TITLE

Predicting treatment effects in unipolar depression: a meta-review

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ABSTRACT

There is increasing interest in clinical prediction models in psychiatry, which focus on developing multivariate algorithms to guide personalized diagnostic or management decisions. The main target of these models is usually the prediction of treatment response to different antidepressant therapies. This is because the ability to predict response based on patients' personal data may allow clinicians to make individualised treatment decisions, and to provide more efficacious or more tolerable medication to a specific patient. Here, we systematically search the literature for systematic reviews about treatment prediction in the context of existing treatment modalities for adult unipolar depression, until July 2019. Treatment effect is defined broadly to include efficacy, safety, tolerability and acceptability outcomes. We first focus on the identification of individual predictor variables that may predict treatment response, and second, we consider multivariate clinical prediction models. Our meta-review included a total of 10 systematic reviews; seven (from 2014-2018) focusing on individual predictor variables and three focusing on clinical prediction models. These identified a number of sociodemographic, phenomenological, clinical, neuroimaging, remote monitoring, genetic and serum marker variables as possible predictor variables for treatment response, alongside statistical and machine-learning approaches to clinical prediction model development. Effect sizes for individual predictor variables were generally small and clinical prediction models had generally not been validated in external populations. We identify the need for rigorous model validation in large external data-sets to prove the clinical utility of models. We also discuss potential future avenues in the field of personalized psychiatry, particularly the combination of multiple sources of data and the potential of the emerging field of artificial intelligence and digital mental health to identify new individual predictor variables.

KEYWORDS

Antidepressant drugs, Prediction; Unipolar depression; Treatment response; Clinical prediction model; Precision psychiatry; Personalized medicine

ABBREVIATIONS

BDI; Beck's Depression Inventory

BDNF; Brain-derived neurotrophic factor

CBASP; Cognitive behavioral analysis system of psychotherapy

CBT; Cognitive behavioral therapy

CRP; C-reactive protein

DOR; Diagnostic odds ratio

DSM; Diagnostic and Statistical Manual of Mental Disorders

EEG; Electroencephalography

HAM-D, HDRS; Hamilton Depression Rating Scale

ICD; International Classification of Diseases

IL-6; Interleukin 6

MADRS; Montgomery–Åsberg Depression Rating Scale

MDD; Major Depressive Disorder

NDST; Non-directive supportive therapy

RCT; Randomised controlled trial

rTMS; Repetitive transcranial magnetic stimulation

SMD; Standardised mean difference

SSRI; Selective serotonin reuptake inhibitor

TCA; Tricyclic antidepressant

tDCS; Transcranial direct current stimulation

TNF-alpha; Tumour necrosis factor alpha

CONTENTS

1. INTRODUCTION

There is an increasing interest into the use of so-called 'precision' (or 'personalized') medicine in psychiatry, particularly to predict treatment effects (Cohen et al, 2018). This has led to the recent development of an increasing number of clinical prediction models, a term used to describe a multivariate algorithm that utilizes patient-level data in order to make individualized clinical predictions (Wessler et al, 2015). It is hoped that clinical prediction models may inform improved clinical decisions and offer patients more efficacious, safer or better tolerated treatments based on their personal data, especially in the context of digital mental health (Shinohara et al., 2019a).

Depression is a psychiatric disorder typically characterised by low mood, reduced energy and anhedonia in addition to a number of associated symptoms. Estimates suggest over 300 million people globally experience depression, making it the single largest factor contributing to disability worldwide (Liu et al., 2019). However, depression also exhibits heterogeneity. Based on DSM-5 criteria alone, there are 227 unique symptom profiles which meet criteria for a diagnosis of Major Depressive Disorder (MDD) (Fried et al., 2015). Likewise, depressive episodes may represent manifestations of different conditions, such as unipolar depression or bipolar affective disorder. Therefore, depression is commonly classified into a number of different categories, based on the severity, nature and type of symptoms present as well as their response to treatment (Table 1).

Precision medicine can be particularly relevant to unipolar depression, where a plethora of treatment modalities exist with potential effectiveness for any given individual (Table 2). In particular, the efficacy and adverse effect profiles of commonly-prescribed antidepressant

treatments may differ between individuals (Cipriani et al., 2019). In the context of pharmacotherapy, a recent analysis of 87 eligible randomized placebo-controlled trials identified significantly more variability in response to antidepressant medications than to placebo, and this variability differed between different classes of medications (Maslej et al., 2020). Consequently, there is increasing interest in using clinical prediction models to better tailor treatment to each individual patient, based on his/her characteristics, to enhance treatment effectiveness, tolerability or acceptability (Tomlinson et al., 2019). This also mirrors interest in predicting long-term response from an individual's initial response in order to avoid protracted courses of potentially ineffective or harmful treatments (Hallgren et al, 2017).

