Master's thesis

Vegetative symptoms predict the treatment outcome of repeated-dose oral esketamine assisted psychotherapy in treatment-resistant depression.

Name and initials:	T.B. Prucker
Student number:	S3572757
E-mail address:	t.prucker@student.rug.nl
First assessor:	Dr. Stefanie Enriquez Geppert
Second assessor:	Prof. Dr. Anna Lichtwarck-Aschoff

External supervisors:	Dr. Jens H. van Dalfsen
	Prof. Dr. Robert A. Schoevers
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Are there deviations of the Master's thesis from the proposed plan?

☐No

☒Yes, please explain below the deviations

The model selection procedure proposed in the proposal did not apply anymore. Since there were only 3 relevant predictors (the dimensions) and two control variable, it was not really necessary to utilize an automated model selection procedure. There is enough evidence from the literature to include all three relevant predictors in the model and examine their predictive value on the outcome.

Abstract

Repeated-dose ketamine assisted psychotherapy alongside treatment as usual was proposed as a novel treatment option for treatment-resistant depression. However, not all patients benefit from the treatment. Determining for which patients this therapy might be effective is vital to prevent years of progressing illness and disability. In a sample of 162 patients diagnosed with treatment-resistant unipolar or bipolar major depression (MD) treated with repeated-dose oral esketamine assisted psychotherapy alongside their usual treatment for 6 weeks, Multiple Logistic Regression was used to determine which symptom dimensions of MD predict treatment effectiveness. Each one unit increase in vegetative symptoms decreased the likelihood of the patient to benefit from the treatment by one fifth. General health should be considered as a potential confounding factor. This study represents a step towards individualized treatment suggestions which might offer the potential for more effective treatment of MD.

Keywords: Precision medicine, Ketamine, Treatment Resistant Depression, Response Prediction

Introduction

Major Depression (MD) is one of the most common mental disorders. MD is diagnosed if a patient shows five or more symptoms of depression over the last two weeks. One of the five experienced symptoms must be 1) depressed mood and 2) loss of interest or pleasure. Other symptoms are changes in appetite and/or weight, cognitive and physical slowing down, fatigue, feelings of worthlessness and/or guilt, diminished ability to think and/or indecisiveness, and recurrent thoughts about death and/or suicide (American Psychological Association, 2022). Globally, around 5% percent of the adult population are affected (Cai et al., 2021; Shorey et al., 2022; Wang et al., 2017; World Health Organization, 2023). In the Netherlands this concerns an approximate total of 877,000 inhabitants. MD is connected to a high disease burden, disability, and heightened healthcare costs per patient (Bosmans et al., 2010; Penninx et al., 2013). Individuals suffering from MD commonly experience low well-being and reduced functioning in family relations, work, or school (Campbell et al., 2022; Gunnarsson et al., 2023; Kessler et al., 2003; Kupferberg et al., 2016; Wickersham et al., 2021). If left untreated, suicide might be a serious consequence of depression (Cai et al., 2021; Rihmer, 2001; World Health Organization, 2023). Thus, it is important to have efficient treatments available.

The treatment of Major Depression (MD)

The current treatment of MD comprises pharmacotherapy, psychotherapy and/or neurostimulation therapy (*Overview | Depression in Adults*, 2022). Pharmacotherapy predominantly concerns the prescription of antidepressants such as selective serotonin reuptake inhibitors (SSRIs) that can be provided individually (monotherapy), in combination (combination therapy), or together with different classes of psychoactive medication (augmentation therapy) such as lithium or atypical antipsychotics (Fava & Targum, 2007). Furthermore, MD is commonly treated with psychotherapy such as cognitive behavioural therapy (CBT) which has shown to be effective as stand-alone treatment, but most effective if

combined with pharmacotherapy (Cuijpers et al., 2013, 2020; *Overview | Depression in Adults*, 2022; Kamenov et al., 2017; Rush, Trivedi, et al., 2006).

The treatment of MD is organized in treatment steps that are selected based on trial and error (Z. D. Cohen & DeRubeis, 2018; Pigott, 2015; Rush, Trivedi, et al., 2006). Whereas the first steps usually comprise monotherapy and/ or psychotherapy, combination or augmentation therapy is reserved for patients that do not benefit sufficiently from the initial antidepressant treatment. Sufficient improvement can be defined in different ways such as the minimally clinically important difference (MCID; the minimal percent reduction in depression score from baseline to end of treatment that is experienced as meaningful by the patient)[1], response (50 percent reduction in depressive symptom score from baseline to the end of treatment), or remission (not meeting the criteria for MD anymore; B. C. Johnston et al., 2015; Rush, Kraemer, et al., 2006; Rush, Trivedi, et al., 2006). If the patient does not report to experience any of these measures of treatment effectiveness the next following treatment step is chosen (Rush, Trivedi, et al., 2006).

Counterintuitively, the more treatment steps a patient goes through the less likely it becomes that they will show clinical improvement during subsequent steps (Muit et al., 2022; Rush, Trivedi, et al., 2006; Sinyor et al., 2010). The STAR*D Trial is the most comprehensive study to date evaluating sequential antidepressant treatment (Pigott, 2015; Rush, Trivedi, et al., 2006; Sinyor et al., 2010). The results demonstrated that the likelihood to achieve remission declined from around 37 percent in the first treatment step to around 13 percent in the fourth treatment step – numbers that worsened with poorer baseline functioning, longer episodes as well as medical and/or psychiatric comorbidities (Rush, Trivedi, et al., 2006; Sinyor et al.,

[1] The percentage reduction that is experiences as meaningful differs per depression scale that is used, but is usually less than the 50 percent reduction that is needed to classify for treatment response (Rush et al., 2003).

2010). Furthermore, the probability to experience a relapse increased the more unsuccessful treatment steps a patient goes through. Ultimately, 20 to 30 percent of the patients did not improve after receiving several steps of antidepressant treatment (Rush, Trivedi, et al., 2006). This group of patients is commonly classified as having treatment-resistant depression (TRD).

Treatment-resistant depression

A treatment-resistant depressive episode is commonly defined as a depressive episode that failed to respond to at least two different conventional antidepressants at an adequate dose and duration consecutively (Gaynes et al., 2020) One pharmacological trial can take up to months, with weeks of dose finding and a waiting period of at least four weeks to see whether the depressive symptoms improve (Quitkin et al., 1984). TRD is not only restricted to MD but can also occur in Bipolar Disorder (BD) I and II (Hidalgo-Mazzei et al., 2019; C.-T. Li et al., 2012).

Generally, the longer the duration of TRD the more the quality of life of the patient decreases and the healthcare costs increase (K. M. Johnston et al., 2019). Following the completion of all recommended treatment-steps, TRD patients usually proceed to neurostimulation therapy, such as electroconvulsive therapy (ECT). ECT is an effective and cost- efficient treatment but is invasive, and carries a high patient burden (Degerlund Maldi et al., 2021; E. L. Ross et al., 2018; Veraart et al., 2021; Voineskos et al., 2020). Therefore, it is important to examine novel, effective, and more patient-friendly treatment strategies for this population as alternatives for ECT.

The use of ketamine in treatment-resistant depression

Over the last two decades ketamine received increasing attention for its efficacious and fast acting antidepressant properties that have been repeatedly reported for TRD (aan het Rot et al., 2012; An et al., 2021; Kishimoto et al., 2016; Smith-Apeldoorn et al., 2022; Veraart et al., 2021; Voineskos et al., 2020). Ketamine is a N-methyl-D-aspartate (NMDA) receptor antagonist that interacts with gamma aminobutyric acid (GABA), serotonin, opioid, dopamine,

and cholinergic receptors (Jelen & Stone, 2021; Zanos et al., 2018). Low doses of ketamine increase glutamate availability, giving rise to its fast acting antidepressant properties (Jelen & Stone, 2021; Kang et al., 2022). These heightened levels of glutamate increase the potential for neurogenesis through downstream effects, counteracting the neurodegeneration that has repeatedly been indicated as a landmark of depression (Price & Duman, 2020; Souza-Marques et al., 2021). As a neuroimaging study has shown, dendritic spines in affected areas increased after ketamine administration (Zhang et al., 2019).

