacotherapy.

### ***Proposed Mechanisms of Change for Combination Treatment***

Psychotherapy and ADM seem to affect distinctly different neural networks (Boccia et al., 2016). Several differences in prefrontal metabolism between psychological and pharmacological treatments for depression indicate there are different mechanisms through

which these treatments attain their clinical effects (Linden, 2006). Thus, combination treatment may provide a cumulative effect where ADM and psychotherapy provide independent but equal contributions on improvement (Cuijpers et al., 2014), possibly because ADM through a bottom-up effect and psychotherapy through a top-down effect target different primary sites that each contribute to producing changes in critical prefrontal-hippocampal pathways (Craighead & Dunlop, 2014; Goldapple et al., 2004; Petersen, 2006). Consequently, both pharmacotherapy and psychotherapy may ultimately lead to reappraisal of emotional experiences, although the initial locus of action may be different (Harmer et al., 2009). Furthermore, the different pathways through which each monotherapy works may augment each other and provide better results in the cases where symptoms are severe, and monotherapy fails to produce the desired effect. For instance, a distinctive feature of chronic depression is that patients usually exhibit severe interpersonal problems (Jobst et al., 2016), and self-critical cognitions that are persistent and difficult to change (Werner et al., 2019). Treatment failure with ADM may be associated with an adverse interpersonal environment or long standing-negative attitudes, such that bottom-up changes in automatic emotional biases are insufficient to produce satisfactory antidepressant effects (Harmer et al., 2009). Conversely, failure of psychotherapy may arise because the primary unconscious automatic biases are too fixed to allow top-down conscious remodeling of appraisal and evaluation (Harmer et al., 2009). In support of this hypothesis, a recent study found that combination treatment outperformed monotherapies for severe depression while psychotherapy performed equally well as combination treatment for moderate depression (Furukawa et al., 2018). Thus, pharmacotherapy and psychotherapy may have different and complementary contributions to psychological recovery (Boccia et al., 2016), and combination treatment may be a preferred option for severe depression rather than increasing the ‘dose’ of either monotherapy when patients do

not respond (Harmer et al., 2009). This mechanism could apply to overall depression but also for specific symptoms. For instance, research indicates self-critical cognitions may respond both to pharmacotherapy and psychotherapy (Chui et al., 2016). Thus, combination treatment may provide accumulated effects also for specific symptoms of depression.

Inspired by the reviewed research the studies in this thesis explore the hypothesis that patients with a combination of psychotherapy and ADM will have better symptom improvement both on overall depression and specific symptoms than patients who only receive psychotherapy, and that patients with more severe depression have greater benefit than patients with moderate depression.

### ***Possible Negative Effects of ADM***

Emerging evidence suggesting ADM might interfere with the long-lasting effects of psychotherapy (Forand et al., 2013; Hollon, 2016), contrast findings suggesting combination therapy produces better effects than monotherapies for chronic depression. This may be especially true for long-term use of ADM. A review of prescribing guidelines revealed that recommendations for maintenance treatment vary from 1 year to lifelong treatment (Piek et al., 2010), and the overall increasing rates of ADM-use in the 21st century can almost entirely be explained by long-term or chronic use (Eveleigh et al., 2017; Mojtabai & Olfson, 2014). However, long-term use of ADM increases the likelihood of developing tolerance where depressive symptoms return during treatment (Fava, 2014). Moreover, as patients experience more depressive episodes, they may develop resistance signified by a lack of response to previously effective ADM when re-administered for a new episode (Fava, 2014; Kaymaz et al., 2008). Furthermore, discontinuing antidepressants can trigger withdrawal symptoms, which can be mistaken for relapse of depressive symptoms (Fava, 2018). In support of this hypothesis, a long-term follow-up study found that patients receiving mental health treatment without medication had fewer symptoms

after 9 years than patients receiving combination treatment, suggesting possible long-term iatrogenic effects of ADM (Vittengl, 2017).

An explanation for these findings may be related to the monoamine-hypothesis of depression that suggests that depression is caused by monoamine-deficiency and that ADMs redress a neurotransmitter deficit. The problem with this notion is that no such deficit has actually been identified, as measuring serotonin levels in the intact living brain is very difficult (Hollon, 2020). A different approach to understanding the role of monoamines in depression is the hypothesis that levels of monoamines are under homeostatic control. Low levels of monoamines may facilitate complex problem solving by directing energy away from pleasurable pursuits, and toward rumination where one is more resistant to distraction and inclined to dwell on concerns related to distress (Hollon, 2020). A homeostatic mechanism will thus reduce the levels of monoamines in response to a perceived problem (Andrews et al., 2011), leading to an altered state of homeostatic equilibrium where monoamines are reduced as long as the problem persists (Andrews & Thomson Jr., 2009). This suggests the symptoms of depression could be a by-product of a naturally evolved mechanism that reduces levels of monoamines to facilitate rumination in the service of complex problem solving (Hollon, 2020). The state of depression thus signifies that individuals perceive themselves to have a complex problem they are unable to solve (Hollon, 2020). Furthermore, hallmark symptoms of chronic depression such as interpersonal problems (Jobst et al., 2016) and self-criticism (Werner et al., 2019) may be examples of perceived problems that leave the individual in a state of perpetual rumination and decreased mood due to downregulation of monoamines.

In such a state, pharmacological interventions that increase the levels of monoamines challenge the altered homeostatic equilibrium aimed at keeping the organism in a problem-solving state while the problem persists. In response to increased levels of



monoamines the homeostatic mechanisms push back by further increasing downregulation, shutting down serotonin synthesis in the presynaptic neuron, and turning down sensitivity in the postsynaptic neuron (Andrews et al., 2015). This mechanism of downregulating monoamines will continue as long as the original problem is perceived to exist and will cause oppositional tolerance to ADM in the sense that ADM will no longer provide its original benefits (Andrews et al., 2011). Furthermore, when ADM is discontinued the oppositional downregulating mechanisms “overshoot” and increase the likelihood of relapse of depression (Andrews et al., 2011). This process of oppositional tolerance may explain why ADMs in many cases lose efficacy when administered over long periods, why discontinuation increases the risk of relapse, and why long-term treatment with ADM may increase chronicity and sensitize to subsequent episodes (Fava, 2014).

Oppositional tolerance suggests ADMs may reduce symptoms for a while but will also trigger further downregulation of the natural synthesis of monoamines. This leads to a need for larger doses and risk of relapse upon discontinuation. Consequently, interventions that facilitate problem-solving skills might do a better job than ADMs, which primarily serve the function of anesthetizing the distress without addressing the cause for reduced levels of monoamines (Hollon, 2020). Also, the symptom relief offered by medication may stand in the way of engaging in psychotherapeutic work aimed at resolving the problems and may thus interfere with the enduring effect psychotherapy may have (Hollon, 2020).

## Aims

As stated above psychotherapy and ADM seem to be equally efficacious when given alone and combination treatment seems to outperform monotherapies in treating chronic and severe depression. This may indicate ADM and psychotherapy act on different symptoms (e.g., psychotherapy acts on dysfunctional cognitions, while ADM acts on somatic symptoms) providing independent and accumulative effect on improvement. Another explanation may be that combination treatment has superior effects on a symptom level (e.g., combination treatment provides more improvement than monotherapies on both cognitive and somatic symptoms respectively), thus providing a stronger improvement on all symptoms and better overall outcomes.

An overarching aim of this thesis was to explore whether chronically depressed patients experience meaningful sub-groups of symptoms, and whether the different treatment groups had different outcomes on these specific symptoms. If combination treatment provided better outcomes also on specific symptoms this could support a hypothesis that combination treatment adds to improvement on a symptom level rather than each treatment acting on separate symptoms. To address these aims, three studies were conducted.

The first aim of this thesis was to examine the hypothesis that combination treatment outperforms monotherapies in treating chronic depression. Thus, we compared the overall depression outcomes of patients using ADM while in psychotherapy to patients not using or discontinuing medication while in psychotherapy. If in fact different treatments in combination provide accumulated effects, we expected to see better overall outcomes for patients using ADM in addition to psychotherapy. We explored this hypothesis in papers 1 and 3. In paper 1 our sample consisted of patients who were all using ADM at the start of treatment. We examined whether patients quitting ADM while in psychotherapy had worse

outcomes on overall depression compared to patients staying on ADM. We hypothesized that patients using medication and then discontinued would have worse outcomes than patients continuing ADM, since they would lose the accumulated benefits of two different treatments. As previous research indicates patients with severe depression may be more in need of the accumulated effects of psychotherapy and ADM, we also explored whether severely depressed patients had different outcomes from continuing or discontinuing ADM compared to patients with moderate depression. We hypothesized that patients with severe depression would benefit more from keeping ADM than patients with moderate to mild depression. In paper 3 our sample consisted of patients using ADM throughout psychotherapy and patients who did not use any medication prior to or during psychotherapy. We explored whether patients using ADM throughout psychotherapy had better outcomes on overall depression than non-medicated patients. We hypothesized patients using ADM would have better outcomes than non-medicated patients as they benefitted from the accumulated effects of two treatments.

The second aim of the thesis was to explore whether meaningful subgroups of symptoms exist within chronic depression. Thus, we explored the structure of depressive symptoms by way of factor analysis (Paper 2). Chronicity was defined both as persistence and recurrence of depression and patients with persistent depressive disorder (PDD) and recurrent major depressive disorder (rMDD) were included. We based our analysis on previous studies indicating symptoms of depression in adult clinical psychiatric samples are best represented either through one global construct with some symptoms constituting specific sub-dimensions (bifactor model) or a two-factor structure. We also examined whether the factor structure was stable across primary diagnoses (i.e., PDD v. rMDD) and presence of comorbid diagnoses.

The third aim of the thesis was to explore potential differences in treatment outcomes between ADM users and non-medicated patients on specific symptom clusters identified in Paper 2. Thus, we explored whether patients using ADM had different outcomes on the sub-factors “self-criticism” and “somatic symptoms” (Paper 3). In accordance with research indicating specific symptoms of depression may respond to both ADM and psychotherapy, we hypothesized that patients with both treatments would have better outcomes on both sub-factors compared to patients only receiving psychotherapy.

## Methods

### Study Design

One function of evidence is to inform decision makers on appropriate use of therapeutic interventions in routine clinical practice (Rawlins, 2008). Clinical guidelines recommending treatment for depression are typically based on evidence derived from various randomized controlled trials (RCT). However, the practice implications from RCTs are limited by the nature of such trials (Deaton & Cartwright, 2018). For instance, to be included in a typical RCT patients are often required to be in remission or recovery for an extended period before they experience the current episode making them eligible for the trial. Also, there are strict criteria for the use of ADM such as how long they have been taken, the type of ADM used, and dosing. Other trials examining ADM and psychotherapy for depression require that patients be experiencing an acute episode of depression and to not be receiving either ADM or psychotherapy, even though many patients receiving combination treatment in clinical settings are not in an acute phase of depression, are on ADMs when they present for psychotherapy, or have been receiving psychological services for some time before beginning a course of ADMs. In addition, most of what is known about treating depression with a combination of ADM and psychotherapy comes from clinical trials with inclusion/exclusion criteria and procedures that make the context of the clinical trial dissimilar to the situations faced by clinicians in naturalistic settings – settings where inclusion/exclusion of patients are based on different criteria such as public health prioritizing rules. Thus, even though RCTs provide unbiased estimates, they only apply to the sample selected and justification is required to extend the results to other groups, including any population to which the trial sample belongs or to any individual (Deaton & Cartwright, 2018). For clinicians in naturalistic settings RCTs provides grounds for predictions on what kind of treatment might be beneficial for patients, but before

implementing them as treatment advice in practice guidelines one must consider that real life health care service provision takes place in different treatment settings with other criteria for inclusion of patients. Also, to comply with principles for evidence-based practice (APA Presidential Task Force on Evidence-Based Practice, 2006) and ethical considerations, health care needs to be conducted in accordance with individual patient characteristics and preferences. For instance, randomizing patients to stop or keep medication, when this is not in accordance with patients' wishes will not be feasible. Thus, there is a need for naturalistic studies examining outcomes for naturally occurring groups of help-seeking patients in real-life treatment settings. In this thesis we used a quasi-experimental design in a naturalistic treatment setting on a group of patients admitted to Modum Bad hospital in Vikersund, Norway. We compared outcomes of patients on ADM with non-medicated patients. Hence, we did not randomize patients to medication or non-medication but collected information and observed patient change as it occurred from assessment through treatment and up to and including one-year follow-up.

### **Study Sample**

Between 2012 and 2017, an estimated 1800 patients were referred to the treatment program. Modum Bad is a small, highly specialized hospital with nation-wide coverage, intended to offer treatment to patients who have not benefitted from regional public health care options. Because they had not tried local health care options 1200 patients were referred back to their local treatment alternatives. The remaining 600 patients were assessed for eligibility. Patients had persistent depressive disorder (PDD) or recurrent major depressive disorder (rMDD) as primary diagnosis. For rMDD, patients with two or more previous episodes were included. A total of 163 patients were excluded for not meeting criteria for PDD or rMDD or for meeting the hospital's exclusion criteria of 1) psychosis, 2) cluster A and B personality disorder, 3) untreated/un-stabilized bipolar disorder, 4)

ongoing substance abuse and 5) organic brain disorders, leaving 437 patients in the treatment program. This was the baseline sample for all three papers, but different subsamples were used in the different papers.

Figure 1 describes the study sample in paper 1. In this study we focused on patients using ADM at start of treatment and examined differences between those continuing throughout treatment and those who discontinued. Thus, we excluded all patients that did not use ADM during waiting list ( $n = 245$ ). We also excluded from analysis those with comorbid diagnoses that could confound interpretation of outcomes (i.e., stabilized bipolar disorder, PTSD, cluster C personality disorder), and patients taking medication for other purposes than depressive symptoms from the analyses (i.e., hyperkinetic medication, dependency medication, anxiety medication). Thus, 80 more cases were excluded from the sample, leaving a total sample of 112 patients in paper 1, with 35 who discontinued ADM and 77 who kept ADM (Høstmælingen et al., 2021a).

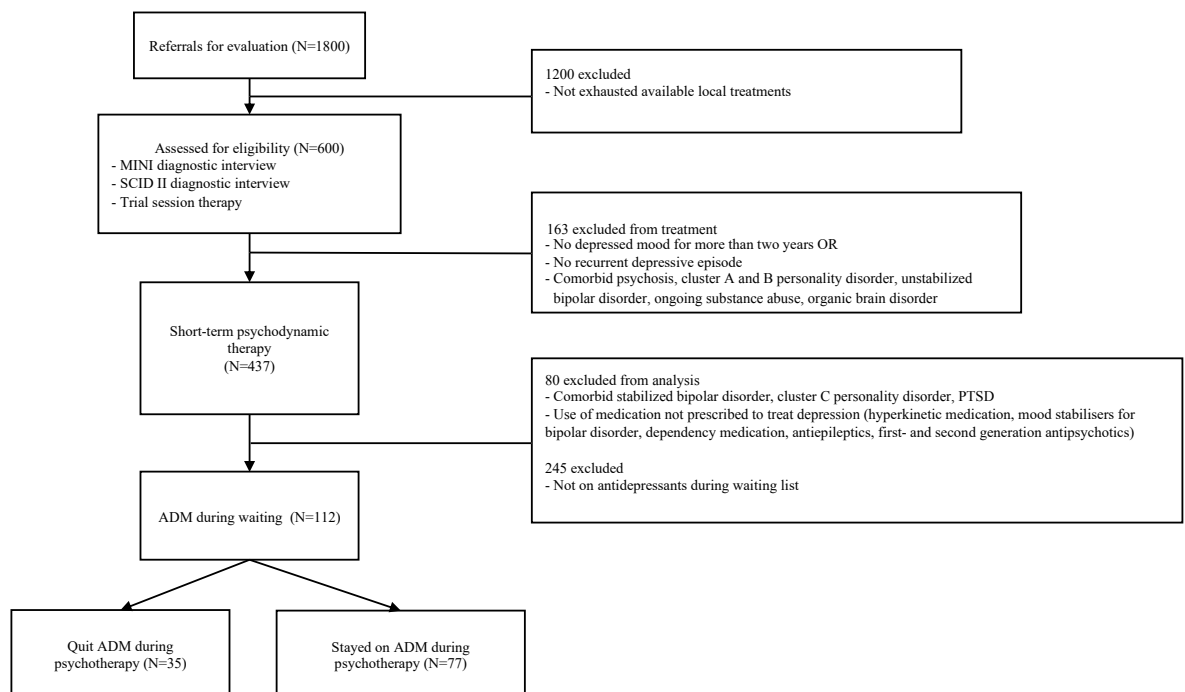


Figure 1: Study sample paper 1

Figure 2 describes the study sample in paper 2. In this paper we conducted a factor analysis of depressive symptoms using Beck Depression Inventory-II (BDI-II; Beck et al., 1996) on the entire sample. Because 60 patients did not complete the BDI-II at start of treatment these were excluded leaving 377 cases in the analysis (Høstmælingen et al., 2021b). (Because we used multilevel modeling for statistical analyses which allows for missing data in papers 1 and 3, these 60 cases could be included in these manuscripts, returning to the original baseline sample of 437 patients.)

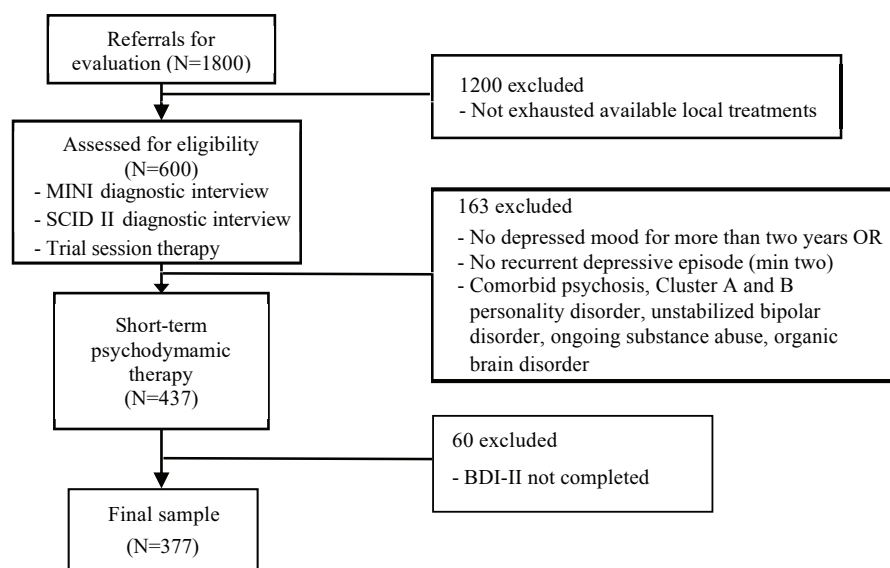


Figure 2: Study sample paper 2

Figure 3 describes the study sample in paper 3. In this paper we explored differences between patients who were using ADM during the whole treatment or not using any medication during treatment. We excluded patients who used medication prescribed for other purposes than treating depression ( $n = 63$ ). Also, patients may discontinue or wish to start pharmacotherapy during treatment for several possible reasons that may confound interpretations of different outcomes between ADM users and non-medicated patients. Thus, patients who either discontinued ( $n = 54$ ) or started ( $n = 13$ ) ADM during treatment were excluded from analysis. These cases were added in supplemental analyses to analyze the robustness of the findings, see supplemental materials in Høstmælingen et al. (2021c).



Also, in this paper there were significant differences between groups on primary outcomes. To ensure that the two groups being compared were as balanced as possible we conducted propensity score matching (PSM), after which some cases were excluded from the ADM group ( $n = 12$ ) and the non-medication group ( $n = 57$ ). This left a final sample of 238 cases with 119 cases in each group (Høstmælingen et al., 2021c)

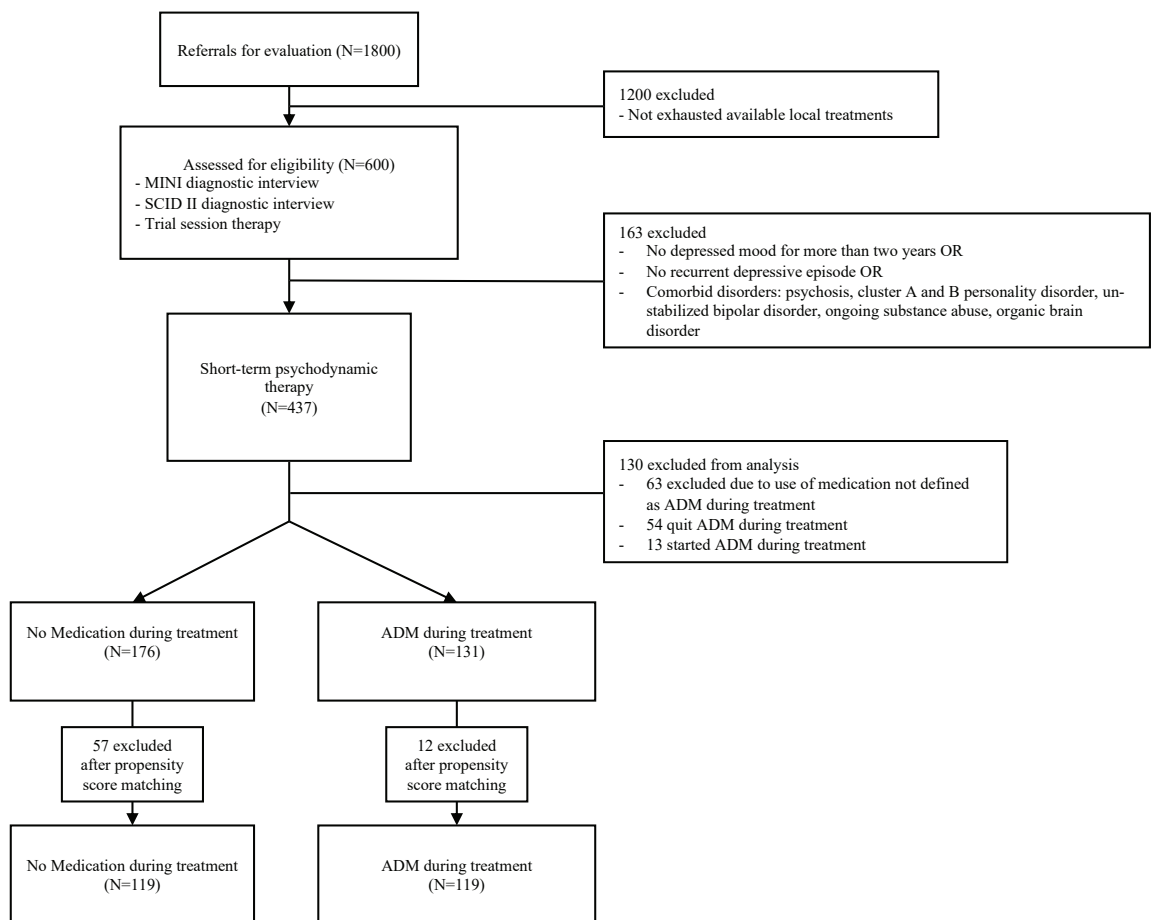


Figure 3: Study sample paper 3

## Procedures

### *Assessment and outcome measures*

Diagnostic assessment was done using the Mini-International Neuropsychiatric Interview (M.I.N.I.; Sheehan et al., 1998) and Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-2; First et al., 1997). Interviews were performed by

specialists in clinical psychology or psychiatry. Demographic information was collected through self-report instruments and assessment interviews. Patients using ADM reported dose, frequency, and additional medication they were taking at assessment, beginning of treatment, termination and at one-year follow-up.