An array of variables have been hypothesised to be useful in informing clinical prediction models in depression. These include sociodemographic, phenomenological, psychological, neuroimaging, genetic, immune, endocrine and remote monitoring data (Perlman et al, 2019). However, the predictive ability of these variables and their reliability across different clinical populations is still unclear (Bzdok & Meyer-Lindenberg, 2018). In this paper, we will employ a three-fold categorization of predictor variables (Simon & Perlis 2010). We will assume that a variable may act as a prognostic factor, a specific predictor of treatment response, or as an effect modifier. These terms are explained below:

- Prognostic factor - A variable is a prognostic factor when it moderates response but does not interact with treatment. It affects the outcome in the same way for all patients, irrespectively of the received treatment (including placebo).
- Specific predictor - A variable is a specific predictor when it affects the outcome in the same way for all patients receiving an active intervention, different however to

the way it affects outcome in patients receiving placebo. For example, a specific predictor moderates the efficacy of a intervention vs. placebo but does not moderate the effect of two different interventions.

- Effect modifier – A variable is an effect modifier when it moderates response and interacts with treatment. This suggests that the relative effects between any two treatments (active or placebo) depend on the value of the effect modifier.

We will also include studies that present data on variables that predict within-group treatment response. It is not possible to conclude that these variables are specific predictors or effect modifiers because they have not been assessed for a differential effect in multiple intervention or placebo arms. As it is not possible to assess the true nature of these within-group predictive variables within a population, we simply provide a description of what can be concluded from the current evidence.

All of the categories described above are formative to model development and in this review we include them under the broad category of "predictive factors" (Simon & Perlis, 2018). We include any patient-specific variable which may predict future treatment response, including both baseline variables and markers of early response following treatment initiation, as either could plausibly inform clinical decisions when deciding to initiate, change or stop treatments. Likewise, clinical prediction models have been developed using a variety of statistical and machine-learning approaches. The data ('training sets') that these models are developed from vary in scope, quality and clinical significance. Stern and colleagues argued that despite promising results, clinical prediction models have often not been extensively cross-validated in novel populations or tested in clinical settings

(Stern et al, 2018). Additionally, clinical prediction models are derived from a variety of different methods and are often evaluated against a variety of different metrics, making quantitative analysis difficult. Previous systematic reviews have been limited in scope to specific technical approaches used to develop clinical prediction models and therefore may not provide a comprehensive overview of the field (Lee et al, 2018).

This meta-review focuses on existing treatments including pharmacological, psychological, neuromodulatory and electroconvulsive therapies and aims to summarize the literature on the prognostic value of individual variables and clinical prediction models that forecast treatment effects in people with unipolar depression. We conceptualise treatment effects broadly, including efficacy, safety, tolerability and acceptability. Although there is overlap between these terms, safety typically refers to the occurrence of specific adverse events, tolerability to the number of people who stop treatment because of adverse events, whereas acceptability refers to dropouts from any-cause (Shinohara et al., 2019b). In our discussion, we also briefly outline the use of prediction in other disorders in psychiatry, as well as in other medical specialties such as oncology, neurology and cardiovascular medicine, to illustrate how predictive models may enhance future clinical practice relevant to psychiatry in general and unipolar depression in specific.

2. METHODS

We conducted a meta-review of the English-language literature on the topic of treatment response prediction in the context of unipolar depression in adults, considering existing systematic reviews and meta-analyses. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) approach (Moher et al, 2009). Our review

focuses on: i) individual predictor variables and ii) clinical prediction models of treatment effects for any treatment intervention in unipolar depression in adults. Our protocol is registered with PROSPERO (CRD42019141425).

2.1. Search strategy:

We searched Ovid MEDLINE, EMBASE and PsycINFO from inception to 15th July 2019, using the following keywords/terms: “prediction”, “antidepressants”, “psychological therapy”, “psychotherapy”, “electroconvulsive therapy”, “transcranial magnetic stimulation”, “vagal nerve stimulation”, “unipolar depression”, “major depressive disorder”. Our complete search strategy is detailed in a freely available data repository (http://dx.doi.org/10.17632/3v49p2dtnx.1). Our search of electronic databases was complemented by a manual search of the reference lists of relevant publications.

2.2 Selection criteria:

The titles and abstracts of all references were screened for eligibility by three authors (GG, AT, AC). Full-texts of potentially eligible references were then retrieved and assessed for inclusion. Inclusion criteria was limited to systematic reviews of male and female adults (≥18 years) with a primary diagnoses of unipolar depression according to standard operationalised criteria such as DSM-III, DSM-III-R, DSM-IV, DSM-5, ICD-10 or Research Diagnostic Criteria who received any treatment modality for depression. Reviews of individuals with schizophrenia, bipolar disorder and dementia were excluded (studies with psychiatric co-morbidities were included only if participants had a primary diagnosis of unipolar depression or results were presented separately for unipolar depression). Reviews considering generic study design or non-patient factors (such as length of treatment, year of

study) as predictor variables were excluded as they were not felt to be relevant to our review's focus. See protocol for further detail.