Ketamine refers to both the S (esketamine) and R (arketamine) enantiomers of ketamine that differ in NMDA receptor affinity. Initially, esketamine received more attention in depression research than arketamine because it shows a three to four times higher affinity to the NMDA receptor and is considered a stronger anesthetic. More recently, research suggests that arketamine shows stronger antidepressant properties with less side effects in preclinical studies (Bahji et al., 2021; Hashimoto, 2020; Jelen et al., 2021). Whereas more research is needed into arketamine, it can be assumed that both es- and arketamine are potent antidepressants (Jelen & Stone, 2021).

The different forms of ketamine can be administered through various routes. Most widespread ways of administration in practice and research include intravenous, intranasal (and oral routes (Table 1). All routes are effective in the treatment of TRD overall, but they vary in bioavailability and response rates (Jelen & Stone, 2021; Meiering et al., 2022; Nuñez et al., 2020). Whereas intravenous administration has been connected to the strongest antidepressant effects, intranasal dispersion is the route that has been officially registered for the treatment of TRD (Bahji et al., 2021; Jelen et al., 2021). More recently, the body of literature is growing for PO administration. The reason for this increase might relate to 1) the familiarity in administration for both patients and practitioner (the oral route recently is widely used in clinical practice), 2) the feasibility for both large scale and home administration and, 3) a milder

side effect profile (Bahji et al., 2021; Jafarinia et al., 2016; Jelen et al., 2021; Schoevers et al., 2016; Smith-Apeldoorn et al., 2022).

Table 1. Response rates and bioavailability of ketamine per administration route.

	Administration route		
	Intravenous	Intranasal	Oral
Response rates	42%[3]	25%[1]	18%[3]
Bioavailability	100%[2]	93%[2]	20%[2]

Note.[1]Meiering et al. (2022), [2] Jelen & Stone (2021), [3]Nuñez et al. (2020).

The heterogeneity in the presentation of Major Depression

While ketamine represents a promising antidepressant agent for the treatment of TRD, the limited response and remission rates demonstrate that it is not efficacious in all patients (aan het Rot et al., 2012; An et al., 2021; Kishimoto et al., 2016; Smith-Apeldoorn et al., 2022; Veraart et al., 2021; Voineskos et al., 2020). This marked variation in the clinical effectiveness of ketamine could be explained by interindividual differences between patients in the clinical presentation of depression. Even though patients are diagnosed with MD if they present with five out of nine symptoms as specified in the Diagnostic and Statistical Manual of Mental Disorders (DSM), in total 227 different combinations of symptoms are possible to meet the criteria for MD (Fried & Nesse, 2015; Goldberg, 2011; Zimmerman et al., 2015). In a sample of 1,500 patients that met the criteria for MD 170 different symptom combinations were present (Zimmerman et al., 2015). Furthermore, subtypes of depression such as atypical or agitated depression which are defined by specific combinations of the symptoms of MD that might vary between different studies (Benazzi, 2006; Bielski & Friedel, 1977; Carragher et al., 2009; Kung et al., 2021; Lam & Stewart, 1996; McGrath et al., 1992).

Precision medicine to uncover predictors of treatment outcome

Given the marked heterogeneity in depression, precision medicine might spare patients from going through many treatment attempts before finding the treatment that works for them (Z. D.

Cohen & DeRubeis, 2018; Lynch et al., 2020). The goal of precision medicine is to uncover whether and which characteristics of a patient (such as socio-demographic aspects, biological markers or clinical characteristics) predict the effectiveness of available treatments beyond trial and error (Simon & Perlis, 2010). A broad range of predictors, such as the number of depressive episodes, age, comorbidities, rapid eye movement (REM) sleep or epigenetic markers have been reviewed for their potential to predict the treatment outcomes for patients diagnosed with MD or BD I and II (Perlman et al., 2019).

In line with the promise's precision medicine has to offer for patients, research has set out to uncover reliable predictors of a successful treatment trajectory for the innovative treatment ketamine. The investigation of neurobiological marker are still in their infancy but have so far been mentioned to be neuroimaging and electrophysiological, sleep and circadian, immunologic, neurotrophic/plastic, metabolic/bioenergetic, genetic/epigenetic markers (Kadriu et al., 2020; Matveychuk et al., 2020). Furthermore, sleep characteristics, history of metabolic syndrome, early symptom improvement, dissociative symptoms during the treatment and a history of alcohol use disorder were found to be predictive of the treatment outcome with esketamine (Dale et al., 2020; Kadriu et al., 2020; Lipsitz et al., 2021; Matveychuk et al., 2020; Rong et al., 2018). Given the heterogeneity hypothesis describes variations in the symptoms of MD it makes them logical targets to examine. Nevertheless, little is known about the predictive value of symptoms as markers of treatment effectiveness.

Adjacent to the heterogeneity hypothesis of MD variations in the symptoms of MD were predictive of the treatment outcome in both conventional antidepressant and ketamine treatment, even though the strength of their predictive quality are widely unreported (Browning et al., 2021; Chekroud et al., 2016; Kadriu et al., 2020; McGrath et al., 1992). However, conventional antidepressants treatment outcomes are for instance predicted by low symptoms of atypical depression such as oversleeping, overeating and pathological rejection sensitivity (Chekroud et al., 2016; McGrath et al., 1992). Insomnia is a widely researched predictor that

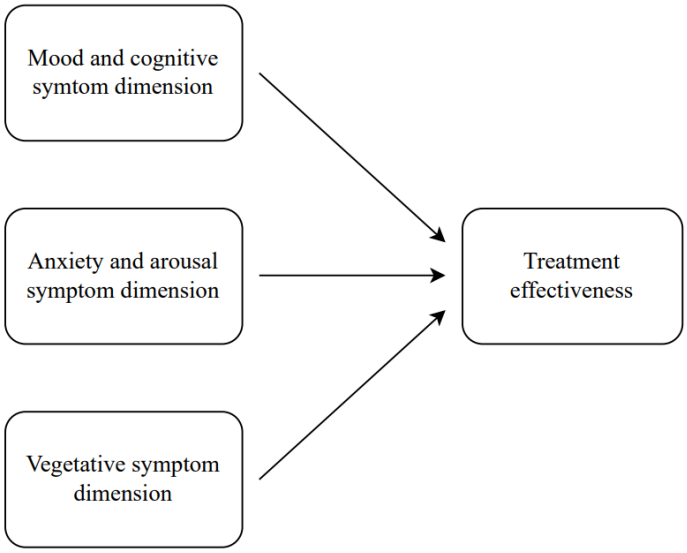
showed a three times higher chance of treatment response compared to placebo (Liu et al., 2020) and improvements in insomnia mediated the treatment response to ketamine (Rodrigues et al., 2022).

While individual depressive symptoms are promising predictors in conventional pharmacological treatment of MD these studies all have the same methodological limitation. On established measures of MD such as the Hamilton Depression Rating Scale (HAMD) or the Inventory of depressive symptoms - self rated (IDS-SR) symptoms were often represented by a single item (Browning et al., 2021; Chekroud et al., 2016; Kadriu et al., 2020; McGrath et al., 1992). Measuring constructs by a single item is prone to unreliability, thereby diminishing their predictive quality, an issue that worsens with small sample sizes. It is suggested that a more effective approach would involve examining dimensions of symptoms, measured by multiple items on MD scales as predictors of the treatment outcomes in both MD and BD I and II (Borsboom, 2006). Increasing the number of items to describe each predictor which in turn increases the reliability and thus quality of the predictor (Diamantopoulos et al., 2012). Consequently, replication studies are necessary to further explore this matter.

The present study

The current study aims to enhance the body of literature on the response prediction for ketamine treatments in TRD by examining whether dimensions of depressive symptoms are predictive of the treatment outcome of ketamine. Rush et al. (1996), describes 3 different symptom dimensions of MD: 1) mood and cognitive symptom domain, 2) anxiety and arousal symptom domain, as well as the vegetative symptom domain, which will be examined for their predictive capacity of the treatment effectiveness of oral esketamine assisted psychotherapy as an add on to patients treatment as usual (Figure 1). Secondary data-analysis will be performed in data from an open-label study without control group that includes 162 in- and outpatients treated with repeated-dose oral esketamine assisted therapy alongside their treatment as usual for six weeks.

Figure 1. Conceptual prediction model of treatment outcome by symptom dimension.



