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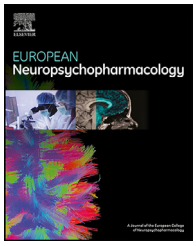

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REVIEW

Biological markers of sex-based differences in major depressive disorder and in antidepressant response

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Abstract
Major depressive disorder (MDD) presents different clinical features in women and men, with women being more affected and responding differently to antidepressant treatment. Specific molecular mechanisms underlying these differences are not well studied and this narrative review aims at providing an overview of the neurobiological features underlying sex-differences in biological systems involved in MDD pathophysiology and response to antidepressant treatment, focusing on human studies. The majority of the reviewed studies were performed through candidate gene approaches, focusing on biological systems involved in MDD pathophysiology, including the stress response, inflammatory and immune, monoaminergic, neurotrophic, gamma-aminobutyric acid and glutamatergic, and oxytocin systems. The influence of the endocrine system and sex-specific hormone effects are also discussed. Genome, epigenome and transcriptome-wide approaches are less frequently performed and most of these studies do not focus on sex-specific alterations, revealing a paucity of omics studies directed to unravel sex-based differences in MDD. Few studies about sex-related differences in antidepressant treatment response have been conducted, mostly involving the inflammatory system, with less evidence on the monoaminergic system and sparse evidence in omics approaches. Our review covers the importance of accounting for sex-differences in research, optimizing patient stratification for a more precise diagnostic and individualized treatment for women and men.

1. Introduction

Major depressive disorder (MDD) differentially affects males and females and sex-based differences in clinical features of MDD are extensively studied. Women are twice as likely as men to develop MDD during their lifetime (Salk et al., 2017) and they are more likely to present recurrent MDD (van Loo et al., 2018). Women diagnosed with MDD present earlier onset of symptoms, longer depressive episodes, greater disease severity (LeGates et al., 2019) and greater frequency of appetite alterations, weight changes and sleep disturbances (Cavanagh et al., 2017), compared to male patients. On their turn, males present more substance abuse, risk taking behaviors and poorer impulse control (Cavanagh et al., 2017).

Furthermore, although data is still limited, several studies have shown that women and men respond differently to antidepressant treatment, particularly to the pharmacological ones. For example, women tend to respond better to selective serotonin reuptake inhibitors (SSRI) and monoamine oxidase (MAO) inhibitors, and are more responsive to fast acting antidepressants such as ketamine, while men usually respond better to tricyclic antidepressants (TCA) (LeGates et al., 2019; Sramek et al., 2016).

From a biological perspective, different factors, such as hormonal changes, particularities in brain structure and function, and inherited traits, seem to increase the risk of MDD in women (Altemus et al., 2014; Kang et al., 2020). Reasons for differential responses to antidepressants between males and females include differences in drug pharmacokinetics profiles and interactions with sex-specific hormones (Sramek et al., 2016).

Nevertheless, despite this data, the specific molecular mechanisms underlying these differences are not well understood. The objective of this narrative review is to provide a broad understanding about the molecular mechanisms underlying sex-based differences in biological systems involved in MDD pathophysiology and response to antidepressant treatment, focusing on human studies.

2. Methods

Electronic searches using MEDLINE/PubMed database were performed combining the following keywords and search terms: “major depressive disorder”, “MDD”, “sex-based differences”, “stress response system”, “biological systems”, “molecular mechanisms”, “inflammatory and immune systems”, “monoaminergic system”, “neurotrophic system”, “GABA and glutamate system”, “oxytocin system”, “endocrine system”, “genetic”, “epigenetic”, “expression”, “transcriptomic”, “omics”, “microRNAs”, “antidepressant treatment” and “antidepressant response”. Narrative reviews, systematic reviews and meta-analyses were also reviewed in order to find further published studies. Inclusion criteria were: a) being a molecular study aimed at analyzing sex-based biological differences in MDD presentation and in antidepressant response performed in humans, b) being an original paper published in a peer-reviewed journal, c) being published in English language.

40 studies were selected from the published literature, from which 34 were directed to the study of biological mechanisms involved in MDD and 6 were focused in antidepressant response.

The selected studies were organized according to the studied biological systems. Studies focusing on molecular changes associated with MDD and relative treatments use different investigation strategies from candidate gene studies to genome-wide, epigenome-wide and transcriptomic approaches, revealing several biological alterations related to MDD and antidepressant response. The next sections will provide an overview on these studies performed on several biological systems at different levels.

3. Human molecular studies: Sex-based differences in MDD

3.1. Stress response system

The stress response system is centered in the hypothalamic-pituitary-adrenal (HPA) axis and its actors, like the corticotropin releasing hormone (CRH), adrenocorticotropin hormone (ACTH), glucocorticoid receptors (GRs) and its regulators, working to regulate stress responses. The following paragraphs focus on sex-based differences relevant for stress-related disorders, especially MDD.

In postmortem brain tissues analyses of depressed patients and controls, depressed women presented increased hippocampal GR protein expression, in comparison with depressed men (Wang et al., 2012). Sex-differences were also found in the amygdala, implicated in emotional regulation and anxiety-related behaviours, in which depressed women, but not men, showed increased GR expression in postmortem amygdala, in comparison to relative controls (Wang et al., 2014). Findings of ACTH peripheral responses to social stress revealed that depressed men and respective controls showed greater ACTH response compared to depressed women and relative controls, while plasma cortisol response remained the same in both sexes (Young and Korszun, 2010; Young et al., 2004). Also, depressed women presented enhanced baseline morning cortisol levels in comparison to relative controls, while this was not always observed in males and respective controls (Young and Korszun, 2010; Young et al., 2004). Depressed women also showed larger salivary cortisol levels in response to negative events in daily life, in comparison with depressed men (Peeters et al., 2003). Overall, these findings show sex-specific regulatory mechanisms in the HPA axis, suggesting diverse stress responses. The studies demonstrate that there are significant differences in the expression of key actors in the stress response system, such as GRs, in different brain regions between males and females. Additionally, the responses to social stress and cortisol levels vary between depressed men and women. In general, females exhibit greater responses to stressful events, but further studies are required to better understand sex-related mechanisms of stress-related disorders. It is relevant to further investigate and comprehend these sex-related mechanisms in the stress response system to enhance our understanding and treatment of stress-related disorders.

3.2. Inflammatory and immune system

The immune system plays a major role in stress-related disorders, with inflammatory markers mediating the relation between stress and MDD (Silva et al., 2021) and being increased in depressed patients (Ma et al., 2016; Osimo et al., 2019). Also, individuals with inflammatory diseases are more likely to develop MDD (Ménard et al., 2017).