For the meta-review of individual predictor variables, studies were classified into seven groups, guided by their search strategy, presentation of results, critical appraisal and quantitative synthesis (Table 3). Our review focuses on the most rigorous systematic reviews, classified as level 4 (Table 4), although we also summarise reviews classified as level 3 (Table 5).

2.3 Data synthesis:

Relevant information was extracted from included reviews, including aim(s), intervention(s), population, variable(s) of interest, outcome predicted, methodology, types of clinical prediction model(s), their evaluation and validation. Data extraction for reviews of clinical prediction models mirrored guidelines set out by standardized checklist such as the CHARMS checklist, a data extraction tool specficially designed for systematic reviews of prediction modelling studies (Moons et al, 2014). We anticipated that, due to the heterogeneity of included studies, a quantitative synthesis would not be possible. We therefore presented a qualitative synthesis of results from the two areas of focus separately; i) individual predictor variables and ii) clinical prediction models.

2.4 Critical appraisal:

The AMSTAR-2 tool (Shea et al, 2017) is a popular instrument used to critically appraise systematic reviews with particular focus on a number of 'critical domains'; pre-registration of the review protocol, adequacy of the literature search, justifications for study exclusion,

the appropriateness of meta-analytical methods, the risk of bias from individual studies, the consideration of this risk and the assessment of publication bias. The instrument was used to critically appraise all the included systematic reviews in this meta-review.

3. RESULTS

Our search returned 1,869 unique references and we retrieved the full-text of 205 articles. 118 references were initially deemed to be relevant to individual predictor variables, of which 21 were classified as level 3 or level 4 (Figure 1). Seven of these were classified as level 4 (including a single, well-defined population or treatment intervention) and are discussed in our results (Table 4). The remaining 14 reviews are summarized in Table 5. Three reviews concerning clinical prediction models were included (Table 6).

3.1 Individual predictor variables:

Of the seven included reviews, two focused on studies comparing cognitive behavioral therapy (CBT) with pharmacotherapy (Cuijpers et al, 2014; Cuijpers et al, 2017a), two focused on studies including all antidepressant medications (Polyakova et al, 2015; Wagner et al, 2017), one focused on two antidepressants, venlafaxine and sertraline (Gibiino et al, 2014), one focused on transcranial direct current stimulation in isolation or in addition to pharmacotherapy (Shiozawa et al, 2014) and one focused on cognitive-behavioral analysis system of psychotherapy (CBASP), pharmacotherapy or a combination of both (Furukawa et al, 2018).

3.1.1 Variables of interest

Variables of interest included demographic variables such as age (3 reviews), gender (3), childhood maltreatment (2), marital status (2), social adjustment (1), job (1), education level (1), clinical variables such as baseline depression severity (3), age of onset (2), duration of episode (2), subtype of depression (2), number of previous episodes (1), prior treatments received (1), treatment resistance (1), baseline anxiety severity (1), family history (1), early clinical improvement following treatment initiation (1) and biochemical variables such as serum and plasma levels of brain-derived neurotrophic factor (BDNF) levels following treatment initiation (1).

3.1.2 Methods

A variety of methods were used to assess possible relationships between predictor variables and outcomes. Two studies (Cuijpers et al, 2014; Cuijpers et al, 2017a) used a one-step individual patient data meta-regression to identify differential response to treatments, differential response to treatment and placebo, or response to individual treatments for a single predictor variable of interest (gender and subtype of depression, respectively). Both reviews reported estimated coefficients to present the relationship between predictor variables and treatment outcomes, adjusted for other covariates which might otherwise act as confounding factors. One study reported coefficients from a meta-regression analysis (Gibiino et al, 2014; Shiozawa et al, 2014). In contrast, Polyakova et al, 2015 assessed the effect of a single predictor variable (BDNF change) and considered treatment responders, remitters and non-responders as categorical groups, comparing BDNF change in each group. This review included studies which attempted to predict treatment response at end-point (week 6) from changes in BDNF levels at day seven; therefore BDNF levels were included as a predictor of future response, although not a baseline variable as considered by the

reviews above (Dreimüller et al, 2012). Similarly, Wagner and colleagues (2017) assessed the role of a single predictor variable (early improvement) and reported outcomes including sensitivity, specificity and odds ratios of responding to treatment for categorical groups of early improvers and non-improvers.

3.1.3 Outcomes

All seven reviews reported outcome data related to efficacy, generally reporting on treatment response or remission as defined using a standardized depression scale including the Hamilton Depression Rating Scale (HAM-D), Beck's Depression Inventory (BDI), and the Montgomery–Åsberg Depression Rating Scale (MADRS). One review also reported on deterioration of depression symptoms (Furukawa et al, 2018). Only one review (Furukawa et al, 2018) considered acceptability (dropout rate) as an outcome, while none were designed to identify predictors of tolerability or the development of specific adverse events.