Note. Left: symptom dimension that represent the predictors of treatment effectiveness; right: dependent variable "treatment effectiveness".

Method

Study description

This study is a secondary analysis of the data obtained during a multicentre six-week off label trial that assessed the effectiveness of repeated-dose oral esketamine assisted psychotherapy as an add on to treatment as usual on depressive symptoms in TRD. The trial aims at providing real world evidence in the treatment of treatment-resistant MD and BD I and II and does not include a control group. In this off-label program in- and outpatients were treated. The trial took place at the University Medical Centre in Groningen (UMCG), Pro-Persona in Nijmegen and Parnassia in Den Haag. The off-label treatment program was approved by the Dutch Medical Ethical Committee in 2017. Upon participation in the program, the patients chose to give their informed consent. Patients were informed that treatment is voluntary and can be discontinued at any time.

Inclusion and exclusion criteria

Patients with moderate to severe treatment-resistant MD or BD according to the Diagnostic and Statistical Manual of Mental Disorders in its fifth edition (DSM-5) were included in this off-label trial. Recruitment took place through referral by a clinical professional of the University Medical Center Groningen (UMCG), Pro Persona in Nijmegen or Parnassia in Den Haag. Most of the patients (60,5%) were referred to Groningen less to Nijmegen (19,8%) and Den Haag (19,1%).

Patients were referred for participation in this off-label program if they were 18 years or older and fluent in the Dutch language. Some of the included patients had already participated in another randomized controlled trial (RCT) "Oral S-ketamine for treatment-resistant depression" before enrolling, but did not sufficiently recover after the RCT, relapsed within three months following the RCT, or fulfilled the inclusion criteria of the RCT but could not take part for other reasons.

Patients were not included in the off-label treatment program if they 1) were not able to give informed consent, 2) had a chronic or acute use of alcohol or 3) active substance use disorder, 4) are currently treated with electroconvulsive therapy (ECT), 5) were prescribed absolute and relative contraindicated medications (e.g., MAO inhibitors) 6) had contraindicated medical conditions (e.g., dementia, pregnancy, hypertension). The inclusion of patients with a history of psychotic disorder, personality disorder, substance, or alcohol use disorder, or that used monoamine oxidase inhibitors (MAO-I) and/or non-prescribed psychoactive substances in the past four weeks were included on a case-to-case basis.

Procedure

The Mini-International Neuropsychiatric Interview (M.I.N.I) structured interview was used to assess whether interested patients fulfilled the criteria of a MDD or BD diagnosis. Furthermore, an echo of their heart, blood collection and a report of the medication use of the patient was administered.

Patients were treated in a quiet room with comfortable chairs (Appendix B). During the sessions patients could choose freely whether they wanted to be alone, with a loved one or with staff, listen to music, have their eyes open or shut and whether the therapist was allowed to give support by touching the patients' underarm or holding their hand (psychological supportive touch). After the acute effects of the ketamine wore off patients could choose to debrief their experience with a professional that was schooled in accompanying ketamine therapy sessions. Twice per session a nurse checked the patient's blood pressure. Patients could choose to plan an extra integration session with the attending psychologist if they wanted to discuss experiences further.

The IDS-SR were assessed once per week from baseline to week six on Tuesday mornings. The HDRS was recorded at baseline and at the end of the treatment in week six.

Treatment

Esketamine

For this trail oral esketamine was used. Esketamine is an officially registered medicine in the Netherlands with low side effect profile, strong antidepressant effects (Fourcade & Lapidus, 2016; Muller et al., 2016; Singh et al., 2016). The oral route was chosen because it has been associated with fewer side effects, is less invasive, and easier to administer on a large scale than other administration routes (Jafarinia et al., 2016). The treatment took place twice weekly for 6 weeks. This frequency and length were chosen because it has been found to be enough to give and maintain antidepressant effects (Han et al., 2016; Irwin et al., 2013; Jafarinia et al., 2016; Kishimoto et al., 2016; Muller et al., 2016; Singh et al., 2016). Over the course of the six-week treatment patients received a total of 11 doses.

The optimal dosage per administration was determined via a tampering schedule. Dosing began by 0.5 mg/kg body weight oral esketamine and could be heightened to a

maximum of 2.0 mg/kg body weight. If the dosage was well-tolerated by the patient the dosing schedule was adapted to a minimum dose of 1 mg/kg and a maximum dose of 3 mg/kg oral esketamine. The final dose was expected to be set after a maximum of 3,5 weeks of tampering. In case of adverse events that were intolerable to the patient the dose was lowered. Paracetamol, ondansetron, or antihypertensive medication could be given additionally to manage mild treatment emergent adverse events such as headaches, hypertension and nausea (Protocol Ketaminebehandeling, 2019).

Psychotherapy

Both in- and outpatients that took part in this trial received supplementary therapy to the esketamine sessions. Patients received psychotherapeutic sessions to discuss the experiences during the esketamine sessions (integration sessions). The therapeutic approach during the esketamine sessions was based on the Yale manual of psylocibin assisted psychotherapy (Guss et al., 2020). The therapeutic approach of this manual is based on the principles of acceptance and commitment therapy (ACT) as well as mindfulness based cognitive therapy (MBCT). Once a week the psychiatric ward offered group cognitive behavioural therapy (CBT), behavioural activation and occupational- and art therapy to the patients (Beck, 2021; Blomdahl et al., 2013; Christie et al., 2021; Dimidjian et al., 2014; J.-M. Li et al., 2018; Probst, 2010).

Measures

Symptom dimensions of the Inventory of depressive symptoms – self rated (IDS-SR)

Depressive symptom dimensions were measured with the self-rated Inventory of Depressive Symptoms (IDS-SR), developed by Rush et al. (1986; 1996) that was designed to measure depressive symptom severity. The IDS-SR is based on the DSM description of depressive symptoms. The patient is asked to rate the symptoms over the past 7 days. Items are

measured on a scale from “0-3” with “0” describing the absence of symptoms and “3” high expression of depressive symptoms. The total score ranges from 0-78 with 27 of the 30 items contributing to this total score. There are other items such as weight and appetite increase or decrease which cannot both occur in the same patient. The optimal cut-off threshold to distinguish clinically relevant depression from healthy control lies by a total score of 18, with scores of 18 or higher signal depression (Rush et al., 1996).

The IDS-SR has been shown to be sensitive to change by differentiating between different severities of depression (Corruble et al., 1999; Trivedi et al., 2004). Concurrent validity has been high when comparing the IDS-SR to the Montgomery Asberg Depression Rating Scale (MADRAS; Trivedi et al., 2004). The IDS-SR has been able to differentiate between depressed patients and healthy or recovered control in both MDD (Corruble et al., 1999; Rush et al., 1986, 1996; Trivedi et al., 2004) and BD (Rush et al., 1986; Trivedi et al., 2004). The measure of Cronbach’s Alpha ranged from Cronbach’s *a*= .76 -.85 (Corruble et al., 1999; Rush et al., 1986; Trivedi et al., 2004). In the current sample the Cronbach’s α was excellent (Cronbachs *a*=.98*).*

The symptom dimensions were established by Rush et al. (1996) through factor analysis in a sample of unipolar major depression, BD, euthymic depression, and other psychiatric disorders. The dimensions were defined as the mood and cognitive symptom dimension with 14 items, the vegetative symptom dimension with 7 items and the anxiety and arousal symptom dimension with 8 items. [2] Cronbach’s Alpha of the subscales varied from *poor* to *excellent* between symptom domains in this sample (mood and cognitive symptom dimension: Cronbach’s *a*= .83; anxiety and arousal symptom domain: Cronbach’s *a*= .60; vegetative symptom domain: Cronbach’s *a*= .93).

[2] For a complete overview of the symptoms included per subscale, please consult appendix A.

Treatment effectiveness: The Minimally Clinically Important Difference on the Hamilton Depression Rating Scale (HDRS)

Treatment effectiveness was measured with the HDRS is a clinician-administered questionnaire that measures depression severity (Hamilton, 1960). The HDRS is administered via a structured interview. Seventeen items are included that describe symptoms of depression and the severity of the depressive episode. The patient is asked to elaborate on the severity of the symptoms considering the last week. Symptoms that show high variability in its strength in different patients such as depressed mood were measured on a scale from 0 to 4. Symptoms that usually show less variability such as illness insight are scored on a scale from 0 to 2. For both scales higher scores represent higher severity. For each item there was a written description of what each score would present in a patient to guide the clinician ratings. Total scores are calculated by summing up the item scores. Scores of 10 to 13 represent mild, 14 to 17 mild to moderate and higher than 17 moderate to severe MD (Hamilton, 1967).

