



# Personalized Psychiatry and Depression: The Role of Sociodemographic and Clinical Variables

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Despite several pharmacological options, the clinical outcomes of major depressive disorder (MDD) are often unsatisfactory. Personalized psychiatry attempts to tailor therapeutic interventions according to each patient's unique profile and characteristics. This approach can be a crucial strategy in improving pharmacological outcomes in MDD and overcoming trial-and-error treatment choices. In this narrative review, we evaluate whether sociodemographic (i.e., gender, age, race/ethnicity, and socioeconomic status) and clinical [i.e., body mass index (BMI), severity of depressive symptoms, and symptom profiles] variables that are easily assessable in clinical practice may help clinicians to optimize the selection of antidepressant treatment for each patient with MDD at the early stages of the disorder. We found that several variables were associated with poorer outcomes for all antidepressants. However, only preliminary associations were found between some clinical variables (i.e., BMI, anhedonia, and MDD with melancholic/atypical features) and possible benefits with some specific antidepressants. Finally, in clinical practice, the assessment of sociodemographic and clinical variables considered in our review can be valuable for early identification of depressed individuals at high risk for poor responses to antidepressants, but there are not enough data on which to ground any reliable selection of specific antidepressant class or compounds. Recent advances in computational resources, such as machine learning techniques, which are able to integrate multiple potential predictors, such as individual/clinical variables, biomarkers, and genetic factors, may offer future reliable tools to guide personalized antidepressant choice for each patient with MDD.

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## INTRODUCTION

The World Health Organization estimates that depression will be the second-most common cause of disease and premature death worldwide by 2020.<sup>1</sup> Moreover, depression is expected to be the largest contributor to disease burden by 2030.<sup>2</sup> Huge personal and societal costs are associated with the disability caused by major depressive disorder (MDD), which frequently arises from the poor response to the current therapeutic options.<sup>3</sup>

Recent guidelines on pharmacological treatments of MDD indicate the use of selective serotonin reuptake inhibitors (SSRIs) or serotonin noradrenaline reuptake inhibitors (SNRIs) as first-line treatment, along with other antidepressants (ADs), including agomelatine, bupropion, mirtazapine, and vortioxetine. Tricyclic antidepressants (TCAs), trazodone, levomilnacipran, and vilazodone are recommended as second-line agents, whereas third-line recommendations include monoamine oxidase inhibitors (MAOIs) and the SNRI, reboxetine.<sup>4</sup> Although concerns of the U.S. Food and Drug Administration (FDA) about antidepressant-associated risk of suicidality in young adults are still a matter of debate, most clinicians and researchers consider that antidepressant-associated benefits outweigh risks in individuals with depression.<sup>5</sup> Despite these pharmacological options, the clinical outcomes are often unsatisfactory. The response to first-line treatment is estimated to be between 40% and 60%,<sup>6-8</sup> while only 30–53% of patients achieve a full remission after antidepressant treat-

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ment.<sup>6-8</sup> Furthermore, approximately 35% of the patients with MDD who fail to respond to first-line treatment obtain a remission after switching to a second-line treatment.<sup>9,10</sup> Finally, between 34% and 48% of depressed patients fail to respond to two or more adequate courses of AD medications.<sup>11,12</sup>

A possible reason for the high rate of unsatisfactory responses to ADs is that MDD is a very heterogeneous disorder with respect to symptom presentation and, possibly, its underlying mechanisms.<sup>13</sup> According to the Diagnostic and Statistical Manual of Mental Disorders–5th ed. (DSM-5) diagnostic criteria,<sup>14</sup> there are more than 60 forms of MDD, given the various possible combinations of symptoms by which a major depressive episode (MDE) can be diagnosed.<sup>15</sup> The symptoms include depressed mood and/or a loss of interest and pleasure (anhedonia), and at least four other symptoms among a list of seven. Furthermore, additional symptomatological features can be considered as specifiers of each MDE.<sup>14</sup>

In this scenario, it is plausible that subgroups of depressed individuals, possibly sharing similar clinical and pathophysiological characteristics, are better suited to some medications, whereas others may obtain limited benefits from the same treatments. Personalized psychiatry can be a crucial strategy to improve pharmacological responses in MDD. This approach attempts to tailor therapeutic interventions according to each patient's unique profile and characteristics, by integrating information from clinical features, biomarkers, genetic/epigenetic factors, and environmental influences, with the final aim of optimizing the choice among treatment options when facing a current MDE, thus overcoming trial-and-error treatment choices. As the lack of full remission of an MDE is associated with high recurrence of episodes, chronic course, and more severe functional impairment,<sup>16,17</sup> increasing the chances of successful therapeutic responses during an MDE can play a key role in making the global course and outcomes of MDD more favorable.

In clinical practice, clinicians already use a somewhat personalized strategy, combining personal experience and scientific evidence, to choose a tailored treatment for each patient. However, personal beliefs and interpretative models, not sufficiently grounded on scientific evidence, may lead to bias in treatment selection. Therefore, efforts to give some evidence-based suggestions in the framework of personalized medicine could have positive effects on clinicians' decisions.

In this narrative review, we evaluated if, and to what extent, some variables easily assessable in clinical practice through clinical interviews may contribute to optimizing the pharmacological choice for each patient with an MDE at the early stage of the disorder. Given the extensiveness of the topic, we focused only on antidepressant medications, while we did not consider combined medications, psychological interventions,

or treatments targeted on non-responder/treatment-resistant patients. Specifically, we considered the influence of some sociodemographic and clinical [i.e., body mass index (BMI), and severity and profile of depressive symptoms] variables on responses to antidepressant classes and/or specific antidepressant compounds.