The primary outcome of the study was the patients’ scores on the Beck Depression Inventory-II (BDI-II; Beck et al., 1996). Also, in paper 3 the BDI-II sub-factor scores on ‘self-criticism’ and ‘somatic symptoms’ (identified as sub-factors in paper 2) were used as primary outcome. Secondary outcomes were Symptom Check List-90-R (SCL-90-R; Derogatis, 1994), Inventory of Interpersonal Problems (IIP-64; Horowitz et al., 2000), Alcohol use disorders identification test (AUDIT; Saunders et al., 1993), and Global assessment of symptoms/function (GAF-S/GAF-F; Pedersen et al., 2018). These measures are self-report instruments, except for GAF-S/GAF-F which is a clinician-rated instrument of the patients’ symptoms and function. Patients were assessed on these measures at initial assessment, start of treatment, termination, and at one-year follow-up. Average time between assessment and treatment start was 12 weeks. Figure 4 describes the data collected and timepoints for data collection.

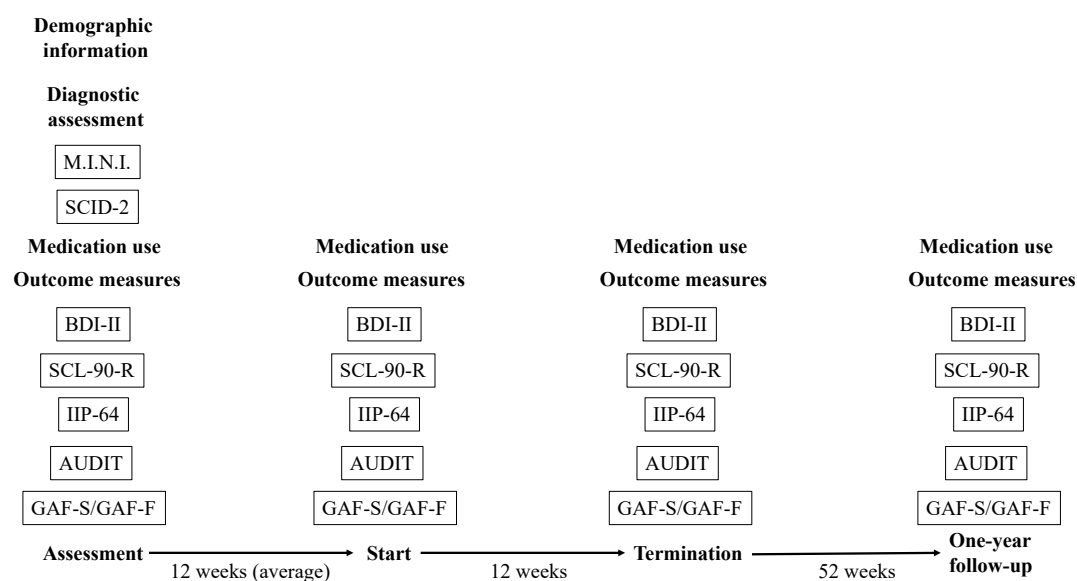


Figure 4: Timeline of data collection

**Beck Depression Inventory-II.** The BDI-II consists of 21-items, with each item scored on a Likert scale from 0-3 (range 0-63). Depression scores are derived by summing the response to each of the items, with scores of 14–19 indicating mild depression, 20–28 moderate depression, and 29–63 severe depression (Beck et al., 1996). BDI-II has demonstrated high reliability, capacity to discriminate between depressed and non-depressed individuals as well as different subtypes of depression, and has demonstrated good to excellent concurrent, content, and structural validity (Beck et al., 1996; Wang & Gorenstein, 2013). Patients completed BDI–II at assessment, start of treatment, at termination, and at one-year follow-up.

**BDI-II sub-factors ‘Self-Criticism’ and ‘Somatic Symptoms’.** The factor analysis of the BDI-II (paper 2) identified a bi-factor model with one general factor and two specific sub-factors labelled ‘self-criticism’ and ‘somatic’. The general factor accounted for 73.4% of the explained variance. ‘Self-criticism’ consisting of four items (‘guilty feelings’, ‘self-dislike’, ‘self-criticism’, and ‘worthlessness’) accounted for 13.1% of the variance. The ‘somatic’ sub-factor (consisting of items ‘changes in sleeping pattern’, ‘changes in appetite’, and ‘tiredness or fatigue’) accounted for 13.5% of the explained variance. Hence, depression could best be explained by one global factor, but that symptoms pertaining to self-critical cognition and somatic symptoms specifically involving sleep problems, appetite, and fatigue, played a special role in the depressive functioning of this sample. In paper 3 we conducted comparisons of outcomes between ADM users and non-medicated patients on these factors. The two factors were separated by summarizing each patient’s score on the items constituting each factor and compared for each measurement time (i.e., assessment, start of treatment, termination, and follow-up).

**Symptom Check List 90-R.** SCL-90-R is a broad measure of symptom distress consisting of 90 items with each item scored on a Likert scale from 0-4. It produces nine

symptom specific subscales, and three global measures of symptom severity (Derogatis, 1994). In the current thesis the global severity index (GSI) was used. It is calculated by dividing total sum score (range 0-360) by number of answered items (Derogatis, 1994). SCL-90-R has demonstrated high internal consistency and concurrent validity in clinical samples (Schmitz et al., 2000), and is well designed for assessing overall mental distress (Siqueland et al., 2016).

**Inventory of Interpersonal problems-64.** IIP-64 is a broad measure assessing a variety of interpersonal problems, consisting of 64 items scored on a Likert scale from 0-4. The IIP-64 yields eight octant sum scores, indicating specific domains of interpersonal functioning and one global score (Horowitz et al., 2000). We used the global score which is calculated by dividing the total sum score (range 0-256) by the number of items. This global score of the IIP-64 has been consistently linked to symptom severity (Tracey et al., 1996), and IIP-64 has demonstrated good convergent validity, test-retest reliability, and internal consistency (Horowitz et al., 2000).

**The Alcohol Use Disorders Identification Test.** AUDIT (Saunders et al., 1993) is a widely used instrument developed by the World Health Organization (WHO) for identifying harmful alcohol consumption (Saunders et al., 1993). The 10-item measure includes questions to assess the amount and frequency of alcohol intake (1-3), alcohol dependence (4-6) and problems related to alcohol consumption (7-10). Items are scored on a Likert scale from 0-4 (range 0-40) and a total score is derived by summing the response to each item. The general accepted cut-off point to identify harmful alcohol intake is 8 (Babor et al., 2001). AUDIT has demonstrated good validity and test-retest reliability (de Meneses-Gaya et al., 2009).

**Global Assessment of Symptoms/Function (GAF-S/GAF-F).** The GAF is a single measure of overall impairment caused by mental factors. It is a clinician rated measure

scored from 1 to 100, where score 1 represents the worst imaginable level of symptom severity and impairment of psychosocial functioning and score 100 represents the most optimal level (Pedersen et al., 2018). It's intended use is to communicate the level of severity and impairment, indicate the need of professional help, and reflect improvement or change over time. It is a generic measure, not related to any specific diagnosis. By reflecting the level of severity, GAF provides important additional information to the categorical diagnostic classifications, and the extensive use of this measure over the years confirms its importance. The reliability of GAF scores has been proven to be acceptable, especially under conditions when raters are experienced and trained (Pedersen et al., 2007; Startup et al., 2002; Vatnaland et al., 2007). As to the validity of GAF, several studies have found significant associations between GAF scores and the presence of axis-II pathology, self-reported symptom distress, interpersonal problems, as well as social functioning (Hilsenroth et al., 2000; Karterud et al., 2003; Pedersen & Karterud, 2012).

### ***Psychotherapy***

A distinctive feature of CD is that patients usually exhibit severe interpersonal problems that may originate from disturbed attachment, invalidating parenting, and interpersonal trauma during childhood (Jobst et al., 2016), and psychotherapies that specifically address interpersonal problems have shown to be efficacious for chronic depression such as cognitive-behavioral analysis system of psychotherapy (CBASP), and interpersonal psychotherapy (IPT; Jobst et al., 2016). Also, some psychodynamic treatments, such as experiential dynamic therapy (EDT; Osimo & Stein, 2012), has a strong interpersonal focus (Lilliengren et al., 2016), and there are clear indications that psychodynamic psychotherapy is effective in alleviating CD (Town et al., 2020; Town et al., 2017). Psychotherapy in the present thesis was provided during an intensive 12-week inpatient treatment program and carried out in accordance with treatment manuals

combining principles of experiential dynamic therapy (EDT), with cognitive and behavioral techniques (Stålsett et al., 2012). EDT is a form of short-term psychodynamic psychotherapy, emphasizing experiential learning, i.e., how to experience and express warded off affects (Osimo & Stein, 2012). The main treatment principles underlying EDT can be summarized using the *triangle of conflict* and the *triangle of person* (Malan, 1979; McCullough et al., 2003). The triangle of conflict illustrates how defenses and anxieties block the experience of true feelings, and the triangle of person refers to how these patterns began with past persons, are maintained with current persons, and may be enacted with the therapist. Thus, EDT therapists strive to a) help patients become aware and let go of maladaptive defenses that generate and perpetuate symptoms; b) track anxiety and regulate it when it is too high; and c) help patients access, process, and integrate previously avoided affects (Lilliengren et al., 2016). Patients were treated by teams of therapists. Each team consisted of a minimum of one psychiatrist, one psychologist specialist, one psychologist, one psychiatric nurse and one nurse. The psychiatrist and psychologist specialist were responsible for assessment, treatment planning and evaluation. While being treated by a team of therapists each patient was the primary responsibility of a two-person team (one psychiatrist, psychologist specialist or psychologist and one psychiatric nurse or nurse). This included following up and adjusting treatment plans, individual therapy, and day-to-day follow-up of the patients' progression. To obtain treatment integrity of the psychotherapy therapists were supervised by trained clinical psychologist specialists, conducting adherence checks throughout the treatment. Pending patient consent, therapy sessions were videotaped.

### ***Inpatient Treatment***

The present thesis was conducted on data collected from inpatient treatment. Compared to single episode depression, patients with chronic forms of depression are also

highly prevalent in inpatient settings (Ley et al., 2011), and need longer durations of inpatient treatment (Köhler et al., 2015). However, few studies on chronic depression are conducted on inpatient samples (Bronswijk et al., 2018). For example, a comprehensive review on the psychometric properties of BDI-II, showed only 3 of 118 studies (2,5%) were on adult inpatient samples (Wang & Gorenstein, 2013). Depressed patients receiving inpatient treatment are more impaired than outpatients in terms of depressive symptomatology, suicidal ideation, physical quality of life, comorbid somatic diagnoses and social and occupational functioning as well as using more antidepressant medication (Zeeck et al., 2015). Thus, depressed inpatient populations may have symptom structures that differentiate them from outpatient populations, and the effect of different treatments may differ between inpatient and outpatient populations.

The inpatient treatment was conducted in closed cohorts of eight. In a typical week the patients received an average of two individual sessions (á 45 minutes), two group therapy sessions (á 75 minutes), one psychoeducational session (á 90 minutes), one art and expression therapy session (á 75 minutes), two physical exercise sessions (á 90 minutes) and one group session discussing means and goals of therapy (90 minutes).

### ***ADM Classification and Medication Management***

While there are many specific ADMs available, a wide range of medications not classified as ADM are also being prescribed for anti-depressive purposes. Lithium has been considered as an effective treatment for depression that has not responded to antidepressants and can also be an effective prophylactic treatment for carefully selected patients with unipolar depression (Abou-Saleh et al., 2017). Second generation antipsychotics (e.g., aripiprazole, olanzapine, quetiapine) have also shown beneficial effects in treating depression and dysthymia (Komossa et al., 2010). Studies have also indicated antiepileptics/anticonvulsants such as lamotrigine, valproate and carbamazepine have

beneficial effects in the treatment of depression (Vigo & Baldessarini, 2009). Thus, in the present thesis we defined ADM broadly and included – in addition to medication formally classified as antidepressants – antipsychotics, antiepileptics and lithium when these medications were prescribed for anti-depressant purposes.

Patients' use of ADM was recorded by medical doctors or psychiatrists. Information on dose, frequency and additional medication was collected at assessment, beginning of treatment, termination and at one-year follow-up. Patients using ADM when entering the program were on treatment regimens prescribed by general practitioners or local secondary mental health care units that had referred the patients. Thus, medication use was part of ongoing treatment efforts initiated outside the clinic. Medication was not an integrated part of the treatment program, but patients were offered help to assess their medication use upon entering treatment by medical doctors or psychiatrists. As part of the general treatment policy of the hospital patients were not actively encouraged to change ongoing medication. If wishing to discontinue pharmacotherapy, they were assisted by a medical doctor to form an individual plan for discontinuation. If patients decided to discontinue ADM, this was initiated at the start of therapy, so the discontinuation could be closely monitored, and for the patient to be stabilized without medication before termination of therapy. Conversely, if patients wanted to start medication during treatment, they were assisted by a medical doctor to initiate pharmacotherapy. Hence, patients changing medication status (i.e., quitting or starting) during treatment initiated this themselves and were assisted by staff to do this, while patients who did not change status were either completely without medication throughout treatment or maintained the ongoing regimen they were on when entering the treatment program.



## **Statistical Analysis**

In the present thesis we utilized several statistical methods. In papers 1 and 3 we used multi-level modeling (MLM; Raudenbush & Bryk, 2002; Hox et al., 2018) to assess the differences in patient outcomes between ADM and no-ADM groups since repeated measurements (level 1) were nested within patients (level 2). Also, due to the naturalistic design we utilized logistic regression analysis (paper 1) and chi-square/t-tests (paper 3) to assess potential baseline differences at start of treatment on key demographic factors. For variables where baseline differences were present these were added as covariates in analysis (paper 1). In the case of significant baseline differences between groups on main outcomes (i.e., BDI-II), propensity score matching was used (paper 3). In paper 2 we used exploratory structural equation modeling (ESEM; Asparouhov & Muthén, 2009) to explore the factor structure of BDI-II, and we conducted tests of invariance (Liu et al., 2017; Meredith, 1993; Meredith & Teresi, 2006) to ascertain the stability of the factor structure across primary diagnoses (i.e., PDD vs. rMDD) and comorbidity (i.e., comorbid diagnosis present vs. not present).

### ***Improving Validity in a Naturalistic Design***

As patients were not randomized to ADM or non-medication in papers 1 and 3, there was a risk of baseline differences on demographic and clinical variables that could confound the results and interpretation of outcomes. If initial testing of group differences revealed significant baseline differences between the ADM group and the non-medicated group on primary outcomes (BDI-II, somatic factor, self-criticism factor), efforts were made to ensure the validity of the results. In paper 1 logistic regression analyses showed there were significant differences between the groups on total ADM-dose and duration of illness, but there were no differences on primary outcome (BDI-II). Thus, we opted to conduct analyses on the original sample but added ADM-dose and duration of illness as

covariates in the analyses. This was done to control for the effect of ADM-dose and duration of illness on depression outcomes. In paper 3 there were significant differences between groups on primary outcomes. To ensure that the two groups being compared were as balanced as possible, we thus opted to conduct propensity score matching (PSM) and conduct further analyses on the matched sample. In PSM a propensity score for each case is estimated to express the likelihood of being in a group given observed covariates such as demographic or clinical characteristic (Thoemmes, 2012). The score is used to match participants from one group (i.e., ADM) to participants in the other (i.e., non-medicated) who have a similar propensity score, thus balancing the groups on possible confounding variables and reducing bias in estimation of group differences during treatment (Thoemmes, 2012). (See Høstmælingen et al. (2021c) for a detailed description of the propensity score matching procedure.)

### ***Papers 1 & 3 – Multi-Level Modeling***

In papers 1 and 3, as repeated measurements on the BDI-II (and the somatic and self-criticism factors in paper 3) were nested within patients, we tested differences in symptom development over time between groups using multilevel modeling (MLM; Raudenbush & Bryk, 2002; Hox et al., 2018).

**Baseline MLM-Model.** For repeated measures, before analyzing group differences, one needs to start with a baseline model that models the measurement occasions in an appropriate manner (Hox et al., 2018). For the model building we started with baseline model and added one parameter at a time testing improvement in model fit for each step. Model fit was estimated and compared using the -2log likelihood test (Fitzmaurice et al., 2004). Thus, for papers 1 and 3 we built a baseline model using the primary outcome (BDI-II in paper 1; BDI-II, ‘self-criticism’ factor, ‘somatic’ factor in paper 3) as separate variables. First, we fitted an intercept only model to serve as a benchmark (Model 0):

$$Y_{ij} = \gamma_{00} + u_{0j} + e_{ij}$$

Model 0: Intercept only model.

Then we included a random effect for the intercept (Model 1):

$$Y_{ij} = \gamma_{00} + \gamma_{10} \text{time}_{ij} + u_{0j} + e_{ij}$$

Model 1: Fixed slope for time, random effect for intercept.

Next, we extended the random intercept model to also include a random slope component (Model 2):

$$Y_{ij} = \gamma_{00} + \gamma_{10} \text{time}_{ij} + u_{0j} + u_{1j} \text{time}_{ij} + e_{ij}$$

$$e_{ij} \sim N(0, \sigma^2)$$

Model 2: Random slope, random intercept.

Model 2 assumes homoscedastic variance (i.e., that a single variance can appropriately represent the variances at all four time points). To test whether a homoscedastic assumption was valid we fitted a model allowing for residual variance at each time point (i.e., heteroscedastic variance, Model 3):

$$Y_{ij} = \gamma_{00} + \gamma_{10} \text{time}_{ij} + u_{0j} + u_{1j} \text{time}_{ij} + e_{ij}$$

$$e_{ij} \sim N(0, \sigma_i^2)$$

Model 3: Random slope, random intercept with heteroscedastic variance.

Lastly, we added a fixed slope for time including linear, curvilinear, and piecewise development over time. The best model fit was arrived at with a linear piecewise timeline model with three timelines to isolate the symptom slopes during waiting list, treatment, and follow-up, using fixed and random effects of intercept and time (Model 4):

$$Y_{ij} = \gamma_{00} + \gamma_{10} \text{waitlist}_{ij} + \gamma_{20} \text{treatment}_{ij} + \gamma_{30} \text{followup}_{ij} + u_{0j} + u_{1j} \text{waitlist}_{ij} + u_{2j} \text{treatment}_{ij} + u_{3j} \text{followup}_{ij} + e_{ij}$$

Model 4: Piecewise linear model.

We also tested different covariance structures and an unstructured model (UN) provided best model fit. As Model 4 provided best model fit for both samples in papers 1 and 3, it was used as baseline model in both papers, to which subsequent predictors and interactions were added.

In Model 4, time was coded as weeks. The first timeline was number of weeks on waiting list. The second timeline was time in active treatment (12 weeks), and the third timeline was time in follow-up (52 weeks). To give the intercept a meaningful value at the start of treatment, time on waiting list was coded negative. Thus, the first timeline for a patient being 12 weeks on waiting list was coded -12 as first-time value and 0 as the value when therapy started, the second timeline was coded 0 at the start of therapy, and 11 at the end of therapy. The third timeline was coded 0 at the end of therapy and 51 at the end of follow up.

For estimation of regression coefficients and variance components in multilevel modeling full maximum likelihood (FML) and restricted maximum likelihood (RML) are robust, produces efficient and consistent estimates, and are robust against mild violations of assumptions (Hox et al., 2018). Although RML is considered to produce less biased estimates, the differences between the two methods are usually small, and FML has the advantage that it allows for comparison between models that differ in regression coefficients as well the variance components, whereas RML only allows for comparisons between the variance components (Hox et al., 2018). In accordance with Bauer and Curran (2012) models with different fixed effects were estimated using FML and models with different random effects were estimated using RML.

**Primary MLM-analysis, paper 1.** In paper 1 all the patients were using ADM at start of treatment, and we analyzed differences between patients continuing vs. discontinuing ADM during treatment. We estimated models by successively adding variables and interactions in accordance with our research questions (Singer & Willet, 2003). As there were significant baseline differences between the groups on total ADM-dose and duration of illness these were added as covariates to the baseline model. In the second model we added ADM group (continuation v. discontinuation) along with two-way interactions between ADM group and timelines (i.e., waiting list, treatment, and follow-up). This was done to investigate whether ADM continuation/discontinuation had an impact on outcome during waiting list, treatment and follow up. In the third model we added initial depression severity along with two-way interactions between severity and the three timelines. This was done to investigate whether depression severity had an impact on outcome during waiting list, treatment, and follow-up. In the third model we also added interaction between ADM group and depression severity to assess whether continuation or discontinuation of ADM during treatment was related to initial depression severity. In the fourth model we added three-way interactions between each of the three timelines and ADM group and depression severity. This was done to assess whether severely depressed patients had different outcomes from continuing or discontinuing ADM compared to patients with mild/moderate depression. (See also Høstmælingen et al. (2021a).)

**Primary MLM-analysis, paper 3.** In paper 3 we compared patients using ADM throughout treatment with patients not using any medication. To test whether patients using or not using ADM had different symptom development over time a dummy coded predictor variable (ADM = 1, no medication = 0) was added to the baseline model. We ran the model separately for BDI-II total scores, and the somatic and self-criticism factors. Also, as the somatic, and self-criticism factors are derived from a measure of one underlying construct

(i.e., depression), we tested the joint effect of the two factors simultaneously allowing for separate examination of the symptom slopes in both factors (i.e., multivariate model). While a univariate model provides separate estimates for a dependent variable, a multivariate model can carry out a single test of the joint effect of an explanatory variable on several dependent variables (Snijders & Bosker, 2012). Multivariate models are particularly suited for examining multiple measurements of one underlying construct (Hox et al., 2018). A model that allows for the simultaneous estimation of growth in both variables offers the opportunity to examine how they covary across different timepoints (Curran et al., 2012). Also, with multivariate analysis the power to detect group differences increases when the outcomes correlate with each other (Schmitz et al., 1998), and are combined in a multivariate model (Tabachnick & Fidell, 2013). Thus, we ran a multivariate multilevel model for the somatic and self-criticism factors with ADM as predictor. (See also Høstmælingen et al. (2021c).)

## ***Paper 2 – Exploratory Structural Equation Modeling (ESEM)***

In paper 2 we explored the factor structure of BDI-II among chronically depressed patients. Studies exploring BDI-II are regularly conducted using variations of exploratory (EFA) and confirmatory (CFA) factor analyses (Huang & Chen, 2015; Wang & Gorenstein, 2013). However, EFA and CFA have methodological limitations (Asparouhov & Muthén, 2009; Marsh et al., 2014). Cross-loadings are traditionally constrained to be zero in CFA but are freely estimated in EFA, so CFA structures are more restrictive than EFA structures. Because of this, in many instances item-level CFAs fail to provide clear support for instruments that have been well established in EFA research (Marsh et al., 2014). Also, the independent cluster model inherent in CFA (ICM-CFA) in which items are required to load on one, and only one, factor, with non-target loadings constrained to zero – could be too restrictive for many multidimensional constructs (Morin et al., 2016). Even when the model

fits well, factor correlations are likely to be inflated unless all non-target loadings are close to zero (Morin et al., 2016). Exploratory structural equation modeling (ESEM; Asparouhov & Muthén, 2009) allows for integration of EFA within a structural equation modeling (SEM) framework. As in EFA, ESEM allows for items to load freely on all factors but at the same time allowing for methodological advances typically reserved for CFA and SEM, such as goodness of fit statistics and comparison of competing models (Marsh et al., 2014; Morin et al., 2013). ESEM has shown to provide better fit to data and less differentiated factors than CFA (Morin et al., 2013), and performs better in terms of construct validity of the interpretation of the factor structure (Marsh et al., 2009).