The HDRS total scores show good overall reliability in measuring global depression severity (Trajković et al., 2011). Based on the evaluation of 5,548 articles on the reliability results demonstrated an acceptable to high reliability estimate (Cronbach's alpha α = .79, inter-rater reliability = .94 and test-retest reliability = .65-.98). In the current sample the Cronbach's α was poor (Cronbachs *a*=.67*).*

Treatment effectiveness in this study was operationalized using the concept of the minimal clinically important difference (MCID) measured on the Hamilton Depression Rating Scale (HDRS). The MCID is determined by a score reduction of ≥27.1 percent in the overall depression score from baseline to end of treatment, as this level of improvement is considered the minimum threshold for patients to perceive the treatment as beneficial. The use of the MCID as an outcome criterion holds greater significance compared to simply examining difference scores, as smaller reductions in symptoms may be statistically useful but lack meaningful value for the patient (Boardman & Dave, 2020).

Secondary measures of treatment effectiveness were response (50% decrease in depressive symptoms on the IDS-SR since treatment entry) and remission absence of sadness or loss of pleasure while showing less than three of the other DSM criteria for depression as assessed by the MINI structured interview (Rush, Kraemer, et al., 2006; Rush, Trivedi, et al., 2006).

Statistical Analysis

Main analysis: Symptom dimensions as the predictors of treatment effectiveness

Multiple logistic regression was used to analyse whether symptom dimensions were predictive of treatment effectiveness. The symptom dimensions anxiety and arousal, mood and cognitive and vegetative symptoms are the independent variables, whereas treatment effectiveness is the dependent variable in this analysis. Treatment effectiveness was operationalised as MCID which was calculated per participant and coded as 1 = effective and 0 = not effective. We controlled for gender (male = 1, female = 0) and type of diagnosis (unipolar =1, bipolar =0). Depression rates were found to be 3 times higher in women than in men, but no gender differences were observed for BD (Dell'Osso et al., 2021; Parker & Brotchie, 2010). Besides the popular approach to control for depression severity at baseline it was decided against it in our sample of *severe* levels of depression, as it was recently indicated that it is not necessary (Hieronymus et al., 2019; Kirsch et al., 2008).

Missing data. Missing data is handled after the steps depicted in Jakobsen et al. (2017) that guide the decision on whether imputation should be considered. Jakobsen et al. (2017) base their advice on the pattern, location, and amount of missing data. The pattern of missing data is assessed by Little's Missing Completely at Random test (MCAR). The null hypothesis of the MCAR test states that the data is missing completely at random (Little, 1988). The assumptions of c*onvergence* of multiple imputation and the *plausibility* of imputed values were examined visually (Austin et al., 2021). The number of imputation rounds was determined with the general rule of thumb to choose ten rounds per predictor (van Buuren, 2018).

Assumptions. The assumptions of multiple logistic regression as defined by Stoltzfus (2011) were examined. The linear relationship between the predictor variables and the log odds transformed outcome variable was inspected via scatterplots. Multicollinearity was checked via the bivariate correlations of the symptom dimensions. Independence of errors was assumed to be warranted by the between subject design and was thus not formally tested. Influential observations defined by a Cook's distance value that deviated more than three standard deviations from the mean cook's distance were excluded (Agresti, 2018).

Model fit and performance. The model fit was assessed with the Hosmer-Lemeshow test draws on the X^2 -distribution with small *p*-values representing poor model fit. The null hypothesis of the test indicates that expected and observed values of the test are the same indicating a good model fit (Hosmer et al., 1980). The performance of the final model was investigated through a Receiver Operating Characteristic (ROC) curve per symptom dimension. Consecutively the area under the curve receiver operating characteristic curve (AUC) was fitted. The AUC can have values between zero and one which represent the probability that a randomly picked subject will be classified in the right group. An AUC value of 1 thus represents perfect discrimination, .5 discrimination at chance level, and 0 an incorrect classification of all subjects (Hajian-Tilaki, 2013). The AUC value can be interpreted as *poor* (*AUC*= .5 - .7), *acceptable* (*AUC*= .7 - .8), *excellent* (*AUC*= .8 - .9) and *outstanding* (*AUC* ≥ .9; (Hajian-Tilaki, 2013).

Sensitivity analysis. To examine the sensitivity of the model to potential outliers the logistic regression model was fitted twice with and without the influential observations. Change in Assumptions, AUC-parameter and predictive capacity of the symptom dimensions, and model fit was examined. Comparative model fit was assessed for the prediction model with and without influential observations. Comparative model fit was operationalized with the Akaike Information Criterion (AIC). A lower AIC indicates better model fit. A model is defined to fit

better if there it has a at least ten points lower AIC than the model it is compared to (Chakrabarti & Ghosh, 2011).

Secondary Analysis 1: The capacity of the symptom dimensions to predict response and remission.

Multiple logistic regression was performed to explore the predictive value of the depressive symptom dimensions on treatment effectiveness if defined by response and remission if controlled for gender and type of diagnosis. Response and remission followed the same coding schema as the MCID with 1= response/remission and 0= non-response/ non-remission.

Secondary analysis 2: The size and significance of the reduction of overall MD scores and specific symptom dimension scores.

To examine how much overall depression and symptom dimension scores reduced in this sample during the treatment period Paired Samples T-Test at α= .05 were conducted. The null hypothesis of a Paired Samples T-Test states that the paired differences between baseline and end of treatment scores across participants do not differ from zero (A. Ross & Willson, 2017). Overall reduction in MD scores compared whether there has been a significant reduction in HDRS scores from baseline and week 6 across all participants. For the symptom dimension the scores on the IDS-SR from baseline to week 6 were examined. The practical importance of the Paired Samples T-Tests were operationalized as Cohen's *d* that specifies small (*d*= .2), medium (*d*= .5) and large (*d*= .8) effects (J. Cohen, 1988).

Assumptions. The assumptions of the Paired Samples T-Test were examined. Normality was not necessary to assess formally, because the number of compared differences was large enough to assume that the Central Limit Theorem applies (Agresti, 2018). Outliers were defined as ±3 standard deviations away from the mean difference across participants. Outliers were examined through boxplots and excluded (Agresti, 2018). Independent sampling of the observations was warranted by the study design of the multicentre trial.

All data analysis was conducted in RStudio version 4.1.1 (R Core Team, 2021).

Results

Demographic characteristics, clinical characteristics, and treatment outcomes

From the initial 162 patients included in the treatment program 15 patients (9%) discontinued prematurely for unknown reasons. This resulted in 147 patients that were included in the analysis. In this sample 105 patients (64,8%) are female. Patients were between 21 and 82 years old, at the start of their treatment with a mean of approximately 32 years (*SD*= 28 years). Most patients in this sample had unipolar depression (89.8%). On average patients that took part in this trial had 10 depressive episodes (*SD*= 19.05). The average length of the current episode was around 54 months (*SD*= 39.24). Patients used a variety of different medications while taking part in this trial (Table 1).

On average the depression scores in this sample exceeded the cut-off score indicating clinical depression on the HDRS and IDS-SR. The average depression severity at baseline was considered *serious* (*M*= 21.31*; SD*= 5.61). Patients scored highest on the Mood/Cognitive dimension (*M*= 2.01*; SD*= 0.51) and lowest on the VSD (*M*= 1.15*; SD*= 0.50). For an overview of demographic and clinical characteristics per group (overall, MCID, response, remission) please consult Table 2.

At the end of the treatment the average MD scores were considered *moderate*. Around one third of patients reached the MCID (33%) at the end of treatment whereas less showed a response (20%) to treatment and even fewer reached remission (12%).