If we find significant results, it may increase the possibility that a personalized medicine approach becomes part of everyday clinical practice in psychiatric settings when more sophisticated, time-consuming, and expensive sources of predictions are unavailable.

## SOCIODEMOGRAPHIC VARIABLES

### Gender

A meta-analysis of 35 historical trials conducted between 1957 and 1991 suggested that men benefited more from the TCA imipramine than premenopausal women.<sup>18</sup> Similarly, a subsequent study in a large sample showed that premenopausal women responded significantly faster and better to the SSRI sertraline than to imipramine, whereas the opposite was found in men, and postmenopausal women had similar rates of response to the two medications.<sup>19</sup> A later review of 15 randomized, placebo-controlled trials (RCTs) supported the possibility of better responses to SSRIs in women when compared to men.<sup>20</sup> Consistently, a meta-analysis suggested a possible better response of females to the SSRI paroxetine,<sup>21</sup> while a meta-regression analysis of 59 studies found a possible better trend in females after 6 weeks-treatment with sertraline.<sup>22</sup> In line with these findings, preliminary results in a small sample of young men and premenopausal women suggested a greater response in females treated with the SSRI citalopram than in females treated with the SNRI reboxetine, while no differences were observed in men.<sup>23</sup> Moreover, the analysis of a pooled dataset from eight RCTs found among women (not men) showed better responses to SSRIs in younger patients (<50 years); hormone replacement therapy appeared to eliminate this difference among women.<sup>24</sup> Higher remission rates in females were found in the large-scale trial Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) (Phase 1) after 14 weeks of treatment with citalopram in psychiatric and primary care “real world” settings.<sup>25</sup> Finally, some indications of more favorable responses to MAOIs<sup>26</sup> and the SNRI venlafaxine in females were found.<sup>20,21</sup> However, many authors claim that these gender differences in treatment response, although statistically significant, are not large enough to suggest that gender should guide the clinical use of antidepressants.<sup>20,21,26,27</sup> Moreover, other findings failed to reveal any gender effects in predicting or moderating differential responses to different antidepressant classes or compounds. Indeed, retrospective

examinations of multiple RCTs did not find gender differences in responses to TCAs, the SSRI fluoxetine,<sup>26,28</sup> or venlafaxine;<sup>24</sup> similarly, no effects of gender or menopausal status on treatment outcomes with venlafaxine or fluoxetine were found in a large, multiphase, multicenter trial.<sup>29</sup> Likewise, a meta-analysis of 30 RCTs found that responses to the TCAs imipramine and amitriptyline were independent of gender, even when considering interactions between gender and age.<sup>30</sup> A more recent meta-analysis of multiple RCTs further supports the lack of associations between gender and responses to TCAs (imipramine, nortriptyline) or SSRIs (paroxetine, escitalopram, fluoxetine).<sup>31</sup> Finally, in the International Study to Predict Optimized Treatment in Depression (iSPOT-D), no gender differences were found after 8 weeks of randomized treatment with escitalopram, sertraline, or venlafaxine.<sup>32</sup>

In conclusion, many studies did not find gender effects on clinical response to antidepressants in MDD and, even when statistically significant differences between females and males were found, they appeared to be small and probably not relevant from a clinical point of view. Therefore, so far, gender does not seem to be a reliable factor to consider when choosing an antidepressant class or specific compound for MDD in clinical practice.

### Age

Studies investigating the relationships between age and response to antidepressants in MDD have yielded inconsistent results. A recent review including RCTs, uncontrolled treatment trials, and observational studies, suggests that older current age and earlier age at onset of MDD may have direct effects on poor overall treatment response.<sup>33</sup> These findings were partly supported by a recent individual participant data (IPD) meta-analysis of Japanese RCTs, comparing bupropion, duloxetine, escitalopram, paroxetine, mirtazapine, and venlafaxine with placebo in the first 6–8 weeks of treatment.<sup>34</sup> Indeed, in line with the review previously mentioned,<sup>33</sup> the IPD meta-analysis indicated that the older the current age, the smaller the difference in depression severity reduction between antidepressants and placebo, while, in the opposite direction, it found that the older the age at onset the smaller the superiority of the antidepressants over placebo.<sup>34</sup> Finally, recent findings from the 8-week multisite EMBARC trial of sertraline versus placebo found that older current age was associated with better outcomes to sertraline than placebo.<sup>35</sup> Conversely, both the STAR\*D (Phase 1)<sup>25</sup> and the iSPOT-D<sup>32</sup> studies failed to find relationships between current age or age at onset and response to antidepressant treatments.

In conclusion, the mixed available results do not allow clinicians to consider current age or age at onset as reliable variables to guide the selection of an antidepressant treatment

for MDD in clinical practice.