Females present larger populations of many innate and adaptive immune cells and higher immunoglobulin levels, resulting in more robust responses to infections and greater vaccine efficacy (Rainville and Hodes, 2019). On the other side, females show greater vulnerability to autoimmune diseases, allergic processes and mood disorders (Klein and Flanagan, 2016; Moulton, 2018; Rainville and Hodes, 2019). Reasons for these dimorphisms involve differential X and Y chromosome gene expression and gonadal hormone metabolism (Dudek et al., 2021; Wang et al., 2016).

Despite the growing interest between the immune system and the known sex-related immunological particularities, few studies reported sex-based differences related to the inflammatory and immune system in the context of MDD. Within the innate immune system, several proinflammatory cytokines were studied. In general, depressed women showed higher interleukin (IL)-6 serum levels than depressed men (Birur et al., 2017; Pallavi et al., 2015), but other findings demonstrate higher blood IL-6 levels in depressed males versus females, relative to respective controls (Vogelzangs et al., 2012). Serum levels of other proinflammatory cytokines, such as IL-1β and tumor necrosis factor alpha (TNF-α), positively correlated with depression severity and suicidal thoughts in depressed females, but not males, in relation to respective controls (Birur et al., 2017). Also, depressed females, but not males, showed higher serum levels of IL-8 and interferon (IFN)-γ than respective controls (Birur et al., 2017). On their turn, males presented some specific proinflammatory markers in mood disorders. In depressed men, but not women, compared to relative controls, TNF receptor 2 serum levels associated with MDD diagnosis (Ramsey et al., 2016) and IL-12 negatively correlated with MDD severity (Birur et al., 2017). Regarding anti-inflammatory markers, depressed females, but not males, presented lower IL-5 serum levels than relative controls (Birur et al., 2017).

C-reactive protein (CRP), an acute phase protein whose circulating levels rise in response to inflammation, also shows evidence of sex-related differences. Among MDD patients, higher CRP serum levels associated with greater depressive symptoms and suicidality in women, but not in men (Köhler-Forsberg et al., 2017). On the contrary, other findings showed associations between higher CRP levels and MDD diagnosis in men, but not in women, in relation to their respective controls (Ramsey et al., 2016; Vogelzangs et al., 2012), and a similar association was found in a cohort of obese participants evaluated for depressive symptoms (Vetter et al., 2013).

Other factors besides cytokines and acute-phase proteins were studied. Depressed females showed higher levels of leptin, which is known for pro-inflammatory properties, and lower levels of the anti-inflammatory adiponectin than controls, while depressed men versus controls showed no differences in these hormone markers (Birur et al., 2017). Finally, analyses of urine metabolites, indirectly related to inflammatory and immune processes, revealed 27 and 36 differential metabolites discriminating women and men with MDD, respectively, from healthy controls. Specifically, the authors have identified women-specific (m-hydroxyphenylacetate, malonate, glycolate, hypoxanthine, isobutyrate and azelaic acid) and men-specific (tyrosine, N-acetyl-D-glucosamine, N-methylnicotinamide, indoxyl sulfate, citrate and succinate) MDD metabolite markers, which could differentiate men and women MDD patients from their respective healthy controls with higher accuracy than sex-nonspecific biomarker panels (Zheng et al., 2016).

These findings highlight the existence of sex-specific immune profiles, but further research is needed to unravel sex-related immune mechanisms in MDD pathophysiology. For example, other inflammatory related markers, like peripheral cytokines and chemokines including IL-13, IL-18, IL-1 receptor antagonist, soluble IL-2 receptor, C-C chemokine ligand 2, known to present alterations in MDD patients versus controls (Köhler et al., 2017), were still not investigated in a sex-specific manner in MDD context. Investigation into other inflammatory markers from a sex-specific perspective may provide valuable insights into the role of the inflammatory and immune system in MDD.

In summary, the results emphasize the close link between inflammation and MDD pathophysiology and shed light on the significant variations in immune responses between females and males, leading to different MDD outcomes. Considering sex-related differences in the inflammatory system and immune profiles, and broadening research in this area, are important for effectively understanding and treating MDD.

3.3. Monoaminergic system

MDD involves regulatory interactions between monoamines like serotonin and noradrenaline, and a decrease in their concentrations are connected with depressive symptoms (Maffioletti et al., 2020; Mulinari, 2012).

Studies on serotonergic system suggest that this system is differentially regulated in both sexes. At the epigenetic level, sex-specific methylation patterns in the serotonin transporter gene *SLC6A4* were found in cord blood of newborns exposed to early life stress, defined as maternal stress during pregnancy, with girls showing higher methylation levels than boys (Dukal et al., 2015). Also, in monozygotic twins assessed for lifetime diagnosis of anxious-depressive disorders, *SLC6A4* promoter methylation was higher in women than men, independently of psychiatric diagnosis, and same methylation differences were found in a sample of postmortem brain tissues of different brain regions (Palma-Gudiel et al., 2019). Other authors found *SLC6A4* promoter hypermethylation in both males and females exposed to childhood maltreatment, but the regions of hypermethylation differed between the sexes. In abused men, there was hypermethylation of the entire *SLC6A4* promoter region compared to those non-abused. In women, two specific loci were significantly hypermethylated among those who experienced child abuse (Beach et al., 2010). In spite of these differences, other findings showed that higher *SLC6A4* promoter methylation associated with childhood adversities, family history of depression and higher perceived stress in depressed patients, but methylation measures were not correlated with sex (Kang et al., 2013). At the gene expression level, mRNA concentrations of the 5-HT (serotonin) 1D receptor and the transcription factors NUDR and REST, regulators of serotonin function, were increased in serotonin-containing neurons of the dorsal raphe nucleus of depressed women versus controls, while no transcript differences were found in depressed men versus controls in postmortem brain specimens (Goswami et al., 2010). At the protein level, sex-specific changes were reported in serotonin receptors and regulators, primarily observed in women in postmortem studies. The concentrations of 5-HT1AR and NUDR protein, serotonin regulators, were decreased in the prefrontal cortex of depressed women versus controls, while this difference was not observed in depressed men relative to controls (Szewczyk et al., 2009). Collectively, these findings show sex-dependent alterations in serotonin functions unraveling molecular mechanisms in the serotonin system associated with MDD.

Finally, another monoaminergic system presenting sex-related differences that exert an effect on MDD vulnerability involves central noradrenaline/norepinephrine regulations, specifically in the locus coeruleus (LC). Indeed, some authors examined microRNAs (miRNAs), small non-coding RNAs that regulate gene expression also involved in psychiatric disorders (Maffioletti et al., 2014), in the LC of depressed suicide completers and controls and found that miR-1179 expression levels were higher in the LC of depressed women suicide subjects in comparison to men (Roy et al., 2017). miR-1179 is related to *GRIA3* and *MAOA*, involved in neuropsychiatric disorders (Roy et al., 2017).