However, one problem with first-order factor solutions is that they fail to represent multidimensionality that occurs when indicators are associated with more than one construct (Morin et al., 2016). This is often the case for items in scales measuring psychological constructs (Morin et al., 2016). For example, in an intelligence test some items might be expected to be associated with a sub-domain (e.g., verbal intelligence) as well as to a hierarchically superior construct (e.g., global intelligence). This raises the question whether some depression symptoms, such as affective symptoms, are part of a global construct while other symptoms constitute specific sub-factors in different subsamples of depressed patients. A bifactor model directly tests whether a global construct (a “g-factor”) exists as a unitary dimension underlying the response to all items and coexists with specific factors explaining the residual variance not explained by the g-factor (Morin et al., 2016). Recent research suggests the structure of psychopathology could be explained by a bi-factor model where a general propensity to experience psychopathology (p-factor) underlies all diagnoses, while clusters of symptoms may explain sub-factors that emerge in different situations or different stages through life (Caspi et al., 2014; Caspi & Moffit, 2018). Also, for depression specifically, some studies have reported that bifactor

solutions of the of BDI-II provide better fit compared to previously identified two-factor solutions in psychiatric outpatients (Brouwer et al., 2013), depressed outpatients (Quilty et al., 2010), and psychiatric inpatients (Subica et al., 2014). Also, re-analyses of data from previous studies finding support for two-factor solutions, have found improved model fit when testing a bifactor model (i.e., with one higher-order general factor and two lower order factors; Ward, 2006). Findings supporting bifactor models for BDI-II, corroborate the theory that BDI-II assesses generalized distress along with more specific features of depression (Subica et al., 2014). We conducted two exploratory analyses comparing a two-factor structure to a bifactor structure with one higher order general factor and two lower order factors. To conduct the analyses, we used exploratory structural equation modeling (ESEM; Asparouhov & Muthén, 2009; Marsh et al., 2014). Thus, we contrasted a first order ESEM model with two factors with a bifactor ESEM specifying one general factor and two sub-factors. All analyses were conducted in Mplus 8 with maximum likelihood estimator (ML; Muthén & Muthén, 1998-2017). (See Høstmælingen et al. (2021b) for a detailed description of the factor analysis procedure.)



## Results

### Demographic and Clinical Characteristics

The total sample ( $N = 437$ ) consisted of nearly 70% women and had a mean age of approximately 50 years ( $SD = 10.89$ ). The patients were characterized by severe depression with a mean BDI-II score of 29.42 ( $SD = 9.423$ ), two decades since first onset of symptoms and ten years since first treatment attempt. Thus, the sample exhibited a pattern of severe symptoms with a long history of persistence and/or recurrence and a long history of previous treatment attempts. About half of the sample was in a relationship, nearly 70 % had higher education, and nearly half were in some form of employment or studies. Table 1 presents the clinical and demographic characteristics of the total sample at time of assessment. (See papers 1, 2, and 3 for demographic and clinical characteristics of the subsamples used.)

### Medication Use

There were several medications present in the sample. At start of treatment 55% were on some form of medication. 54.8% were on one or more medication used for antidepressant purposes: 34% were on medication classified as antidepressants, 2.5% were on lithium, 8.7% were on antipsychotics, and 9.6% were on anticonvulsants/antiepileptics. In addition, several patients were using anxiolytics/hypnotics (10.7%), hyperkinetic medication (1.6%), substance dependency medication (1.0%), antihistamines (4.1%), pain medication (5.3%), or medication not otherwise specified (4.3%). To avoid confounding of possible effects of these medications when comparing users and non-users of ADM, patients who were on these medications but not any form of medication used for antidepressant purposes were excluded from analysis in papers 1 and 3. Table 2 describes the use of medication in the total sample.

**Table 1***Demographic and clinical characteristics*

	<i>N</i> = 437
Age	47.5 (10.89)
Years since first episode	23.5 (13.63)
Years since first treatment attempt	12.2 (9.77)
Sex (Women)	299 (68.4%)
Having one or more children	306 (70.0%)
Relationship status	
Single	109 (24.9%)
Married, cohabiting or in a romantic relationship	241 (55.1%)
Divorced or widowed	87 (19.9%)
Education	
No known education	10 (2.3%)
Primary or secondary	28 (6.4%)
High school	101 (23.2%)
Bachelor	282 (64.5%)
Master or higher	16 (3.7%)
Employment status	
Full time work	62 (14.2%)
Part time work	130 (29.7%)
No work	234 (53.6%)
Student	10 (2.3%)
Unknown	1 (0.2%)
BDI-II score	29.42 (9.423)
Primary diagnosis	
Recurrent major depressive disorder	263 (60.2%)
Persistent depressive disorder	174 (39.8%)
Second comorbid diagnosis	212 (48.5%)

*Note:* Data are from time of assessment. Data are mean (SD), or n (%). BDI=Beck depression inventory-II.

**Table 2***Medication at start of treatment*

	<i>N</i> = 437
No medication	194 (44,4%)
Any medication present	243 (55,6%)
Antidepressants (ADM)	150 (34,3%)
SSRI	81 (18,6%)
SNRI	30 (6,9%)
TeCA	15 (3,4%)
NDRI	14 (3,2%)
TCA	4 (0,9%)
SMS	3 (0,7%)
MAOI	1 (0,2%)
RIMA	1 (0,2%)
Melatonin-/serotonin antagonist	1 (0,2%)
No. of patients on two or more ADMs	28 (6,4%)
Anxiolytics/hypnotics*	47 (10,7%)
Buspirone	1 (0,2%)
Hydroxyzine	3 (0,7%)
Melatonin	7 (1,6%)
Nitrazepam	1 (0,2%)
Oxazepam	7 (1,6%)
Zolpidem	6 (1,4%)
Zopiclone	22 (5,0%)
Hyperkinetic medication*	7 (1,6%)
Atomoxetine	1 (0,2%)
Methylphenidate	6 (1,4%)
Mood stabilizers - Lithionit	11 (2,5%)
Antiepileptics	42 (9,6%)
Gabapentin	1 (0,2%)

Clonazepam	2 (0,5%)
Lamotrigine	35 (8,0%)
Pregabalin	1 (0,2%)
Valproate	3 (0,7%)
Substance dependency medication*	4 (1,0%)
Disulfiram	2 (0,5%)
Naltrexone	2 (0,5%)
Antipsychotics	38 (8,7%)
Aripiprazole	2 (0,5%)
Flupentixol	1 (0,2%)
Chlorprothixene	2 (0,5%)
Quetiapine	28 (6,4%)
Levomepromazine	3 (0,7%)
Olanzapine	1 (0,2%)
Prochlorperazone	1 (0,2%)
Antihistamines* - Alimemazine	18 (4,1%)
Pain medication*	23 (5,3%)
Diclofenac	3 (0,7%)
Etoricoxib	1 (0,2%)
Ibuprofen	2 (0,5%)
Naproxen	1 (0,2%)
Naproxen-esomeprazole	3 (0,7%)
Paracetamol	10 (2,3%)
Paracetamol-codeine	1 (0,2%)
Tramadol	2 (0,5%)
Unknown medication*	19 (4,3%)

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Note: Total number exceeds 100% as patients may be using more than one type of medication. SSRI= selective serotonin reuptake inhibitor, SNRI= serotonin-norepinephrine reuptake inhibitor, TeCA= tetracyclic antidepressant, NDRI= norepinephrine-dopamine reuptake inhibitor, TCA= tricyclic antidepressant, SMS= serotonin modulator and stimulator, MAOI= monoamine oxidase inhibitor, RIMA= reversible inhibitor monoamine oxidase A. \* Patients not using medication for antidepressant purposes but still using these were excluded from analyses.

## **Results Paper 1**

As research indicates combination of psychotherapy and antidepressant medication (ADM) have cumulative effects in treating chronic depression, we explored symptom change for patients with chronic depression treated with ADM when presenting for psychotherapeutic inpatient treatment. We compared outcomes through treatment and follow-up of patients who continued medication with those who discontinued. We also examined whether severely depressed patients had different outcomes from continuing or discontinuing ADM compared to patients with mild/moderate depression. We hypothesized that patients who continued ADM and thus received two different treatments (i.e., medication and psychotherapy) would have better outcomes, and that patients with more severe depression would benefit more from keeping ADM than patients with moderate depression. Of 112 patients, 35 patients discontinued ADM during treatment while 77 continued. Both continuers and discontinuers had a significant treatment effect that was maintained at one-year follow up. There was no difference in outcome between continuers and discontinuers of ADM. Patients with severe depression had significantly more symptom improvement than patients with moderate depression, but depression severity did not affect outcomes across continuers and discontinuers of ADM differently. The results could indicate that patients had developed resistance and/or tolerance to the prophylactic effects of medication and that ADM did not contribute to the reduction of depressive symptoms. The findings may also indicate that psychotherapy alone in some instances can be a viable alternative to continued combined treatment, and that psychotherapy may provide a secure context that helps patients prevent relapse when discontinuing ADM.

## **Results Paper 2**

The purpose of paper 2 was to explore the factor structure of Beck Depression Inventory-II in patients with chronic depression presenting for inpatient treatment. We

explored whether a two-factor solution or a bifactor solution provided best model fit for a sample of 377 patients, and the best fitting model was assessed for stability with invariance tests across primary diagnosis and presence of comorbidity. We found that a bi-factor model with one general factor and two specific factors provided best model fit. Invariance analyses provided support for measurement invariance and stability of the factor solution. The factor structure in our sample was best explained by a general depression factor, one specific factor pertaining to self-criticism, and one consisting of the somatic items fatigue, disturbance of sleep, and appetite.

### **Results Paper 3**

In paper 3 we explored outcomes between users of ADM vs non-medicated patients while undergoing intensive inpatient psychotherapeutic treatment on the subfactors identified in the factor analysis in Paper 2 (i.e., self-criticism and somatic symptoms), and on overall depression outcomes. After adjusting for baseline differences with propensity score matching, we analyzed whether the two groups had different outcomes on overall BDI-II scores, “self-criticism”, and “somatic symptoms” using multilevel modeling. The results showed chronically depressed patients not using ADM while in psychotherapy reduced self-critical thought content more than patients using ADM, while there was no difference between groups on the somatic factor or overall BDI-II scores. A reason for this could be that the effects of ADM make patients less accessible to psychotherapeutic interventions addressing dysfunctional rumination or emotional processing thus making application of new problem-solving strategies harder.

## Discussion

Depression is the most common mental disorder worldwide (Liu et al., 2020), and is ranked as the third cause of burden of disease worldwide (WHO, 2008). Detection, diagnosis, and management of depression causes challenges because of its various presentations, unpredictable course and prognosis, and variable response to treatment (Malhi & Mann, 2018). Chronic depression is one of the most challenging types to treat and is responsible for a considerable part of the disease burden of depression (Cuijpers et al., 2017). Still, the nature of the disorder and its underlying mechanisms are not well understood (Cuijpers, Stringaris, et al., 2020), and only a small number of trials have examined the effects of treatments of chronic depression (Cuijpers et al., 2017).

The aim of this thesis was to examine the hypothesis that combination treatment outperforms monotherapies in treating chronic depression. To explore this, we 1) compared outcomes of patients using ADM while in psychotherapy to patients only receiving psychotherapy on overall depression outcomes, 2) explored whether there were meaningful sub-groups of depressive symptoms within chronic depression, and 3) examined whether the different treatment groups had different outcomes on the subfactors identified. We found there was no difference in overall outcome between continuers and discontinuers of ADM, or between non-medicated patients and patients using ADM throughout psychotherapy. As to the question of possible sub-groups of depressive symptoms the results indicated a bi-factor model provided the best fit, where the structure of depression symptoms corresponded to one global depression factor and two sub-factors. One sub-factor consisted of self-critical cognitions, and the other consisted of somatic items related to sleep, appetite, and fatigue. As to the question of possible differences in outcome on specific symptoms the results showed chronically depressed patients not using medication while in psychotherapy reduced self-criticism more than patients using ADM, while there

was no difference between groups on the somatic factor. These findings are further discussed below.

### **Treatment Outcomes for Overall Depression**

A key issue in depression research is to understand why different treatments such as ADM and psychotherapy seem to be equally efficacious in treating depression (Cuijpers, Noma, et al., 2020) and why combination treatment seems to outperform either monotherapy (Craighead & Dunlop, 2014; Cuijpers et al., 2011; Cuijpers, Dekker, et al., 2009; Cuijpers et al., 2014; Cuijpers, van Straten, et al., 2009; Forand et al., 2013). The main hypothesis for the antidepressant effect of ADM suggests that depression is caused by monoamine-deficiency and that ADMs thus redress a neurotransmitter deficit (Hollon, 2020). Through a “bottom-up” effect, ADM is thought to provide clinical effect by influencing automatic processing of stimuli which in turn modulates the conscious appraisal and experiencing of these stimuli (Boccia et al., 2016; Harmer et al., 2009; Rosier et al., 2012). Conversely, psychotherapy may work through a “top-down” effect where changes in conscious evaluation of emotional experiences in turn influences automatic patterns of processing (Boccia et al., 2016; Harmer et al., 2009; Rosier et al., 2012). In many cases, especially for chronic or severe depression, monotherapies may provide inferior results compared to combination treatment (Furukawa et al., 2018). For instance, altering biases in automatic processing through ADM may not be sufficient for patients struggling with serious interpersonal problems or long standing negative attitudes. Conversely, conscious remodeling of emotional experiences through psychotherapy may be insufficient if automatic processing is too fixed. Thus, in cases of severe or chronic depression the cumulative effects of both treatments working simultaneously through both pathways may be required to achieve satisfactory effect (Harmer et al., 2009). If beneficial effects of both



treatments are present, one would expect superior outcomes compared to those who only receive psychotherapy for patients with chronic depression.

This hypothesis was explored in the current thesis by comparing patients using ADM while undergoing a 12-week inpatient psychotherapy program with patients not using ADM, thus examining potential differences between patients receiving the presumed benefits of two efficacious treatments compared to only one. Also, patients starting out on ADM but discontinuing during treatment were compared to patients keeping ADM throughout treatment to examine the potential impact of losing a presumably efficacious treatment compared to continuing with two treatments. In both cases we hypothesized patients on ADM would benefit from the addition of medication and have better outcomes than patients who were not medicated or discontinued.

The results indicated the 12-week therapy program had an overall significant treatment effect that was maintained at one-year follow-up, and the reduction of depression symptoms on the BDI-II constituted a meaningful clinical change according to criteria described by Button et al. (2015). Contrary to our hypothesis, there was no difference between ADM users and non-medicated patients, indicating that ADM did not provide added effect to treatment. In addition, there was no difference between ADM users who continued or discontinued their antidepressant medication, indicating that removing a presumably efficacious treatment did not produce worsening of symptoms compared to those who stayed on medication. These results contrast findings suggesting combination treatment is better than psychotherapy for chronically depressed patients. One explanation for this finding is that ADM did not produce beneficial effects for the patients. Support for this explanation may be found in the hypothesis that levels of monoamines are under homeostatic control and will change in response to perceived stressors or problems (Andrews et al., 2011). According to this idea depressed mood can be explained as a

byproduct when monoamine levels are reduced to enable complex problem solving (e.g., rumination, reduced desire for hedonistic pursuits). Thus, depression is caused by the brain's response to a perceived problem, and the low levels of monoamines (and resulting depressed mood) will persist as long as the perceived problem is present (Andrews & Thomson Jr., 2009). This new state of homeostatic equilibrium may explain why ADM will cease to produce beneficial effects when used long term. As the homeostatic mechanism works to keep the levels of monoamines low to enable problem solving it will push back in response to ADM increasing the levels, shutting down monoamine synthesis in the presynaptic neuron and turning down sensitivity in the postsynaptic neuron (Andrews et al., 2015). This process of oppositional tolerance may explain why ADMs in many cases lose efficacy when administered over longer periods and may account for the fact that we did not find any added benefit of ADM in the current sample. This is in line with findings indicating that 30–50% of long-term ADM users will not benefit from continuing their ADM treatment (Maund, Dewar-Haggart, et al., 2019). Furthermore, even though ADM is not perceived as helpful many patients are reluctant to discontinue (Eveleigh et al., 2017), possibly for fear of worsening symptoms (Cartwright et al., 2016). The lack of supportive guidance during discontinuation also seems to be a barrier for many patients to attempt discontinuation (Bosman et al., 2016). Thus, an explanation for the lack of better outcomes for patients on ADM compared to non-medicated patients could be that these patients because of oppositional tolerance were using medication that was no longer beneficial when starting psychotherapy.

If patients on ADM were indeed experiencing oppositional tolerance which caused ADM to be ineffective, one would also expect to see a worsening of symptoms when discontinuing medication (Andrews et al., 2011; Andrews et al., 2015), typically within 3 days of stopping medication (Fava, 2014). This is because the mechanism that

downregulates monoamines in response to the increase caused by ADM will “overshoot” when ADMs are removed and increase the likelihood of relapse (Andrews et al., 2011). More than half of antidepressant users experience withdrawal symptoms after discontinuation, and many experience them for more than two weeks and up to several months (Davies & Read, 2019). The finding that patients discontinuing ADM did not have worse outcomes compared to patients keeping ADM, could indicate that the process of psychotherapy provided patients with supportive environment and problem-solving strategies to address and handle symptoms resulting from discontinuing. As a homeostatic mechanism will reduce the levels of monoamines to facilitate problem solving (i.e., reduced activity, increased rumination, decreased pleasure seeking; Andrews et al., 2011; Hollon, 2020), it is possible that the psychotherapeutic process provided patients with problem solving strategies that were successful in addressing the perceived problem and thus providing the grounds for re-establishing a normal homeostatic equilibrium. For instance, if the process of psychotherapy enables the individual to work effectively with issues of self-criticism or relational difficulties, the need to be put in a problem-solving state could be reduced. This idea is in line with recent research indicating that psychotherapy can help patients discontinue antidepressants without increasing the risk of relapse/recurrence and that psychotherapy can be a viable alternative to continued combined treatment (Karyotaki et al., 2016; Maund, Stuart, et al., 2019). This is further supported by our finding that severely depressed patients had significantly better outcomes from psychotherapy than moderately depressed patients with no difference between ADM-groups. One explanation for this could be that the psychotherapy provided was particularly suited to address the specific needs of this patient group. Driessen et al. (2010) argued that psychotherapy works better for patients with severe depression than for patients with less severe depression, when the psychotherapy provides ingredients that target the patients’ specific symptoms.

On the other hand, for patients with low levels of depression it may be sufficient with non-specific treatments that offer more generalized coping strategies (Driessen et al., 2010). Thus, the psychotherapy may have provided ways of targeting the specific issues that the patients in the study struggled with. Although not directly tested in this study, these findings may support research indicating psychodynamic treatments are suited to address chronic depression (Town et al., 2020; Town et al., 2017). A common goal for short-term psychodynamic treatments is to contribute to changing the patients' dysfunctional overarching schemas and relational patterns (Nielsen & Binder, 2014). Within the short-term dynamic psychotherapy method (i.e., EDT) used in the current study symptoms of depression are assumed to be a byproduct of an individual's attempt to regulate strong emotions, typically associated with adverse experiences in key attachment relationships during childhood (Lilliengren et al., 2016). In later relationships, these maladaptive responses (e.g., self-criticism) contributes to relational difficulties, which in turn contributes to maintaining symptoms in "cyclical dysfunctional patterns" (Nielsen & Binder, 2014). The combined focus in EDT to become aware of and let go of maladaptive defenses and working to analyze how these are maintained in current relationships (Lilliengren et al., 2016) may thus be particularly suited to address key features found in patients with chronic depression, such as self-criticism (Werner et al., 2019) and interpersonal problems (Jobst et al., 2016).

There could also be another possible explanation for the lack of difference between ADM and non-medicated patients. If patients on ADM experienced positive effects from the medication, they could be balanced out by negative side effects. Commonly reported negative side effects of ADM include sexual problems, weight gain, emotional numbness, reduction in positive feelings, and adverse effects on interpersonal relations, work or study and social life (Cartwright et al., 2016; Read et al., 2017, 2019; Read & Williams, 2018).

Thus, if patients experienced prophylactic effects from ADM use, this could have been counterbalanced by negative side effects that resemble the symptoms that make up the diagnosis of depression (Fried & Nesse, 2015b). This is supported by the finding that ADM users who discontinued medication did not experience a worsening of symptoms. Thus, discontinuing ADM may have caused loss of beneficial effects of the drug that was balanced out by also losing the negative side effects of the same drug. In sum, this could have resulted in similar outcomes for patients continuing and discontinuing ADM.

In sum, the results indicate that patients with chronic depression using ADM may experience oppositional tolerance and not benefit from continued use. Also, EDT may be an effective treatment for chronic depression, and may also provide a secure context that help patients prevent relapse when discontinuing ADM. This further suggests that psychotherapy in some cases may be a viable alternative to combination treatment.

### **Structure of Chronic Depression**

Although treatment results for overall depression seem to be similar for ADM and psychotherapy, there is an increasing amount of research suggesting depression may be better understood as a collection of different sub-types or symptom clusters and that various treatments have different effects on these subtypes. Hence, it is important to examine whether the structure of depressive symptoms differ in different populations and explore possible differential effects of various treatments on specific symptom groups. Depression has been consistently described as consisting of affective (e.g., sadness), somatic (e.g., fatigue) and cognitive (e.g., self-criticism) symptoms, but factor analytic research investigating the structure of depression rarely identifies three distinct factors (see Høstmælingen et al., 2021b). In the current thesis, the structure of chronic depression was explored by means of factor analysis of BDI-II. We found a bi-factor model provided best fit where BDI-II items corresponded to one global depression factor and two sub-factors

where one consisted of self-critical cognitions, and one consisted of somatic items related to sleep, appetite, and fatigue. Also, all the items typically labelled “affective” loaded on the general factor but did not form a separate factor independent from the general factor. This bi-factor model for chronic depression structurally resembles the p-factor model for psychopathology identified by Caspi et al. (2014). They found a bi-factor model of psychopathology where general psychopathology (i.e., p-factor) constitutes a factor that directly influences all symptoms while specific expressions of psychopathology were represented by sub-factors influencing a smaller subset of symptoms (i.e., externalizing and internalizing symptoms; Caspi et al., 2014). For example, alcohol symptoms loaded both on the general p-factor and the externalizing factor, indicating alcohol use can be attributed to one overall vulnerability as well as a tendency to express this vulnerability through an externalizing behavior style (Caspi et al., 2014). In addition, Caspi et al. (2014) found that thought disorder symptoms unlike externalizing and internalizing symptoms could not form a separate sub-factor independent of p. Rather, thought disorder symptoms loaded very highly on and was thus subsumed in p, suggesting these symptoms are key indicators of a general vulnerability to develop mental disorders (Caspi et al., 2014).

In our study, we found symptoms typically labeled as affective were subsumed in the general factor. Thus, applying the same line of thinking as Caspi et al. (2014), this could be indicative of one general depression factor that directly influences all depression symptoms, where affective symptoms constitute cardinal symptoms. Furthermore, the sub-factors may represent specific processes of chronic depression which influence the symptom clusters of self-criticism and somatic symptoms. The finding of a general factor wherein affective symptoms play a key role is consistent with findings indicating a general state of negative emotionality may constitute a key risk factor for developing mental disorders (Schaefer et al., 2017). For instance, strong negative emotions in childhood seem

to be a key factor differentiating people who are likely to experience multiple mental disorders from people that experience enduring mental health without mental disorders (Schaefer et al., 2017). Thus, among the phenomena Caspi and Moffit (2018) hypothesize as potential causes for a general p-factor (i.e., negative emotionality, poor impulse control, deficits in intellectual function, or disordered thought), our findings indicate negative emotionality may be a key underlying vulnerability for chronic depression specifically and possibly also for mental disorders.