With regards to efficacy, Cuijpers et al, 2014, 2017a found no evidence that either subtype of depression (melancholia, atypical) or gender were associated with treatment response to CBT or pharmacotherapy as an effect modifier, specific predictor or within-group predictive variable. Gibiino et al, 2014 found that female gender (standardized mean difference (SMD) between groups: 1.43, p=0.007) was a within-group predictive vairable of response to venlafaxine, as were shorter duration of illness (SMD 0.98, p=0.001) and Caucasian ethnicity (SMD 2.57, p=0.0212), but there was weaker evidence of an association at week 6 (SMD 2.21, p=0.125). There was no evidence that baseline depression severity was associated with venlafaxine response. There was very weak evidence of an association with recurrent depression (SMD 1.58, p=0.352). None of the variables were strongly associated with

sertraline response. Furukawa et al, 2018 found evidence that baseline depression and anxiety severity and use of prior medications were effect modifiers for CBASP, pharmacotherapy or combination therapy (predicted relative treatment effects ranged between -3.9 and 9.4 on HAM-D scores in sub-groups defined by these three variables). No variables were found to be predictors of deterioration in this analysis. There was little evidence that baseline depression severity can be used to predict antidepressant response or remission in the Wagner et al, 2017 review (explained variance in odds ratios: 0.6%, p=0.744 and 8.1%, p=0.285 respectively).

Polyakova and colleagues (2015) identified that serum, but not plasma, BDNF increased more in responders (Cohen's d=1.33, 95% CI 0.69–1.97) and remitters (d=0.85, 95% CI 0.39–1.29) following antidepressant medication including Selective Serotonin Reuptake Inhibitors (SSRIs), Selective Noradrenergic Reuptake Inhibitors, Tricylcic Antidepressants (TCAs) and atypical antidepressants compared to non-responders, while Wagner et al, 2017 found that patients with early improvement were more likely to achieve response (pooled OR 8.37, 95% CI: 6.97; 10.05) or remission (pooled OR 6.38, CI: 5.07; 8.02) compared to those without early improvement. Cohen's d is an estimate of effect size, and is often interpreted as small where effect size is >0.2, medium where effect size is >0.5 or large where effect size >0.8 (Cohen, 1988). Confidence intervals quantify the uncertainty estimated effects, by providing a range of values within which the true effect size is expected to lie 95% of the times. In the context of transcranial direct current stimulation, one study found no evidence of association between age, gender, baseline depression severity or treatment-resistance and treatment response (Shiozawa et al, 2014).

With regards to acceptability, Furukawa et al, 2018 found evidence that age and subtype of depression modify the effect of CBASP compared to combination of CBASP and pharmacotherapy, although it is difficult to disentangle the effects of individual covariates as this study modelled interactions between different combinations of predictor variables rather than considering each variable as a predictive factor in isolation.

3.1.4 Critical appraisal

AMSTAR-2 assessements are summarised in Table 4, with full details for each study available in a data repository (http://dx.doi.org/10.17632/3v49p2dtnx.1). All seven reviews contained two or more flaws in critical domains and therefore were considered to have "critically low" quality. Common areas of weakness included a lack of explicit statement detailing that methods were established prior to review commencement, failure to provide a list of excluded studies and a lack of consideration of risk of bias when interpreting results.

3.2 Clinical Prediction Models:

Our search returned three reviews meeting our inclusion criteria for assessment of clinical prediction models (Table 6). Bos et al, 2015 presented a broad review on the role of experience sampling and ecological momentary assessment in prescribing of psychotropic medications in MDD. The authors identified one study involving a sample of 49 patients receiving the tricyclic antidepressant imipramine, which found a clinical prediction model combining measures of early change in HDRS with early measures of positive affect (measured by experience-sampling) improved prediction of response and remission compared to single variables alone (Geschwind et al, 2011). The model accounted for 28 and 40% of explained variance in response and remission respectively. However, given that

the clinical prediction model was developed using information of relatively few patients and also given that it was not validated in an external sample, its clinical usefulness remains questionable.

Lee et al, 2018 presented a review of clinical prediction models in the context of depression. Although criteria included both bipolar and unipolar depression, components of the qualitative and quantitative syntheses presented results exclusively from participants with unipolar depression. Twenty-six studies were included, two of which featured both bipolar and unipolar depression, with the remainder featuring solely unipolar depression. Clinical prediction models predicted a range of proxy-markers of treatment response, including patient- or observer-rated symptom scales, frequency of hospital admission or suicidal ideation. The majority (92%) of models used supervised-learning algorithms, including logistic regression, support vector machines, decision trees, linear discriminant analysis, gradient boosting machines, random forest algorithm and mixture of factor analysis (Iniesta et al., 2016, Redlich et al., 2016, Korgaonkar et al., 2015, Al-Kaysi et al., 2017, Chekroud et al., 2017, Kautzky et al., 2017, Khodayari-Rostamabad et al., 2013). Unsupervised approaches included neural networks (Serretti et al., 2007).