Additionally, other researchers have found intriguing results regarding the impact of sex differences on depressive symptoms, related to differential sex-based effects in monoaminergic function. This study assessed the effects of sex on mood responses to acute serotonin and catecholamine depletion in individuals in clinical remission from MDD and found a significant increase in depressive symptoms following both depletions, with depressive symptoms being significantly greater in women during serotonin depletion, while no significant sex differences were found during catecholamine depletion (Moreno et al., 2006).

In summary, these studies explore the sex-dependent alterations in the monoaminergic system in MDD pathophysiology, contributing to our understanding of the molecular mechanisms underlying MDD and the potential role of sex in its development. These findings indicate sex-related differences in the serotonergic and norepinephrine system, but further human translational studies are necessary for more targeted and effective clinical applications and treatment approaches.

3.4. Neurotrophic system

The neurotrophic system and its main actors, including the neurotrophin family member brain derived neurotrophic factor (BDNF), are involved in MDD (Mosiołek et al., 2021) and studies have reported sex-based neurotrophic regulations in stress-related diseases in different levels.

At the genetic level, a genetic variant in the *BDNF* promoter gene, the single nucleotide polymorphism (SNP) Val66Met, influence BDNF activity, changing its regulation, cellular localization and secretion (Hing et al., 2018), and it is known that this SNP is involved in the association between early life stress and MDD (Kundakovic et al., 2015). A genetic study combined different *BDNF* polymorphism analyses, including Val66Met, with BDNF serum measures in depressed individuals and controls and found higher serum BDNF in female methionine carriers and in males homozygous for valine, in contrast to lower serum BDNF levels in male methionine carriers and females homozygous for valine (Elfving et al., 2012). Although none of the SNPs associated

with MDD, BDNF was increased in depressive subjects versus controls and the findings showed genotype and gender as significant determinants for serum BDNF (Elfving et al., 2012). At the expression level, a study in postmortem brain samples of depressed subjects and controls reported sex-specific changes for BDNF-dependent genes and the BDNF tyrosine receptor kinase B (TrkB), with decreased brain expression, more pronounced in men than in women, relative to respective controls (Tripp et al., 2012). At the protein level, BDNF was reduced in the prefrontal cortex of female depressed suicide completers versus controls, contrary to men, who presented decreased hippocampal BDNF compared to controls (Hayley et al., 2015). In spite of these findings, BDNF serum levels were significantly decreased in males and females depressed adolescents relative to respective controls, with no sex-related differences (Pallavi et al., 2013).

Other neurotrophic factors involved in sex-based differences in MDD are the VGF (non-acronymic) and the Nerve Growth Factor (NGF). VGF is a protein and neuropeptide precursor involved in neuronal homeostasis and synaptic plasticity, regulated by BDNF/TrkB signaling (Alder et al., 2003). VGF mRNA levels were downregulated in the prefrontal cortex and hippocampus of male and female depressed patients relative to respective controls, but its downregulation in the nucleus accumbens was only seen in depressed men versus controls (Jiang et al., 2019, 2018). Nerve growth factor (NGF) is a neurotrophin involved in neuronal growth, differentiation, death and synaptic plasticity (Rocco et al., 2018). A study aiming at addressing differences in serum neurotrophic levels in depressed patients and controls found a positive correlation between NGF and depressive-anxiety symptoms and disease duration, and a negative correlation between BDNF and disease duration in women, while in men there was a negative correlation between NGF and disease duration (de Azevedo Cardoso et al., 2014). Also, in depressed adolescents, females presented lower serum levels of NGF and neurotrophin-3, in comparison to males, a finding not observed between male and female controls (Pallavi et al., 2013).

In general, women and men with MDD differ in markers of the neurotrophic system, although results remain conflicting. Overall, these findings demonstrate the significance of sex-based molecular alterations within the neurotrophic system, particularly BDNF and related factors, in MDD pathophysiology, and the necessity for further studies designed to compare males and females paving the way for potential targeted clinical applications in the management of MDD.

3.5. Gamma-AminoButyric Acid (GABA) system and glutamate system

Dysfunctions in GABAergic and glutamatergic systems are involved in MDD, with GABA being part of the brain inhibitory system responsible for controlling excitatory neurotransmission (Duman et al., 2019) and regulating mood responses in normal and pathological states (Nuss, 2015), while the glutamatergic system controls excitatory projection neurons being involved in antidepressant responses (Cui et al., 2019; Lener et al., 2017).

Depressed suicide completers showed increased frontopolar cortex expression of DNA methyltransferases (DNMTs), greater in females than in males relative to respective controls for the DNMT3B, and enhanced methylation with decreased expression of $GABA_A$ receptor alfa-1 subunit in males versus controls, revealing epigenetic sex-related alterations affecting GABAergic gene expression (Poulter et al., 2008). Sex-based effects were also seen in a gene array meta-analysis, demonstrating a decreased somatostatin expression, marker of GABA neuron subtype, in postmortem corticolimbic brain areas, more evident in depressed females than in depressed males relative to respective controls (Seney et al., 2013). Somatostatin and GABA-synthesizing enzyme expression was influenced by X-linked chromosome polymorphisms (Seney et al., 2013). Finally, lower $GABA_A$ receptor mRNA levels were found in the frontopolar cortex of depressed suicide completers, in comparison to controls, but with no apparent sex-differences (Merali et al., 2004). At the glutamate system, glutamatergic gene expression analyses in postmortem brain tissues revealed increased prefrontal cortex expression of many glutamate-related genes in depressed females but not in males, while depressed males versus controls presented only glutamate metabotropic receptor 5 (GRM5) downregulation, indicating a more pronounced glutamate receptors dysregulation in depressed females (Gray et al., 2015).

The results support evidence that demonstrates hypothetical alterations in GABAergic and glutamatergic systems, with a slight tendency for more intense alterations in females, in respect to males. These studies provide insights into sex-based differences in GABAergic and glutamatergic systems, demonstrating a dimorphic role of these systems in the pathophysiology of MDD.

3.6. Oxytocin system

The oxytocin system mediates social behaviors, is involved in stress regulations and anxiety responses (Neumann and Slattery, 2016), and imbalances in its physiology associate with social dysfunctions and MDD (Dumais and Veenema, 2016).

In general, oxytocin expression is higher in females, whereas oxytocin receptor expression is higher in males (Dumais and Veenema, 2016). For example, males, relative to females, present higher oxytocin receptor binding densities in the nucleus accumbens, stria terminalis, medial preoptic area, insular cortex, medial amygdala and ventromedial hypothalamus (Dumais et al., 2013; Dumais and Veenema, 2016), implying on diverse social behaviors. Also, oxytocin is implied in social recognition in both sexes, with females being less sensitive to exogenous oxytocin than males (Dumais and Veenema, 2016).