Table 1. Patients' pharmacological treatment as usual

	Pharmacological agent and/or strategy							
	Selective Serotonine Reuptake Inhibitors (SSRI)	Selective Norephinedrine Reuptake Inhibitors (SNRI)	Tricyclic Antidepressants (TCA)	Lithium	Monoamine Oxidase Inhibitors (MAOI)	Augmentation strategies (e.g., anti-psychotic)	Other (e.g., Saint John's wort)	Unknown
Ammount	23	12	24	3	9	17	55	63

Note. Unknown = No information of the patients' treatment as usual was indicated. The amount is indicated in counts. A patient can use multiple medications/strategies.

Table 2. Clinical characteristics, demographic characteristics, and depression scores at baseline

Characteristic	Overall	MCID	Response	Remission
|Group size, *n (%)*	147 (100)	54 (33)	32 (20)	19 (12)
Demographic characteristics				
Male sex, *n (%)*	48 (33)	19 (44)	15 (47)	9 (47)
MD diagnosis, *n* (%)	79 (91)	35 (92)	21 (91)	13 (87)
Age in years, *M (SD)*	52.49 (13.38)	51.97 (13.37)	53.53 (11.85)	57.90 (9.53)
Psychiatric history				
Number of lifetime depressive episodes, *M (SD)*	9 (17.91)	7.68 (7.40)	7.23 (7.62)	8.80 (9.51)
Length of current depressive episode in months, *M (SD)*	54.21 (38.89)	54.88 (39.56)	57.92 (41.78)	68.93 (42.29)
Depression scores				
Overall Hamilton Depression Rating Scale, *M (SD)*	21.31 (5.61)	20.63 (4.99)	19.88 (4.74)	17.53 (4.01)
Mood and cognitive symptom dimension, *M (SD)*	2.01 (.51)	1.96 (0.49)	1.86 (.51)	1.77 (0.91)
Anxiety and arousal symptom dimension, *M (SD)*	1.24 (.49)	1.24 (0.52)	1.25 (0.5)	1.12 (0.50)
Vegetative symptom dimension, *M (SD)*	1.15 (0.50)	1.06 (0.44	0.98 (0.4)	0.91 (.39)

Note. MD = Major Depression.

Main analysis: Symptom dimensions as the predictors of treatment effectiveness

The mood and cognitive symptom dimension, the anxiety and arousal symptom dimension and the vegetative symptom dimension were examined as predictors of treatment effectiveness (MCID) when controlling for the age and type of diagnoses of the patients. Vegetative symptoms predicted treatment effectiveness significantly (z= -2.0, p= .046). The effect of the vegetative symptom dimension on treatment effectiveness with every one-point increase in vegetative symptoms the odds of achieving the MCID decreased by around one fifth (*OR*= .22, *OR-95% CI* [.05, .97]). The patient group with no to low symptom expression (IDS-SR vegetative symptom score = 0 - 1.5) did indeed show the highest amount of MCIDs (low = 41 MCIDs, other = 5 MCIDs). Thus, the lower the level of vegetative symptoms at baseline the higher the likelihood of the treatment with ketamine to be effective.

The mood and cognitive symptom dimension (z= -1.36, p= .17) as well as the anxiety and arousal symptom dimension (z= *.81*, p= .42) did not significantly predict treatment effectiveness (Table 3).

Missing data. Across the dataset 19 percent of data was missing due to the failure to a failure to collect it by staff or the patients. On each of the dependent and independent variables missing data was more than five percent. The null hypothesis that the data is missing completely at random was rejected (X^2 (29, 10) = [32.7], p= .291). If the prediction model was fitted the amount of missing data increases to 48 percent due to listwise deletion which warrants imputation (Jakobsen et al., 2017). 50 rounds of data were imputed. There was no reason to assume that the convergence assumption was violated. The imputed values seemed plausible. There was no striking difference if the prediction model was built on the imputed versus the non-imputed data set. The standard errors for the estimates of the imputed and non-imputed model did not differ up to the 5th decimal place. Therefore, the final model was fitted on the complete cases data set, due to its higher degree of parsimony.

Assumptions. There was no reason to assume a violation of linearity between the predictors and the log odds transformed outcome values when examined in scatterplots. There was also no evidence of multicollinearity because correlations between the independent variables were negligible (Table 3). Six observations were deemed influential and excluded.

Model fit and performance. The Hosmer-Lemeshow test did not indicate poor model fit (X^2 (8,70) = [7.62], p= .47). The model shows *acceptable* capacity to discriminate between patients for whom the treatment was effective versus patients where the treatment was not effective based on their gender, diagnosis, and the scores on the symptom dimensions (*AUC* = .7). The POC curve can be found in Appendix D (Figure D1).

Sensitivity analysis. Including influential observations did have an impact on the significance of the model estimates. If influential observations were included in the analysis the VSD did not remain significant (z= -1.53, p= .125). There was no evidence of poor model fit as indicated by the Hosmer-Lemeshow test (X^2 (8,70) = [8.63], p= [.37]). As expected, the AIC of the model without the influential information was around 13 points lower than the model with influential information pointing towards better model fit (*AIC*= 113 vs. *AIC*= 100). Model

performance as operationalized as AUC also decreased to *AUC*= .63 indicating poor discrimination. Please consult Appendix D for the POC curve (Figure D2).

Including the influential observations into the analysis did not lead to any notable changes in the assumptions. If included many correlations between the predictors changed, but never by more than .1, or led to a belief that multicollinearity might occur (Table 4). Linearity was not violated by including influential observations.

Table 3. *Correlation matrix of the prediction symptom clusters and control variables.*

Measure	1	2	3	4	5
1. Mood and cognitive symptom domain	-				
2. Anxiety and arousal symptom domain	.43	-			
3. Vegetative symptom domain	.41	.39	-		
4. Diagnosis	-.01	.08	-.07	-	
5. Gender	-.13	.06	.06	-.14	-

Note. Correlations between quantitative variables are represented by Pearson r Correlations, quantitative and qualitative by point biserial correlation coefficient and qualitative-qualitative by phi.

Table 4. *Correlation matrix of the prediction symptom clusters and control variables with influential observations.*

Measure	1	2	3	4	5
1. Mood and cognitive symptom domain	-				
2. Anxiety and arousal symptom domain	**.44**	-			
3.Vegetative symptom domain	**.48**	**.41**	-		
4. Diagnosis	**-.06**	**.07**	.07	-	
5. Gender	**-.07**	**.03**	.06	**.22**	-

Note. Correlations that changed due to the exclusion of influential observations are printed in **bold.**

Secondary analysis 1: The capacity of the symptom dimensions to predict response and remission.

Response was significantly predicted by the mood and cognitive symptom dimension (z= -2.08, p=.037). The lower the mood and cognitive symptoms of a patient the higher their likelihood to respond to the repeated-dose oral esketamine assisted psychotherapy. With every one-point increase in mood and cognitive symptoms the odds of responding to the treatment decreased by one fifth (*OR*= .20, *OR-95% CI* [.05, .91]). The vegetative (z= -1.68, p= .09) as well as the anxiety and arousal (z= 1.94, p= .51) symptom dimensions were not predictive of treatment response. *Remission* was not significantly predicted by either of the mood and cognitive (remission: z= -1.55, p= .12), anxiety and arousal (z= -.60, p= .55) or vegetative (z= -.73, p= .47) symptom dimension. For a detailed overview please conduct appendix C (Table C2: response, Table C3: remission)

Both response (*AUC*= .72) and remission (*AUC*= .80) showed *acceptable* discrimination. The corresponding ROC-curves can be found in Appendix D (Figure D3: response; Figure D4: remission). There was no evidence of poor model fit as defined by the Hosmer-Lemeshow test for neither response (X^2 (8, 84) = [8.63], p= [.52]) nor remission (X^2 (8, 86) = [5.10], p= [.75]). The number of observations needed per category to allow for five predictors was grossly violated for both response (n= 32) and remission (n= 19). Other assumptions of Multiple Logistic Regression did not seem to be violated.

Secondary analysis 2: The size and significance of the reduction of overall MD scores and specific symptom dimension scores

Overall there was a significant reduction of depression scores between baseline and the end of the treatment at week six on the HDRS (t(121) = 8.97, p <.001). This reduction resembled about 5 points (95% CI [3.97, 6.21]), which represents a *large* effect (d =.81). At the end of treatment the patients report a significant reduction (t(102) = -8.02 , p <.001) on the mood and

cognitive symptom dimension of about -.38 points (95% CI [-.48, -.29]) representing a *large* effect (Cohen's d= .79). Anxiety and arousal symptoms did also reduce significantly across participants (t(103)= -3.36 , p= .001). The reduction spanned -.12 points (95% CI [-.18, -.05]) which can be interpreted as a *medium* effect (d= .33). On the vegetative symptom dimension patients also experienced a significant reduction (t(104)= -5.71 , p <.001) in symptoms of about -.24 points (95% CI [-.33, -.16]) resembling a *medium* effect (d= .56).