### Race and ethnicity

Older studies, performed with very different methodology concerning design, settings, outcome measures, and types/doses of medications, provided inconsistent results about the possible influence of ethnic differences on antidepressant treatment outcomes in MDD. Some findings suggested that African-Americans and Latinos may respond to lower doses of antidepressants when compared with Caucasian patients,<sup>36,37</sup> whereas others found poorer global outcomes for minority patients than Caucasians.<sup>38,39</sup> More recently, pooled analyses of large pharmacy-sponsored databases found similar response and remission rates to paroxetine and duloxetine treatments in Latino, African American, and Asian American patients compared with whites,<sup>40,41</sup> even though these findings may not be fully representative of treatment effectiveness in clinical settings. Partly in line with these findings, the “real world” clinical study STAR\*D (Phase 1) found only few indications in blacks, and no indications in Hispanics, of poorer outcomes to citalopram treatment compared with whites, after adjustment for many baseline clinical, demographic, and socioeconomic differences.<sup>42</sup> Specifically, remission rate remained worse for blacks in only one of several outcome measures, i.e., the self-report version of the 16-item Quick Inventory of Depressive Symptomatology.<sup>42</sup> A prospective 8-week, open-label clinical trial with citalopram found similar outcomes in African-American and Caucasian patients with MDD, despite several baseline differences in demographic/socioeconomic variables and depression severity.<sup>43</sup> Similar findings were obtained in the Combining Medications to Enhance Depression Outcomes (CO-MED) trial, which examined if outcomes differed by race-ethnicity (i.e., non-Hispanic whites, blacks, and white Hispanics) in the acute (12 weeks) and continuation (12–28 weeks) phases of randomized treatment with escitalopram (plus placebo) or one of two antidepressant combinations (bupropion plus escitalopram/venlafaxine plus mirtazapine). Although black participants had greater baseline psychiatric and medical comorbidities, there were no significant differences in clinical outcomes between groups.<sup>44</sup> Likewise, the iSPOT-D study did not find associations between response to antidepressant treatment and race.<sup>32</sup> Taken together, the results of these studies suggest that socioeconomic disparities were likely contributors to the ethnic differences in treatment outcomes found in older studies; hence most differences may be overcome by improving access to and quality of care for minority groups.<sup>44</sup> However, it should be noted that subsequent re-analyses of STAR\*D data to examine independent contributions of race and genetic ancestry to citalopram response found that, although socio-

economic and baseline clinical factors drove racial differences in antidepressant response, genetic African ancestry, rather than self-reported race, explained a significant fraction of the residual differences between blacks and whites.<sup>45</sup>

In conclusion, no specific indications based on race/ethnicity are available when choosing an antidepressant treatment in clinical practice. However, the possible influence of low socioeconomic status and genetic African ancestry on poorer outcomes, as well as some indications of higher attrition rates of blacks in both clinical trials and clinical sites of care,<sup>44,46</sup> should be considered in clinical practice when selecting optimal setting and intensity of care for ethnic minority groups.

### Socioeconomic variables

A large body of literature supports the association between low socioeconomic status (SES) and both higher prevalence of depression and higher risk of developing it over time.<sup>47,48</sup> Several studies suggest that SES also influences the outcomes of antidepressant treatments. In the STAR\*D study (Phase 1), socioeconomic factors, such as low income, education, and unemployment, were highly discriminative in predicting a poor response to citalopram, even with disparities in access to care accounted for;<sup>25,49</sup> whereas reviews of several studies found that high income and SES, as well as living with a spouse/partner, were predictive of a better response to antidepressants.<sup>50,51</sup> If unemployment is consistently considered a risk factor of poorer antidepressant response, recent findings suggest that even the occupational level of patients in employment may play a role in treatment outcome. In a large multicenter and multinational study project [Group for the Study of Resistant Depression (GSRD)], patients with high occupational level (OL) (e.g., higher executives/business managers/administrative personnel) showed lower response/remission with the last treatment (SSRIs, SNRIs, and NRIs) for the current depressive episode, compared with those with middle or low occupational level. Moreover, the high OL group contained a higher proportion of patients who suffered from at least two consecutive failures of treatment.<sup>52</sup> A following study, with an independent sample, confirmed that managers and white-collar workers had higher rates of non-response and resistance to antidepressant treatments than blue-collar workers.<sup>53</sup> These unexpected results may be partly explained by some specific stressful psychosocial factors related to high OL that may hinder the healing process, such as high demand and workload, pressure, competition, social isolation at work, work-life imbalance, and personal attributes leading to difficulties in adapting to the depressive state or stigma of mental illness.<sup>53</sup>

In conclusion, the available findings suggest that assessment of SES and OL in clinical practice can help to select patients

that need special care over the course of treatment for increased risk of poor responses to antidepressants, whereas no indications are available to guide a personalized class- or medication-specific selection.

## CLINICAL VARIABLES

### Body mass index

Obesity is one of the most prevalent comorbidities of MDD, in particular among women,<sup>54</sup> and it is associated with more severe and chronic MDD.<sup>55</sup> This relationship raises the question if being overweight or obese may be associated with a poor response to antidepressants, and if BMI may inform the selection of antidepressant treatment.

In an older meta-analysis of three clinical trials (all double-blind, active-controlled comparisons of marketed SSRIs and SNRIs, conducted between 2003 and 2006), being overweight (i.e., BMI between 25.0 and 29.9) and, to a greater extent, obese (i.e., BMI  $\geq$  30) were predictive of poor outcomes compared to normal weight.<sup>56</sup> Subsequent studies confirmed the association between higher weight and poorer responses to antidepressants in MDD, while the findings regarding specific classes or compounds were heterogeneous. A pooled analysis of Phase II-IV SSRIs-clinical trials, involving obese/non-obese participants, showed that the subgroup of depressed obese men had little or no therapeutic benefit with SSRIs compared with the rest of the depressed sample.<sup>57</sup> Similarly, increased BMI was associated with poorer outcomes in two short-term trials with the SSRI fluoxetine.<sup>58,59</sup> Conversely, overweight and obesity did not seem to influence responses to the SSRI escitalopram in a very large sample participating in the Genome Based Therapeutic Drugs for Depression (GENDEP) project (a 12-week open-label, part-randomized, multicenter trial comparing treatment with escitalopram or nortriptyline),<sup>60</sup> while in the same sample, these features predicted poor responses to the TCA nortriptyline.<sup>60</sup> More recently, two reviews supported the association between obesity/overweight and poor antidepressant responses, even though it was difficult to draw definitive conclusions due to the methodological differences among studies.<sup>61,62</sup> Subsequent findings from the iSPOT-D trial revealed that venlafaxine monotherapy was more effective than escitalopram in obese II (BMI between 35.0 and -39.9) and obese III (BMI  $\geq$  40) depressed outpatients, while escitalopram was more effective than venlafaxine in those with normal BMI.<sup>63</sup>