Neuroimaging analyses assessing social cognition shows that oxytocin administration produces greater female amygdala responses to angry faces and threatening scenes (Domes et al., 2010; Lischke et al., 2012; Rupp et al., 2014), suggesting differential modulation of neural activities by oxytocin, serving to detect socially relevant and threatening stimuli in women, while males present reduced threat sensitivity. Also, depressed women showed higher methylation rates in the oxytocin promoter region, in comparison to

depressed men, suggesting that oxytocin is less activated in depressed females (Sanwald et al., 2020).

In general, these findings show that there are sex differences in the regulation and functioning of the oxytocin system, which can contribute to sex-specific vulnerabilities to MDD. Women with MDD may have dysregulated oxytocin systems, resulting in lower oxytocin levels or reduced sensitivity to oxytocin. This dysregulation can contribute to the development and persistence of depressive symptoms in women. Given the importance of oxytocin in stress responses and its potential use as a treatment option for mood disorders, it is relevant investigating whether its use may reduce stress-related disturbances in women and men.

3.7. Endocrine system

Sex-based differences in MDD pathophysiology are influenced by the endocrine system, specially by sex-hormones. Indeed, mutual influences of gonadal and adrenal hormones act in stress response regulations and may explain sex-differential responses to stress and mood disorders vulnerability (Eid et al., 2019; Sheng et al., 2003).

In women, menstrual cycle phase, menopause and hormone use induce variable changes in studies evaluating sex-differences in stress responses, like on cortisol suppression after dexamethasone administration, showing that ovarian hormones do regulate HPA axis responsivity (Kokras et al., 2019; Young and Korszun, 2010). Female metabolism, with gonadal hormone cycles and lifetime variations, strongly influence stress responsiveness and consequent susceptibility of women to stress-related disorders. Increased ovarian hormones circulation in particular periods of a woman's life following puberty may play a role in the higher incidence of MDD in women. Moreover, lower estrogen levels during luteal phase of the menstrual cycle, postpartum period or menopause, can also precipitate depressive symptoms, leading to the hypothesis that dramatic alterations in estrogen levels may be involved in MDD pathophysiology and contribute to sex-differential incidence of depressive symptoms (Bangasser and Valentino, 2014). Testosterone levels also contributes to sex-differences and its role in regulating CRH expression and influencing the stress response system should also be considered. Sexually dimorphic behaviours and differential responses to stressful stimuli are a consequence of complex interactions between organizational gonadal hormones, pubertal and lifetime hormonal changes in males and females (Bangasser and Valentino, 2014).

In summary, evidence support the influence of sex hormones and the endocrine system on sex-based differences in the pathophysiology of MDD. For example, the mutual influences of gonadal and adrenal hormones play a role in stress response regulations and may explain why men and women have different responses to stress and vulnerability to mood disorders. Overall, sex differences in the pathophysiology of MDD may be a result of complex interactions between hormonal changes in males and females throughout their lifetime.

3.8. Omics studies

Advances in high-throughput technologies with hypotheses-free approaches enables the investigation of multiple levels of a neurobiological system, like genomics, epigenomics and transcriptomics alterations, contributing to the understanding of diseases characterized by multifactorial and polygenic nature, like MDD. Indeed, omics studies have contributed to the identification of sex-specific molecular features associated with MDD and indicated dimorphic features in its mechanisms. At the epigenome level, a methylomic study in blood (812 MDD patients and 320 controls) and postmortem prefrontal cortex tissues (30 MDD patients and 31 controls) showed sex-differential DNA methylation signatures, highlighting the Fibulin 2 (*FBLN2*) gene, involved in cell differentiation, which was differentially methylated according to sex (Aberg et al., 2020). At the transcriptome level, Labonté and colleagues studied global transcription patterns in postmortem brain regions of 26 depressed patients and 22 controls, finding significant changes in all examined regions, with little overlap (5-10%) in expression patterns of depression-related genes between sexes. Employing co-expression network analyses to study MDD-associated gene modules, they identified around 150 depression-associated gene modules for each sex, most of them sex-specific. These modules were enriched for genes expressed in several cell types in men, like neurons, astrocytes and microglia, while for women, the modules were mainly enriched for neuronal genes (Labonté et al., 2017). Similarly, another study found homologous results, employing a large-scale gene expression meta-analysis of corticolimbic regions from 50 MDD patients and 50 controls. Findings showed little overlap in depression-related expression changes between sexes, with synapse-related genes downregulated in men and upregulated in women and microglia and oligodendrocyte-related genes upregulated in men, but downregulated in women (Seney et al., 2018). Other transcriptional regulators like long non-coding RNAs presented sex-differences in depressed patients. Indeed, in the same dataset studied by Labonté and colleagues (Labonté et al., 2017), LINC00473 was found to be downregulated in the medial prefrontal cortex of depressed women, but not men, a finding confirmed in animal models and human-derived neural-like cells in culture (Issler et al., 2020). Taken together, these findings show that transcriptional patterns in MDD present many sex-distinctive features, pointing to sex-differences in disease pathophysiology.

Overall, the aforementioned findings indicate that high-throughput technologies have allowed for the investigation of multiple levels of various neurobiological systems, such as genomics, epigenomics, and transcriptomics, in the understanding of MDD pathophysiology. Omics studies have identified sex-specific molecular features associated with MDD, indicating dimorphic functioning, paving the way for a broader understanding of its mechanisms with potential clinical targeted applications.

Table 1 summarizes the main findings concerning sex-based differences in diverse biological systems included in this review.

Table 1 Main findings of sex-based biological differences related to the diverse revised systems in the context of MDD.