Discussion

A secondary analysis of a six-week multicentre off-label repeated-dose oral esketamine assisted psychotherapy trial as an addition to treatment as usual for patients with treatment-resistant unipolar and bipolar depression was conducted. The goal was to examine which symptom dimensions of treatment-resistant depression could predict which patients will experience the treatment as beneficial to them. Predicting who will benefit from ketamine treatment might enable more individualized treatment recommendations to match patients and treatment options more effectively. The results, their embedding in the existing body of literature, strengths and limitations of this study and future directions will be discussed.

Depending on the operationalisation of treatment effectiveness the predictors changed. The MCID was predicted by low levels of vegetative symptoms at treatment begin if controlled for gender and type of diagnosis. Per one point increase in vegetative symptoms the odds of achieving clinical effectiveness decreased by one fifth. The mood and cognitive symptom domain as well as the anxiety and arousal symptom domain did not reach significance in predicting which patient will experience an effective treatment with esketamine. If treatment effectiveness was operationalized as treatment response the mood and cognitive symptom dimension and not the anxiety and arousal or vegetative symptom dimension was predictive of patients that were likely to benefit from the repeated-dose oral esketamine assisted psychotherapy. A one-point increase in mood and cognitive symptoms at baseline decreased the odds to respond to the repeated dose oral esketamine assisted psychotherapy by one fifth. If treatment effectiveness was operationalized as remission none of the symptom dimensions were predictive. Lastly, treatment effectiveness defined by remission was predicted by neither of the three-symptom dimension.

Besides the changing predictors of different operationalizations of treatment effectiveness patients experienced significant reductions on both overall MD scores and each single symptom dimensions. Repeated-dose oral esketamine assisted psychotherapy patients'

had a significant and large effect on the reducing of the overall depression score of patients. Similar effect size was observed for the reduction in the mood and cognitive domain. The anxiety and arousal and vegetative symptom dimensions also reduced significantly throughout the treatment but showed a slightly smaller, that is, a medium sized decrease. Overall, this demonstrates that even though the repeated dose oral esketamine assisted psychotherapy was effective in treating overall MD severity as well as all symptom domains of MD, symptom domains might possess a finite ability as indicators of which patients will experience a meaningful reduction in MD severity.

Connecting the findings to current research

These findings are puzzling in the light of the distinct role insomnia plays in the prediction of treatment effectiveness of repeated- dose oral esketamine assisted psychotherapy. Compared to Liu et al. (2020) as well as Rodrigues et al. (2022) the dimension in which most insomnia items were included did not show to be predictive of an effective treatment. It might be plausible that the effects of insomnia as predictors are offset by the role of other symptoms included in the anxiety/arousal domain such as sympathetic arousal or panic/phobic symptoms as examples (Coltman et al., 2008; Fayers & Hand, 2002). This might have been the case because the IDS-SR for which the latent constructs have been defined assume equal weights of the items onto the total score on the symptom domain (Rush et al., 2006; Wardenaar et al., 2010). It might be plausible that insomnia has a bigger influence on the score on the latent anxiety/arousal construct which was not accounted for in the scoring of the IDS-SR. Therefore, insomnia might play an important role in predicting treatment effectiveness if examined on its own compared to a part of the latent construct anxiety arousal symptomatic pattern.

In alignment with past findings for the conventional antidepressants imipramine and escitalopram symptoms of atypical depression may be predictive of treatment effectiveness (Chekroud et al., 2016; McGrath et al., 1992). Particularly higher expressions of the symptoms of oversleeping, overeating and anergy (feeling tired) at baseline have been indicated as

predictive of poorer treatment outcomes in the past as well as the present study (Chekroud et al., 2016; McGrath et al., 1992). Otherwise, the vegetative symptom dimension also included the symptoms of weight change, early morning awakening and leaden paralysis which have not been examined previously (Chekroud et al., 2016; McGrath et al., 1992; Rush, Trivedi, et al., 2006). Concluding that whereas some of the predictive symptoms coincided the reflected latent variable was defined differently and included other ancillary symptoms.

Judging from the similarity in finding between conventional antidepressants and the repeated- dose oral esketamine assisted psychotherapy it might be the case that there is a commonality explaining these effects. Usually, agents such as imipramine and escitalopram are assumed to have distinct working mechanisms by affecting mainly the serotonin (SSRI's & SNRI's) versus the glutaminergic (ketamine) system (Fourcade & Lapidus, 2016; Jelen et al., 2021). Since vegetative symptoms mostly define the physical maintenance of the body, patients with low vegetative symptoms at baseline might have better physical functioning and therefore can mitigate and benefit from the drug effects better independent of the type of antidepressant treatment they are getting (Griffin, 1990; Niederberger & Parnham, 2021). Furthermore, higher age has been associated with an increase in vegetative symptoms (Faustman et al., 1990). Since the patients in this sample were around 50 years of age on average the patients that did not exhibit this expected pattern of high vegetative symptoms might have higher levels physical health and could therefore benefit from the repeated doses oral esketamine assisted psychotherapy better (Seals et al., 2016). Nevertheless, age without the connection to vegetative symptoms has so far not been associated with a greater effectiveness of ketamine (Pennybaker et al., 2021).

The role of the low expression of mood and cognitive symptoms in treatment resistant MD and BD type I and II as an predictor of treatment response blends in with the existing body of literature. A great expression of cognitive symptoms are commonly associated with worse outcomes in MD (Kaser et al., 2017). Similarly, patients with a high profile of cognitive

symptoms show an impaired response to SSRIs (Gonda et al., 2015; Groves et al., 2018). Furthermore, some antidepressant pharmacological agents were indicated to have negative impacts on cognitive functioning which might mean that patients with a lower profile of cognitive symptoms did not receive as much antidepressant pharmacological treatment yet (Roca et al., 2015). This might be an indicator that their depressive episode is less severe or long-lasting then from patients with substantial antidepressant pharmacological treatment and therefore have a greater capacity to respond to any further pharmacological treatment (Rush, Trivedi, et al., 2006; Shilyansky et al., 2016).

Cognitive impairments may also prevent patients from being able to benefitting from CBT in which learning plays a central role (Beck, 2021; Dobson, 2009; Farmer & Chapman, 2016; J.-M. Li et al., 2018). CBT uses cognitive processes such as rationalization to treat misconceptions that give rise to depressive symptoms such as the negativity bias (LeMoult & Gotlib, 2019; Murrough et al., 2011). If the cognitive functioning of patients is worse, it may hold true that also these evaluation processes in CBT therapy do not work as well as in patients with better cognitive functioning. It might be imaginable that patients that can benefit from CBT therapy due to sufficient functioning can also "fill" the newly grown neurons more effectively with knowledge contradiction the misconceptions in MD (Price & Duman, 2020; Souza-Marques et al., 2021). Nevertheless, it remains unclear whether the capacity for neurogenesis due to the repeated-dose oral esketamine assisted psychotherapy allows them for making new connection due to CBT or whether the neurogenesis is a prerequisite to gain enough capacity to use CBT successfully. Cognitive impairments might also interact with the motivation to take part in CBT therapy and thus, impair the chance to benefit from the therapy (Rock et al., 2014). Overall, this capacity to be motivated, attentive, and learning in CBT due to lower cognitive impairments might lead to more profound changes such as treatment response instead of MCID.

Overall, the difference in predictors between the different groups of patients that reached the MCID, response, or remission, did not seem to be brought about by demographic or clinical characteristics of the current sample. The patients in this sample did not show any striking differences at baseline that might explain the discrepancies between the predictors of the MCID, response and remission (Table 2). Therefore, the reasons for the varying predictors of treatment effectiveness remain open for further investigation.