Candidate predictors in clinical prediction models were most commonly neuroimaging (defined as Magnetic Resonance Imaging (*MRI), functional* Magnetic Resonance Imaging *(fMRI) or Electroencephalography (EEG)*, phenomenological (defined as baseline symptom scores, functioning, number of previous depressive episodes and sociodemographic variables including employment, education, household income). Two studies focused exclusively on candidate genetic predictors (Belzeaux et al., 2016, Serretti et al., 2004) and

three studies used phenomenological predictors in combination with genetic or neuroimaging predictors (Guilloux et al., 2015, Kautzky et al., 2015, Dysdale et al., 2017). Studies generally evaluated their models using classification accuracy. All studies reported a percentage rate of correct classification, apart from one study (Iniesta et al., 2016) that reported the area under the receiver-operator characteristic curve, a commonly used measure in medical decision-making to determine how well a model or tool distinguishes between groups (Hoo et al., 2017). Sensitivity and specificity were also commonly reported. Importantly, only four of 20 studies evaluated models in an external dataset and one study evaluated performance with hold-out validation. Quantitative pooling of phenomenological and combined prediction models reported classification accuracy of 0.76 (CI: 0.63; 0.87) and 0.93 (CI: 0.86;0.97) respectively, but pooled classification accuracy of neuroimaging and genetic prediction models were presented separately for participants with bipolar and unipolar illness. The authors note that application of commonly-used methods (Egger's test and funnel plot asymmetry) provided some indication of small study effects and publication bias in their included studies, suggesting that smaller studies gave larger estimates. This might be the case for example when studies with negative results were less likely to be published than those with positive findings.

Five studies included in the review by Lee et al, 2018 compared results from machine-learning approaches with conventional statistical analyses of the same dataset (Bailey et al., 2018, Liu et al., 2012, Serretti et al., 2004, Serretti et al., 2007, van Waarde et al., 2014,). *Three* neuroimaging studies failed to identify baseline predictors of treatment response with univariate analysis while the machine-learning algorithms predicted response with a classification accuracy of between 78–91% (Bailey et al., 2018, Liu et al., 2012, van Waarde

et al., 2014,). However, multiple regression analysis in another study did identify clinical and demographic predictor variables such as the number of previous depressive episodes, age of onset and the duration of the current episode, consistent with machine-learning methodology (Serretti et al., 2007).

Finally, Rosenblat et al, 2017 presented another approach to clinical prediction models in a review focusing on whether pharmacogenomic clinical prediction models improved treatment response. The review included five studies from three separate commercial pharmacogenomic models featuring a variety of candidate predictor genetic variants. Due to these tools' commercial nature and study of design, the exact outcome predicted, or advice outputted, by each tool is poorly reported but guided treatment selection and dosing. However, the reviewers focused on the clinical validation of these tools, assessing changes in depression severity, response or remission rates among participants whose clinician used the tool. While no tolerability or acceptability data were reported in the review, the candidate predictor variables included genes supposedly associated with adverse reactions, alongside those associated with treatment efficacy and drug metabolism. The review included four controlled trials (two randomized and two non-randomized) and one naturalistic study lacking a control group (Hall-Flavin et al., 2012, Hall-Flavin et al., 2013, Winner et al., 2013, Singh, 2015, Brennan et al., 2015). Two open-label non-randomized trials showed an improvement in response and remission rates when using a pharmacogenomic tool, however this result was not replicated for the same tool in a randomized-control blinded study (Hall-Flavin et al., 2012, Hall-Flavin et al., 2013, Winner et al., 2013). A randomized-controlled double-blinded trial of a different tool did show improvements in remission compared to an unguided group, however reviewers caution

interpreting results due to the study funding arising from the developers of the tool (Singh, 2015). Results were not independently replicated. The naturalistic study suggested improvement compared to baseline but lacked a control group for comparison.

In terms of critical appraisal using AMSTAR-2, all three reviews contained two or more flaws in critical domains and therefore were considered to have "critically low" quality (Table 6). Common areas of weakness were a lack of explicit statement detailing that methods were established prior to review commencement, failure to provide a list of excluded studies and a lack of consideration of risk of bias when discussing results.

4. DISCUSSION

4.1 Individual predictor variables:

This meta-review identified seven reviews meeting our inclusion criteria for individual predictor variables. No single variable was found to consistently predict treatment response across multiple reviews. It is possible that this finding represents specificity of individual predictive variables to specific treatments (Simon & Perlis 2010). Alternatively, due to the high number of retrospective analyses performed for a variety of candidate predictor variables, it is also possible that some of the studies' findings arose from chance (Head et al, 2015). However, the lack of consistent statistically significant findings across different studies does not in itself demonstrate disagreement, as it may simply result from meta-analyses being under-powered to detect the effects of the explored variables to the outcome of interest. Also of particular note are cases where the effects estimated for the individual predictor factors had small effect sizes. In such cases, the clinical significance of predictor variables might be questionable. For example, Gibiino et al, 2014 found that older

age predicted worse outcome when considered as a continuous variable, but the difference in outcome associated with older age was so small that it would unlikely be recognized by patients or clinicians without the use of numerical rating scale.