Type of study	Protein/gene/biological system studied	Population	Comorbidities	Main findings	References
		Stress response sytem			
Protein studies	GR protein expression	9 MDD patients (5 F and 4 M) and 9 controls (5 F and 4 M) Postmortem tissues	N/A	Increased hippocampal GR expression in depressed women versus depressed men.	Wang et al., 2012
	GR protein expression	10 MDD patients (5 F and 5 M) and 8 controls (4 F and 4 M) Postmortem tissues	Epilepsia, pulmonary carcinoma	Increased GR expression in the amygdala only in depressed females versus relative controls.	Wang et al., 2014
	ACTH	33 MDD patients (21 F and 12 M) and 48 controls (29 F and 19 M)	Anxiety disorders, panic disorders	Upon social stress, depressed men and controls showed greater ACTH response than depressed women and controls.	Young et al., 2004; Young and Korszun, 2010 (review)
	Cortisol	45 MDD patients (26 F and 19 M) and 39 controls (23 F and 16 M)	N/A	Larger salivary cortisol levels in depressed women in response to negative events, in comparison with depressed men.	Peeters et al., 2003
		Inflammatory and immune system			
Protein studies	IL-6	103 MDD patients (61 F and 42 M) and 97 controls (67 F and 30 M)	No comorbidities	Higher IL-6 serum levels in depressed women than depressed men, relative to respective controls.	Birur et al., 2017
		77 (28 F and 49 M) and 54 controls (29 F and 25 M)	No comorbidities	Higher IL-6 serum levels in depressed women than depressed men, relative to respective controls.	Pallavi et al., 2015
		1921 MDD patients (1314 F and 607 M) and 494 controls (301 F and 193 M)	Diabetes, cardiovascular diseases	Higher IL-6 blood levels in depressed males versus females, relative to respective controls.	Vogelzangs et al., 2012
	IL-1β, TNF-α	103 MDD patients (61 F and 42 M) and 97 controls (67 F and 30 M)	No comorbidities	IL-1β and TNF-α serum levels positively correlated with depression severity only in depressed females versus controls.	Birur et al., 2017
	IL5, IL-8, IFN-γ	103 MDD patients (61 F and 42 M) and 97 controls (67 F and 30 M)	No comorbidities	Higher serum levels of IL-8, IFN-γ and lower levels of IL-5 only in depressed women, relative to controls.	Birur et al., 2017

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Table 1 (*continued*)

Type of study	Protein/gene/biological system studied	Population	Comorbidities	Main findings	References
	TNF receptor 2	MDD patients and controls (total sample comprised 1243 participants, including 838 F and 405 M)	High blood pressure, anxiety disorders	In depressed men only, TNF receptor 2 serum levels associated with MDD diagnosis.	Ramsey et al., 2016
	IL-12	103 MDD patients (61 F and 42 M) and 97 controls (67 F and 30 M)	No comorbidities	In depressed men only, IL-12 negatively correlated with MDD severity.	Birur et al., 2017
	CRP	231 MDD patients (142 F and 89 M)	Inflammatory/ autoimmune diseases	Higher CRP serum levels associated with greater depressive symptoms only in women.	Köhler-Forsberg et al., 2017
		MDD patients and controls (total sample comprised 1243 participants, including 838 F and 405 M)	High blood pressure, anxiety disorders	Higher CRP levels associated with MDD diagnosis only in men.	Ramsey et al., 2016
		1921 MDD patients (1314 F and 607 M) and 494 controls (301 F and 193 M)	Diabetes, cardiovascular diseases	Higher CRP levels associated with MDD diagnosis only in men.	Vogelzangs et al., 2012
		Obese participants evaluated for depressive symptoms (total sample comprised 390 participants, including 311 F and 79 M)	Obesity	Higher CRP levels associated with depressive symptoms only in men.	Vetter et al., 2013
	Leptin and adiponectin	103 MDD patients (61 F and 42 M) and 97 controls (67 F and 30 M)	No comorbidities	Higher leptin levels and lower adiponectin levels only in depressed females versus controls.	Birur et al., 2017
	Urine metabolites	93 MDD patients (43 F and 50 M) and 123 controls (48 F and 75 M)	No comorbidities	Differential urine metabolites differentiating women and men with MDD.	Zheng et al., 2016
			Monoaminergic system		
Epigenetic studies	Serotonergic system (*SLC6A4* methylation)	Newborns exposed to maternal stress during pregnancy (51 F and 39 M)	Depression and anxiety in mothers Hypoxia and preterm birth in infants	Analyses of cord blood of newborns exposed to maternal stress showed higher *SLC6A4* methylation levels in girls than in boys.	Dukal et al., 2015

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Table 1 (*continued*)

Type of study	Protein/gene/biological system studied	Population	Comorbidities	Main findings	References
	Serotonergic system (*SLC6A4* methylation)	Monozygotic twins assessed for anxious-depressive disorders (total of 148 participants, including 90 F and 58 M)	Anxiety disorders, psychotic disorders, eating disorders	*SLC6A4* promoter methylation levels were higher in women than in men.	Palma-Gudiel et al., 2019
	Serotonergic system (*SLC6A4* methylation)	192 adults assessed for childhood maltreatment in the Iowa Adoption Study (96 F and 96 M)	N/A	Overall *SLC6A4* promoter hypermethylation observed in abused men versus non-abused, while in abused women two specific loci were hypermethylated.	Beach et al., 2010
	Serotonergic system (*SLC6A4* methylation)	108 MDD patients assessed for childhood maltreatment (81 F and 27 M)	No comorbidities	Higher *SLC6A4* methylation associated with childhood adversities in MDD patients, but methylation status did not correlate with sex.	Kang et al., 2013
Expression and protein studies	Serotonergic system (serotonin regulators transcripts)	12 MDD patients (6 F and 6 M) and 12 controls (6 F and 6 M) Postmortem tissues	Cardiovascular diseases, pneumonia, diabetes	Increased serotonin regulators transcripts found in the dorsal raphe nucleus in depressed women, but not in men, in comparison to respective controls.	Goswami et al., 2010
	Serotonergic system (5-HT1A receptor expression.)	24 MDD patients (13 F and 11 M) and 25 controls (13 F and 12 M)	Cardiovascular diseases, asthmatic bronchitis	Decreased 5-HT1A receptor expression in the prefrontal cortex of depressed women, but not men, in comparison to relative controls.	Szewczyk et al., 2009
	Noradrenergic system (miR-1179 expression)	9 depressed suicide completers (3 F and 6 M) and 11 controls (2 F and 9 M) Postmortem tissues	N/A	miR-1179 expression was higher in the LC of depressed women suicide subjects, in comparison to men.	Roy et al., 2017
		Neurotrophic system			
Genetic and protein study	BDNF	162 MDD patients (135 F and 27 M) and 289 controls (231 F and 58 M)	Other psychiatric disorders	Higher serum BDNF in female methionine carriers and in males homozygous for valine. Lower serum BDNF levels in male methionine carriers and females homozygous for valine.	Elfving et al., 2012

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Table 1 (*continued*)