A recent secondary analysis of data from the CO-MED trial found that normal- or under-weight participants (BMI < 25) appeared to be less likely to remit with the bupropion-escitalopram combination than with escitalopram monotherapy or the venlafaxine-mirtazapine combination, whereas

obese II+ participants (BMI $\geq$ 35) were more likely to remit with bupropion-escitalopram than the other two treatment options.<sup>64</sup> These results support and extend those of Green and colleagues.<sup>63</sup> Indeed, the dopaminergic and noradrenergic antidepressant bupropion in combination with escitalopram was supposed to have a pharmacological profile similar to that of venlafaxine, which provided greater benefits than escitalopram in iSPOT-D.<sup>64</sup> Taken together, these studies provide very preliminary suggestions of personalized, medication-specific, antidepressant selection in clinical practice based on BMI measurements. Bupropion-escitalopram combination should be avoided in normal-/under-weight depressed outpatients, as compared to escitalopram monotherapy or venlafaxine-mirtazapine combination, while it should be preferred in those with BMI $\geq$ 35. The latter group may also benefit from venlafaxine monotherapy, which, conversely, may be less efficacious in normal-/under-weight depressed patients, as compared to escitalopram monotherapy. Finally, fluoxetine and nortriptyline may be less efficacious in overweight/obese depressed patients.

In conclusion, most findings point to associations between overweight/obesity and poorer responses to antidepressants, which suggest careful monitoring of symptoms during the course of treatment in depressed patients with these features. Only preliminary indications are available concerning antidepressant-specific selection based on BMI.

### Severity of depressive symptoms

One of the most studied clinical predictors of antidepressant treatment outcome is pretreatment depressive symptom severity. A meta-analysis by Khan and colleagues<sup>65</sup> found that greater baseline depression severity was associated with significantly greater magnitude of symptom reduction during antidepressant treatment compared to placebo. In line with these results, a subsequent meta-analysis<sup>66</sup> concluded that lower depressive symptom severity predicted minimal to no advantage of antidepressants over placebo. Conversely, the magnitude of the advantage in taking antidepressants increased as the severity of pretreatment depression increased,<sup>35,66</sup> although the very severely depressed patients had lower probabilities of achieving a full remission of depressive symptoms than a clinical response (i.e., symptom reduction), and displayed less favorable global outcomes.<sup>51,67</sup> In line with these findings, recent results from the European GSRD indicated that great depressive symptom severity, as well as early age of onset ( $\leq$ 18 years), are predictors of resistance to AD treatment.<sup>68</sup>

In conclusion, the greater the pretreatment symptom severity of patients in an MDE, the greater the expected treatment response to the whole class of antidepressants, even if, in patients with severe depressive symptoms, full remission

seemed to be more difficult to achieve than response and poorer treatment outcomes are more likely. Patients with very low depressive symptom severity may not require antidepressants, while non-pharmacological interventions, such as cognitive behavioral therapy (CBT), may be sufficient for symptom remission.<sup>69</sup> No indications were available for personalized selection of specific antidepressant class or compound based on the range of depressive severity.

### Symptom profiles

Symptom profile-based predictors and moderators of treatment response were widely investigated in research studies, as the examination of symptomatological expression of an MDE is usually part of the psychiatric interview. Symptom profiles include single specific depressive symptoms, such as anhedonia, symptom dimensions (i.e., groups of co-occurring symptoms identified through factor analyses of depression rating scales), subtypes, and specifiers. However, while the definition of single depressive symptoms is more univocal, considerable variations were found in the literature for the definition of depressive subtypes/specifiers, with risk of subjective and idiosyncratic interpretations. As an example, although both the DSM-IV-TR and DSM-5 made a distinction between subtypes (i.e., mutually exclusive and jointly exhaustive phenomenological subgroupings) and specifiers (i.e., non-mutually exclusive or jointly exhaustive phenomenological subgroupings),<sup>14,70</sup> these two terms are often used interchangeably in scientific studies. Furthermore, both the criteria used to define the same construct, such as melancholic depression, and methods of assessment (e.g., clinical interview/psychometric tools; self-administered/clinician-administered scales) vary considerably across studies, thus making the results not always directly comparable. Therefore, the available findings should be interpreted keeping in mind the limitations affecting this body of research.

Given the extensiveness of the topic, we specifically focused on anhedonia, a core symptom of major depression, and MDD with melancholic features, with atypical features and with anxiety symptoms.