All seven included reviews focused on efficacy, with only one review presenting acceptability data (Furukawa, et al., 2018). Broadening our search to include level 3 reviews (Table 5), identified one further review of tolerability in the context of amitriptyline (Chen et al, 2018) and two further reviews of acceptability in the context of psychotherapy (Karyotaki et al, 2015, Cooper et al, 2015). This may represent a relatively unexplored area in this field, especially given the variety of potentially under-utilized treatments licensed for unipolar depression (Table 2) which exhibit potentially clinically relevant differerences in terms of efficacy and acceptability (Cipriani et al, 2018). Other medical specialties, such as cardiovascular medicine, have struggled to predict adverse effects due to their relatively low frequency in clinical trial data (van der Leeuw et al, 2014), although there is limited precedent for doing so, with the example of natalizumab (Tysabri) in multiple sclerosis. In this case, data from postmarketing sources, clinical studies, and a national registry identified antibodies which predicted occurrence of a rare but potentially life-threatening progressive multifocal leukoencephalopathy (PML) following treatment with the drug (Bloomgren et al, 2012).

Only three of the seven reviews of individual predictor variables listed in Table 4 were designed to identify variables acting as effect modifiers, with gender, subtype of depression and clinical factors (such as age of onset, number of precious depressive episodes) investigated in this manner (Cuijpers et al, 2014, 2017a; Furukawa et al, 2018). Three

reviews reported on specific predictors, by assessing variables which may predict differential response in the intervention arm compared to a placebo arm. All seven reviews assessed for within-group predictive variables, whereby the predictive efficacy of variables were not compared with a second active intervention or placebo arm. Variables investigated in such a way, including age, gender, ethnicity and duration of depressive episode, may therefore represent prognostic factors, specific predictors or effect modifiers (Gibiino et al, 2014). Furthermore, we found that these terms were used inconsistently, with some studies reporting on "moderator" variables without an appropriate study design to distinguish effect modifiers from prognostic factors (Gibiino et al, 2014). For example, while female gender was shown to be associated with response to venlafaxine and there was no evidence of an association with response to sertraline, this cannot be considered evidence of effect modification. For this, a formal statistical analysis would be required (Cuijpers et al, 2014, 2017a and Furukawa et al, 2018). Indeed, in this example it is possible that gender may be a generic prognostic factor and that certain samples were underpowered to detect an association, rather than there being a differential effect.

Likewise, in our broader search (Table 5) we identified a number of reviews assessing whether variables predicted response in a pooled grouping of multiple treatment interventions or placebo. Such analyses are not adequate to elucidate prognostic factor, specific predictor or within-group effects since they do not clarify whether variables affect response differentially in each treatment arm or placebo as they only present the pooled effect size for all component treatment arms or placebo. Analyses containing hetergenous treatment interventions not assessed independently are therefore of limited value and are not the focus of our reported results. The importance of study design to identify and classify

effect modifiers, specific predictors and prognostic factors in order to isolate the individual relationships between predictor variables and specific treatments rather than more generic predictors of outcome has been discussed in the literature previously (Simon and Perlis, 2010).

There was also heterogeneity in how treatment response was conceived and reviewed across different studies. Approaches included categorical variables (response defined as an >50% improvement symptoms) or continuous variables (symptom severity change pre- and post-intervention using a variety of different rating scales), measured at different time-points and using different cut-offs. Heterogeneity also existed in the individual predictor variables themselves. For serum and plasma markers such as BDNF, samples were drawn at different time-points between studies (Polyakova et al, 2015). In particular, the clinical utility of the results presented in that review may be questionable due to the heterogeneity of time-points where treatment response and BDNF levels were measured, since BDNF can only be used as a predictor of future response if it is measured significantly in advance of clinical response measurements. Heterogeneity in study population and treatment setting also exist, raising questions about the specific contexts in which individual predictor variables and models are valid.

4.2 Clinical prediction models:

This meta-review identified three reviews of clinical prediction models (Bos et al., 2015, Lee et al., 2018, Rosenblat et al., 2017). The clinical prediction models we identified were generally poorly validated, and commonly not evaluated on a separate data-set to that which the models were derived from. Even in the rare cases that models were externally

validated, the test data was often derived from clinical trial settings with similar methodology and populations, raising questions about its external validity. The importance of internal-external and external validation has been discussed in the literature and is important to avoid over-fitting and to improve external validity (Steyerberg and Harrell, 2016). Therefore, caution should be advised when interpreting results for clinical prediction models which haven't been properly validated.