Type of study	Protein/gene/biological system studied	Population	Comorbidities	Main findings	References
	BDNF	51 MDD patients (25 F and 26 M) and 51 controls (25 F and 26 M) Postmortem tissues	N/A	Sex-specific changes for BDNF-dependent genes and the BDNF receptor TrkB, more robust in depressed men than in women, versus relative controls.	Tripp et al., 2012
	VGF	22 MDD subjects (13 F and 9 M) and 28 controls (12 F and 16 M) for hippocampus analysis	N/A	VGF was downregulated in the hippocampus of depressed men and women, versus respective controls.	Jiang et al., 2018
Expression studies		23 MDD subjects (10 F and 13 M) and 26 controls (14 F and 12 M) for nucleus accumbens analysis Postmortem tissues		VGF downregulation in the nucleus accumbens was seen only in depressed men, relative to controls.	
		28 MDD subjects (13 F and 15 M) and 27 controls (11 F and 16 M) Postmortem tissues	N/A	VGF was downregulated in the prefrontal cortex of depressed men and women, versus respective controls.	Jiang et al., 2019
	BDNF	19 MDD suicide completers (9 F and 10 M) and 19 controls (10 F and 9 M) Portmortem tissues	No comorbidities	Reduced prefrontal cortex BDNF in depressed females, but not in males, relative to respective controls. Hippocampal BDNF reduction in depressed males, but not females, versus relative controls.	Hayley et al., 2015
		84 MDD patients (28 F and 56 M) and 64 controls (35 F and 29 M)	No comorbidities	Decreased BDNF serum levels in depressed adolescents versus controls, with no sex-based differences.	Pallavi et al., 2013
Protein studies	NFG	120 MDD patients (95 F and 25 M) and 120 controls (95 F and 25 M)	No comorbidities	Positive correlation between NGF levels and depressive symptoms and disease duration in depressed women. Negative correlation between NGF levels and disease duration in depressed men.	de Azevedo Cardoso et al., 2014
		84 MDD patients (28 F and 56 M) and 64 controls (35 F and 29 M)	No comorbidities	Lower NGF levels in depressed women, in comparison to depressed men, not observed in controls.	Pallavi et al., 2013

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Table 1 (*continued*)

Type of study	Protein/gene/biological system studied	Population	Comorbidities	Main findings	References
		GABA and glutamate system			
Epigenetic and expression study	GABA system (DNMT and GABA expression)	MDD suicide completers and controls (dimorphic analyses reported on number of sample tissues) Postmortem tissues	N/A	Increased frontopolar cortex DNMT3B expression, greater in depressed females versus controls. Enhanced methylation and decreased frontopolar cortex $GABA_A$ receptor expression in males versus controls.	Poulter et al., 2008
Expression studies	GABA system (SST expression)	51 MDD suicide completers and 50 controls (dimorphic analyses reported on number of sample tissues) Postmortem tissues	N/A	Decreased SST expression in corticolimbic brain areas, more evident in depressed women than men, relative to respective controls	Seney et al., 2013
	GABA system (GABA expression)	12 suicide completers with affective disorders (1 F and 11 M) and 12 controls (6 F and 6 M) Post mortem tissues	No comorbidities	Lower brain $GABA_A$ receptor expression in depressed suicide completers in comparison to controls, with no sex-based differences.	Merali et al., 2004
	Glutamate system (glutamate-related genes expression)	34 MDD suicide completers (18 F and 16 M), 19 non-MDD suicide completers (9 F and 10 M), and 32 controls (13 F and 19 M) Post mortem tissues	Cardiovascular diseases, pneumonia, pulmonary embolism	Increased prefrontal cortex expression of glutamate-related genes in post-mortem tissues in depressed females, but not in males.	Gray et al., 2015
		Oxytocin sytem			
Epigenetic study	Oxytocin system	146 MDD patients (98 F and 48 M)	N/A	Women showed higher oxytocin methylation in comparison to men, in a sample of MDD patients.	Sanwald et al., 2020
		Endocrine system			
Protein studies	Stress-related system and gonadal hormones	Human studies, various populations	Various populations	Hormonal status in women promoted different responses to stress exposure.	Young and Korszun, 2010 (review); Kokras et al., 2019 (review)

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Table 1 (*continued*)

Type of study	Protein/gene/biological system studied	Population	Comorbidities	Main findings	References
	Gonadal hormones	Human studies, various populations	Various populations	Increased ovarian hormones associates with higher incidence of MDD in women. Lower estrogen levels, during luteal phase, postpartum period or around menopause associates with depressive symptoms.	Bangasser and Valentino, 2014 (review)
			Omics studies		
Epigenome-wide association study	*FBLN2*	Postmortem tissues (30 samples from MDD patients and 31 samples from controls) Blood samples (812 samples from MDD patients and 320 samples from controls)	N/A	Differential sex-based methylation patterns of *FBLN2* in depressed men and women in postmortem blood and brain tissues.	Aberg et al., 2020
Transcriptome studies	MDD-associated gene modules	26 MDD patients (13 F and 13 M) and 22 controls (9 F and 13 M) Postmortem tissues	No comorbidities	Network analyses revealed MDD-associated modules enriched for genes expressed in neurons, astrocytes and microglia in men, and neuronal genes in women.	Labonté et al., 2017
	Synapse-related, microglia and oligodendrocyte-related genes	50 MDD patients (24 F and 26 M) and 50 controls (24 F and 26 M) Postmortem tissues	Psychotic features	Synapse-related genes downregulated in men and upregulated in women, and microglia and oligodendrocyte-related genes upregulated in men and downregulated in women.	Seney et al., 2018
	Long non-coding RNAs	26 MDD patients (13 F and 13 M) and 22 controls (9 F and 13 M) Postmortem tissues	No comorbidities	LINC00473 downregulation in the medial prefrontal cortex of depressed women, but not men	Issler et al., 2020

ACTH: adrenocorticotropin hormone; BDNF: brain-derived neurotrophic factor; CRP: C-reactive protein; DNMT: DNA methyltransferase; F: females; *FBLN2*: Fibulin 2; GABA: Gamma-AminoButyric Acid; GR: glucocorticoid receptor; IFN-γ: interferon gamma; IgG: immunoglobulin G; IL: interleukin; LC: locus coeruleus; M: males; MDD: major depressive disorder; MiR: micro-RNA; N/A: not available; NGF: Nerve growth fator; SST: somatostatin; TNF-α: tumor necrosis factor

4. Human molecular studies: Sex-based differences related to antidepressant response

Few studies evaluated molecular mechanisms potentially underlying sex differences in exposure or response to pharmacological treatment in patients with MDD. Overall, even though it is not possible to draw definitive conclusions on which molecular mechanisms might underly the sex differences observed in the efficacy of antidepressants, this represents an emerging research topic as most related studies were published in the last five years. Most of the available studies were conducted in patients with treatment-resistant depression (TRD) and focused on molecular markers involved in the inflammatory response.