The finding that one subfactor in chronic depression influences self-criticism aligns with previous findings that self-criticism may play a particularly important role in chronic depression. In an early study, Dent and Teasdale (1988) found self-criticism contributed significantly to chronicity of depression. Additionally, self-criticism has been linked to severity of depression (Luyten et al., 2007), and higher rates of depressive relapse (Hawley et al., 2014; Mongrain & Leather, 2006). Finally, less self-criticism and/or greater reduction during inpatient or hospital day treatment predicted rapid and sustained improvement after one year for depressed patients (Zeeck et al., 2020). Harsh forms of self-criticism are persistent and difficult to change and may thus represent an important treatment target for psychotherapeutic treatment of chronic depression (Werner et al., 2019). Furthermore, the finding that one sub-factor influences the symptoms of changes in sleep pattern, changes in appetite, and tiredness/fatigue is consistent with factor analytic research on BDI-II indicating these items most consistently load on a somatic factor (Manian et al., 2013). One study found that sleep symptoms may play a central role in a “true” symptom cluster in depression (Chekroud et al., 2017), indicating sleep may affect both appetite and fatigue forming a set of somatic symptoms that should be specifically addressed in treatment.

In sum, these findings indicate chronic depression could be understood as caused by an underlying vulnerability of negative emotionality that influence all depressive

symptoms, while at the same time specific independent sub-factors cause expressions of self-criticism and somatic symptoms which could be regarded as relevant treatment targets for this patient group.

### **Treatment Outcomes for Specific Symptoms**

The results of the present thesis indicated that for overall depression the psychotherapeutic treatment provided clinically meaningful results. Also, this effect did not seem to differ between patients using or not using ADM, possibly because oppositional tolerance balanced out beneficial effects of ADM. After establishing that self-criticism and somatic symptoms (sleep, appetite, fatigue) seemed to constitute key symptoms in chronic depression for the patients in the study, we explored whether different treatment conditions (i.e., ADM in combination with psychotherapy vs. psychotherapy alone) were associated with different treatment outcomes for these symptoms.

Several studies comparing psychotherapy to ADM on specific symptoms indicate that both treatments produce changes in both cognitive and somatic symptoms (Dunlop et al., 2018; Stewart & Harkness, 2012). One explanation for this may be that the treatments provide both direct and indirect effects. For instance, somatic symptoms may be directly influenced by ADM, as they are thought to influence processing of psychosomatic sensation (Boccia et al., 2016), and thus change automatic affective attention biases (Harmer et al., 2009). In addition to the direct effects on symptoms of ADM, Boschloo et al. (2019) found that some symptoms improved only when other symptoms also improved. Thus, the improvement of cognitive symptoms in response to ADM may be an indirect effect, and for symptoms such as self-criticism to respond to ADM other symptoms may need to improve first. For instance, if ADM contributes to improve sleep disturbance, the improved quality of sleep may also facilitate improvement in cognitive symptoms (Fried & Nesse, 2015b). Conversely, psychotherapy may directly affect cognitive symptoms such as



dysfunctional attitudes, rumination, and worry (Lemmens et al., 2016), as it is thought to facilitate changes in conscious evaluation of emotional experience (Harmer et al., 2009). Furthermore, such changes may also indirectly contribute to increased affective control which in turn influences automatic patterns of processing (Harmer et al., 2009). Thus, it is likely that depressive symptoms are inter-dependent when it comes to an individual's treatment response (Stewart & Harkness, 2012). This could also explain how specific symptoms may respond differently to different treatment options (Cohen & DeRubeis, 2018; DeRubeis et al., 2014; Kessler et al., 2017; Simmonds-Buckley et al., 2021), while at the same time different treatments over time ultimately lead to similar results (Boschloo et al., 2019; Dunlop et al., 2018; Stewart & Harkness, 2012). Consequently, different treatments may end up producing similar overall outcomes but through different pathways. One hypothesis following this logic could be that ADM directly affects somatic symptoms but also indirectly facilitate changes in negative cognitive schemas, whereas psychotherapy directly influences cognitive schemas and indirectly contribute to changing somatic symptoms (Fournier et al., 2013).

We hypothesized that patients using ADM in addition to psychotherapy would have better outcomes on both somatic symptoms and self-criticism as somatic symptoms could benefit from direct effects of ADM and indirect effect of psychotherapy, and self-criticism could benefit from direct effects of psychotherapy and indirect effects of ADM. In comparison, patients with only psychotherapy would only have the direct effects of psychotherapy on cognitive symptoms and the indirect effects of psychotherapy on somatic symptoms. Contrary to our hypothesis, though, on the somatic factor ADM-users did not have better results than non-medicated patients. This is in line with our findings on overall depression indicating oppositional tolerance may have counteracted the beneficial effects of ADM, and that patients entered psychotherapy using ADM that did not provide added

beneficial effects. Thus, rather than having a direct positive effect on somatic symptoms ADM seemed not to provide an effect at all.

On the self-criticism factor, non-medicated patients had better outcomes than patients on ADM. This was also contrary to our hypothesis and indicated patients using ADM in addition to psychotherapy were at a disadvantage with regards to improving self-criticism compared to patients only receiving psychotherapy. There may be several reasons for this. Even when ADMs are experienced not to be helpful, many patients believe that they cannot cope with their depression without them and have had relapse of symptoms when attempting to discontinue (Maund, Dewar-Haggart, et al., 2019). A re-emergence of symptoms upon discontinuation may be a result of oppositional tolerance (Andrews et al., 2011; Andrews et al., 2015), but from a patient's perspective it may seem as though they are dependent on ADM to prevent relapse. If patients regard themselves as dependent on ADM it may also cause them to trust less in their own capacity to cope with their distress by means of the strategies offered to them by psychotherapy. Hence, the use of ADM in addition to psychotherapy may have had the negative effect of worsening self-critical schemas.

Furthermore, some negative side effects of ADM such as emotional blunting (Goodwin et al., 2017) could make it harder for patients to evoke and engage in emotions that need to be addressed in psychotherapy. Depression may be understood as an evolved mechanism which facilitates complex problem solving by increasing rumination and decreasing mood and activity (Hollon, 2020). For self-criticism this includes the tendency to set high and unrealistic standards and to adopt a punitive outlook of oneself (Blatt et al., 1982). Thus, the gap between unrealistic expectations and capacities along with harsh self-punishment when failing to bridge it may present an unsolvable problem, keeping the person in a perpetual problem-solving state. The use of ADM in such a state will serve the

function of anesthetizing the pain, while the use of psychotherapy may offer strategies to solve the problems inducing depression in the first place (Hollon, 2020). However, the process of psychotherapy is hard and challenging work, and the anesthetizing effect of ADM could also lead to decreased motivation to engage in changing self-critical schemas (i.e., a person may be just as self-critical, but without it hurting so much when on ADM). Thus, the end goal of finding strategies that allow for less self-criticism (e.g., lowering expectations and/or becoming more self-compassionate towards oneself), could be hindered by the use of ADM reducing the motivation to engage in such processes. Instead of having a positive indirect effect on self-criticism ADM could thus have had a negative indirect effect.

In sum, self-criticism may be a key factor in chronic depression and our findings indicated that patients on ADM had worse outcomes on self-criticism than non-medicated patients. The effects of ADM, especially for long term users where the risk of oppositional tolerance increases, could interfere with psychotherapeutic interventions that target self-criticism through top-down processing of their own emotions and cognitions, and thus make application of new problem-solving strategies harder.

### **Strengths and limitations**

This thesis had some notable strengths, addressing a question of clinical importance, using comprehensive diagnostic assessment (using the M.I.N.I), multiple measurement points (assessment, start, discharge, and follow-up) and a naturalistic setting where we observed a sample of naturally occurring groups as they proceeded through therapy. Other strengths include the use of up-to-date statistical approaches and a large sample size. In spite of this there were also notable limitations.

The sample consisted of patients with rMDD and PDD as primary diagnosis. Patients with comorbid psychosis, cluster A and B personality disorder, untreated/un-

stabilized bipolar disorder, ongoing substance abuse and organic brain disorders were excluded due to the hospital admission criteria to the treatment program. As comorbidity is the norm rather than the exception (e.g., Gadermann et al., 2012), patients in the general population with chronic depression may also have other comorbid diagnoses than those included in this study. Thus, there is a risk that findings for this sample cannot be generalized to other samples with chronic depression. Also, we did not conduct specific analyses for patients with comorbid diagnoses, such as personality disorders. There may be differences between these groups that are not accounted for in the present study.

Furthermore, we did not conduct separate analysis for patients with PDD vs. rMDD as primary diagnoses. Although several studies have found several shared risk factors shared between PDD and rMDD, there may also be differences between them not accounted for in the present analyses. In cases where rMDD was primary diagnosis, patients on their second episode were excluded, thus including patients with two or more prior episodes. However, evidence suggests that any past episode is associated with an increased risk of recurrence (Monroe et al., 2019). Also, there may be differences between patients with recent past episodes and those that had some episodes in earlier life followed by a long period free from depression. Thus, the inclusion criteria may have introduced biases in the sample that do not fully capture the nuances of chronicity. Also, we only included patients with chronic depression. Hence, we were unable to assess whether our results were specific to chronically depressed compared to patients with non-chronic depression.

Another limitation is that the psychotherapy offered was part of a program also offering group therapy sessions, psychoeducation, art and expression sessions and physical exercise sessions. Although there was a significant clinical effect of the program, and the results were in line with research indicating psychodynamic therapy may be an effective treatment for chronic depression, the specific effect of the psychotherapy sessions were not

isolated. Thus, there may have been specific contributions from other elements than psychotherapy that contributed to improvement. There may also have been interaction effects between these other elements and ADM groups that consequently are not accounted for.

In this study BDI-II was used as a measure of depression. A possible limitation is that this outcome measure is too narrow to fully capture the complexity of symptoms in the patient sample. Using more comprehensive symptom measures would perhaps reveal a different symptom structure or other subfactors. Also, self-report measures of symptoms have limited use when it comes to describing the mechanisms that are involved in improvement and/or worsening of symptoms. For instance, there are likely aspects in the phenomenology of depression that could shed light on potential differences between users and non-users of ADM that the BDI-II does not capture.

A further limitation is we did not have information about the patients' earlier experiences with duration and number of earlier treatments. It could have been especially useful to have information about earlier use of medication, and qualitative data about patients experiences with using ADM and motivation to keep on using or discontinuing. Although we tested whether differences between the groups were systematically related to a variety of demographic and clinical variables, there could be other factors related to ADM use than those available to us and accounted for in the analyses.

Also, there are caveats with naturalistic studies. As patients were not randomized to treatment conditions there is uncertainty regarding possible systematic differences between the patients on demographic and clinical factors. Without an RCT design, we cannot claim that other factors that may influence outcome are randomly distributed in the two groups, and the grounds for making causal inferences about treatment and improvement in depression are thus limited. Hence, it might well be that patients not using or discontinuing

ADM possessed some kind of psychological or psycho-social resource that we did not account for and that the groups because of this were not entirely comparable. Conversely, the generalizability of RCTs to real-world patient populations can be problematic (Rawlins, 2008). In routine clinical practice, RCTs provide grounds for choosing between forms of treatment – giving some level of certainty that a treatment backed by RCTs has merit as they have been shown to be beneficial for people under controlled conditions. However, the challenge remains for clinicians to judge whether or not a treatment supported in RCT studies might be beneficial for the individuals and subgroups in their clinic. Although our study design prevents us from forming generalizable statements based on our results, they show that the assumption derived from many RCTs and meta-studies that combination treatment has an advantage over monotherapy, is not necessarily met in this particular sample. This underscores the need for further research on the conditions under which patients might benefit from either monotherapy or combination treatment.

In paper 2 we used logistic regression to assess baseline differences. There are weaknesses to this approach. To run a logistic regression with all factors with a limited sample size reduces the chance of finding differences between the groups. However, when assessing baseline differences with chi-square- and t-tests, we replicated the findings (i.e., there were differences between groups on total ADM dose and duration of illness). Thus, it seems the covariates entered in the model based on logistic regression analysis were correct.

### **Conclusions and implications**

The results of this thesis indicated patients with chronic depression using ADM may experience oppositional tolerance and not benefit from continued use. Also, short-term psychodynamic therapy such as EDT may be an effective treatment for chronic depression and could be a viable alternative to combination treatment for patients who run the risk of

tolerance after prolonged ADM use. In addition, such therapy may provide a secure context that help patients prevent relapse when discontinuing ADM. The results suggest clinicians should carefully assess the effects of ongoing ADM use for chronically depressed patients presenting for treatment and be prepared to provide them with an opportunity to discontinue if the desired effects of medication are not present.

The results also indicated chronic depression may be understood as characterized by an underlying vulnerability of negative emotionality that influence all depressive symptoms, while at the same time specific independent sub-factors cause expressions of self-criticism and somatic symptoms. The findings thus add to the literature suggesting there may exist meaningful subgroups of symptoms within depression that could serve as relevant treatment targets for different treatments. In chronic depression somatic symptoms and self-criticism may be prominent maintaining factors that should be specifically targeted in treatment.

Furthermore, our findings indicated that patients using ADM during psychotherapy had worse outcomes on self-criticism than non-medicated patients. This suggests long term ADM use could have negative effects that interfere with psychotherapeutic interventions that target self-criticism through top-down processing of emotions and cognitions, and thus make application of new problem-solving strategies harder. The findings add to the growing amount of research indicating ADM could have negative side effects that interfere with the healing process psychotherapy may provide. This challenges the assertion that combination treatment is better than monotherapy for patients with chronic depression and suggests that many patients with a long history of ADM-use need help discontinuing and should be offered psychotherapy instead.

It is important to further the understanding of the complex phenomenon of depression. However, the thesis also had weaknesses that may limit the generalizability of

the findings, and more research is needed to corroborate the findings. Further efforts should be made to establish whether meaningful sub-groups of symptoms exist that are particularly prevalent for patients with chronic depression. In addition, further research efforts should explore under which conditions and for which specific symptoms different treatment options are most effective.



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## Appendix – Papers

### Paper 1

Høstmælingen, A., Ulvenes, P., Nissen-Lie, H. A., Eielsen, M., & Wampold, B. E. (2021). Comparing outcomes in chronic depression following inpatient psychotherapy for patients continuing versus discontinuing antidepressant medication. *Clinical Psychology and Psychotherapy*, 28(5), 1111–1127. <https://doi.org/https://doi.org/10.1002/cpp.2561>

### Paper 2

Høstmælingen, A., Ulvenes, P., Nissen-Lie, H. A., Eielsen, M., & Wampold, B. E. (2021). Do self-criticism and somatic symptoms play a key role in chronic depression? Exploring the factor structure of Beck depression inventory-II in a sample of chronically depressed inpatients. *J Affect Disord*, 283, 317–324.  
<https://doi.org/https://doi.org/10.1016/j.jad.2021.01.066>

### Paper 3

Høstmælingen, A., Ulvenes, P., Nissen-Lie, H. A., Eielsen, M., & Wampold, B. E. (2021). Trajectories of Change in Chronic Depression: Differences in Self-Criticism and Somatic Symptoms Between Users of Antidepressants and Nonmedicated Patients. *Journal of Counseling Psychology*, Advance online publication. <https://doi.org/10.1037/cou0000572>







## RESEARCH ARTICLE

WILEY

# Comparing outcomes in chronic depression following inpatient psychotherapy for patients continuing versus discontinuing antidepressant medication

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## Abstract

Research indicates that combination of psychotherapy and antidepressant medication (ADM) provides cumulative effects and thus outperforms monotherapy in treating chronic depression. In this quasi-experimental study, we explored symptom change for patients with chronic depression treated with ADM when presenting for a 12-week psychotherapeutic inpatient treatment programme. We compared outcomes through treatment and follow-up of patients who continued medication with those who discontinued. We also tested possible moderator effects of initial depression severity on change between the groups. Based on prior research, we hypothesized that combination treatment would yield better results (i.e., more reduction in depression). Patients ( $N = 112$ ) were referred from general practitioners or local secondary health care. Outcome was measured by Beck Depression Inventory-II (BDI-II), and comparisons were carried out using multilevel modelling. Although 35 patients discontinued ADM during treatment, 77 continued. Both continuers and discontinuers had a significant treatment effect that was maintained at 1-year follow-up. There was no difference in outcome between continuers and discontinuers of ADM. Patients with severe depression had significantly more symptom improvement than patients with moderate depression, but depression severity did not affect outcomes across continuers and discontinuers of ADM differently. The results could indicate that patients had developed resistance and/or tolerance to the prophylactic effects of medication and that ADM did not contribute to the reduction of depressive symptoms. The findings may also indicate that psychotherapy alone in some instances can be a viable alternative to continued combined treatment. Clinicians should carefully assess benefits of patients' ongoing use of antidepressant medication when entering psychotherapy.

## KEYWORDS

antidepressants, chronic depression, inpatients, psychotherapy

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## 1 | INTRODUCTION

Chronic depression (CD) is ranked among the top 20 leading causes of years lost to disability (Vos et al., 2013), and is associated with severe impairment of daily functioning (Arnow & Constantino, 2003). However, it is not defined as a separate diagnosis in current diagnostic guidelines, and debate remains on how chronicity should be conceptualized.

The Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) differentiates between 'persistent depressive disorder' (PDD) and 'recurrent major depressive disorder' (rMDD; American Psychiatric Association, 2013). PDD is a consolidation of the DSM-IV-defined chronic major depressive disorder (MDD) and dysthymic disorder (American Psychiatric Association, 2013), but there is also significant overlap between PDD and rMDD on diagnostic validation criteria such as co-morbidity, clinical course trajectories and treatment response (Rhebergen & Graham, 2014). The key features distinguishing PDD from rMDD are duration of symptoms and symptom-free periods. In order for patients to be diagnosed with PDD, they must experience persistence of depressive symptoms for at least 2 years (where full criteria for MDD may or may not be met) but with possible intervals of remission for up to 2 months followed by relapse. A diagnosis of rMDD would be appropriate if patients have experienced phases of remission between symptoms extending beyond 2 months (American Psychiatric Association, 2013). According to criteria set forth by Frank et al. (1991) which have become standard in the literature (Burgum & Iacono, 2007), recurrence of symptoms during 'remission' is assumed to constitute 'relapse' of the same episode, whereas a return of symptoms after remission would constitute a new episode (i.e., 'recurrence'). Remission is operationalized as a period of at least 2 months where the patient only experiences minimal symptoms (i.e., no symptoms or only one or two symptoms to a mild degree; American Psychiatric Association, 2013). Hence, for patients struggling with depressive symptoms on and off for more than 2 years, the question of whether they should be diagnosed with PDD or rMDD becomes essentially a question of duration of symptom free periods. If symptoms re-emerge *before* 2 months have passed, one assumes relapse of the same episode and PDD would be proper. If symptoms re-emerge *after* 2 months have passed, one assumes recurrence of a new episode and rMDD would be proper.

However, the idea of differentiating between relapse and recurrence based on duration criteria lacks empirical support (de Zwart, Jeronimus, & de Jonge, 2019). Also, it is difficult to confirm whether patients' past symptoms constitute relapse or recurrence as they often have trouble recalling the precise nature, severity and timing of their symptoms (Harris et al., 2020). Third, similar risk factors predict both persistence and recurrence of depressive episodes (Hoertel et al., 2017; ten Have et al., 2018). Thus, it could be argued that a valid categorization of chronic versus nonchronic depression should be between patients experiencing just one or few episodes of MDD and patients that experience either repeated recurrence or persistence of depression. Thus, many studies on chronicity of depression include recurrent MDD as well as PDD but vary on whether two or

### Key practitioner messages

- Psychotherapy and antidepressant medication are thought to have cumulative effects and are therefore expected to yield better results than monotherapy in treating chronic depression.
- Our results indicated that patients discontinuing their medication did not have inferior outcomes in treatment compared to those patients who continued using ADM.
- A lack of added effect of ADM to psychotherapy could indicate tolerance and/or resistance against the prophylactic effects of medication.
- Psychotherapy alone could in some instances be an alternative to continued combined treatment.
- Our results suggest the need to carefully assess whether ongoing use of antidepressant medication is still beneficial for patients when entering psychotherapy.

more (DeRubeis et al., 2020; Hollon et al., 2014; Ma & Teasdale, 2004), three or more (Barnhofer et al., 2009), or five or more (Bockting et al., 2005; Humer et al., 2020) episodes constitute a pattern of chronicity. In sum, these findings indicate that PDD and rMDD should be investigated together in studies exploring chronic forms of depression, as is the case in the present study.

A distinctive feature of CD is that patients usually exhibit severe interpersonal problems that may originate from disturbed attachment, invalidating parenting and interpersonal trauma during childhood (Jobst et al., 2016). Hence, cognitive-behavioural analysis system of psychotherapy (CBASP) and interpersonal psychotherapy (IPT) which specifically address interpersonal problems are recommended as first- and second-line treatment for CD (Jobst et al., 2016). Also, some psychodynamic treatments, such as the variant used in the present study called experiential dynamic therapy (EDT; Osimo & Stein, 2012), have a strong interpersonal focus (Lilliengren, Johansson, Lindqvist, Mechler, & Andersson, 2016). A fundamental underlying assumption in EDT is that depression is a by-product of attempts to regulate strong negative emotions typically evoked in adverse experiences of early attachment relationships. When the attachment system and associated affects are triggered in later relationships, the individual may resort to a type of maladaptive coping leading to symptom formation (i.e., depression) and relational difficulties (Lilliengren et al., 2016). There are clear indications that psychodynamic psychotherapy is effective in treating depression in general (Driessen, Cuijpers, de Maat, et al., 2010; Driessen et al., 2013; Leichsenring et al., 2015), and CD in particular (Town et al., 2020; Town, Abbass, Stride, & Bernier, 2017). Although more high standard trials are needed, psychodynamic treatments are recommended as a viable option in treating CD (Jobst et al., 2016).

A combination of antidepressant medication (ADM) and psychotherapy (i.e., combination treatment) has shown significantly larger effects on symptom reduction relative to psychotherapy or ADM

alone for patients with chronic depression (Cuijpers, Andersson, Donker, & van Straten, 2011; Cuijpers, Dekker, Hollon, & Andersson, 2009; Cuijpers et al., 2014; Cuijpers, van Straten, Warmerdam, & Andersson, 2009). The superiority of combination treatment in alleviating depression may be explained by the fact that psychotherapy and ADM seem to contribute independently and with an approximately equal effect to improvement (Cuijpers et al., 2014), thus creating a cumulative effect on symptom reduction. A recent study comparing psychotherapy, pharmacotherapy or combination for PDD showed that combination treatment on average was superior to psychotherapy alone or pharmacotherapy alone. However, the study also identified subgroups of patients for whom this general finding did not apply (Furukawa et al., 2018); for patients with severe depression, combination treatment was better than pharmacotherapy alone, which in turn outperformed psychotherapy. On the other hand, for patients with moderate depression, combination of treatment and psychotherapy alone performed equally well, and both were better than pharmacotherapy. These findings suggest that psychotherapy alone may be the preferred choice for moderate levels of chronic depression, being equally efficacious as combination treatment, less costly and often matching patient preference (Furukawa et al., 2018).

