

**RESEARCH ARTICLE**

# 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.)

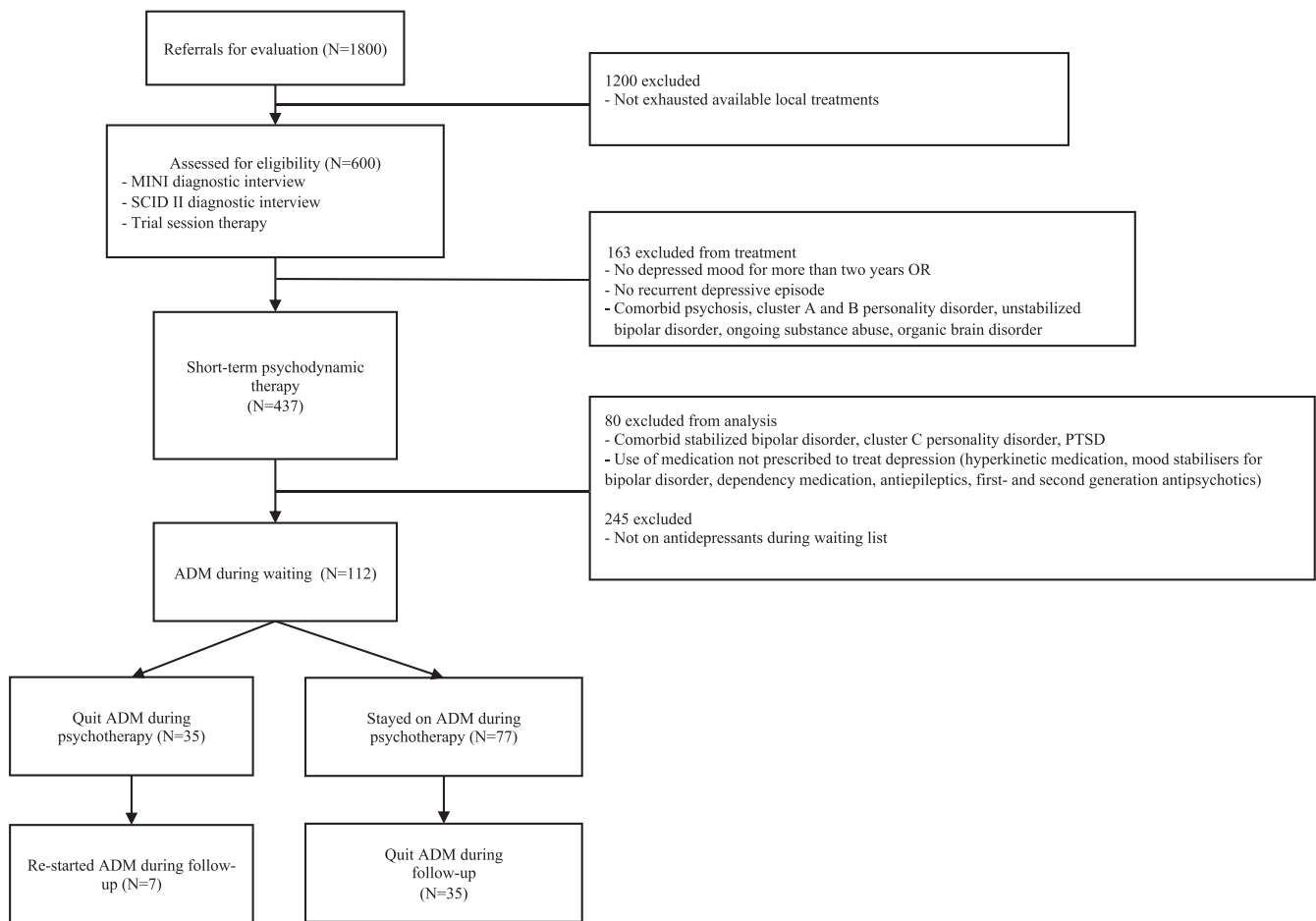
#### 3.2 | Procedures

##### 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 II 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.

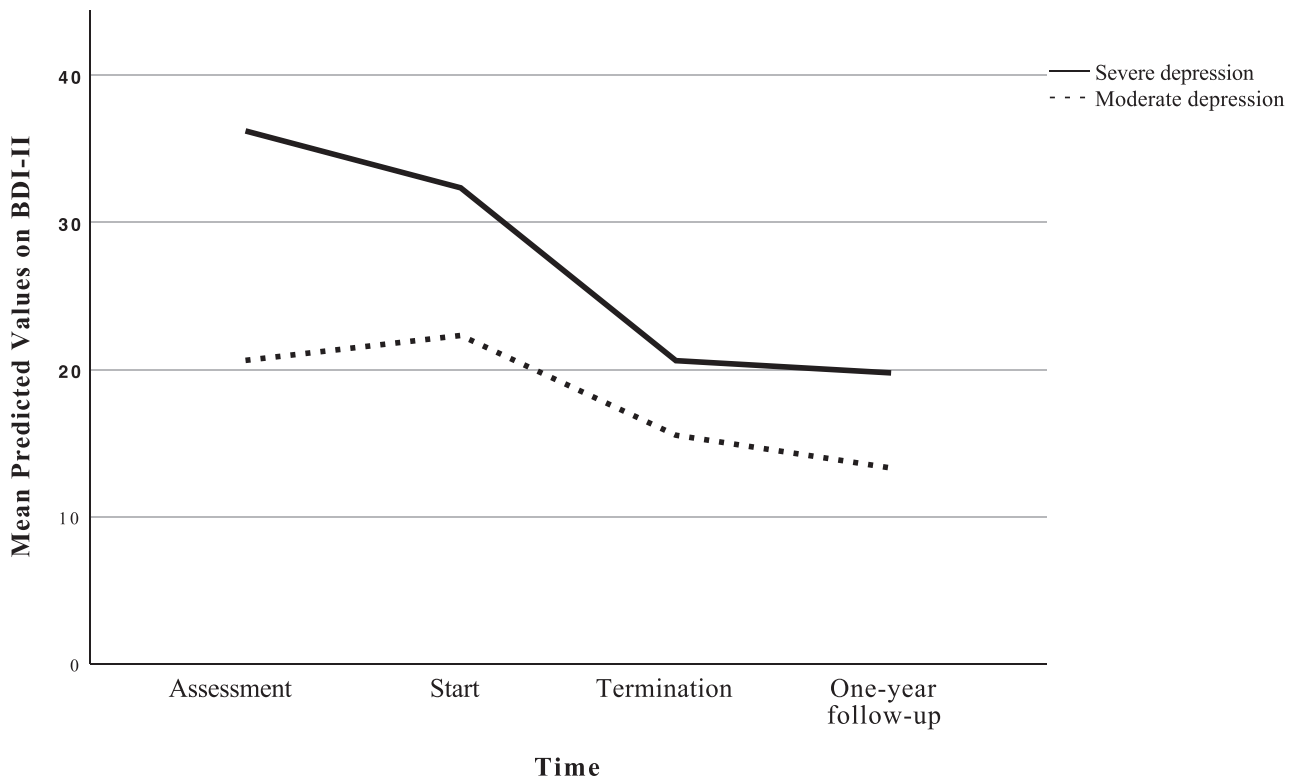