### Anhedonia

Anhedonia (i.e., the loss of pleasure in activities, and/or lack of reactivity to usually pleasurable stimuli) is considered a cardinal symptom of MDD, and it was proposed as a possible endophenotype of depression.<sup>71</sup> Anhedonia is thought to reflect the dysfunction of the brain reward circuits, which are crucial for both the motivational drive and the ability to feel pleasure in response to events/activities (i.e., consummatory pleasure).<sup>71-73</sup> Findings from preclinical and clinical studies suggest the centrality of dopamine in motivational aspects of

reward processing, while endogenous opioids may be involved in the hedonic experience.<sup>74,75</sup> More recently, other neurotransmitters, such as glutamate, have broadened the picture of mediation of reward and anhedonia at neurotransmitter level.<sup>73,76</sup>

From a clinical point of view, some studies point to relationships between anhedonia and severe behavioral and somatic MDD-related events.<sup>58,77,78</sup> For these reasons, it is of great importance when treating MDD to consider the therapeutic effectiveness of medications on this critical aspect of the disorder. Unfortunately, at present, there are no approved medications specifically targeting anhedonia, which is associated with poorer responses to treatments and poorer short-/long-term outcomes.<sup>79,80</sup> In the GENDEP and STAR\*D (Phase 1) studies, higher interest-activity symptom dimension at baseline, mainly reflecting anhedonia, was the most robust predictor of a poor response to escitalopram or nortriptyline (GENDEP), and to citalopram (STAR\*D), irrespective of overall depression severity and multiple sociodemographic variables.<sup>81</sup> Likewise, other studies found that the current standard antidepressant treatments, particularly SSRIs, did not seem to be fully effective in treating reward-related symptoms of depression,<sup>82,83</sup> and anhedonia often seemed to persist despite the resolution of other symptoms of depression.<sup>84</sup> Moreover, several studies suggested that SSRIs may induce some clinical features close to anhedonia in depressed patients, such as emotional blunting and restriction in the range of emotions,<sup>85</sup> possibly related to SSRI induced dampening of dopaminergic/noradrenergic activity.<sup>86</sup> This possibility may also partly explain why anhedonia and fatigue often remained in some depressed patients with an overall positive response to SSRIs.<sup>87</sup>

In this context, a recent systematic review<sup>88</sup> examined the issue whether specific antidepressants may be particularly suitable to treat anhedonia and provided some preliminary results from relatively few comparative pharmacological studies that used reliable measures of anhedonia. The antidepressant agomelatine, which has melatonergic activity, increases serotonin and dopamine levels in the frontal cortex, and enhances expression of brain-derived neurotrophic factor (BDNF),<sup>89,90</sup> reduced emotional blunting and affective flattening in some open-label studies,<sup>88</sup> and it displayed greater efficacy on measures of anhedonia when compared with the SNRI venlafaxine extended-release (ER),<sup>91</sup> or the SSRI escitalopram.<sup>92</sup> Conversely, no significant differences in antianhedonic properties were found in a randomized double-blind trial comparing the SSRI fluoxetine with ER venlafaxine.<sup>93</sup> The reversible MAOI-A moclobemide, which has pro-dopaminergic properties, had earlier and greater antianhedonic effects when compared with the serotonergic TCA clomipramine in a 4-week double-blind multicenter study.<sup>94</sup> Similarly, the norepinephrine-dopamine

reuptake inhibitor, bupropion, appears to alleviate anhedonia by improving reward response, interest, and energy when compared with placebo.<sup>95</sup> Recent findings of an open-label trial<sup>96</sup> suggest that a single infusion of ketamine (0.5 mg/kg), a medication targeting the glutamatergic system through its NMDA receptor antagonistic properties, may provide rapid (i.e., during the first three days post-infusion) antianhedonic effects, which was maintained for up to 28 days post-infusion. Overall, there was significant methodological heterogeneity across the studies included in the qualitative review of Cao and colleagues,<sup>88</sup> such as trial duration, illness severity, medication dose, and assessment measure. Additionally, the number of available studies was limited. For these reasons, the results should be considered preliminary, and more research is needed to provide any ranking of the antianhedonic properties of different antidepressants.

In conclusion, the association between anhedonia and poorer responses to antidepressants suggest to clinicians a careful monitoring of patients with this prominent symptom during the course of antidepressant treatment to select the intensity of care and consider complementary strategies, such as behavioral activation, physical exercise, and/or pharmacotherapeutic combination or augmentation strategies.<sup>81</sup> Only very preliminary indications are available for clinicians concerning possible antidepressant-specific selection based on the presence of anhedonia.

### MDD with melancholic features

According to the DSM-IV-TR and DSM-5,<sup>14,70</sup> MDD with melancholic features (MDD-MF) is characterized by pervasive anhedonia, accompanied by at least three other symptoms among a distinct quality of depressed mood (e.g., profound despondency/moroseness), worse depression in the morning, early morning awakening, psychomotor agitation/retardation, significant anorexia/weight loss, and inappropriate guilt.

Studies comparing efficacy of antidepressants between melancholic and non-melancholic depression provided controversial results concerning both the outcome to antidepressants considered as a group and to different types of antidepressants. These discrepancies were thought to be related to methodological differences across studies concerning design, definition/assessment of melancholia, differences in baseline features of patients, and statistical power.