Most psychotherapies (with or without combined ADM treatment) are delivered in outpatient clinics. A recent meta-analysis investigating the effectiveness of psychotherapy for treatment resistant depression found that two of 22 trials were conducted in an inpatient setting (Bronswijk, Moopen, Beijers, Ruhe, & Peeters, 2018). Thus, there is little research investigating outcomes for CD in inpatient settings, although some studies on inpatients have found combination treatment to outperform ADM for depressed (Köhler et al., 2013) and chronically depressed patients (Schramm et al., 2008).

The purpose of the current study was to explore how patients with CD and ongoing ADM treatment responded to a 12-week inpatient psychotherapy treatment programme where some continued and others discontinued ADM during treatment. There are several reasons why this study may be important. First, 40% of patients with depression do not or only partially respond to treatment (Cuijpers & Christensen, 2017), and chronic depression is one of the most challenging types of depressive disorders to treat (Cuijpers, Huibers, & Furukawa, 2017). Thus, more research is needed on effective treatments (both inpatient and outpatient) and factors that may moderate treatment response in different subgroups. Second, although most treatment guidelines recommend a combination of pharmacotherapy and psychotherapy for treatment of chronic depression (Cuijpers et al., 2017), there are growing concerns over the increasing use of ADM. The increasing rates of ADM-use in the 21st century can almost entirely be explained by long-term or chronic use (Eveleigh et al., 2017; Mojtabai & Olfson, 2014), and the likelihood of developing *tolerance* to ADM (e.g., depressive symptoms returning while on maintenance antidepressant treatment) increases with the duration of treatment (Fava, 2014). Also, as patients experience more depressive episodes, they may develop *resistance* (e.g., lack of response to previously effective ADM when readministered for a new episode) to the prophylactic properties of ADM (Fava, 2014; Kaymaz, van Os,

Loonen, & Nolen, 2008). Moreover, discontinuing antidepressants can trigger withdrawal symptoms, which can be mistaken for relapse of depression, thus leading to an erroneous impression that combination treatment is the better option (Fava, 2018). In support of this hypothesis, a long-term follow-up study found that patients receiving mental health treatment without medication had fewer symptoms after 9 years than patients receiving combination treatment, suggesting possible long-term iatrogenic effects of ADM (Vittengl, 2017). Thus, adding ADM to psychotherapy might interfere with its enduring effect (Forand, DeRubeis, & Amsterdam, 2013; Hollon, 2016). This suggests the need for further research on long-term outcomes for patients with chronic and recurrent depression receiving combination treatment. Thirdly, most of what is known about treating depression with a combination of ADM and psychotherapy comes from clinical trials with inclusion/exclusion criteria and procedures that are dissimilar to the situations in naturalistic settings where factors such as public health care prioritizing rules come into play. In clinical practice, interventions are likely to be used in a more heterogeneous population, frequently with co-morbid disorders, greater chronicity and a variety of past and ongoing treatments (Rawlins, 2008). It is not certain whether the benefits achieved by 'average' patients in RCTs can be extrapolated to patients receiving clinical care from an array of public and private health care providers (Rawlins, 2008). Real-life health care provision takes place in different treatment settings (e.g., inpatient vs. outpatient) with other criteria for inclusion of patients than what is typical in RCTs. Also, to comply with principles for evidence-based practice (APA Presidential Task Force on Evidence-Based Practice, 2006) and ethical considerations, health care needs to be conducted in accordance with individual patient characteristics and preferences. For instance, randomizing patients to continue/discontinue medication, when this is not in accordance with patients' wishes, will not be feasible. Thus, there is also a need for naturalistic observational studies to evaluate how predictions from randomized controlled efficacy studies play out in real-life treatment settings.

## 2 | RESEARCH QUESTIONS AND HYPOTHESES

In this study, we compared the symptom trajectories of patients who chose to discontinue their ADM during treatment with patients who continued their medication. Consequently, all patients used at least one kind of medication prescribed for depression from assessment to the start of treatment, but some decided to discontinue medication during treatment. We thus compared change in symptoms in these naturally occurring groups. Data and ADM-status were recorded at assessment, start of therapy, termination of therapy and at 1-year follow-up. Given the current evidence on ADM and psychotherapy for CD suggesting that combination treatment is the better option over either monotherapy, we hypothesized that (a) symptom reduction would be larger among patients continuing ADM while undergoing inpatient treatment compared to patients discontinuing ADM and (b) patients who continued ADM during inpatient treatment would

have better outcomes at 1-year follow-up compared to those who discontinued.

In line with the findings of Furukawa et al. (2018), we hypothesized that initial depression severity would have a moderating effect and that (c) patients with more severe depression would benefit relatively more from keeping ADM than patients with moderate to mild depression who might do equally well, even if their ADM was discontinued.

### 3 | METHODS

#### 3.1 | Study design and participants

This study of patients with chronic depression undergoing ADM treatment while presenting for a 12-week inpatient treatment programme (masked reference for anonymous review), examines the symptom development of patients who continued their use of ADM and patients who chose to discontinue ADM while undergoing treatment. Hence, we conducted a quasi-experimental study in a naturalistic treatment setting where we collected information and observed patient change as it occurred from assessment through treatment and a follow-up period of 1 year.

The clinic has a nation-wide catchment area and patients were referred from general practitioners or local secondary mental health care units across the country. The hospital is part of publicly funded health care and offers treatment to patients who have exhausted available local treatment options, typically including both pharmacotherapy and/or psychotherapy. Patients were assessed for the treatment programme during a 4-day assessment stay prior to inclusion in the programme. Eligible individuals had PDD or rMDD as primary diagnosis. As the risk of recurrence increases progressively with each new episode (de Jonge et al., 2018), and patients on their third or more episode approaches 100% chance of subsequent recurrence (Gelenberg et al., 2010), patients with at least two previous episodes (i.e., current episode is third or more) were included in the study. Exclusion criteria for the treatment programme were (1) psychosis, (2) cluster A and B personality disorder, (3) untreated/unstabilized bipolar disorder, (4) ongoing substance abuse and (5) organic brain disorders. Of the patients admitted to the treatment programme, we further excluded from analysis those with comorbid diagnoses that could confound interpretation of outcomes (i.e., stabilized bipolar disorder, PTSD, cluster C personality disorder). We also excluded patients taking medication for other purposes than depressive symptoms from the analyses (i.e., hyperkinetic medication, mood stabilizers for bipolar disorder, dependency medication, antiepileptics, first- and second-generation antipsychotics). Patients using medication not formally classified as antidepressants for the purpose of treating depression (e.g., lamotrigine, quetiapine) were included in the analyses. All patients were over 18 years of age.

Between 2012 and 2017, 1800 patients were referred to the treatment programme, of which 1200 were excluded because they

had not exhausted local treatment alternatives. The remaining 600 patients were assessed for eligibility. A total of 163 patients met the exclusion criteria for the treatment programme or were excluded for not meeting criteria for chronic or recurrent depression, leaving 437 patients receiving treatment. Furthermore, 80 cases that met the exclusion criteria for the analysis were removed. The sample was further reduced to 112 patients undergoing treatment with ADM during the waiting list period ( $M = 5.68$  months,  $SD = 3.43$ ). (See Figure 1 for study profile.)

#### 3.2 | Procedures

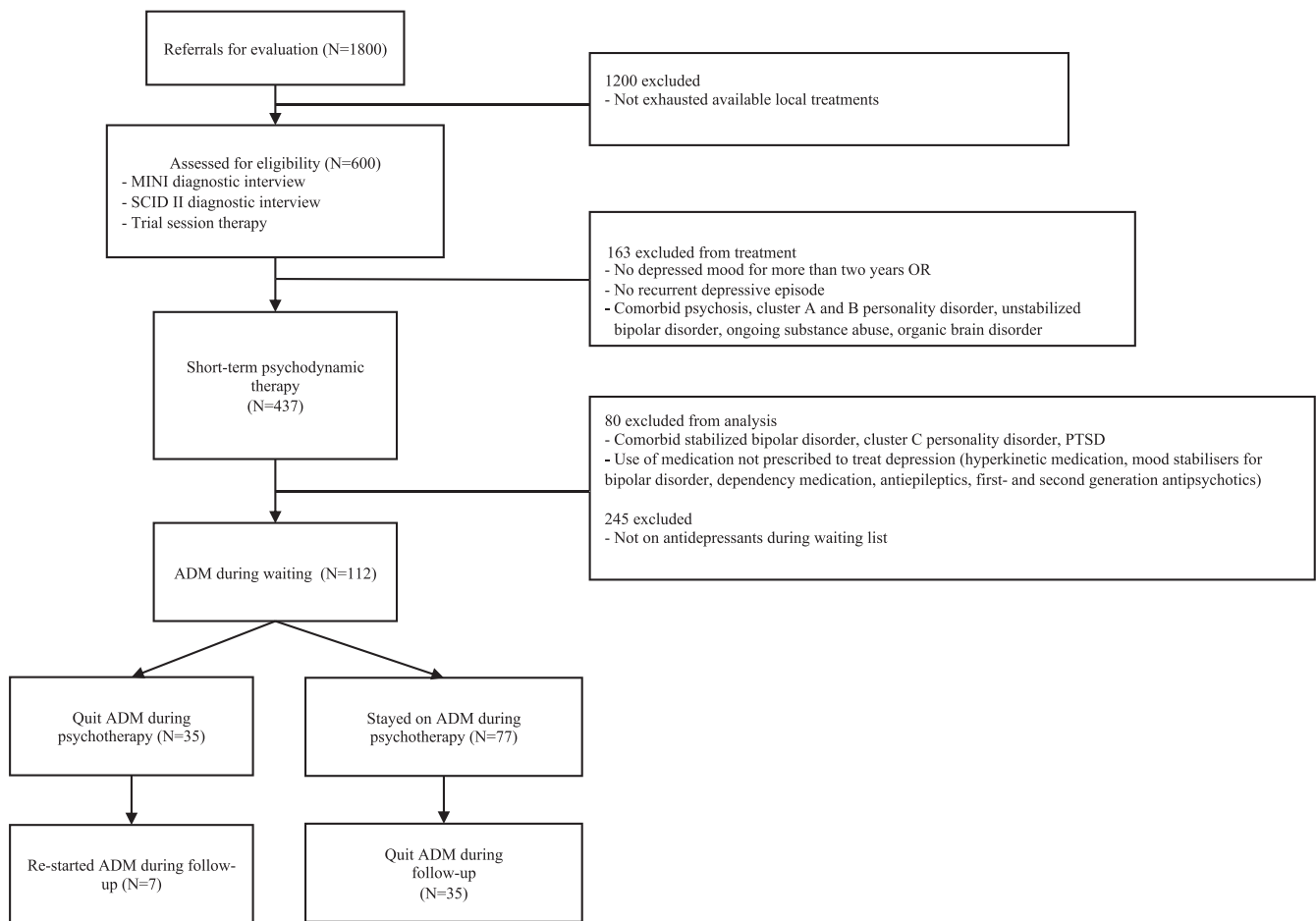
##### 3.2.1 | Assessment

Diagnostic assessment was done using the Mini-International Neuropsychiatric Interview (M.I.N.I.; Sheehan et al., 1998) and Structured Clinical Interview for DSM-IV Axis I Personality Disorders (SCID-2; First, Gibbon, Spitzer, Williams, & Benjamin, 1997). Interviews were performed by specialists in clinical psychology or psychiatry. Demographic information was collected through self-report instruments and assessment interviews. Patients using ADM reported dose and frequency and additional medication they were taking at assessment, beginning of treatment, termination and at 1-year follow-up. Patients were assessed on self-report instruments at initial assessment, start of treatment, termination and at 1-year follow-up with Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996), Symptom Checklist-90-R (SCL-90-R; Derogatis, 1994), Inventory of Interpersonal Problems (IIP-64; Horowitz, Alden, Wiggins, & Pincus, 2000) and alcohol use disorders identification test (AUDIT; Saunders, Aasland, Babor, De la Fuente, & Grant, 1993). Average time between assessment and treatment was 12 weeks.

##### 3.2.2 | Psychotherapy

Psychotherapy was provided during an intensive 12-week inpatient treatment programme and carried out in accordance with treatment manuals combining principles of experiential dynamic therapy (EDT), with cognitive and behavioural techniques (Stålsett, Gude, Rønnestad, & Monsen, 2012). EDT is a form of short-term psychodynamic psychotherapy, emphasizing experiential learning, that is, how to experience and express warded off affects (Osimo & Stein, 2012). The main treatment principles underlying EDT can be summarized using the *triangle of conflict* and the *triangle of persons* (Malan, 1979; McCullough et al., 2003). The triangle of conflict illustrates how defences and anxieties block the experience of true feelings, and the triangle of persons refers to how these patterns began with past persons, are maintained with current persons and may be enacted with the therapist (Lilliengren et al., 2016). Thus, EDT therapists strive to (a) help patients become aware and let go of maladaptive defences that generate and perpetuate symptoms; (b) track anxiety and regulate it when it is too high; and (c) help patients access, process and





**FIGURE 1** Study profile

integrate previously avoided affects (Lillengren et al., 2016). Patients were treated by teams of therapists. Each team consisted of a minimum of one psychiatrist (minimum 6-year medical school, 5-year specialization including attending courses, receiving supervision, writing research papers and gaining experience in psychiatry), one psychologist specialist (minimum 6-year university degree in psychology and psychotherapy, 5-year specialization including attending courses, receiving supervision, writing research papers and gaining experience in psychology and psychotherapy), one psychologist (minimum 6-year university degree in psychology and psychotherapy), one psychiatric nurse (3-year bachelor degree in nursing, 2-year specialization including attending courses, receiving supervision, writing research papers and gaining experience in psychology and psychotherapy) and one nurse (3-year bachelor degree in nursing). Staff without a specialist title (i.e., psychologist and nurse) was working towards qualifying for such a title. The psychiatrists and psychologist specialists were responsible for assessment, treatment planning and evaluation. Whereas being treated by a team of therapists each patient was the primary responsibility of a two-person team (one psychiatrist, psychologist specialist or psychologist and one psychiatric nurse or nurse). This included following up and adjusting treatment plans, individual therapy and day-to-day follow-up of the patients' progression. To obtain treatment integrity of the psychotherapy, therapists were

supervised by trained clinical psychologist specialists, conducting adherence checks throughout the treatment. Pending patient consent, therapy sessions were videotaped.

The therapy was provided in an inpatient context where treatment units accepted patients in closed cohorts of eight. In a typical week the patients received an average of two individual sessions (á 45 min), two group therapy sessions (á 75 min), one psycho-educational session (á 90 min), one art and expression therapy session (á 75 min), two physical exercise sessions (á 90 min) and one group session discussing means and goals of therapy (90 min).

### 3.2.3 | Medication management

As part of the general treatment policy of the hospital, patients were not actively encouraged to change ongoing medication but were offered help to assess their medication use upon entering treatment by medical doctors or psychiatrists. If wishing to discontinue pharmacotherapy, they were assisted by a medical doctor to form an individual plan for discontinuation. All patients were on ADMs as the treatment started. If patients decided to discontinue ADM, this was initiated at the start of therapy, in order for the discontinuation to be closely monitored during their stay, and for the patient to be stabilized

without medication before termination of therapy. Analyses were conducted comparing the patients' ADM-status (i.e., continued or discontinued) at termination of psychotherapy.

### 3.3 | Outcomes and measures

Primary outcome was the patients' scores on the BDI-II (Beck et al., 1996). Secondary outcomes were SCL-90-R (Derogatis, 1994), IIP-64 (Horowitz et al., 2000) and AUDIT (Saunders et al., 1993).

#### 3.3.1 | Beck Depression Inventory-II

The BDI-II consists of 21-items, with each item scored on a Likert scale from 0–3 (range 0–63). Depression scores are derived by summing the response to each of the items, with scores of 14–19 indicating mild depression, 20–28 moderate depression and 29–63 severe depression (Beck et al., 1996). BDI-II has demonstrated high reliability, capacity to discriminate between depressed and nondepressed individuals as well as different subtypes of depression and has demonstrated good to excellent concurrent, content and structural validity (Beck et al., 1996; Wang & Gorenstein, 2013). Patients completed BDI-II at assessment, start of treatment, at termination and at 1-year follow-up.

#### 3.3.2 | Symptom Checklist-90-R

SCL-90-R is a broad measure of symptom distress consisting of 90 items with each item scored on a Likert scale from 0 to 4. It produces nine symptom specific subscales and three global measures of symptom severity (Derogatis, 1994). In the current study, the global severity index (GSI) was used. It is calculated by dividing total sum score (range 0–360) by number of answered items (Derogatis, 1994). SCL-90-R has demonstrated high internal consistency and concurrent validity in clinical samples (Schmitz et al., 2000) and is well designed for assessing overall mental distress (Siqueland, Moum, & Leiknes, 2016).

#### 3.3.3 | Inventory of Interpersonal Problems-64

IIP-64 is a broad measure assessing a variety of interpersonal problems, consisting of 64 items scored on a Likert scale from 0–4. The IIP-64 yields eight octant sum scores, indicating specific domains of interpersonal functioning and one global score (Horowitz et al., 2000). In the current study, we used the global score which is calculated by dividing the total sum score (range 0–256) by the number of items. This global score of the IIP-64 has been consistently linked to symptom severity (Tracey, Rounds, & Gurtman, 1996), and IIP-64 has demonstrated good convergent validity, test-retest reliability and internal consistency (Horowitz et al., 2000).

### 3.3.4 | The alcohol use disorders identification test

AUDIT (Saunders et al., 1993) is a widely used instrument developed by the World Health Organization (WHO) for identifying harmful alcohol consumption (Saunders et al., 1993). The 10-item measure includes questions to assess the amount and frequency of alcohol intake (1–3), alcohol dependence (4–6) and problems related to alcohol consumption (7–10). Items are scored on a Likert scale from 0–4 (range 0–40), and a total score is derived by summing the response to each item. The general accepted cut-off point to identify harmful alcohol intake is 8 (Babor, Higgins-Biddle, Saunders, & Monteiro, 2001). AUDIT has demonstrated good validity and test-retest reliability (de Meneses-Gaya, Zuardi, Loureiro, & Crippa, 2009).

A reliability analysis was carried out on all outcome measures from the study sample at time of assessment. Cronbach's alpha showed good reliability for BDI-II ( $\alpha = 0.88$ ), AUDIT ( $\alpha = 0.84$ ), IIP-64 ( $\alpha = 0.93$ ) and SCL-90-R ( $\alpha = 0.96$ ).

### 3.4 | Statistical procedures

We calculated means and standard deviations for clinical and demographic variables.

We correlated total ADM-dose at assessment with BDI-II, AUDIT, SCL-90-R and IIP-64 to examine whether total ADM-dose was associated with symptom severity on these measures. In line with Furukawa et al. (2019), the total dose of ADM was calculated using the review of Hayasaka et al. (2015) to convert different ADMs to fluoxetine equivalents. Where no empirical data for dose conversion were available, we assumed the average maintenance dose per day calculated from the dose recommendations in each drug's product information according to WHO (WHO Collaborative Centre for Drug Statistics Methodology, 2006). Also, some patients were using quetiapine and lamotrigine for antidepressant purposes in the sample. The optimal dose of quetiapine for depression was set to 300 mg per day (Ignácio, Calixto, da Silva, Quevedo, & Réus, 2018). The optimal dose of lamotrigine for depression was set to 200 mg per day (Goldsmith, Wagstaff, Ibbotson, & Perry, 2003; Zavodnick & Ali, 2012). We converted all medication used for antidepressant purposes at assessment to equivalents of 40 mg fluoxetine (Hayasaka et al., 2015) and correlated total ADM-dose with initial symptom severity on the symptom measures (see Table 1 presenting conversion rates for medication used for antidepressant purposes in the sample).

As patients were not randomized to continuing or discontinuing medication, logistic regression was performed to assess whether key demographic and key clinical variables predicted continuation or discontinuation of ADM during treatment. Tested variables were (1) sex, (2) being currently in work (yes/no), (3) in a relationship (yes/no), (4) education level, (5) age/birth year, (6) duration of illness, (7) time since first treatment, (8) total dose of ADM at assessment, (9) depression severity on BDI-II, (10) global score of interpersonal problems on IIP-64, (11) Global symptom severity (GSI) on SCL-90-R and (12) AUDIT score.

**TABLE 1** Antidepressant dose equivalent to 40 mg fluoxetine<sup>a</sup>

Citalopram <sup>b</sup>	20
Escitalopram	18
Paroxetine	34
Sertraline	98.5
Duloxetine <sup>b</sup>	60
Venlafaxine	149.4
Mianserin	101.1
Mirtazapine	50.9
Bupropion	348.5
Amitriptyline	122.3
Clomipramine	116.1
Vortioxetine <sup>b</sup>	10
Phenelzine <sup>b</sup>	60
Moclobemide	575.2
Quetiapine <sup>c</sup>	300
Lamotrigine <sup>d</sup>	200

<sup>a</sup>Hayasaka et al. (2015).

<sup>b</sup>WHO Collaborative Centre for Drug Statistics Methodology (2006).

<sup>c</sup>Ignácio et al. (2018).

<sup>d</sup>Zavodnick & Ali. (2012); Goldsmith et al. (2003).

The difference in outcome between patients continuing or discontinuing ADM was assessed by comparing BDI-II scores for patients who at termination of psychotherapy had discontinued their ADM with the patients who continued. The analyses were conducted using multilevel models since repeated measurements (level 1) were nested within patients (level 2; Raudenbush & Bryk, 2002). All analyses were conducted using SPSS v 25. The model was built by successively adding predictors of time and intercept to fixed and random effects and testing model fit. Model fit was assessed comparing the  $-2$  log likelihood test for each model. Thus, we subtracted the deviance (i.e.,  $-2$  log likelihood) of the less restricted model from that of the more restricted model, and this difference was distributed as a chi-square with degrees of freedom defined as the difference in the number of estimated parameters (Fitzmaurice, Laird, & Ware, 2004; Bauer & Curran, 2019).

In accordance with Bauer and Curran (2012), models with different fixed effects were estimated using full estimation maximum likelihood, and models with different random effects were estimated using restricted estimation maximum likelihood. Model fit was also examined with homoskedastic and heteroskedastic error variance, linear and curvilinear effect of time and a piecewise timeline.

The best model fit was obtained using fixed and random effects of intercept and time, with an unconditional covariance structure, and a piecewise model with three timelines. Time was coded as weeks. The first timeline was number of weeks on waiting list. The second timeline was time in active treatment (12 weeks), and the third timeline was time in follow-up (52 weeks). In order to give the intercept a meaningful value at the start of treatment, time on waiting list was coded negative. Thus, the first timeline for a patient being 12 weeks on waiting list was coded  $-12$  as first-time value and 0 as the value

when therapy started, the second timeline was coded 0 at the start of therapy, and 11 at the end of therapy. The third timeline was coded 0 at the end of therapy and 51 at the end of follow-up. Finally, a dummy-coded group variable was entered as a predictor (patients continuing ADM were coded as 1 and patients discontinuing were coded as 0), to investigate if outcome was predicted by belonging to one category or the other. Also, a dummy-coded group variable for depression severity on BDI-II at assessment was entered as a covariate. Patients with BDI-II scores 0–28 was coded as 0 ('mild/moderate') and scores 29–63 was coded as 1 ('severe').