Strengths and Limitations

The findings of the present study should be interpreted with caution. Due to the lack of a control group in the multicentre trial MCID, response and remission rates might have been attributed to a placebo effect. The most lenient estimated to classify treatment effectiveness the MCID was 33 percent in this sample, with lower rates for the more conservative operationalizations treatment effectiveness. Because, spontaneous recovery rates from MD are estimated to lie in between 23 to 55 percent within three to 12 months they might have been responsible for the observed treatment effectiveness in this sample (Demyttenaere & Van Duppen, 2018; Whiteford et al., 2013). Nevertheless, these spontaneous recovery rates for MD might not fully apply to this study since here treatment- resistant patients were included for who estimations are likely to be more conservative (Fekadu et al., 2012; Whiteford et al., 2013).

Another limitation of this multicentre off label treatment paradigm is that high amounts of missing data are a typical challenge (Ford, 2006). In the current study almost half of the patients could not be included in the model due to missing data. The smaller sample size of the study may also be connected to the lack of robustness of the prediction models (Agresti, 2018; Kim, 2009). If previously flagged influential observations remained in the data, significance predictors did not sustain. This change in significance due to the removal of influential data allows for the possibility that the results were found by chance (Agresti, 2018). Lastly, the limited number of patients that achieved the MCID, response or remission decreased even more due to the listwise deletion of patient data due to the missingness.

Otherwise, the strength of an off-label study is its high ecological validity (Ford, 2006). Off-label studies represent the reality of the treatment-resistant patients that are treated with oral esketamine assisted psychotherapy on top of the treatment as usual (aan het Rot et al., 2012; An et al., 2021; Kishimoto et al., 2016; Smith-Apeldoorn et al., 2022; Veraart et al., 2021; Voineskos et al., 2020). In RCTs the antidepressants are usually faded out for the purity of the data, which puts a lot of strain on the patients. The off-label treatment procedure is more patient friendly with the potential to lighten some of the ethical concerns of experimenting with novel treatments in vulnerable patient groups (Borysowski et al., 2019; Evenblij et al., 2019).

Future directions

To bring the field of precision medicine for patients with TRD forward, further steps need to be taken. Future studies might consider validating the symptom dimensions by Rush et al. (1996) in samples with TRD. Rush et al. (1996) originally did not include treatment-resistant MD and BD I and II. Additionally, the analysis should be repeated in samples with higher response and remission rates to warrant the validity of the results for these operationalizations of treatment effectiveness. Furthermore, other methods of analysis that are able to handle large amounts of missing data, such as elastic net regularisation prediction modelling might be considered, since missing data can be expected in longitudinal treatment studies (Chekroud et al., 2016; Ibrahim & Molenberghs, 2009; Zou & Hastie, 2005).

Lastly, a method to inspect the role of single symptoms of depression as predictors of the treatment outcome of oral esketamine assisted psychotherapy as an add on to treatment as usual should be considered to make the results more comparable with previous literature. Since conventional scales measuring symptoms of depression such as the IDS-SR, HAMD or Montgommary Asperger Depression Rating Scale (MADRAS) do have the limitation of examining single symptoms with only one item the construction of a new scale that includes at least three items per symptom might be recommended (Ibrahim & Molenberghs, 2009). Another approach might be to use clinician administered depression scales as predictor and

outcome scales. In practitioner rated scales such as the HAMD and MADRAS a single item is rated after the clinician asks various questions to the patients to judge the severity of the symptoms of the patient and scores the item. A single item is rated after the practitioner asks various questions to the patients to judge the severity of the symptoms that might behave in a similar way to multiple items on a self-report measure. Therefore, it might be that the single item is reliable due to the practitioners' experience and the variety of questions that are asked to make this judgement.

Conclusion

Whereas predictors of treatment response varied per operationalization of treatment effectiveness especially a low profile of vegetative symptoms seemed to increase the chances to experience a meaningful reduction in depressive symptoms with repeated-dose oral esketamine assisted psychotherapy as an add on to treatment as usual for TRD patients. Predictors of treatment response and remission need to be replicated in bigger samples due to the small number of patients that achieved response and remission in this study before further consideration. The influence of a placebo effect remained unclear. The knowledge gap that needs to be bridged to be able to provide individual treatment recommendations to patients is substantial. More knowledge about which markers flag treatment effectiveness per pharmacological agent for patients with TRD needs to be acquired and synthesised. Ultimately, this might mean that many patients that will experience symptoms of depression in future will be spared the "treatment-resistant" label, because the right treatment option for them was found upon the first visit to their doctor's office.

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APPENDIX A

The symptom dimensions of the Inventory of Depressive Symptoms – Self Rated (IDS-SR).

Table A1. Overview of the items per symptom dimension on the Inventory of Depressive Symptoms – Self Rated (IDS-SR).

Dimension	Items
Cognitive mood	Interest in people/activities
	Pleasure/enjoyment (not sex)
	Reactivity of mood
	Feeling sad
	Energy/fatiguability
	Concentration/ decision making
	Interest in sex
	Quality of mood
	Future pessimism
	Suicidal thoughts
	Psychomotor retardation
	Self-criticism and blame
	Interpersonal sensitivity
	Feeling irritable
Anxiety/Arousal	Sympathetic arousal
	Psychomotor agitation
	Constipation/diarrhoea
	Panic/phobic symptoms
	Middle insomnia
	Feeling anxious or tense
	Initial insomnia
	Diurnal variation of mood

Vegetative symptoms	Sleeping too much
	Weight gain
	Weight loss
	Leaden paralysis/physical energy
	Increased appetite
	Decreased appetite
	Early morning awakening

APPENDIX B

Picture of the treatment room where the esketamine treatment sessions took place.

APPENDIX C

Table C1. Estimates for the final model predicting treatment effectiveness (*Minimally Clinically Important Difference*) from the mood cognitive symptom dimension, vegetative symptom dimension and anxiety and arousal symptom dimension controlling for gender and type of diagnosis

Predictor	*b*	*se*	*z*	*p*	*Z - 95% CI lower bound*	*Z - 95% CI upper bound*	*Odds ratio*	*95% CI odds ratio lower bound*	*95% CI odds ratio upper bound*
Intercept	3.23	1.65	1.96	.06	-.01	6.47	25.33	0.99	647.06
Mood and cognitive symptom domain	-0.87	0.64	-1.36	.17	-2.11	0.28	0.42	0.12	1.47
Anxiety and arousal symptom domain	0.55	0.68	0.81	.42	-0.79	1.89	1.74	0.45	6.64
Vegetative symptom domain	-1.50	0.75	-1.998	.046*	-2.98	-0.03	0.22	0.05	0.97
Gender	0.28	0.55	-0.52	.61	-1.36	0.79	0.75	0.26	2.21
Diagnosis	-0.52	1.12	-0.46	.64	-2.71	1.67	0.60	0.07	5.32

Table C2. Estimates for the final model predicting treatment effectiveness (*Response*) from the mood cognitive symptom dimension, vegetative symptom dimension and anxiety and arousal symptom dimension controlling for gender and type of diagnosis

Predictor	*b*	*se*	*z*	*p*	*Z - 95% CI lower bound*	*Z - 95% CI upper bound*	*Odds ratio*	*95% CI odds ratio lower bound*	*95% CI odds ratio upper bound*
Intercept	-14.28	2238.46	-0.02	.995	-4401.57	4373.01	0.00	0.00	Infinite
Mood and cognitive symptom domain	-1.59	0.76	-2.08	.037*	-3.08	-0.09	0.20	0.05	0.91
Anxiety and arousal	1.69	0.87	194	.051	-0.01	3.38	5.40	0.99	29.51

symptom domain									
Vegetative symptom domain	-1.55	0.92	-1.68	.09	-3.35	0.26	0.21	0.03	1.30
Gender	0.38	0.66	0.58	.56	-0.90	1.66	1.46	0.41	5.28
Diagnosis	15.5905	2238.46	0.007	.99	-4371.70	4402.88	590051.58	0.00	Infinite