In both the STAR\*D (Phase 1)<sup>97</sup> and iSPOT-D<sup>98</sup> studies, unadjusted analyses found a lower rate of remission in patients with MDD-MF than those without melancholic features, but differences became non-significant after adjusting for baseline characteristics. Furthermore, no indications were found that the melancholic/non-melancholic features may guide antidepressant selection.<sup>99</sup> Similarly, secondary analyses of data

from the CO-MED trial found no evidence of differential remission or response rates to antidepressant combination or monotherapy between melancholic/non-melancholic MDD patients.<sup>100</sup> Conversely, in a prospective, naturalistic, multi-center, nationwide epidemiological Spanish study,<sup>101</sup> outpatients with MDD-MF, compared with non-melancholic outpatients, showed lower rates of remission after both 6–8 and 14–20 weeks of different antidepressant treatments (SSRIs, SNRIs, and TCAs), even after considering baseline differences between the two groups. A secondary analysis of data from the GENDEP study found that MDD-MF had slightly worse outcomes than non-melancholic MDD, which was relatively specific to escitalopram, but not to nortriptyline. However, the melancholia-drug interaction was not statistically significant on the primary outcome measure, and significant results for secondary measures were not confirmed in sensitivity analyses restricted to randomly allocated individuals; hence the authors concluded that MDD-MF was not a sufficiently robust differential predictor of outcome to guide clinicians in choosing between SSRIs and TCAs.<sup>102</sup> In the opposite direction, in a nationwide Korean naturalistic study, patients with MDD-MF who received 12-week, clinician-determined, antidepressant intervention had faster and higher rates of remission, especially when SSRIs were used, than those without melancholic features, even after adjustment for baseline status.<sup>103</sup>

The group of studies that specifically focused on the clinical response to different types of antidepressants provided inconsistent results. Briefly, older studies initially discouraged the use of MAOIs in MDD-MF, while subsequent results did not find differences between MAOIs and TCAs. First studies with SSRIs suggested lower effectiveness of these compounds in MDD-MF compared with TCAs, while more recent studies found heterogeneous results ranging from better outcomes with TCAs to no differences, or to better response with SSRIs. Finally, inconsistent results were also found in comparisons between SSRIs and newer antidepressants such as venlafaxine. For a detailed list of these studies, please refer to the review cited below.<sup>104</sup>

Recently, a comprehensive meta-analysis attempted to clarify this heterogeneity. It included randomized and non-randomized trials that were published between 1980 and 2017 and using validated measures to define melancholic/non-melancholic MDD.<sup>104</sup> Considering antidepressants as a group, MDD-MF, compared with non-melancholic MDD, was less likely to show response to placebo (weighted mean follow-up period, 5.8 weeks) and was significantly associated with decreased likelihood of remitting from the MDE (weighted mean follow-up period, 10.6 weeks), even taking into account the higher baseline severity of depressive symptomatology found

in MDD-MF. Conversely, MDD-MF was not associated with a decreased likelihood of responding to antidepressants during a weighted mean follow-up period of 10 weeks. A possible explanation of this discrepancy is that MDD-MF may take a longer time to remit than non-melancholic MDD, as found in a previous study,<sup>105</sup> while the mean duration of trials was sufficient for a 50% reduction in baseline depressive symptoms (i.e., “response”), thus making the odds of response in melancholic/non-melancholic MDD similar.<sup>104</sup> Comparing the odds of remission to different types of antidepressants in MDD-MF, melancholic patients treated with SSRIs had significantly lower odds of achieving remission than those treated with TCAs, while no differences were found between SSRIs and venlafaxine.<sup>104</sup>

In conclusion, considering the relative shortage of studies specifically focusing on MDD-MF, and the methodological limitations of this body of research, the available findings should be considered preliminary and further research is needed.<sup>104</sup> Due to the central role of anhedonia in MDD-MF, future studies should also evaluate the efficacy of compounds that seem promising when tested on anhedonia considered as a single symptom, as described in the previous section. So far, provisional conclusions suggest that MDD-MF may have lower rate of remission than non-melancholic MDD with antidepressant treatments, and TCAs may have higher efficacy than SSRIs in patients with MDD-MF. However, due to the well-known less favorable side effect profile of TCAs compared with SSRIs, clinicians should carefully consider the advantages and disadvantages of using TCAs for each individual patient with MDD-MF.

### MDD with atypical features

MDD with atypical features (MDD-AF) describes a condition with significant mood reactivity in response to positive events, and at least two of the following symptoms: interpersonal rejection sensitivity, increased appetite/weight, hypersomnia, and leaden paralysis.<sup>14,70</sup> Similar to MDD-MF, a mixed picture has arisen for outcomes for antidepressants in MDD-AF, especially concerning the value of atypical features for antidepressant selection. Regarding the global outcome for antidepressants, although some results suggest lower remission rates in MDD-AF than in MDD without atypical features,<sup>101</sup> most other studies failed to find outcome differences after adjustment for pretreatment baseline differences, including large trials such as iSPOT-D, STAR\*D, and GENDEP.<sup>99,102,106</sup> Concerning preferential response to specific antidepressants, older studies suggest a poorer response to the TCA imipramine in MDD-AF,<sup>107</sup> and higher efficacy of the irreversible MAOI phenelzine and the reversible MAOI moclobemide compared with imipramine<sup>108</sup> or the SSRI fluox-

etine,<sup>109</sup> respectively. However, another study did not find outcome differences between moclobemide and the SSRI sertraline in MDD-AF.<sup>110</sup> A meta-analysis of double-blind, 6- to 12-week controlled studies, covering the years from 1966 through 2004, supported the higher efficacy of phenelzine and moclobemide over imipramine in MDD-AF, while it provided preliminary suggestions, based on a limited number of studies, that fluoxetine and sertraline may have similar efficacy to MAOIs.<sup>111</sup> More recently, a 6-week, randomized, double-blind trial found that moclobemide was superior to the TCA clomipramine in MDD-AF, thus supporting the higher efficacy of MAOIs over TCAs in patients with atypical features.<sup>112</sup> However, as the current use of MAOIs in clinical practice is limited, some subsequent studies focused on SSRIs or other antidepressants newer than MAOIs. Unfortunately, this body of research is still limited. In the GENDEP study, the SSRI escitalopram and the TCA nortriptyline were equally effective in treating MDD-AF,<sup>102</sup> and no differences were found in the iSPOT-D study when the effectiveness of escitalopram, sertraline, and venlafaxine in MDD-AF were compared.<sup>99</sup>