4.1. Inflammatory system

Among inflammatory markers, promising evidence is available for IL-8. Lower baseline peripheral levels of this pro-inflammatory cytokine had been suggested to be associated with response to antidepressants by a recent meta-analysis that did not specifically evaluate sex differences (Liu et al., 2020). Based on this evidence, Kruse and colleagues examined the relationship between IL-8 plasma levels and response to ketamine (Kruse et al., 2021), a drug for which potential sex differences in the therapeutic or adverse effects have been suggested (Ponton et al., 2022). The study from Kruse and colleagues included 46 patients with TRD (29 men and 17 women) in which clinical response was defined as a reduction $\geq$ 50% in the 17-item Hamilton Depression Rating Scale (HAMD-17) at 24 hours following ketamine infusion compared with baseline (Kruse et al., 2021). The authors observed a non-significant trend for an association between lower baseline IL-8 levels and differential clinical response based on sex (responder status $\times$ sex interaction: $p = 0.096$). Interestingly, the study also reported a significant interaction between sex and change in IL-8 levels in the prediction of clinical response or change in HAMD-17 score. When stratifying the analyses based on sex, decreasing IL-8 levels were associated with decreasing HAMD-17 scores in men ($p = 0.02$), while a trend in the opposite direction was observed in women. Similar results were observed in a previous study conducted by the same research group including 40 patients with TRD (22 women and 18 men) characterized for response to electroconvulsive therapy (ECT) (Kruse et al., 2020). In this study, lower baseline IL-8 plasma levels were associated with better response to ECT, exclusively in women. In addition, the change in IL-8 levels from baseline to end of treatment was significantly negatively correlated with the change in the HAMD-17 score in women, but not in men. In both studies no significant association was identified in other inflammatory markers (IL-6, IL-10, TNF-α and CRP). A secondary analysis of a previously conducted clinical trial (Minocycline in Depression, MINDEP), which included 39 patients with TRD, evaluated the potential role of serum CRP and IL-6 levels in sex differences in the efficacy of a 4-week adjunctive treatment with minocycline, an antibiotic with anti-inflammatory properties (Lombardo et al., 2022). The original study was a double-blind, randomised, placebo-controlled clinical trial that had suggested minocycline to be effective in patients with MDD and of low-grade inflammation (defined as serum CRP levels $\geq$ 3 mg/L) (Nettis et al., 2021). The secondary analysis showed that CRP levels had an effect on response to minocycline in women (22, of which 10 randomised to minocycline and 12 to placebo) but not in men (17, of which 8 randomised to minocycline and 9 to placebo). Specifically, women with CRP levels $\geq$ 3 mg/L showed a greater improvement based on the change of the HAMD-17 score compared with women with CRP levels $<$ 3 mg/L. Conversely, higher IL-6 levels were associated with response to minocycline in both men and women (Lombardo et al., 2022).

While the still limited number of studies does not allow to draw final conclusions, molecular players involved in the inflammatory system, especially IL-8 and CRP, seem to represent promising candidates for further exploration.

4.2. Monoaminergic system

A recent secondary analysis of the Do Antidepressants Induce Metabolic Syndromes (METADAP) study examined the association between two SNPs located in the two MAO encoding genes, *MAOA* and *MAOB*, with clinical response up to six months after beginning treatment with antidepressants in patients with MDD (Chappell et al., 2022). The original METADAP investigation was a prospective, multicentric, observational cohort study enrolling patients with a current major depressive episode in the context of MDD, treated with monotherapy with either SSRIs (41%), serotonin norepinephrine reuptake inhibitors (SNRI, 40%), TCAs (7%), other antidepressants (9%) or ECT (3%). The authors tested the association between the *MAOA* rs979605 and *MAOB* rs1799836 SNPs and change in the HAMD-17 score in 378 participants for which clinical and genetic data were available. A significant sex x genotype interaction was identified for rs979605. Men carrying the A allele (n = 24, 10.9 $\pm$ 1.61) showed a lower HAMD-17 score at six months compared with women with the AA genotype (n = 14, 18.1 $\pm$ 1.87, $p = 0.007$) (Chappell et al., 2022), while no significant sex interaction was identified for response or remission. In this study, analyses were conducted assuming random X-chromosome inactivation (i.e., men coded the same as homozygous women), as the two investigated genes are located on the X chromosome. While this finding represents preliminary evidence that the *MAOA* rs979605 SNP might be associated with the HAMD-17 score in a sex-dependent way, the low number of participants carrying the tested allele, as well as the lack of a replication cohort, limit the generalizability of this result. Nonetheless, this study underlines the importance of including in the analyses variants located in genes within the X chromosome, as these genes are sometimes omitted from genome-wide association studies (GWAS) due to increased complexity of the analytical approaches.

4.3. Omics studies

In recent years, pharmaco-metabolomics has emerged as a promising approach to predict response to pharmacological therapy. Caspani and colleagues investigated sex

Table 2 Main findings of sex-based biological differences in the context of response to antidepressants or ECT

Type of study	Protein/gene/biological system studied	Population	Comorbidities	Main findings	References
		Inflammatory system			
Protein studies	IL-8	46 TRD patients (17 F and 29 M) characterized for response to ketamine	No comorbidities	Significant interaction between sex and change in plasma IL-8 levels in the prediction of change in the HAMD-17 score 24 hours after ketamine infusion. Decreasing IL-8 levels associated with decreasing HAMD-17 scores in men ($p = 0.02$), while a trend in the opposite direction observed in women.	Kruse et al., 2021
		40 TRD patients (22 F and 18 M) characterized for response to ECT	No comorbidities	Lower baseline IL-8 plasma levels associated with ECT response exclusively in women. Change in IL-8 levels from baseline to end of treatment significantly negatively correlated with HAMD-17 score change in women, but not men.	Kruse et al., 2020
	CRP, IL-6	39 (22 F and 17 M) TRD patients characterized for response to minocycline	No comorbidities	Women with CRP serum levels $\geq$ 3 mg/L showed a greater improvement based on HAMD-17 score change after 4 weeks compared with women with CRP levels $<$ 3 mg/L. Conversely, higher serum IL-6 levels associated with response to minocycline in men and women.	Lombardo et al., 2022
		Monoaminergic system			
Genetic studies	*MAOA*	378 MDD patients (259 F and 119 M) treated with different antidepressants or ECT	No comorbidities	A significant sex x genotype interaction was identified for the *MAOA* rs979605 SNP. After treatment with different antidepressants, men carrying the A allele showed a lower HAMD-17 score at six months compared with women with the AA genotype.	Chappell et al., 2022
		Omics studies			
Protein study	Plasma metabolites	211 MDD patients (133 F and 78 M) treated with escitalopram alone or augmented with aripiprazole	No comorbidities	Different lipoprotein signatures predicted response to escitalopram in men or to escitalopram augmented with aripiprazole in women.	Caspani et al., 2021
Genetic study	Drug targets of antidepressants specific for female or male patients with MDD	UK Biobank, population-based cohort (127.867 M and 146.274 F)	N/A	Targets of antidepressants may be related to epigenetic processes and inflammation in men, and to neuronal migration, neurotrophic factors, synaptic plasticity and dopamine in women.	Silveira et al., 2023