\*Significant at  $p \leq .05$ .

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.

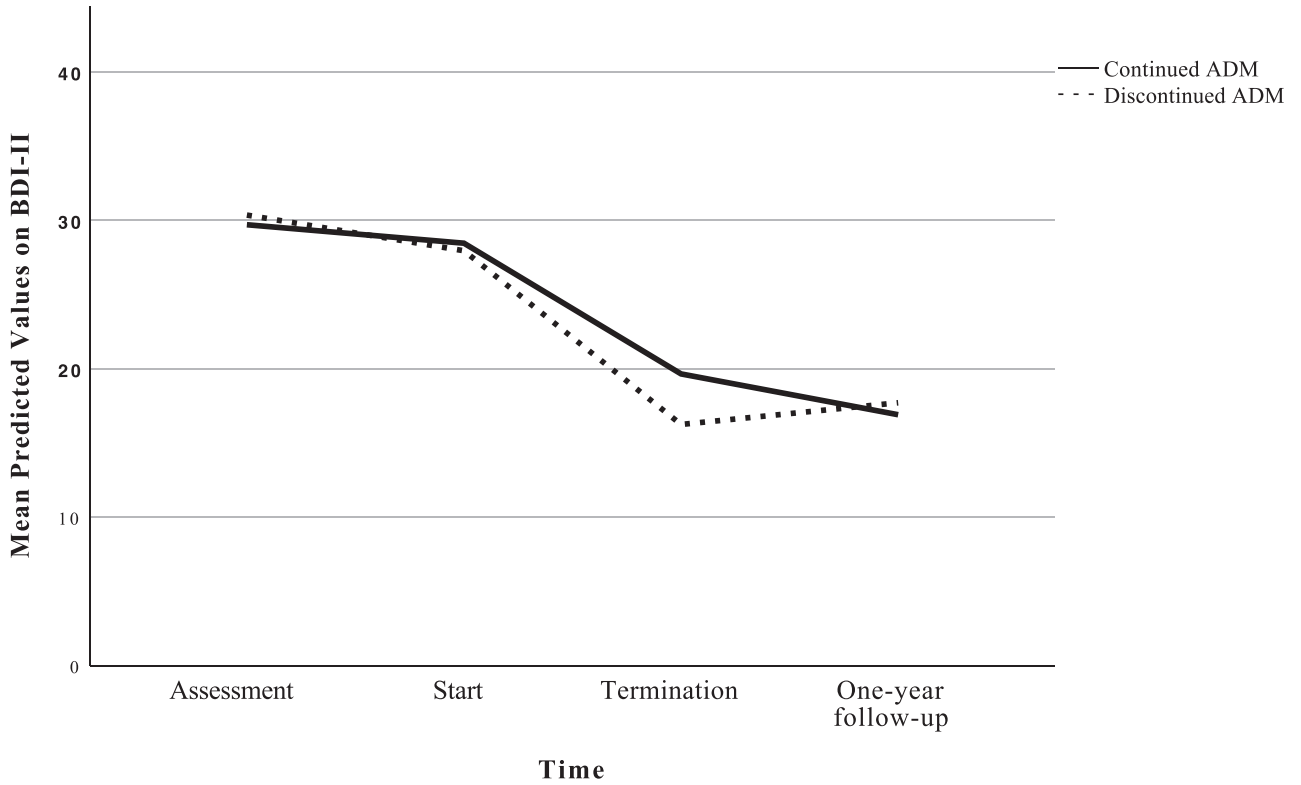
## 5 | DISCUSSION

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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