In conclusion, beyond the older findings of the superiority of MAOIs compared to TCAs in treating MDD-AF, so far, no specific indications are available to help clinicians in selection among newer antidepressants.<sup>113</sup> However, as associations between atypical depression and bipolarity were found, which can have therapeutic implications,<sup>114</sup> careful information about possible risk factors for bipolarity should be collected in clinical practice before starting treatment when atypical features are present. Likewise, some associations found between atypical depression, overweight/obesity, and resistance to leptine<sup>114,115</sup> suggest that clinicians should consider antidepressants with limited effects on appetite and/body weight when treating patients with MDD-AF.

### MDD with anxiety symptoms

To take into account the presence of significant anxiety condition in MDD, the DSM-5 introduced the anxious distress specifier, defined as the occurrence, during most days of an MDE, of at least two of five anxiety symptoms.<sup>14</sup> Before the development of this relatively new DSM-5 specifier, the concurrence of anxiety symptoms in depression was generally denominated as “anxious depression.” This term was used interchangeably across studies to indicate heterogeneous definitions that had poor agreement<sup>116</sup> and made it more difficult to compare the results. The most common definitions of “anxious depression” included MDD with comorbid full-blown anxiety disorders (AnxDs), or MDD with clinically significant anxiety symptoms measured on different anxiety dimensional rating scales. For the dimensional definition of “anxious depression,” the most common criteria were a cut-off score of

at least seven on the Hamilton Depression Rating Scale (HAM-D) anxiety/somatization factor (ASF), or varying cut-off scores on the Hamilton Anxiety Rating Scale (HAM-A).<sup>117</sup> Despite heterogeneity in definitions and assessment tools, “anxious depression” was reported in 42–78% of patients with MDD, and it was generally associated with greater depression chronicity and severity, higher suicide ideation/risks, greater functional disability, lower quality of life, and poorer outcomes compared with MDD without anxiety.<sup>117</sup> Recently, the DSM-5 anxious distress specifier appeared to outperform the presence of comorbid DSM-IV-AnxDs as a longitudinal predictor of depression outcome, suggesting that it may represent a general marker of anxiety able to capture a specific construct with clinical validity and not fully overlap with the co-occurrence of AnxDs in MDD.<sup>118</sup> In the following paragraphs, we specifically focus on MDD with significant anxiety symptoms (MDD-AS), as identified by both the DSM-5 specifier and previous dimensional measurements, because the therapeutic implications of comorbidity of MDD with AnxDs require a dedicated review.

Most studies suggest that MDD-AS has poorer outcomes with antidepressants compared to MDD without anxiety symptoms. A review of pharmacological studies (with different designs/compounds), covering the years from 1949 through the beginning of 2013, found that patients with MDD-AS, mostly defined as HAM-D-AFS score  $\geq 7$ , did not maintain sustained response or remission following initial successful treatments with SSRIs, SNRIs, or TCAs, and, moreover, they were at greater risk of side effects.<sup>119</sup> In the Phase 1, STAR\*D study, MDD-AS (HAM-D-AFS score  $\geq 7$ ) was associated with delayed and less likely remission compared with MDD without anxiety symptoms. Similarly, in Phase 2, MDD-AS was associated with poorer outcomes in both the switching (sustained-release bupropion/sertraline/venlafaxine ER), or augmentation (sustained-release bupropion/buspirone) options.<sup>120</sup> Consistently, a pooled analysis of 13 double-blinded, randomized, controlled trials (including SSRIs and SNRIs) found that patients with MDD-AS (HAM-D-AFS score  $\geq 7$ ) had lower remission rates than those without anxiety symptoms.<sup>121</sup> In the GENDEP study, MDD-AS, based on HAM-D-AFS score, was not a predictor of outcome in the whole sample of participants; however, in secondary analyses restricted to randomly allocated participants, MDD-AS was associated with overall poorer outcomes.<sup>102</sup> Multiple re-analyses of data from the iSPOT-D study<sup>32,116,122</sup> found that greater anxiety symptoms at baseline, as measured with the anxiety subscale of the Depression, Anxiety and Stress Scale (DASS-42), were associated with lower response/remission rates across all medications, independent of depression severity and after adjustment for multiple covariates. The factor “somatic anxiety” appeared to



be particularly related to worse outcomes. Conversely, no relationships between anxiety symptoms and outcome were found using the HAM-D-AFS scores.<sup>32,99,116,122</sup> Finally, a recent longitudinal cohort study, the Netherlands Study of Depression and Anxiety, revealed that the DSM-5 anxious distress specifier significantly predicted poorer outcomes with adequate antidepressant treatments in MDD, including SSRs, TCAs, and other antidepressants. Poorer outcomes were represented by higher depression severity (at 1-year and 2-year follow-up), lower remission rates (at 2-year follow-up), and greater burden of antidepressant side effects during treatment. Conversely, comorbidity with AnxDs did not predict treatment outcome.<sup>118,123</sup> Across all the studies described above, no evidence of preferential response of MDD-AS to a specific antidepressant class or compound was found.