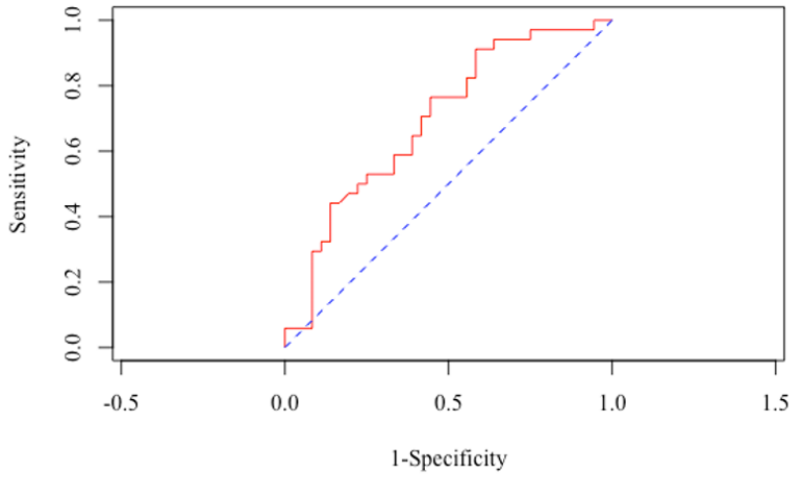
Table C3. Estimates for the final model predicting treatment effectiveness (*Remission*) from the mood cognitive symptom dimension, vegetative symptom dimension and anxiety and arousal symptom dimension controlling for gender and type of diagnosis

Predictor	*b*	*se*	*z*	*p*	*Z - 95% CI lower bound*	*Z - 95% CI upper bound*	*Odds ratio*	*95% CI odds ratio lower bound*	*95% CI odds ratio upper bound*
Intercept	-14.90	1855.78	-0.01	.99	-3652.16	3622.36	0.00	0.00	Infinite
Mood and cognitive symptom domain	-1.22	.79	-1.55	0.12	-2.76	.32	0.30	0.02	1.38
Anxiety and arousal symptom domain	-.62	1.03	-0.60	.55	-2.64	1.41	0.54	0.07	4.08
Vegetative symptom domain	-0.75	1.02	-1.73	.47	-2.75	-1.26	.47	.06	3.52
Gender	1.17	0.76	1.53	.13	-0.32	2.67	3.22	0.72	14.37
Diagnosis	16.38	1855.78	0.01	.993	-3620.88	3653.64	12982620.25	0.00	Infinite

APPENDIX D

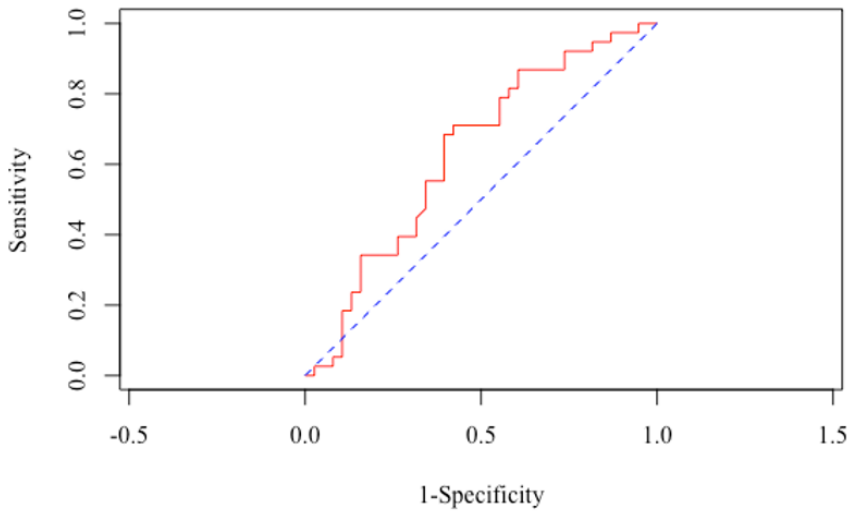
Perceiver Operating Characteristic (POC) - Curves

Figure D1. POC-curve of regressing diagnosis, gender, mood cognitive symptom dimension, vegetative symptom dimension and anxiety and arousal symptom dimension on treatment effectiveness (*Minimally Clinically Important Difference*).



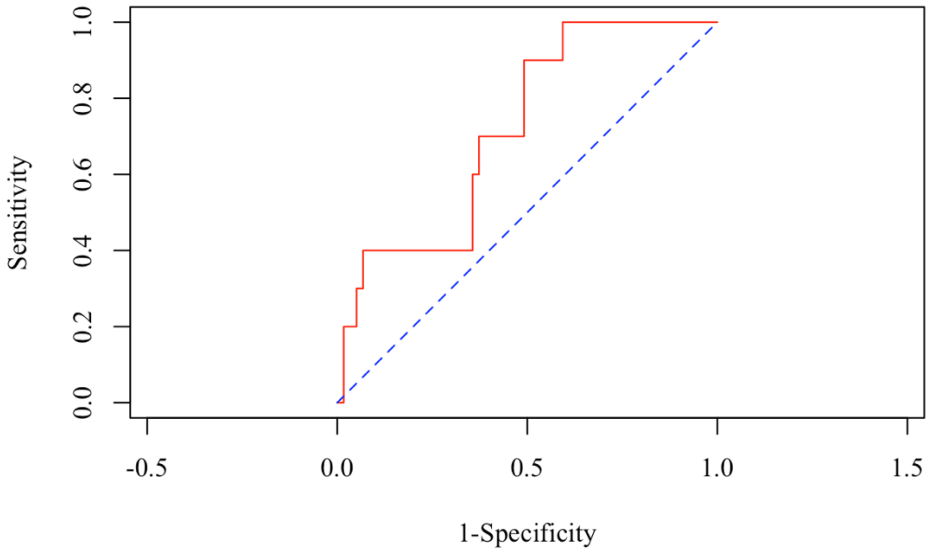
Note. The blue curve represents the model's performance at chance level. The red curve represents the performance of the fitted prediction model

Figure D2. POC-curve of regressing diagnosis, gender, mood cognitive symptom dimension, vegetative symptom dimension and anxiety and arousal symptom dimension on treatment effectiveness (*Minimally Clinically Important Difference*) if influential observations are included.



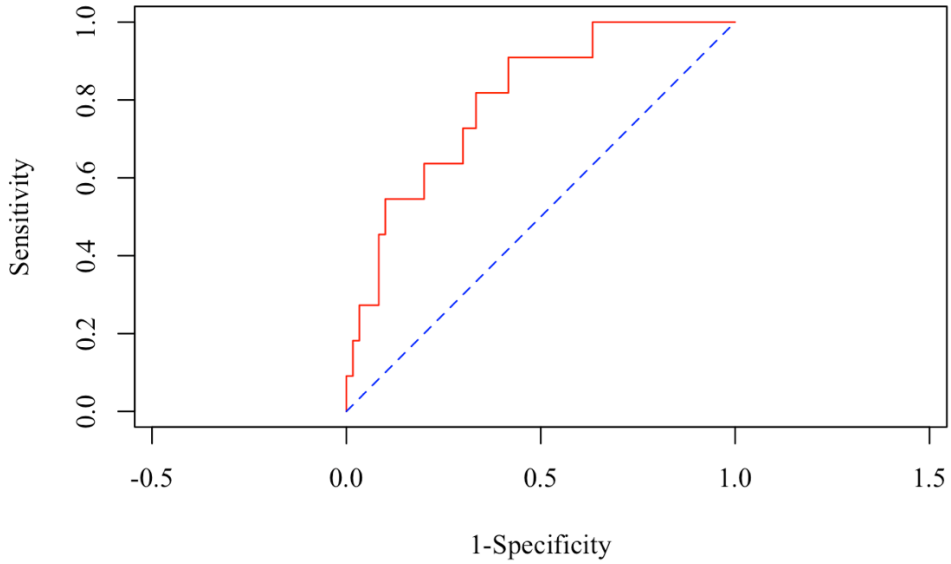
Note. The blue curve represents the model's performance at chance level. The red curve represents the performance of the fitted prediction model.

Figure D3. POC-curve of regressing diagnosis, gender, mood cognitive symptom dimension, vegetative symptom dimension and anxiety and arousal symptom dimension on treatment effectiveness (*response*).



Note. The blue curve represents the model's performance at chance level. The red curve represents the performance of the fitted prediction model.

Figure D4. POC-curve of regressing diagnosis, gender, mood cognitive symptom dimension, vegetative symptom dimension and anxiety and arousal symptom dimension on treatment effectiveness (*remission*).



Note. The blue curve represents the model's performance at chance level. The red curve represents the performance of the fitted prediction model.