The lack of external validation is compounded by the need of large datasets to develop clinical prediction models. There is evidence that training-sample size is the most robust predictor of model performance (Popovici et al, 2010). Therefore, while it is possible to split data-sets into training, cross-validation and test sets in order to better evaluate and validate models, doing so reduces the sample size which the model is built from, potentially compromising its performance. A compromise must often be reached between optimising model performance and rigorous validation, especially given that data-set size is already a major limitation in precision psychiatry. Indeed, Cuijpers et al, 2012 estimated that in order to perform sufficiently powered analyses of individual predictor variables predicting pharmacotherapy or psychotherapy response, another 254 studies would have to be conducted.

Another limitation of clinical prediction model development is that they do not neccessarily inform our understanding of which candidate predictor variables are significant. For instance, clinical prediction model development using machine-learning methods such as neural networks do not provide individual coefficients for each variable inputted into the model. These models also often include high order interactions between covariates, such

that one cannot identify the effect of a single covariate to the outcome. Meanwhile commercially developed models often do not share the weight assigned to each predictor variable in model development. These factors limit our understanding of which candidate predictor variables deserve further research interest. This is especially important, given that in oncology the selection of candidate predictor variables and data inputted has been shown to be a more significant determiner of model performance than the type of algorithm used (Jang et al, 2014).

The vast majority of prediction models identified in our meta-review focused on individual predictors of just one domain, such as genetic, neuroimaging, demographic or clinical data. This raises the difficulty of how to combine prediction models from different domains to make more accurate predictions. While an ensemble method using stacking may prove useful in combining the predictions of a number of separate prediction models into one, our meta-review did not identify any examples of this within the context of unipolar depression (Wan et al, 2014). Therefore, in depression, a significant challenge exists in standardizing and combining predictor variables of different domains to predict treatment response, compared to other specialties such as oncology where pathology is thought to arise primarily from genetics (Kelloff and Sigman, 2012).

Finally, similarly to reviews of individual predictor variables, we found that significant heterogeneity exists in reviews of clinical prediction models. Alongside heterogeneity in the definitions of treatment response and candidate predictor variables, there is heterogeneity in the specific context in which a clinical prediction model is valid in. For instance, it is possible that a model which accurately predicts treatment response to a drug after two

failed interventions would fail to accurately predict response to the same drug in the context of a new presentation of unipolar depression, or vice versa. This consideration emphasises the importance of rigorous model validation in different populations and clinical contexts.

All included reviews of individual predictor variables and clinical prediction models were deemed to be *"critically low"* according to the AMSTAR-2 instrument, which is the label given to reviews with flaws in at least two critical domains and indicative that reviews "should not be relied on to provide an accurate and comprehensive summary of the available studies" (Shea et al., 2017). However, it is worth noting that this was often the result of not providing a list of excluded studies, which no review did, or not explicitly referencing a pre-registered protocol in the article, which only one review did. While these criteria represent good practice they are not necessarily evidence that the reviews contained bias or were of poor quality. Furthermore, the suitability of the AMSTAR-2 tool for some of our included studies could be questioned. Although we felt it is important to systematically use a single tool to standardize quality assessment across included reviews, it can be argued that AMSTAR-2 does not comprehensively capture all the quality issues relevant to each review, and may assess aspects not relevant to some reviews. For instance, reviews developing a model (such as Furukawa et al, 2018) might be better assessed by the CHARMS checklist, a tool specifically designed for critical appraisal of prediction modelling studies (Moons et al, 2014). Furthermore, although a review might be classified as high quality, the included studies within that review may be of low quality and therefore review quality alone may present a deceiving impression of the overall quality of evidence. In particular, many of our included reviews failed to consider their risk of bias assessment

results when interpreting their results, raising the possibility that meta-analytic findings may conceal biases present in individual component studies.

4.3 Limitations:

Although our meta-review is wide-ranging in its scope, it exhibits limitations. Our focus on treatment response and remission meant that it was not possible to include reviews focusing on prediction of relapse following treatment cessation. Most of our included reviews measure treatment response within eight weeks of commencing an intervention, a relatively short time in the context of unipolar depression (Penninx, 2011). However, an equally relevant question is which variables predict relapse or durability of response following the cessation of an intervention and how we might design clinical prediction models to guide clinical decisions to discontinue treatments (Berwian et al, 2017, Kedzior et al, 2015). These reviews are not discussed in detail here but are worthy of consideration due to the known chronicity of unipolar depression.

Another limitation of our meta-review is our focus on the most rigorous reviews featuring a single, well-defined population or treatment intervention. This may compromise external validity, given that the well-defined populations of our included reviews may be dissimilar to the wider clinical population. However, this approach was necessary due to the heterogeneity of the studies, the methodological rigour of our meta-review and the need to clarify the effects of candidate predictor variables. Nonetheless, this concern emphasises the importance of proper validation of clinical prediction models in external samples prior to their use in clinical practice.