In conclusion, studies considering the dimensional definitions of anxiety in MDD point to associations between MDD-AS and poorer responses to antidepressants, with a greater burden of side effects, suggesting careful monitoring of patients with these features during the course of antidepressant treatment. No indications are available for possible antidepressant-specific selection based on the presence of significant anxiety symptoms during an MDE.

## CONCLUSION AND FUTURE DIRECTIONS

In the framework of personalized medicine in psychiatry, our review aimed to evaluate if some easily assessable sociodemographic and clinical variables may help clinicians to optimize selection of the most effective possible antidepressant treatment for each patient with MDD, at the early stage of the disorder. Unfortunately, gender, age, race/ethnicity, and SES, as well as BMI, severity of depressive symptoms, and symptom profiles (i.e., presence of anhedonia; MDD with melancholic features/atypical features/anxiety symptoms), when considered independently as separate variables, failed to provide value to predict reliable differences in benefits of alternative antidepressants for each patient. Several variables were associated with poorer outcomes to the whole group of antidepressants, such as low SES, genetic African ancestry, overweight/obesity, very severe pretreatment depressive symptoms, depression with melancholic symptoms, or with significant anxiety symptoms. However, only sparse and preliminary associations were found between some clinical variables (i.e., BMI, anhedonia, and MDD with melancholic/atypical features) and possible benefits with some specific antidepressants, not sufficient to be considered as guidelines in choosing antidepressant treatment.

In conclusion, in clinical practice, the assessment of the

sociodemographic and clinical variables considered in our review can be valuable for early identification of depressed individuals at high risk for poorer responses to antidepressants, who may require a particular setting and a higher intensity of care and monitoring. However, so far, there is not enough data on which to ground any reliable selection of specific antidepressant class or compound.

As discussed throughout the paper, the lack of reliable conclusions may be partly explained by limitations that this body of studies suffered from, including heterogeneity in design, duration, setting, features of the sample, statistical power, criteria and/or tools used to assess clinical symptoms or profiles, and the limited number of comparative studies testing the differential efficacy of specific antidepressants. In addition, it should be noted that our review focused only on a limited set of variables, while other individual/clinical factors, relatively easy to assess in clinical practice, may play a role, such as childhood maltreatment/adversities,<sup>124-126</sup> inflammatory markers,<sup>127,128</sup> other symptom profiles or individual features. Among the latter, alexithymia, reflecting difficulty with identifying and expressing emotions, seems to be associated with higher severity of depression, increased suicide risk, and pro-inflammatory imbalance;<sup>129-133</sup> thus its potential contribute to selection of specific antidepressant class/compound may be worth investigating. Finally, we did not include combined pharmacotherapies, augmentation strategies, or non-pharmacological interventions. However, even if these limitations are overcome in the future, it appears unlikely that single variables, considered separately, may provide reliable indications for personalized treatment selection, as has been previously noted by others. Furthermore, it is claimed that refining the phenotypes of MDD beyond traditional psychiatric nosography, taking into account biomarkers, functional systems, neural circuits, and environmental factors, may be a crucial step in providing more reliable results both in pharmacological and genetic studies.<sup>134</sup> Likewise, future use of biomarkers, such as neural markers in neuroimaging measures, may help clinicians distinguish depression in bipolar disorder from MDD.<sup>135</sup> Indeed, mainly at the early stage of the disorder, this distinction, which is crucial for choosing appropriate treatments, is difficult when solely based on clinical information.

In this framework, the National Institute of Mental Health Research Domain Criteria (RDoC) initiative<sup>136</sup> is ongoing, with the final aim of defining more reliable phenotypes for each depressed individual, based on which personalized therapies may be selected in the future.<sup>137,138</sup>

Consistent with this view, recent approaches have pointed to the development of composite prediction models that integrate multiple potential predictors through new technological acquisitions and computational resources, such as ma-

chine learning and related techniques.<sup>139,140</sup> Some promising attempts were performed, showing that this paradigm may offer relevant advances toward personalized treatments. A deep learning prediction approach, resulting from the integrated analysis of genetic (i.e., single nucleotide polymorphisms), sociodemographic, and clinical factors in a large sample of patients with MDD, seems to be suitable to distinguish responders from non-responders to SSRI treatment.<sup>141</sup> A machine learning model recently developed using data from STAR\*D (Phase 1) and CO-MED studies performed significantly-above-chance in predicting clinical remission to citalopram, escitalopram, and escitalopram-bupropion treatment, but not to venlafaxine-mirtazapine treatment, suggesting specificity of the model to identify patients who are likely to respond to a specific antidepressant.<sup>142</sup> Similarly, a combination of demographic and clinical variables, obtained with a machine learning approach on data from the GENDEP study, provided a significant contribution in predicting response and remission in MDD during treatment with escitalopram, but not with nortriptyline, suggesting a potential for individualized prescription of this specific antidepressant.<sup>143</sup> In a subsequent re-analysis of the data from the same sample, significant drug-specific predictions of remission for both escitalopram and nortriptyline were obtained, using statistical learning on a larger number of factors, including not only clinical variables but also common genetic variants.<sup>144</sup> These encouraging results offer hope for the future, when predictions that are more reliable may guide personalized choices for each patient with MDD.

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### Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

### Author Contributions

All authors equally contributed to the selection and reviewing process of the scientific articles and the writing of the manuscript.

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