F: females; ECT: electroconvulsive therapy; HAMD-17: 17-item Hamilton Depression Rating Scale; M: males; *MAOA*: monoamine oxidase A; MDD: major depressive disorder; N/A, not available; TRD: treatment-resistant depression

differences in metabolic association with response to escitalopram, either alone or augmented with aripiprazole, in the Canadian Biomarker Integration Network in Depression (CAN-BIND) cohort (Caspani et al., 2021). The CAN-BIND cohort included 211 patients with MDD who underwent a 16-week two-phase treatment protocol. Phase I consisted in treatment with escitalopram for 8 weeks, followed by assessment of response based on a $\geq$ 50% reduction in the Montgomery-Åsberg Depression Rating Scale compared with baseline. In Phase II, responders continued treatment with escitalopram alone, while non-responders with escitalopram augmented with aripiprazole from week 9 to 16. A panel of 112 plasma lipoproteins and 50 urinary metabolites was assessed using ^{1}H nuclear magnetic resonance. The study identified significant sex-specific plasma metabolic signatures of antidepressant treatment, taking into account body mass index, age and inflammation. Specifically, low baseline levels of 8 lipoproteins, including apolipoprotein A1, A2 and HDL lipoproteins, predicted response to escitalopram in men. These associations were not correlated with the norescitalopram/escitalopram ratio and showed a modest accuracy (72.4%) in the discrimination of male responders vs non-responders to escitalopram (Caspani et al., 2021). On the other hand, high baseline levels of apolipoprotein A2, HDL and VLDL subfractions predicted response to escitalopram augmented with aripiprazole exclusively in women. The identified features positively correlated with the dehydroaripiprazole/aripiprazole ratio at week 16, suggesting a potential relationship between higher circulating amounts of lipoprotein subfractions and a higher breakdown of aripiprazole to its active metabolite dehydroaripiprazole. A lipoprotein signature comprising the identified lipoproteins showed an 88.5% accuracy in the discrimination of female responders to aripiprazole augmentation compared with non-responders (Caspani et al., 2021).

A recent sex-stratified GWAS analysis for broad depression conducted in the UK Biobank provided promising evidence of a potential sex-specific genetic architecture of this trait (Silveira et al., 2023). While no data related to clinical response to antidepressants are available in this cohort, the authors conducted an *in-silico* analysis using the drug-target network-building tool Drug Targetor, to identify potential drug targets of antidepressants specific for female or male patients with depression. Results from this analysis suggested targets of antidepressants to be related to epigenetic processes and inflammation in men, and to neuronal migration, regulation of neurotrophic factors, synaptic plasticity and dopamine neurotransmission in women, supporting potential sex-dependent therapeutic pathways in depression (Silveira et al., 2023).

Compared to studies focused on the MDD pathophysiology, omics studies focused on the evaluation of sex-based differences in response to pharmacological and non-pharmacological therapy in patients with MDD are still in their infancy, although promising results support the potential utility of lipoprotein signatures to discriminate responders and non-responders. In addition, some of the targets of antidepressants might differ between men and women. Overall, the majority of studies investigating response to pharmacological treatments in patients with MDD did not report stratified findings for men and women, thus leading to limited available evidence. Nonetheless, the topic has seen a great expansion in the last few years, leading to novel findings in support of a potential role of peripheral levels of inflammatory markers as well as pharmacometabolomic signatures in the prediction of response to antidepressants in a sex-specific way.

Table 2 summarizes the main findings concerning sex-based differences in antidepressant response included in this review.

5. Conclusions

MDD is a heterogenous disease, and it has been suggested that sex-based differences are underlying its pathophysiology. In recent years, there have been many studies dedicated to depict sex-specific molecular changes within different neurobiological systems involved in MDD. In spite of the emerging data, some issues need to be addressed. Most of the studies in humans were done in postmortem samples of suicide completers, with data being compared with subjects without psychiatric disorders who died by other causes and with a lack of studies with non-suicide MDD subjects. The presence of psychiatric comorbidities, previous treatments and substance abuse may influence the findings in the MDD group. Hormonal variations and menstrual cycle phases greatly influence the results and should always be accounted for in research. The majority of studies were performed using candidate gene approaches, focusing on selected genes and pathways most related to MDD pathophysiology, including the stress response system, monoaminergic system, neurotrophic system, and GABA and glutamatergic system. Genome, epigenome and transcriptome-wide approaches are much less frequently performed and most of these studies do not focus on sex-specific alterations, revealing a paucity of omics studies directed to unravel sex-based differences in MDD. More studies on this level, comparing data in males and females, are needed.

Regarding sex-related differences in antidepressant treatment response, few studies addressing this topic have been conducted, mostly involving the inflammatory system, with less evidence focused on the monoaminergic system. A recent promising approach is pharmacometabolomics, directed to find potential clinically relevant signatures of response prediction to pharmacological therapy and sparse omics evidence identified sex-specific biochemical markers of antidepressant response in MDD and TRD patients. Of note, while enzymes form part of the cytochrome P450 system and play a central role in the metabolism of antidepressants, and sex-based differences in the activity of some of these enzymes have been described (Scandlyn et al., 2008), to our knowledge no study explored whether the observed sex differences in the clinical efficacy of these drugs might be at least partly explained by differences in the activity of enzymes involved in their metabolism.

A comprehensive understanding of the sex-specific neurobiological mechanisms underlying MDD and how these different systems operate together can lead to future translation research and clinical practices, including personal-

ized treatments based on hormonal cycles or the use of hormonal therapy. Additionally, the potential use of oxytocin in clinical practice should be investigated due to the importance of the oxytocin system in stress responses and mood-related disorders, for example. Moreover, the exploration of sex-related biomarkers of MDD, such as inflammatory and metabolic markers, can have predictive, diagnostic, and targeted therapeutic applications. Analysis including sex variable stratification should be one of the main goals of every biomarker research performed in MDD.

For a better understanding of the MDD pathophysiology, it is important to include both sexes in research, accounting for their particularities. Understanding the biological mechanisms leading to particular responses to stress and individual susceptibilities for stress-related disorders will help translating research into clinical practice, optimizing patient stratification, precise diagnostic, disease outcomes and individualized treatment for women and men.

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Author contributions

AM and AS conceived of the study and participated in its design; RCS, CP, EM, VM and AM co-wrote the manuscript; BB, MG, AS, MB and AM helped draft the manuscript and critically reviewed it for intellectual content. All authors read and approved the final manuscript.

Conflict of interest

The authors declare no conflicts of interest.

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