To facilitate interpretation when testing hypothesis, we estimated models by successively adding variables and interactions in accordance with our research questions (Singer & Willet, 2003). In Model 1, we tested fixed slopes for waiting list, treatment and follow-up including as covariates potential variables that were shown to differ among the continuers and discontinuers of ADM in the previous logistic regression analysis. In Model 2, we added ADM group (continuation vs. discontinuation) along with two-way interactions between ADM group and timelines (i.e., waiting list, treatment and follow-up). This was done to investigate whether ADM continuation/discontinuation had an impact on outcome during waiting list, treatment and follow-up. In Model 3, we added initial depression severity along with two-way interactions between severity and the three timelines. This was done to investigate whether depression severity had an impact on outcome during waiting list, treatment and follow-up. In Model 3, we also added interaction between ADM group and depression severity to assess whether continuation or discontinuation of ADM during treatment was related to initial depression severity. In Model 4, we added three-way interactions between each of the three timelines and ADM group and depression severity. This was done to assess whether severely depressed patients had different outcomes from continuing or discontinuing ADM compared to patients with mild/moderate depression.

To test if we had sufficient statistical power to detect difference between groups, post hoc power analysis was conducted with a single tailed *t* test assuming effect size of .50 using the 'G\*Power'-application (Faul, Erdfelder, Buchner, & Lang, 2009; Faul, Erdfelder, Lang, & Buchner, 2007).

To test whether reduction in BDI-II score constituted meaningful clinical change, we calculated the minimal clinically important difference (MCID; Button et al., 2015). This was done by calculating the percentage reduction of BDI-II score from start to end of therapy using 32% or higher reduction as a cut-off to denote clinically meaningful improvement (Button et al., 2015). Furthermore, we tested whether the proportion of patients who improved during treatment differed between the groups (i.e., ADM continuers vs. discontinuers). This was done by performing a multilevel binary logistic regression with MCID (i.e., improved vs. not improved) as our outcome. We computed a dummy variable (0, 1) where patients with an improvement of 32% or higher were coded as 1 ('improved') and improvement of less than 32% was coded as 0 ('not improved'). To obtain the grand mean across ADM-groups of the proportion of improved patients, the dummy coded ADM variable (continued = 1, discontinued = 0) was

entered as fixed effect. Also, depression severity (coded 0 for 'mild/moderate' depression and 1 for 'severe' depression) was entered as predictor, and variables from the logistic regression analyses showing significant differences among those continuing versus discontinuing ADM during treatment were entered as covariates. To identify whether there was significant variation in proportion of patients in each ADM-group who improved, random intercepts were added. The covariance structure used was variance components (VC).

### 3.5 | Statement on ethics

Patients were informed of the study upon entering treatment and all those participating in the study provided written informed consent. The study was reviewed and approved by the (masked for anonymous review) regional committee for medical and health research ethics (application number 2014/2355 and 2016/2003). The study with primary hypothesis and description of outcome variable was preregistered at 'aspredicted.org' (#7854) and is publicly available at <https://aspredicted.org/cr8v2.pdf>.

## 4 | RESULTS

### 4.1 | Descriptive statistics

See Table 2 for a description of the study sample on demographic and clinical characteristics. The mean age of the patients was 51 years ( $SD = 12.20$ ), 74.1% were women, 60.7% had children, 49.95% were in a relationship, 64.3% had higher education (i.e., bachelor-degree or higher) and 36.5% were in full-time or part-time employment. All patients had PDD or rMDD as their primary diagnosis, and 52 patients (46.43%) qualified for a second diagnosis. At time of assessment the average depression score on BDI-II was 27.54 ( $SD = 9.40$ ), with an average illness history of 21.75 years ( $SD = 13.52$ ), and a long history of previous treatment attempts, averaging 16.45 years ( $SD = 10.30$ ) since first treatment attempt.

There were eight classes/types of ADM present in the sample at start of treatment, the most prevalent being selective serotonin reuptake inhibitor (SSRI; 50%), serotonin-norepinephrine reuptake inhibitor (SNRI; 16.1%) tetracyclic antidepressant (TeCA; 8%) and norepinephrine-dopamine reuptake inhibitor (NDRI; 8%). Also, 4.5% used the antipsychotic quetiapine, and 7.1% used the antiepileptic lamotrigine for antidepressive purposes. Thirty-seven patients (33%) were taking two antidepressants at start of treatment whereas six (5.4%) patients were taking three ADM. Total ADM dosages at start of treatment ranged from 6.54 to 293.82 mg with a mean dose of 45.78 mg ( $SD = 35.32$ ).

The sample included 112 patients undergoing treatment with ADM during the waiting-list period. During the 12-week treatment, 35 patients discontinued ADM whereas 77 continued. Four of the patients who discontinued were on two different ADMs. Of the 35 patients who discontinued ADM during treatment, seven (20%)

**TABLE 2** Demographic and clinical characteristics

Age	51.0 (12.20)
Years since first depressive episode	21.75 (13.52)
Years since first treatment attempt	16.45 (10.30)
Sex	
Women	83 (74.1%)
Men	29 (25.9%)
Children	68 (60.7%)
Marital status	
Single	33 (29.5%)
Relationship	6 (5.3%)
Married or cohabiting	50 (44.6%)
Divorced or widowed	23 (20.6%)
Education	
Secondary or lower	11 (9.8%)
High school	29 (25.9%)
Bachelor or higher	72 (64.3%)
Employed	41 (36.5%)
BDI-II score	27.54 (9.402)
Second comorbid diagnosis	52 (46.43%)
F40-F48 neurotic, stress-related and somatoform disorders	35/52 (67.31%)
F30-F39 mood disorders	6/52 (11.54%)
F60-F69 disorders of adult personality and behaviour	6/52 (11.54%)
F50 eating disorders	3/52 (5.77%)
F10-19 mental and behavioural disorders due to psychoactive substance abuse	2/52 (3.84%)

Note: Data are mean ( $SD$ ), or  $n$  (%). Data are from assessment.

"F" = diagnosis codes in ICD-10, chapter V (World Health Organization, 1993).

Abbreviation: BDI, Beck Depression Inventory-II.

restarted during follow-up. Of the 77 patients continuing ADM during psychotherapy, 35 (45.5%) discontinued during follow-up (see Figure 1). A McNemar's test determined that there was a significant difference in the number of patients changing ADM status from termination to follow-up ( $p < .001$ ). BDI-II data from 39 patients (34.82%) were missing at time of follow-up. Patients could not be contacted for reanalysis because the local ethics committee approval of the study did not include admission to contact patients after such extended time periods.

### 4.2 | Correlations and regression analyses

Results of the Pearson correlations indicated that there was no significant association between ADM-dose (40-mg fluoxetine equivalents) at assessment and symptom severity on AUDIT ( $r(88) = 0.092$ ,  $p = .391$ ), BDI-II ( $r(82) = -0.028$ ,  $p = .803$ ), IIP-64 ( $r(86) = -0.060$ ,  $p = .579$ ) or SCL-90-R ( $r(85) = -0.070$ ,  $p = .517$ ).

The logistic regression analysis showed increased duration of illness (stand.  $\beta = 1.067$ ,  $p = .026$ ), and total ADM dose at assessment (stand.  $\beta = 1.045$ ,  $p = .011$ ) significantly predicted keeping ADM during treatment. None of the other demographic, clinical or symptom measure variables predicted continuing or discontinuing ADM (see Table 3).

### 4.3 | Multilevel growth curve modelling of BDI-II outcomes

Because increased duration of illness and increased total ADM-dose at assessment predicted keeping ADM during treatment, these variables were entered as covariates in the multilevel growth curve analysis.

Table 4 presents the results for the multi-level models. Model 1 showed a general significant weekly reduction of BDI-II symptoms during treatment (est. =  $-0.829$ ,  $p < .001$ ). The effect of treatment was maintained during follow-up as there was no significant deterioration or improvement in the follow-up phase (est. =  $-0.035$ ,  $p = .158$ ). There was no significant effect of ADM dose (est. =  $0.015$ ,  $p = .538$ ) or duration of illness (est. =  $-0.051$ ,  $p = .352$ ) on BDI-II scores at start of treatment (i.e., intercept).

Model 2 showed that patients discontinuing ADM did not have different outcomes from patients continuing ADM (est. =  $0.425$ ,  $p = .0503$ ). This was maintained during follow-up as there was no significant difference between the groups on symptom development during this phase (est. =  $-0.100$ ,  $p = .055$ ).

Model 3 included ADM and initial depression severity as predictors and showed that patients categorized as having severe depression (i.e., above 28 on BDI-II) experienced significantly more symptom improvement than patients categorized as having mild/moderate depression (est. =  $-0.452$ ,  $p = .037$ ; see Figure 2). This effect was maintained during follow-up as there was no significant difference

between the groups on symptom development during this phase (est. =  $0.028$ ,  $p = .627$ ). As in Model 2, Model 3 also showed that there was no significant difference on symptom slopes between continuers and discontinuers of ADM (est. =  $0.265$ ,  $p = .234$ ; see Figure 3). Also, there was no interaction between ADM group and depression severity (est. =  $1.234$ ,  $p = .664$ ), indicating no systematic relationship between initial depression severity and whether or not ADM was continued. Model 3 also showed that patients with severe depression had more symptom improvement during waiting list than patients with moderate depression (est. =  $-0.221$ ,  $p = .003$ ).

Model 4 showed that ADM continuation did not interact with the effect of initial depression severity and treatment on outcome (est. =  $-0.458$ ,  $p = .316$ ), indicating that continuing or discontinuing ADM did not predict differential outcomes for severely depressed patients compared to patients with mild/moderate depression. As in Model 3, Model 4 also showed patients with severe depression had more symptom improvement during waiting list than patients with moderate depression (est. =  $-0.223$ ,  $p = .030$ ).

Post hoc analysis showed an achieved statistical power ( $1 - \beta$  err. prob.) of 0.79, which indicated sufficient power to detect differences between the groups.

### 4.4 | Multilevel binary logistic regression analysis of MCID outcomes

The results showed that 51.8% of the patients experienced clinical improvement. Since increased duration of illness and increased total ADM-dose at assessment predicted keeping ADM during treatment, these variables were entered as predictors in the multilevel binary logistic regression analysis along with initial depression severity. The multilevel binary logistic regression analysis showed that the random (individual) effect variation in intercepts (i.e., level of depression scores) for patients discontinuing versus continuing ADM was not

**TABLE 3** Regressions for possible predictors for discontinuing medication during treatment

	B	S.E.	Sig.	Exp (B)
Sex	-0.671	0.816	.411	0.511
Having work (yes/no)	0.623	0.632	.324	1.864
In a relationship (yes/no)	0.771	0.618	.212	2.162
Education level	-0.011	0.153	.941	0.989
Birthyear	0.045	0.029	.119	1.046
Duration illness	0.065	0.029	.026*	1.067
Time since first treatment	-0.017	0.038	.662	0.983
ADM total dose at start of assessment	0.044	0.017	.011*	1.045
AUDIT	-0.131	0.072	.068	0.877
BDI-II	0.063	0.049	.195	1.065
IIP-64	-0.731	0.763	.338	0.481
SCL-90-R	-0.945	0.866	.275	0.389

Abbreviations: AUDIT, alcohol use disorders identification test; BDI-II, Beck Depression Inventory-II; IIP-64, Inventory of Interpersonal Problems 64; SCL-90-R, Symptom Checklist-90 Revised.

\*Significant at  $p \leq .05$ .

**TABLE 4** Treatment effects

Fixed effects	Model 1					Model 2				
	Slopes for waiting list, treatment and follow-up with covariates					Model 1 with ADM groups				
	Est.	S.E.	df	C.I.	p	Est.	S.E.	df	C.I.	p
Intercept	28.257	1.877	129.114	(24.543, 31.970)	<.001*	28.633	2.168	130.723	(24.345, 32.921)	<.001*
Waiting list	-0.069	0.037	43.878	(-0.143, 0.006)	.070	-0.087	0.060	37.901	(-0.209, 0.035)	.157
Treatment	-0.829	0.010	97.361	(-1.027, -0.631)	<.001*	-1.125	0.179	96.963	(-1.480, -0.769)	<.001*
Follow-up	-0.035	0.024	86.353	(-0.083, 0.014)	.158	0.033	0.042	83.601	(-0.050, 0.117)	.428
ADM dose	0.015	0.025	105.255	(-0.034, 0.064)	.538	0.013	0.026	106.387	(-0.038, 0.064)	.619
Duration of illness	-0.051	0.054	103.574	(-0.158, 0.057)	.352	-0.056	0.056	104.622	(-0.166, 0.055)	.320
ADM group						-0.205	2.127	114.671	(-4.419, 4.008)	.923
Waiting list * ADM group						0.028	0.077	41.325	(-0.128, 0.183)	.720
Treatment * ADM group						0.425	0.214	97.019	(-0.001, 0.851)	.0503
Follow-up * ADM group						-0.100	0.051	83.984	(-0.202, 0.002)	.055
Severity										
Waiting list * severity										
Treatment * severity										
Follow-up * severity										
ADM group * severity										
Waiting list * ADM group * severity										
Treatment * ADM group * severity										
Follow-up * ADM group * severity										
-2 log likelihood	2562.663					2563.201				
Fixed effects	Model 3					Model 4				
	Model 2 with depression severity					Model 3 with three way interactions between slopes, ADM groups and depression severity				
	Est.	S.E.	df	C.I.	p	Est.	S.E.	df	C.I.	p
Intercept	22.909	2.609	99.251	(17.732, 28.086)	<.001*	23.871	2.650	110.597	(18.621, 29.122)	<.001*
Waiting list	0.024	0.069	43.902	(-0.116, 0.163)	.734	0.070	0.081	84.725	(-0.091, 0.232)	.390
Treatment	-0.796	0.219	72.123	(-1.232, -0.360)	.001*	-0.988	0.284	93.400	(-1.552, -0.423)	.001*
Follow-up	0.012	0.058	56.324	(-0.103, 0.128)	.832	0.006	0.074	53.661	(-1.142, 0.155)	.933
ADM dose	0.001	0.022	76.780	(-0.043, 0.046)	.950	0.006	0.023	73.980	(-0.039, 0.051)	.793
Duration of illness	-0.024	0.050	76.494		.639	-0.027	0.051	73.823		.607



TABLE 4 (Continued)

Fixed effects	Model 3					Model 4				
	Model 2 with depression severity					Model 3 with three way interactions between slopes, ADM groups and depression severity				
	Est.	S.E.	df	C.I.	p	Est.	S.E.	df	C.I.	p
				(-0.124, 0.076)					(-0.129, 0.076)	
ADM group	-0.136	2.654	103.104	(-5.399, 5.128)	.959	-2.294	2.856	120.996	(-7.949, 3.360)	.423
Waiting list * ADM group	0.064	0.070	40.848	(-0.078, 0.206)	.370	-0.027	0.103	89.483	(-0.232, 0.178)	.796
Treatment * ADM group	0.265	0.221	72.424	(-0.175, 0.705)	.234	0.591	0.350	94.822	(-0.103, 1.285)	.094
Follow-up * ADM group	-0.083	0.059	58.019	(-0.200, 0.035)	.165	-0.075	0.090	53.961	(-0.255, 0.105)	.409
Severity	9.107	2.712	99.288	(3.727, 14.487)	.001*	7.884	2.946	115.685	(2.049, 13.718)	.009*
Waiting list * severity	-0.221	0.070	44.724	(-0.361, -0.081)	.003*	-0.223	0.101	86.789	(-0.423, -0.022)	.030*
Treatment * severity	-0.452	0.212	73.685	(-0.875, -0.030)	.037*	-0.178	0.371	91.096	(-0.914, 0.559)	.633
Follow-up * severity	0.028	0.057	58.661	(-0.086, 0.141)	.627	0.036	0.097	54.874	(-0.158, 0.230)	.710
ADM group * severity	1.234	2.828	72.830	(-4.401, 6.870)	.664	3.579	3.580	116.196	(-3.512, 10.670)	.320
Waiting list * ADM group * severity						0.011	0.129	90.973	(-0.245, 0.266)	.933
Treatment * ADM group * severity						-0.458	0.454	91.650	(-1.361, 0.444)	.316
Follow-up * ADM group * severity						-0.010	0.120	56.346	(-0.250, 0.231)	.936
-2 log likelihood	2051.485					2066.146				

Note: Dependent variable is BDI-II. Intercept centred at start of treatment. Treatment slope = estimated change in BDI-II scores from start to termination of therapy. Follow-up slope = estimated change in BDI-II scores from termination of therapy to 1-year follow-up. ADM dose = total dose of antidepressant medication at assessment. Duration of illness = years since first symptom emergence. ADM group = patients discontinuing (coded 0) vs. continuing (coded 1) ADM during therapy. Severity = mild/moderate depression (coded 0) vs. severe depression (coded 1) at assessment.

Abbreviations: Est., estimated values of the parameters in the multilevel models; S.E., standard error; *df*, degrees of freedom; C.I., 95% confidence interval; *p*, *p* value.

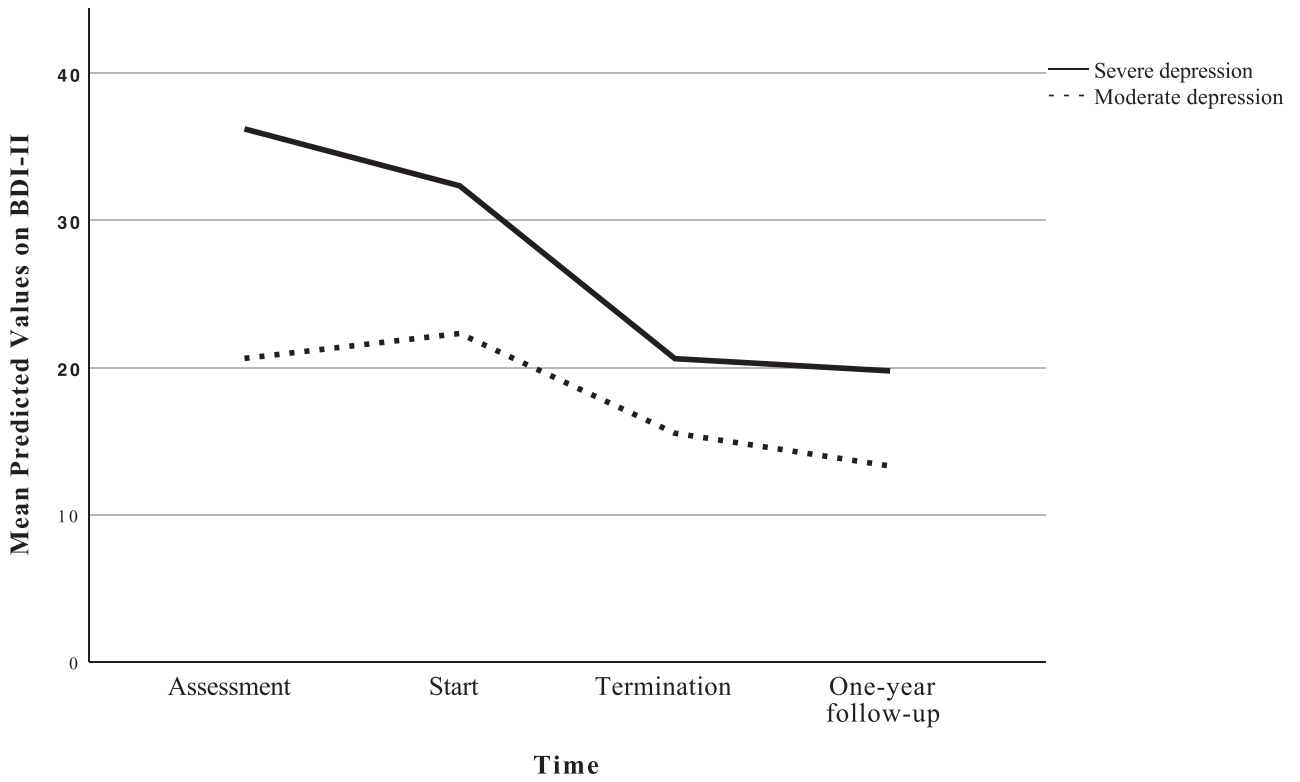
\*Significant at  $p \leq .05$ .

significant (est. = 0.315,  $p = .537$ ). This indicated there was not a different proportion of patients improving in the two groups. Also, patients with severe depression at assessment exhibited a 1.28 times greater likelihood to improve compared to those with mild/moderate depression (stand.  $\beta = 1.281$ ,  $p < .001$ ). There was no significant effect of ADM-dose or duration of illness.

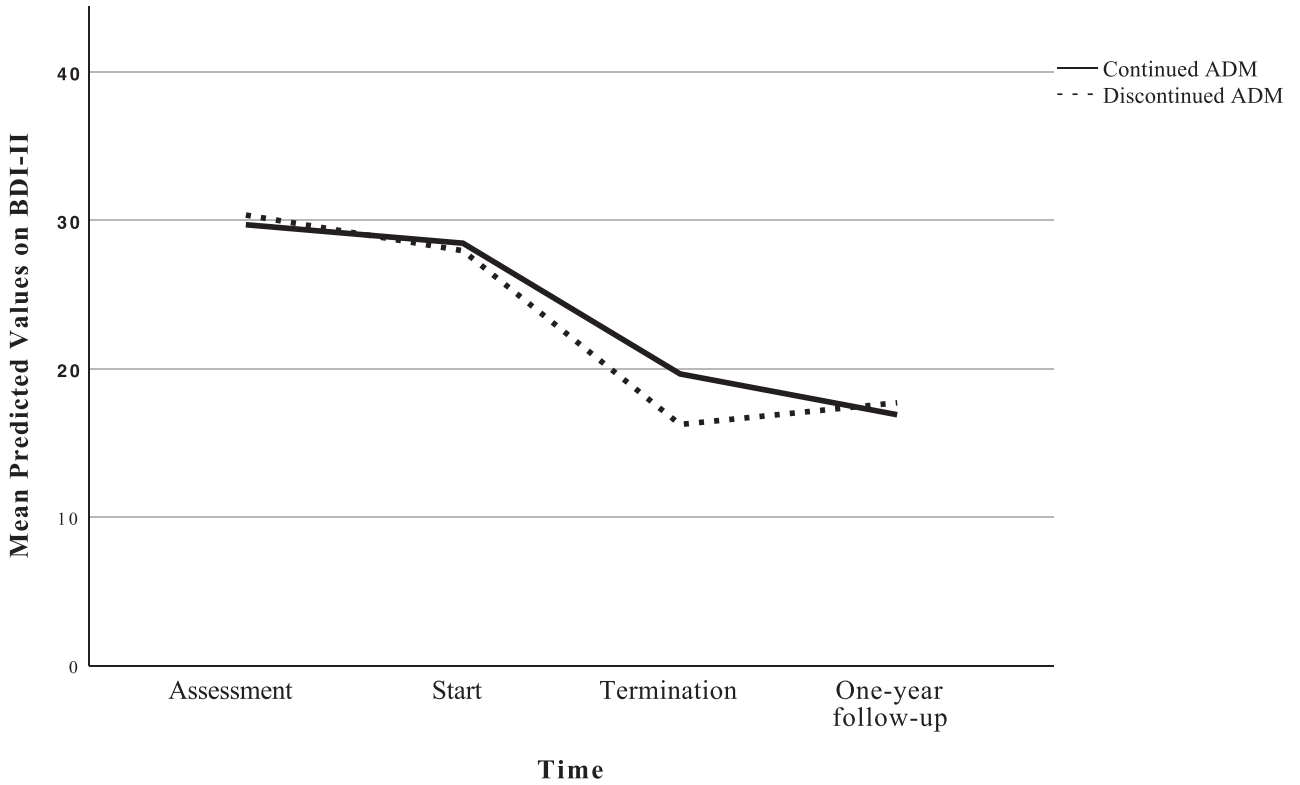
## 5 | DISCUSSION

This quasi-experimental study examined patients with chronic depression who presented for inpatient psychotherapeutic treatment in a naturalistic setting. We compared the symptom

trajectories of patients who chose to discontinue ADM during treatment with those who continued. Based on current evidence indicating that combination treatment (i.e., medication and psychotherapy combined) is the most effective treatment for this patient group, we tested the hypothesis that patients continuing ADM while undergoing inpatient psychotherapy would have better outcomes on BDI-II compared to patients discontinuing ADM, due to an added effect of the medication. We also investigated whether initial depression severity had a moderating effect on BDI-II outcomes for patients discontinuing or continuing ADM based on prior research indicating that severely depressed patients benefit more from combination treatment compared to those who are moderately affected (Furukawa et al., 2018).