Finally, this meta-review is limited in the clinical prediction models it identified. It is likely that recent clinical prediction models have been published that have not yet been identified by systematic reviews and were therefore missed by our literature search. Likewise, clinical prediction models may be derived from meta-analysis, such as the Furukawa et al, 2018 review, which was included in our review of individual predictor variables since it focused on relative effectiveness research rather than performance of multiple clinical prediction models. While an updated search of primary studies would likely be fruitful in identifying further clinical prediction models, it was deemed to be beyond the scope of this review. Rather, our meta-review presents a broader overview of the synthesized literature on individual predictor variables and clinical prediction models in unipolar depression.

4.4. Recommendations for future research

Our findings highlight encouraging efforts towards the prediction of treatment response in unipolar depression, in-keeping with the wider interest of applying precision medicine methods in psychiatry more generally (Cipriani and Tomlinson, 2019). Our meta-review leads us to the following recommendations for future research.

First, we believe the field would benefit from more consistent terminology when characterising predictor variables. Here, we use the terms “prognostic factor,” “specific predictor” and “effect modifier” to distinguish types of predictor variables, although heterogeneity exists in the literature (Simon & Perlis 2010). Similarly, we believe the field may benefit from the use of more consistent and clinically meaningful definitions of treatment outcomes. Prediction of safety and tolerability appear to be relatively

underexplored areas worthy of more structured and standardised investigation that can take into account preferences and values of end users (Kernot et al., 2019).

Second, it is noteworthy that the majority of data in our included reviews come from randomized-controlled trials. Combining data from other sources, such as observational studies and "real-world" clinical data, may aid the identification and development of new and possibly stronger candidate variables associated with treatment outcomes and prediction models (Tomlinson et al., 2019). If these variables exhibit true effects, we would expect findings from randomized study populations to be replicated in large observational clinical dataset. Obtaining information from multiple sources would not only provide opportunity to optimise model performance and identify further predictor variables, but to also thoroughly assess the clinical utility of models and elucidate the specific clinical contexts and populations in which they are valid (Vaci et al., 2020). A recent study in cardiology highlighted that differences between the population in which prognostic models are developed and the populations in which models are tested represents a key determinant of model validity (Iwakami et al., 2020). We therefore emphasise the pressing need to undertake external validation of clinical prediction models to thoroughly assess their performance, clinical utility and to guide their appropriate clinical application.

Other specialties may inform methods to increase access to large data-sets. Oncology has benefitted from public repositories of genomic data in its development of targeted therapies, while neurology has benefitted from international patient databases when developing personalized therapies for multiple sclerosis (Azuaje, 2017, Kalincik et al, 2017). Oncology has also used novel trial designs such as adaptive clinical trials to more efficiently

identify predictive response biomarkers (Kelloff and Sigman, 2012). Meanwhile networks have been designed based on similarities in genomics and drug structures to predict drug response, methods which may prove useful in overcoming limited data (Zhang et al, 2015). However, it is worth noting that while cancer may be understood as a "genetic disease" (Kelloff and Sigman, 2012), the same may not be true of psychiatric disorders where a more diverse array of predictor variables are likely to contribute to the treatment response (Gómez-Carrillo, 2018). Consequently, while personalized therapies in oncology benefitted from methods such as co-clinical trials with mouse models, such approaches may not prove as successful in psychiatry (Huang et al, 2014).

One particularly exciting area is digital mental health. The emerging field of digital phenotyping offers a wealth of behavioral data which is both cost-effective and practical to collect (Torous et al, 2018). Although our meta-review identified just one example of a prediction model using remote monitoring featuring active data collection (Bos et al, 2015), the role of passive data collection not requiring continuous active patient engagement may provide abundant clinically relevant data to inform future prediction models (Gillett & Saunders, 2019). Such data may prove useful in implementing measurement-based-care, in which a patient's response to a treatment could inform further predictions on a continuous basis (Lewis et al, 2019). Our meta-review identified one example of using early improvement (Wagner et al, 2017) as a predictor of future response, although this was based on established standard symptom rating scales (HAM-D or MADRS) rather than remotely collected data. If properly validated, the emergence of clinically-relevant digital data may therefore identify new candidate predictor variables and allow clinical prediction models to be validated on large digital datasets. We therefore welcome interest into the

identification of standardised digital metrics as candidate variables in the prediction of treatment effects.

4.5 Conclusions:

To conclude, this review summarized the evidence on a number of predictive factors for treatment response in adult unipolar depression and identified interest in an array of predictor variables, especially in the context of efficacy. We found that clinical prediction models had generally not been validated in external populations and discuss potential future avenues in the field, particularly the need for rigorous external validation, the combination of multiple sources of data and the emerging field of digital mental health.

5. CONFLICT OF INTEREST STATEMENT

Two authors (AC & OE) are authors on one of the systematic reviews included in our meta-review (Furukawa et al, 2018). The authors have no other conflicts of interest to disclose.

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8. AUTHORSHIP AND CONTRIBUTORSHIP

Protocol was designed and registered by GG, AT, AC and OE. Search was performed by GG and reference screening undertaken by GG, AT and AC. Data extraction performed by GG. The manuscript was written by GG and reviewed by AT, AC and OE. All authors gave final approval for the work to be published.

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