**FIGURE 2** Mean of predicted values on BDI-II across time by initial depression severity



**FIGURE 3** Mean of predicted values on BDI-II across time by ADM-group



We found both patients continuing and discontinuing ADM had a significant treatment effect that was maintained at 1-year follow-up (Model 1). There was no difference in outcomes between discontinuers and continuers of ADM (Models 2 and 3). Instead, we found patients with severe depression had better outcomes than patients with moderate levels of depression (Model 3). Also, patients with severe depression had more symptom improvement during waiting list than patients with moderate depression. Thus, contrary to our hypothesis, patients continuing ADM did not have better outcomes than patients discontinuing. Also contrary to our hypothesis, we did not find that patients with severe depression benefitted more from keeping ADM than patients with moderate levels of depression. Hence, our results indicated patients discontinuing ADM had similar outcomes to those continuing, regardless of initial depression severity.

Our results are in line with previous research finding that patients with severe depression benefit more from psychotherapy than patients with moderate levels of depression (Driessen et al., 2010). General treatment strategies seem to benefit those with mild to moderate levels of depression more than the severely affected. However, Driessen et al. (2010) argue that treatment specifically targeting the issues that are relevant to the patient's disorder may benefit severely depressed patients more than moderately affected. Our finding may provide indirect support of this assertion in the sense that since our treatment provided more relief for the severely distressed, it seems to have been effective in addressing the specific problems of the disorders in our sample. Moreover, that severely depressed patients benefitted more than moderately depressed patients also supports prior findings that psychodynamic treatment may be especially suited to address chronic depression (Town et al., 2020; Town et al., 2017). Also, patients with difficult-to-treat depression seem to need higher doses of treatment in terms of number of sessions to respond to psychotherapy and experience a clinically significant change (Robinson, Kellet, & Delgado, 2020). In light of this, the high intensity/high dose nature of the treatment programme offered here may have been especially beneficial for the more severely depressed patients in our sample. Finally, the superior improvement of those with high depression severity could also be due to regression to the mean (i.e., the higher the depression level, the bigger the potential decrease in symptoms). This could also explain why patients with higher depression severity improved more than moderately depressed during waiting list.

There may be several reasons why keeping ADM did not seem to provide an added benefit to the patients in our sample. First, in spite of ongoing treatment with ADM, many of the patients still had severe depression symptoms at the time of assessment, indicating possible tolerance and/or resistance to the prophylactic effects of the medication. The fact that patients who kept ADM during psychotherapy did not show superior outcomes could be caused by the fact that the positive effect of ADM was not present at start of treatment. Hence, keeping ineffective ADM would not provide an added effect on treatment. Also, many patients stay on ADM that are not perceived as helpful for fear of withdrawal symptoms (Cartwright, Gibson, Read,

Cowan, & Dehar, 2016). Our results showed a large proportion of patients that kept ADM during treatment discontinued during follow-up (45.5%). This could indicate that successfully completing therapy may have provided additional confidence for some patients to overcome fear of withdrawal symptoms and discontinue ADM that were not perceived as helpful.

Second, users of ADM typically report negative side effects such as sexual problems, weight gain, emotional numbness, reduction in positive feelings, and adverse effects on interpersonal, work or study and social life (Cartwright et al., 2016; Read, Gee, Diggle, & Butler, 2017, 2019; Read & Williams, 2018). If patients continuing ADM retained some prophylactic effect from ADM use, this could have been counterbalanced by negative side effects that resemble the symptoms that make up the diagnosis of depression (Fried & Nesse, 2015). Conversely, patients discontinuing ADM may have lost some of the therapeutic or prophylactic effect of their ADM but at the same time benefitted from a possible decrease of negative side effects. In sum, discontinuing ADM did not seem to negatively impact the effect of psychotherapeutic treatment.

Third, the results may suggest a differential receptiveness to the specific psychotherapeutic interventions among the patients. For instance, as much as 50% of patients using ADM report emotional blunting as a side effect (Goodwin, Price, de Bodinat, & Laredo, 2017). Thus, discontinuing medication could make some of our patients more receptive to psychotherapeutic interventions aiming at getting access to their emotions and facilitating emotional processing and interpersonal functioning, balancing out the lack of positive effects of ADM.

Our findings are in line with previous research suggesting patients with a long history of depression and ADM may develop tolerance and/or resistance to the prophylactic effects of the medication and actually experience minimal benefits from maintaining their medication even though many are reluctant to discontinue (Fava, 2014; Kaymaz et al., 2008).

Our results could also lend support to findings indicating psychotherapy can help patients discontinue antidepressants without increasing the risk of relapse/recurrence (Maund et al., 2019) and that psychotherapy can be a viable alternative to combined treatment (Karyotaki et al., 2016).

To draw firm conclusions about the pattern and rate of symptom reduction for the two groups in the current study would be speculative. However, we believe these findings give rise to important questions regarding interactions between psychological and biological mechanisms in treating depression that warrant further exploration. Furthermore, clinicians should carefully assess the effects of ongoing ADM use for chronically depressed patients presenting for treatment and be prepared to provide them with an opportunity to discontinue under safe and controlled conditions if the desired effects of medication are not present. There is a need for more research on potential benefits of continuing ADM when initiating psychotherapy, and on differential factors that might contribute to patient's motivation to stay on or discontinue medication.

## 5.1 | Limitations of the study

The current study has some notable strengths, such as the comprehensive diagnostic assessment (using the M.I.N.I.), multiple measurement points (assessment, start, discharge and follow-up) and a naturalistic setting where we observed a sample of naturally occurring groups as they proceeded through therapy. Despite this, there are also limitations that limit the conclusions that can be drawn. Patients who initiated discontinuation did so by their own accord and proceeded with the assistance of medical doctors. As we did not have data on the exact timing of the discontinuation of ADM, outcomes may have differed across patients discontinuing at the beginning of treatment compared to patients discontinuing at the end of treatment. Consequently, the potential positive and/or negative effects of discontinuing medication might not have manifested themselves at termination of treatment. It should be noted that the risk for this is fairly low. Due to the high levels of depressive symptoms in our sample, we suspect that the patients already had developed tolerance and/or resistance to the prophylactic effects of ADM. Therefore, the potential observable effects on outcome would be expected to be due to loss of negative side effects, which should manifest itself in better outcomes for the discontinuation group (Fava, 2014). Although we tested whether the choice to discontinue was systematically related to a variety of demographic and clinical variables, there could be other factors related to discontinuation than those available to us and accounted for in the analyses. Without an RCT design, we cannot claim that other factors that may influence outcome are randomly distributed in the two groups, and the grounds for making causal inferences about treatment and improvement in depression are limited. Conversely, the generalizability of RCTs to real-world patient populations can be problematic (Rawlins, 2008). In routine clinical practice, RCTs provide grounds for choosing between forms of treatment—giving some level of certainty that a treatment backed by RCTs has merit as they have been shown to be beneficial for people under controlled conditions. However, the challenge remains for clinicians to judge whether or not a treatment supported in RCT studies might be beneficial for the individuals and subgroups in their clinic. Although our study design prevents us from forming generalizable statements based on our results, they show that the assumption derived from many RCTs and meta-studies that combination treatment has an advantage over monotherapy is not necessarily met in this particular sample. In our view, this underscores the need for further research on the conditions under which patients might benefit from either monotherapy or combination treatment.

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### CONFLICT OF INTEREST

All authors have completed International Committee of Medical Journal Editors (ICMJE) form for disclosure of potential conflict of interests and have nothing to disclose.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are not publicly available due to privacy or ethical restrictions. Pending approval from the treatment facility that all data are made anonymous and in compliance with GDPR and other local regulations, the data may be made available on request from the corresponding author.

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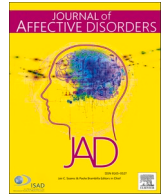
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## Research paper

## Do self-criticism and somatic symptoms play a key role in chronic depression? Exploring the factor structure of Beck depression inventory-II in a sample of chronically depressed inpatients.

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## ABSTRACT

**Background:** The factor structure of depression differs for different sub-samples. The purpose of this study was to explore the factor structure of Beck Depression Inventory-II in patients with chronic depression presenting for inpatient treatment. **Methods:** Using exploratory structural equation modeling (ESEM), we explored whether a two-factor solution or a bifactor solution provided best model fit for a sample of 377 patients. For the best fitting model stability was assessed with tests for invariance across primary diagnosis (persistent depressive disorder v. recurrent major depressive disorder), and presence of comorbidity. **Results:** A bifactor solution with one general factor and two specific factors provided best model fit. Invariance analyses provided support for measurement invariance and stability of the factor solution. **Limitations:** The naturalistic study design implies some uncertainty regarding possible systematic differences between the patients on demographic and clinical characteristics. **Conclusion:** The factor structure in our sample was best explained by a general depression factor, one specific factor pertaining to self-criticism, and one consisting of the somatic items fatigue, disturbance of sleep, and appetite. Clinicians could benefit from paying special attention to the subfactors identified, as these findings may have implications for treatment choice for patients with chronic depression.

## Introduction

Subsamples of depressed patients seem to vary in symptom profiles reflecting possible subtypes of depression that in turn might respond differently to treatment (Huang & Chen, 2015; Shafer, 2006). It is therefore important to extend the body of literature describing the underlying structure of depression in different patient subsamples. A common approach to understanding the disorder involves examining its latent structures via factor analysis of symptom measures. Descriptions of depression as consisting of depressed affects, self-deprecating cognitions and somatic symptoms can be traced back to Hippocrates (Spielberger, Ritterband, Reheiser, & Brunner, 2003). However, the factor analytic literature on Beck Depression Inventory-II (BDI-II), the most commonly used depression instrument (Lemmens, Müller, Arntz, & Huibers, 2016), rarely identifies three distinct factors in clinical

psychiatric samples. The original study by Beck, Steer, and Brown (1996) identified a two-factor solution consisting of a 9-item cognitive factor and a 12-item somatic-affective factor. Reviews of subsequent studies show three-factor solutions have been identified in samples of substance abusers, post-partum women, students, chronic pain patients, patients with intellectual disabilities and other medical samples, but two-factor solutions are typically identified in clinical psychiatric and depressed samples (Huang & Chen, 2015; Wang & Gorenstein, 2013).

The two-factor solutions are variations of cognitive, somatic and affective elements making up the factors, but different item compositions interfere with straightforward interpretation (Vanheule, Desmet, Groenvynck, Rosseel, & Fontaine, 2008). While some items are consistent indicators of the cognitive dimension, and some consistently define the somatic dimension, other items variably load on one factor or the other to produce either a Cognitive-affective factor or a

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Somatic-affective factor (Ward, 2006). Using the nomenclature of Beck et al. (1996), these shifting items could be classified as “affective” (Ward, 2006). One reason for the instability of the affective items (such as “sadness”, “agitation”, “irritability”, and “loss of pleasure”) across samples might be that they are ambiguous in nature with the ability to add salience to both thought content and non-verbal bodily sensations. Different negative thoughts (e.g., “I am disappointed in myself”, “I feel guilty”) can add meaning to the circumstances under which negative affect is experienced, and thus become depressive thoughts (Spielberger et al., 2003). Conversely, symptoms such as tiredness/fatigue, changes in sleeping pattern or changes in appetite, may shift from neutral to negative experiences when they appear in conjunction with negative affect. Thus, rather than functioning as a separate factor in depression, affective symptoms (i.e., negative feelings) may add salience to thought content or bodily sensations in different subsamples, making up either cognitive-affective or somatic-affective factors.

One problem with first-order factor solutions is that they fail to represent multidimensionality that occurs when indicators are associated with more than one construct (Morin, Arens, & Marsh, 2016). This is often the case for items in scales measuring psychological constructs (Morin et al., 2016). For example, in an intelligence test some items might be expected to be associated with a sub-domain (e.g., verbal intelligence) as well as to a hierarchically superior construct (e.g., global intelligence). This raises the question whether some depression symptoms, such as affective symptoms, are part of a global construct while other symptoms constitute specific sub-factors in different subsamples of depressed patients. A bifactor model directly tests whether a global construct (a ‘g factor’) exists as a unitary dimension underlying the response to all items and coexists with specific factors explaining the residual variance not explained by the g factor (Morin et al., 2016). Some studies have reported that bifactor solutions of the BDI-II provide better fit compared to previously identified two-factor solutions in psychiatric outpatients (Brouwer, Meijer, & Zevalkink, 2013), depressed outpatients (Quilty, Zhang, & Bagby, 2010), and psychiatric inpatients (Subica et al., 2014). Also, re-analyses of data from previous studies finding support for two-factor solutions, have found improved model fit when testing a bifactor model (i.e., with one higher-order general factor and two lower order factors; Ward, 2006). Findings supporting bifactor models for BDI-II, corroborate the theory that BDI-II assesses generalized distress along with more specific features of depression (Subica et al., 2014).

Chronic depression (CD) is not a formal diagnosis in current diagnostic classification manuals, but the term is frequently used to describe patients who experience a repeated pattern of recurrent episodes as well as persistence of symptoms (e.g., Jobst et al., 2016; Köhler, Chrysanthou, Guhn, & Sterzer, 2019). It is likely that the pathogenesis of single episode depression is different from that of recurrent and persistent depression, which is characterized by long-term declines in functioning and cognition (Belmaker & Agam, 2008). Also, similar risk factors (e.g., initial depressive and comorbid symptom severity, failure to seek treatment at baseline), predict both persistence (i.e., continuity of symptoms over at least two years) and recurrence of depressive episodes (Hoertel et al., 2017; ten Have et al., 2018). Thus, patients diagnosed with persistent depressive disorder (PDD) and recurrent major depressive disorder (rMDD) are often included in studies exploring chronic forms of depression (Barnhofer et al., 2009; Bockting et al., 2005; DeRubeis et al., 2020; Hollon et al., 2014; Humer et al., 2020; Ma & Teasdale, 2004). On the other hand, PDD and rMDD are clearly separated as two distinct disorders in current diagnostic manuals (American Psychiatric Association, 2013), and there is little agreement on the number and nature of depression subtypes (Fried & Nesse, 2015). Whether clustering of PDD and rMDD is a valid way of conceptualizing chronicity of depression thus remains an open question. Examining whether patients with these diagnoses share similar symptom structures may contribute to the debate on how best to conceptualize chronicity of depression.

For patients diagnosed with depression, prevalence estimates indicate 93.5 percent of them experience at least one other comorbid physical or mental disorder, and patients’ evaluations of their own burden of disease are dramatically improved when adjusting for comorbidity (Gademann, Alonso, Vilgaut, Zaslavsky, & Kessler, 2012). This suggests condition specific severity varies significantly depending on the presence or absence of comorbidity (Moussavi et al., 2007). Also, failure to identify underlying causes of mental disorders suggests they could be understood as clusters of mutually re-enforcing symptoms (Borsboom & Cramer, 2013; Kendler, Zachar, & Craver, 2011). Hence, the presence of comorbid conditions in conjunction with depression may constitute large clusters of re-enforcing symptoms affecting overall symptom severity, functioning and perceived wellbeing, raising the question whether depressed patients with comorbid diagnoses may have different factor structures than patients without comorbidity.

To summarize, it is important to extend the body of literature describing the factor structure of commonly used depression screening instruments for different patient subsamples. Specifically, there is a need to explore the underlying constructs for patients with chronic depression, and whether symptom structure differs between patients with PDD v. rMDD and comorbidity v. no comorbidity.

Previous studies exploring BDI-II have regularly been conducted using variations of exploratory (EFA) and confirmatory (CFA) factor analysis (Huang & Chen, 2015; Wang & Gorenstein, 2013). However, EFA and CFA have methodological limitations (Asparouhov & Muthén, 2009; Marsh, Morin, Parker, & Kaur, 2014). Cross-loadings are traditionally constrained to be zero in CFA but are freely estimated in EFA, so CFA structures are more restrictive than EFA structures. Because of this, in many instances item-level CFAs fail to provide clear support for instruments that have been well established in EFA research (Marsh et al., 2014). Also, the independent cluster model inherent in CFA (ICM-CFA) in which items are required to load on only one factor, could be too restrictive for many multidimensional constructs (Morin et al., 2016). Exploratory structural equation modeling (ESEM; Asparouhov & Muthén, 2009) allows for integration of EFA within a structural equation modeling (SEM) framework. As in EFA, ESEM allows for items to load freely on all factors but at the same time allowing for methodological advances typically reserved for CFA and SEM, such as goodness of fit statistics and comparison of competing models (Marsh et al., 2014; Morin, Marsh, & Nagengast, 2013). ESEM has provided better fit to data and less differentiated factors than CFA (Morin et al., 2013), and performs better in terms of construct validity of the interpretation of the factor structure (Marsh et al., 2009). However, a first order ESEM model will likely ignore the presence of hierarchically superior constructs, which will end up being expressed through inflated cross-loadings. To fully capture the hierarchical and multidimensional nature of instruments incorporating sources of psychometric multidimensionality bifactor ESEM is a viable option (Morin et al., 2016).

The purpose of this study was to explore the factor structure of BDI-II in a sample of hospitalized inpatients with chronic depression (i.e., primary diagnosis PDD or rMDD), using updated statistical methods. We based our analysis on previous studies indicating BDI-II in adult clinical psychiatric samples is best represented either through one global construct with some symptoms constituting specific sub-dimensions (bifactor model) or a two-factor structure. Hence, we tested whether a two-factor structure or a bifactor structure with one general factor and two lower order factors provided best fit for our data, applying ESEM. We also conducted invariance analyses to examine whether factor structure was stable across primary diagnosis and presence of comorbid disorders. To our knowledge no studies on the factor structure of BDI-II have been made on chronically depressed inpatients using ESEM.

## Methods

### Study design & treatment context

The factor analysis was conducted as part of a naturalistic study of patients presenting for a 12-week inpatient treatment program for chronic depression at Modum Bad hospital in Vikersund, Norway, comparing outcomes of patients that were taking antidepressant medication (ADM) in addition to undergoing inpatient psychotherapeutic treatment with patients who were not taking ADM. Modum Bad has a nation-wide catchment area and patients were referred from general practitioners or local secondary mental health care units across the country. Patients who had exhausted available local treatment options, typically including both pharmaco- and/or psychotherapy, were assessed for the treatment program during a 4-day assessment stay prior to inclusion in the program. Eligible individuals had PDD or rMDD as primary diagnosis. As the risk of recurrence increases progressively with each new episode (de Jonge et al., 2018), and patients on their third or more episode approaches 100% chance of subsequent recurrence (American Psychiatric Association, 2010), patients with a recurrent depressive episode with at least two previous episodes (i.e., current episode is third or more) were included in the study. Exclusion criteria for the treatment program were 1) psychosis, 2) cluster A and B personality disorder, 3) untreated/unstabilized bipolar disorder, 4) ongoing substance abuse and 5) organic brain disorders. All patients applying for the treatment program were diagnostically assessed with the Mini-International Neuropsychiatric Interview (M.I.N.I.; Sheehan et al., 1998) and Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-2; First, Gibbon, Spitzer, Williams, & Benjamin, 1997) the first day of the 4-day assessment stay. The same diagnostic instruments were used throughout the period patients were admitted to the program (from 2012 to 2017). A specialist in clinical psychology or psychiatry conducted the interviews and made initial assessment of primary and secondary diagnoses. Then, each diagnosis was discussed in a team of psychiatrists and psychologists before final diagnostic assessment was recorded.

### Participants

Between 2012 and 2017, 1800 patients were referred to the treatment program, of which 1200 were excluded because they had not

exhausted local treatment alternatives. These were referred back to alternative local health care alternatives. The remaining 600 patients were assessed for eligibility. Some patients (N=163) were excluded for not meeting criteria for persistent or recurrent depression or met exclusion criteria for the treatment program (see above). Thus, 437 patients received treatment. Because 60 patients did not complete the BDI-II at start of treatment, 377 cases were included in the present analyses (see Fig. 1).

### Measures

To assess levels and change of depressive symptoms, patients completed BDI-II at assessment, start of treatment, at termination, and at one-year follow-up. In this study, we used the BDI-II data from start of treatment. The BDI-II consists of 21-items, scored on a Likert scale from 0 to 3 (range 0-63), and has demonstrated high reliability and good concurrent, content, and structural validity for screening depression in outpatient and student samples (Beck et al., 1996). Cronbach's alpha showed good reliability for BDI-II in the current sample ( $\alpha=0.88$ ).

### Statistical procedures

We based our analysis on comprehensive reviews of BDI-II most commonly identifying two-factor solutions in adult clinical psychiatric and depressed samples (Huang & Chen, 2015; Wang & Gorenstein, 2013), and findings suggesting that bifactor solutions provide better fit than previously identified two-factor solutions (Brouwer, Meijer, & Zevalkink, 2013; Quilty, Zhang, & Bagby, 2010; Subica et al., 2014; Ward, 2006). Thus, we conducted two exploratory analyses comparing a two-factor structure to a bifactor structure with one higher order, general factor and two lower order factors. To conduct the analyses, we used exploratory structural equation modeling (ESEM; Asparouhov & Muthén, 2009; Marsh et al., 2014). Thus, we contrasted a first order ESEM model with two factors with a bifactor ESEM specifying one general factor and two sub-factors.

All analyses were conducted in Mplus 8 with maximum likelihood estimator (ML; Muthén & Muthén, 1998-2017). First, an exploratory analysis using ESEM was conducted specifying the extraction of two factors. The factors were correlated under the oblique geomin rotation (Muthén & Muthén, 1998-2017). Secondly, a bifactor exploratory analysis was conducted using ESEM, specifying one general factor and

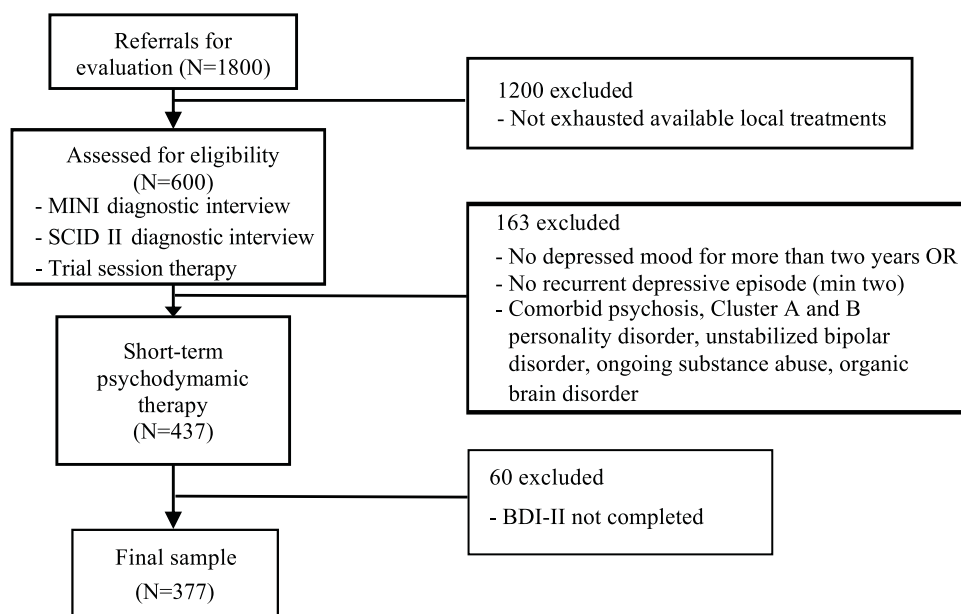


Fig. 1. Study profile.

two specific factors. In bifactor estimation it is assumed that the general and group factors are orthogonal (Reise, 2012). Thus, we specified a bi-geomin orthogonal rotation where the specific factors were uncorrelated. In both models, item loadings were freely estimated, the intercepts and residual variances of the factor indicators were estimated, and the residuals were not correlated. The variances of the factors were fixed at 1 as the default.

For the bifactor model, the independent contributions of general and specific factors to common item variance were determined by calculating the percentage of explained common variance (ECV) for each factor. For each factor the ECV is the sum of the squared standardized factor loadings for that factor divided by the sum of all squared factor loadings for the model (Rodriguez, Reise, & Haviland, 2016). Thus, ECV is the percent of variance explained by each factor.

With a sample size of 377 cases, factor loadings were interpreted as salient when greater than or equal to .30 (Hair, Tatham, Anderson, & Black, 1998). Goodness of fit of the factor model was assessed by means of chi square ( $\chi^2$ ), comparative fit index (CFI), root mean square error of approximation (RMSEA) and standardized root mean square residual (SRMR; Schweizer, 2010). For the CFI cut-offs for acceptable and good model fit we used  $\leq .90$  and  $\leq .95$ , whereas cut-offs for acceptable and good model fit on the RMSEA were set to below .08 or .05 respectively (Marsh et al., 2010). For SRMR, values were expected to stay below 0.10 (Kline, 2005). We used Akaike information criterion (AIC) to compare model fit between the two models.

It is important to establish whether questionnaires measure the same constructs in all subgroups of the population for whom the measure will be used (Brown, 2013). Tests of measurement invariance evaluate the extent to which measurement properties generalize over multiple groups, situations or occasions (Morin, Marsh, & Nagengast, 2013). We tested invariance of the most optimal model across patients with different primary diagnosis (PDD v. rMDD), and comorbidity (comorbid diagnosis present v. not present). First, model fit of the selected model was tested separately in each sub-group (Brown, 2013). Then we sequentially tested configural, weak, strong and strict invariance (Liu et al., 2017; Meredith, 1993; Meredith & Teresi, 2006). Invariance testing was done in MPlus Version 8 following the procedure outlined in Morin et al. (2013, see supplemental materials for Mplus syntax). For analysis of configural invariance factor structures are freely estimated in each group with only the number of factors being the same in both groups. The latent variances are fixed to 1 and the latent means to 0 in both groups to freely estimate all factor loadings and items intercept. Weak invariance tests whether the factor loadings are the same in both groups by fixing the loadings to equality across groups, and fixing factor variance to 1 in a selected reference group while freely estimating it in the other. Strong invariance tests whether intercepts in addition to factor loadings are invariant across groups (i.e., whether individuals with the same score on a latent factor answer the items in a similar way). The intercepts are constrained to equality in both groups, while latent means are constrained to 0 in a selected reference group and freely estimated in the other. Strict invariance requires invariance of item uniqueness (i.e., item-level measurement errors are equivalent across groups) in addition to the invariance of factor loadings and intercepts. This is done by adding equality constraints to item uniqueness in both groups (Morin et al., 2013).

If configural invariance was established, further analysis was conducted to check weak factorial invariance, if weak factorial invariance was established analysis for strong was conducted, and if strong factorial invariance was established, we analyzed for strict factorial invariance. If for any step invariance was not established further analysis was not conducted. If strict invariance is established, this would imply that group differences in means, variances, and covariances of the measured indicators are entirely attributable to group differences in the latent common factors (Millsap, 2011). For purposes of model comparison, tests of the relative fit of models are of greater importance than the absolute level of fit for any one model (Marsh et al., 2009). Differences in

comparative fit index (CFI) and root mean square error of approximation (RMSEA) were used as they appear to be equally sensitive to lack of invariance (Chen, 2007). If a difference in CFI is smaller than or equal to .01, this indicates that the hypothesis of invariance is supported (Chen, 2007; Cheung & Rensvold, 2002). For the RMSEA a difference smaller or equal to .015 would support the hypothesis of invariance (Chen, 2007).

**Results**

The mean BDI-II total score for the sample was 29.47 ( $SD = 9.49$ ) at assessment. The mean age of the patients was 47.5 years ( $SD = 10.83$ ). Years since first episode was 23.5 ( $SD = 13.6$ ), mean ‘years since first treatment attempt’ was 11.9 ( $SD = 9.8$ ). The primary diagnosis was rMDD for 221 patients (58.6%), and PDD for 156 patients (41.4%). Comorbid psychiatric diagnosis (one or more) was present for 185 patients (49.1%). See Table 1 for additional demographics and clinical characteristics.

Table 2 presents model fit indices for the tested models. Both models provided adequate fit, with the bifactor model achieving the best fit ( $\chi^2(150) = 250.676$ ,  $p < .001$ ;  $RMSEA = 0.042$ , 90% C.I. [0.033, 0.051];  $CFI = 0.956$ ;  $SRMR = 0.034$ ). Table 3 and Fig. 2 show the factor loadings for the bifactor model. All items except item 16 (“changes in sleeping pattern”) loaded saliently (above 0.3) on the general factor. For the first sub-factor, four items loaded saliently (item 5, “guilty feelings”; item 7, “self-dislike”; item 8, “self-criticalness”; item 14, “worthlessness”). As these items all reflect self-devaluating thought content, we labeled this factor “self-criticism”. For the second sub-factor, three items loaded saliently (item 16, “changes in sleeping pattern”; item 18, “changes in appetite”; item 20, “tiredness or fatigue”). We labeled this factor

**Table 1**  
Demographic and clinical characteristics.

	Baseline characteristic (N=377)	
	n	%
Sex		
Female	255	67.6
Male	122	32.4
Having children	268	71.1
Marital status		
Single	93	24.7
Relationship	17	4.5
Married or cohabiting	188	49.8
Divorced or widowed	79	21
Education		
No known education	9	2.4
Primary or secondary	24	6.4
High school	87	23.1
Bachelor or higher	257	68.1
Employment status		
Full time work	53	14.1
Part time work	117	31.0
No work	198	52.5
Student	8	2.1
Unknown	1	0.3
Medication at start of treatment		
No medication	171	45.4
Any medication present	206	54.6
Antidepressants	125	33.2
Anxiolytics/hypnotics	38	10.1
Hyperkinetic medication	6	1.6
Mood stabilizers	10	2.7
Antiepileptics	38	10.1
Substance dependency medication	2	0.5
Antipsychotics	34	9.0
Antihistamines	16	4.2
Pain medication	21	5.6
Unknown medication	16	4.2
Primary diagnosis		
Recurrent major depressive disorder (rMDD)	221	58.6
Persistent depressive disorder (PDD)	156	41.4
Comorbid diagnosis	185	49.1



**Table 2**  
Summary of goodness of fit statistics.

	$\chi^2(df)$	RMSEA	90% C.I.	CFI	SRMR	AIC	$\Delta$ RMSEA	$\Delta$ CFI
ESEM	331.376* (169)	0.05	[0.042, 0.058]	0.928	0.04	17673.78		
BI-ESEM	250.676* (150)	0.042	[0.033, 0.051]	0.956	0.034	17631.081		
Invariance comorbid								
Configural	432.748* (300)	0.048	[0.038, 0.058]	0.942	0.043	17686.445		
Weak	504.949* (354)	0.048	[0.038, 0.057]	0.933	0.057	17650.645	0	0.009
Strong	528.601* (372)	0.047	[0.038, 0.056]	0.931	0.059	17638.298	0.001	0.002
Strict	547.486* (393)	0.046	[0.036, 0.055]	0.932	0.061	17615.183	0.001	-0.001
Invariance PDD v. recurrent MDD								
Configural	450.177* (300)	0.052	[0.041, 0.061]	0.936	0.043	17708.110		
Weak	523.473* (354)	0.05	[0.041, 0.059]	0.928	0.055	17673.406	0.002	0.008
Strong	542.173* (372)	0.049	[0.040, 0.058]	0.928	0.057	17656.106	0.001	0
Strict	569.460* (393)	0.049	[0.040, 0.057]	0.925	0.06	17641.393	0	0.003

Note. Invariance comorbid: patients with one or more comorbid diagnosis compared to patients with only one diagnosis. Invariance PDD v. recurrent MDD: patients with PDD as primary diagnosis compared to patients with recurrent MDD as primary diagnosis. Estimator is maximum likelihood (ML); ESEM=Exploratory structural equation modeling; BI-ESEM=bifactor ESEM; RMSEA=root mean square error of approximation; C.I.=confidence interval; CFI=comparative fit index; SRMR=standardized root mean square residual; AIC=akaike information criterion;  $\Delta$ =difference previous model; \* $p < 0.01$ ; ESEM estimated with geomin oblique rotation; Bifactor ESEM estimated with bi-geomin orthogonal rotation.

**Table 3**  
Results from factor analysis of BDI-II.

BDI-II item	Bi-factor ESEM		
	General factor	«Self-criticism»	«Somatic»
1. Sadness	<b>.624</b>	-.001	-.187
2. Pessimism	<b>.557</b>	.071	-.193
3. Past failure	<b>.529</b>	.297	-.100
4. Loss of pleasure	<b>.660</b>	-.100	.104
5. Guilty feelings	<b>.522</b>	<b>.443</b>	.001
6. Punishment feelings	<b>.438</b>	.178	-.019
7. Self-dislike	<b>.556</b>	<b>.473</b>	-.050
8. Self-criticalness	<b>.521</b>	<b>.470</b>	.107
9. Suicidal thoughts or wishes	<b>.413</b>	.154	-.239
10. Crying	<b>.394</b>	-.015	.116
11. Agitation	<b>.389</b>	.053	.194
12. Loss of interest	<b>.640</b>	-.252	.006
13. Indecisiveness	<b>.625</b>	.019	.229
14. Worthlessness	<b>.619</b>	<b>.300</b>	-.197
15. Loss of energy	<b>.643</b>	-.142	.266
16. Changes in sleeping pattern	.261	.047	<b>.418</b>
17. Irritability	<b>.351</b>	-.032	.154
18. Changes in appetite	<b>.358</b>	.065	<b>.346</b>
19. Concentration difficulty	<b>.631</b>	-.093	.290
20. Tiredness or fatigue	<b>.609</b>	-.129	<b>.431</b>
21. Loss of interest in sex	<b>.320</b>	-.105	.289

Note. N = 377. The extraction method was exploratory structural equation modeling with maximum likelihood estimator (ML) and orthogonal bi-geomin rotation. Factor loadings above .30 are in bold. Standardized model results.

“somatic”. ECV showed 73.4% of the variance of the bifactor model was explained by the general factor, indicating a strong general factor. 13.1% of the variance was explained by the “self-criticism” factor, and 13.5% was explained by “somatic” factor.

Invariance tests for the bifactor model were conducted for presence of comorbid diagnosis v. no comorbid diagnosis, and for primary diagnosis PDD v. recurrent MDD. The bifactor model showed good fit for patients without comorbid diagnosis ( $\chi^2(150) = 208.514$ ,  $p < .001$ ; RMSEA=0.045, 90% C.I. [0.029, 0.059]; CFI=0.945; SRMR=0.043), and for patients with one or more comorbid diagnosis ( $\chi^2(150) = 224.234$ ,  $p < .001$ ; RMSEA=0.052, 90% C.I. [0.037, 0.065]; CFI=0.939; SRMR=0.043). For rMDD v. PDD, model fit was good for patients with rMDD as primary diagnosis ( $\chi^2(150) = 221.197$ ,  $p < .001$ ; RMSEA=0.046, 90% C.I. [0.033, 0.059]; CFI=0.949; SRMR=0.039), and acceptable for patients with PDD as primary diagnosis ( $\chi^2(150) = 228.980$ ,  $p < .001$ ; RMSEA=0.058, 90% C.I. [0.042, 0.073]; CFI=0.917; SRMR=0.048). For the tests of measurement invariance, the goodness of fit indices suggested good model fit at each stage for all groups (see Table 2). Changes in the goodness of fit indices did not decrease below

the limits indicating strong support for measurement invariance and stability of the factor solution (see Table 2).

**Discussion**

In this study, we explored the factor structure of BDI-II in a sample of inpatients with chronic depression, also testing for invariance between patients with PDD or rMDD as primary diagnosis, and presence of comorbid diagnoses. In our sample we found a high level of symptom severity, a long history of depression, and a long history of treatment attempts. A bifactor model provided best fit, suggesting that psychometric multidimensionality may be present in the BDI-II ratings from our sample. Invariance testing indicated stability of the model across primary diagnosis, indicating the same factor structure for patients with PDD and recurrent MDD. This supports including patients with both diagnoses in studies of chronic depression. The invariance testing also indicated the same factor structure of depression for patients with and without comorbidity. Even though comorbid diagnoses affect symptom severity and perception of burden of disease (Gadernann et al., 2012; Moussavi et al., 2007), our results show that depression remains a stable construct with or without comorbidity present.

Our results further suggest that BDI-II items correspond to one global depression factor, where all items loaded saliently except item 16 (“changes in sleeping pattern”). In addition, some of the items seem to constitute separate sub-dimensions where items revolving around self-critical cognitions (items 5, 7, 8, and 14) load on one specific factor, and somatic items connected to sleep, appetite and fatigue (items 16, 18, and 20) load on another. Also, all of the items typically labelled “affective” loaded on the general factor, but none of the specific factors. Our results indicate depression is mostly explained by a general factor, where affective symptoms are part of the more fundamental (global) construct while cognitive symptoms pertaining to being self-critical and somatic items pertaining to sleep, appetite and fatigue, may play a special role for the current subsample of chronically depressed inpatients.

Among the cognitive aspects of depression, such as helplessness, worrying about the future, ruminating over past problems and self-critical thoughts (Blatt, Quinlan, Chevron, McDonald, & Zuroff, 1982; Pearson, Brewin, Rhodes, & McCarron, 2008), self-criticism may play a particularly important role in chronic/recurrent depression. In an early study Dent and Teasdale (1988) found thought content, specifically devaluing the self, contributed to chronicity of depression. Also, self-criticism has been linked to severity of depression (Luyten et al., 2007), and higher rates of depressive relapse (Hawley, Zuroff, Brozina, Ho, & Dobson, 2014; Mongrain & Leather, 2006). In addition, less self-criticism and/or greater reduction during inpatient or hospital day

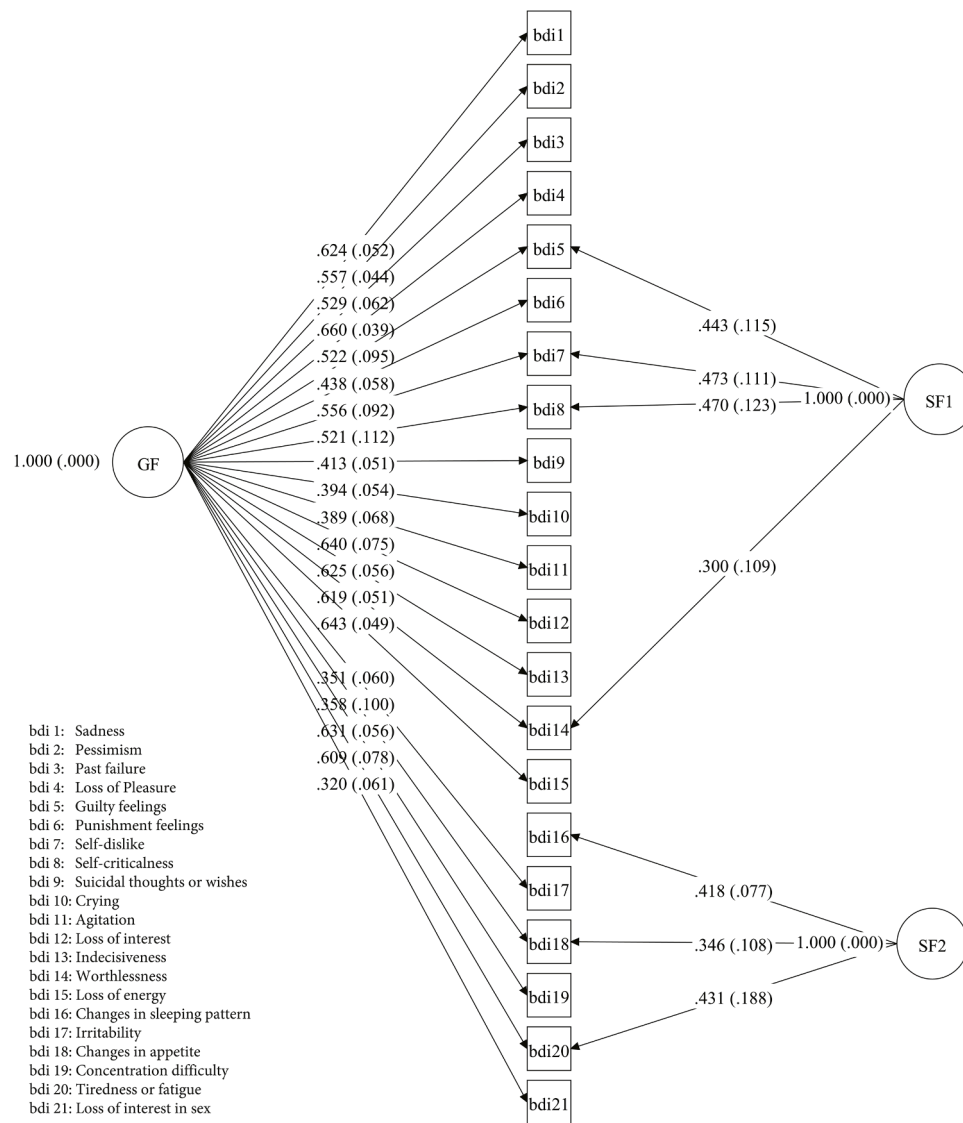


Fig. 2. Bifactor ESEM model.

treatment predicted rapid and sustained improvement after one year for depressed patients (Zeck et al., 2020). Harsh forms of self-criticism are persistent and difficult to change and may represent a possible specific target for psychotherapeutic treatment (Werner, Tibubos, Rohrmann, & Reiss, 2019).

The three items 16 (“changes in sleeping pattern”), 18 (“changes in appetite”) and 20 (“tiredness/fatigue”) are the most consistent items regularly loading on a somatic factor (Manian, Schmidt, Bornstein, & Martinez, 2013). One study found that sleep symptoms might be a candidate for one symptom cluster in a “true” symptom structure for depression (Chekroud et al., 2017). From a theoretical perspective, sleep symptoms could directly affect appetite and fatigue forming a set of somatic symptoms that should be specifically addressed in treatment.

Our results could have practical clinical implications. First, the general factor in a bifactor model represents the single source of common variance running through all items in an instrument and can be interpreted as representing the psychological construct the instrument was created to measure (Reise, 2012). According to Beck et al. (1996) the total BDI-II score provides an estimate of the overall severity of depression. Thus, our results indicate that the total BDI-II score is a valid indicator for depression severity in chronically depressed inpatients. However, overall symptom improvement may obscure whether different treatments target different symptoms. Overall, both psychotherapy and

antidepressants (ADM) work about equally well for depression (Hollon, 2016), but regardless of treatment type, only 30-40% will achieve remission (Craighead & Dunlop, 2014). In other words, a large number of patients do not respond to either ADM or psychotherapy, and there is a need to identify indicators that predict which patients will respond to different available treatment options (DeRubeis et al., 2014). Specific symptom profiles could serve as indicators for treatment choice (Stewart & Harkness, 2012), and assessing scores on the subfactors self-criticism and somatic items may be useful in guiding treatment choice. For example, positive change due to psychotherapy is most often associated with changes in dysfunctional attitudes, rumination and worry (Lemmens et al., 2016), whereas different ADMs have differential effects on core emotional and sleep symptoms (Chekroud et al., 2017). Also, as depressive symptoms seem to be interconnected in complex networks, improvement or worsening of one type of symptom can causally affect others (Borsboom & Cramer, 2013; Boschloo et al., 2019). For instance, the somatic item sleep disturbance can lead to cognitive impairment (Fried & Nesse, 2015). Thus, targeting specific cognitive or somatic symptoms with treatment options specifically suited for that symptom cluster could lead to overall faster and more stable remission. Further research should explore whether targeting symptom clusters of self-criticism and sleep/appetite/fatigue with different treatment options could provide beneficial outcomes for patients with

chronic/recurrent depression. For instance, if self-criticism is especially salient, therapists may consider exploring psychotherapeutic interventions targeting self-compassion (Neff & Vonk, 2009). If, on the other hand somatic symptoms are particularly salient, one might consider focusing on treatment with antidepressant medication (Chekroud et al., 2017). We believe our results contribute an important clinical nuance in the use and interpretation of BDI-II for chronically depressed patients. Clinicians could benefit from paying special attention to the subfactors identified, as these findings may have implications for the treatment choice for patients with chronic depression.

### Limitations

Despite the strengths of this study such as using new statistical approaches and the large sample size of a heterogeneous, naturalistic sample of depressed patients with severe symptomatology, our study has some shortcomings that should be taken into account. First, as this was a naturalistic study, patients were not randomized to treatment conditions leaving uncertainty regarding possible systematic differences between the patients on demographic and clinical characteristics. However, as we did find factorial invariance, any difference between the groups did not affect the main findings of this study. Second, even if our inclusion criteria were liberal, we did exclude those with Cluster B or C personality disorders and those with substance abuse, and so the generalizability of the findings to other samples of depressed patients with these comorbid diagnoses might be compromised. Third, ESEM may have potential limitations, such as not being applicable to complex models unless sample size is sufficiently large (Marsh, et al., 2014). Also, ESEM might confound constructs that need to be kept separate in relation to theory, and ESEM, like EFA, suffers from rotational indeterminacy (i.e., different rotation strategies result in different solution that all fit the data equally well; Marsh, Guo, Dicke, Parker, & Craven, 2020). Lastly, even though we replicated findings from prior studies on BDI-II in a sample of chronic depression, there could be differences in phenomenology of depression that the BDI-II does not capture that may distinguish this group from other groups of depressed patients, and potentially also differentiate between those using ADM from those who do not.

### Author contributions

Andreas Høstmælingen was responsible for designing and initiating the study, planning and performing the analyses, interpreting the results and writing the report, and was involved in managing the study and collecting the data.

Pål Gunnar Ulvenes was responsible for designing, initiating and managing the study, collecting the data, planning and performing the analyses, interpreting the results and was involved in writing the report.

Helene Amundsen Nissen-Lie was responsible for initiating and managing the study and was involved in designing the study, planning the analyses, performing the analyses, interpreting the results and writing the report.

Mikkel Eielson was responsible for collecting the data and was involved in designing the study, planning and performing the analyses, interpreting the results and writing the report.

Bruce E. Wampold was involved in designing and initiating the study, interpreting the results and writing the report.

All authors approved the final version of the manuscript.

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The study was funded by the University of Oslo and Modum Bad. The funder had no role in study design, data collection, -analysis, -interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

### Statement of ethics

The study was conducted in compliance with APA ethical standards and IRB standards, and was reviewed and approved by the Norwegian regional committee for medical and health research ethics (application number 2014/2355 and 2016/2003).

### Declaration of Competing Interest

All authors have completed the International Committee of Medical Journal Editors (ICMJE) form for disclosure of potential conflict of interest and declare that there is no conflict of interest.

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### Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2021.01.066.

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