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Review

Beyond One-Size-Fits-All: Personalized Medicine and Future Directions in Sex-Based Psychopharmacological Treatment

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Abstract: Sex-related differences in psychopharmacology present unique challenges in both clinical and research settings. Recognition of sex differences in psychopharmacological treatment has increased in recent years, but a significant research gap regarding variations between men and women still exists. Biological factors, including hormonal fluctuations, genetic factors, and brain structure differences, contribute significantly to differential drug responses. Moreover, social determinants can influence the differential burden of psychiatric disorders between the sexes and may impact treatment plans. Incorporating sex as a key variable in personalized treatment programs and plans holds the potential to optimize efficacy and minimize adverse effects in psychopharmacology. Sex-related challenges in psychopharmacology necessitate a nuanced approach to treatment. Further research is needed to fully understand these differences and to develop guidelines for personalized medication management. By addressing these challenges, clinicians can improve treatment outcomes and enhance the quality of life of patients with psychiatric disorders.

Keywords: psychopharmacology; women; antidepressants; antipsychotics; mood stabilizers; psychiatric disorders; personalized medicine

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1. Introduction

Gaining insight into the epidemiology of psychiatric disorders by examining sex differences is crucial for creating effective treatment plans and enhancing mental health outcomes. Building on the importance of understanding sex disparities, research in epidemiology has repeatedly demonstrated that the prevalence, onset, and progression of numerous psychiatric conditions differ markedly between men and women [1]. These variations are shaped by a multifaceted interaction of biological, psychological, and sociocultural influences [2,3]. Understanding sex variations in mental health is essential. Sex roles, societal expectations, and access to support systems can all impact how men and women experience mental health issues [4–6]. Novel insights suggest that biological factors, including hormonal influences and genetic predisposition, interact with environmental variables to shape mental health outcomes differently for males and females.

Men and women may experience the same condition differently. For instance, depression might manifest as social withdrawal in men and fatigue in women [7]. Accurate acknowledgement of such variations may ensure proper diagnosis and treatment. Additionally, considering treatment preferences (e.g., medication vs. therapy) can enhance adherence and overall success [8,9].

The prevalence of mental disorders has increased significantly in the past 25 years, with an increase of 48.1% between 1990 and 2019. This rise constitutes a significant public health concern. In the same period, the global burden of mental disorders has also grown considerably, increasing from 3.1% in the 1990s to 4.9% in 2019. Depressive disorders are the leading cause (37.3%), followed by anxiety disorders (22.9%) and schizophrenia (12.2%), with prevalence rates varying across countries. Moreover, depression represented the second highest cause of years lived with disability (YLDs) in 2019. Sex disparities are evident in the burden of mental disorders, as reflected by disability-adjusted life years (DALYs) [10–14]. Women exhibit a higher propensity for mood and anxiety disorders, including depression, post-traumatic stress disorder (PTSD), and eating disorders [15–17]. On the other hand, men demonstrate a greater susceptibility to substance use disorders (SUDs) and certain neurodevelopmental disorders, such as attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) [13,18–23]. While bipolar disorder (BD) shows a relatively equal prevalence across sex, there are noteworthy sex-specific differences in its presentation and course. Women are more prone to rapid cycling and mixed episodes, while men more frequently experience manic episodes [24–26]. Schizophrenia, though showing similar overall prevalence across sexes, presents with earlier onset in males. Additionally, males with schizophrenia typically exhibit poorer long-term outcomes compared to females [8,10,25,27]. Sex differences are further evident in personality disorders. Women demonstrate a higher prevalence of borderline personality disorder; in contrast, males are more likely to be diagnosed with antisocial personality disorder. These variations may be rooted in a complex interplay of biological and social factors. Socialization processes can influence how men and women learn to express and manage emotions, potentially shaping their susceptibility to certain disorders and their preferred coping mechanisms. Additionally, potential biases within diagnostic criteria and assessment practices might contribute to the observed sex differences in prevalence rates. Biological factors, particularly hormonal fluctuations, likely play a significant role [8,12,28,29]. Women experience hormonal shifts throughout their lifespan, including during the menstrual cycle, pregnancy, the postpartum period, and the menopause [6,30–32]. These fluctuations can influence neurotransmitter activity and brain function, potentially increasing vulnerability to certain mental health conditions. Beyond influencing physical development and reproduction, sex hormones, particularly estrogen and progesterone, exert a profound effect on mood and behaviour. This influence is mediated through their interaction with key neurotransmitter systems, including serotonin, dopamine, and GABA. Animal models demonstrate that estrogens exert antidopaminergic properties, potentially mitigating the effects of dopamine. Conversely, human studies reveal a synergistic relationship between estradiol and the dopaminergic system. Estrogens seem to play a protective role, which weakens following the menopause when estrogen levels decline [12,28]. This hormonal fluctuation may contribute to the observed sex disparities in the course of certain mental illnesses. Schizophrenia provides a compelling example. While the overall prevalence is relatively equal between the sexes, the age of onset differs significantly. Men typically experience the initial symptoms in their late teens to early twenties, whereas women often present later, in their late twenties to early thirties. Furthermore, men with schizophrenia tend to exhibit a more severe clinical course, characterized by a higher incidence of negative symptoms and poorer long-term outcomes compared to women [8–10,27,33].

Social factors contribute to the differential burden of psychiatric disorders between the sexes. Women typically face higher levels of stress due to factors like demanding caregiving responsibilities, workplace discrimination, and societal expectations regarding their roles. These chronic stressors can activate stress response systems and contribute to the development or exacerbation of mental health conditions [11,34–38]. The COVID-19 pandemic served as a stark illustration of how social factors can intensify these sex disparities [11,39,40].

There is an increasing recognition of the need for sex-disaggregated data in clinical trials to ensure that therapeutic interventions are appropriately tailored. As the field moves toward a more nuanced understanding of these variations, it becomes paramount for researchers and clinicians to adopt an integrative approach that encompasses biological, psychological, and socio-cultural factors, ultimately aiming to enhance the efficacy of mental health care across diverse populations.

2. Biological Differences in Psychopharmacological Treatment Response

Animal models play an important role in elucidating the mechanisms underlying genetic variants and variable drug-response phenotypes and represent the most practical tools for pre-clinical drug screening before application in clinical trials. The study of gender-based differences in the pharmacokinetics of compounds tested in animal models has received greater attention, particularly in recent years. For example, estrogen and progesterone have been involved in many aspects of drug abuse and animal models of depression, anxiety, post-traumatic stress disorder, substance-related disorders, obsessive–compulsive disorder, schizophrenia, bipolar disorder, and autism [2,3,15].

Accounting for sex differences in drug metabolism is paramount for optimizing psychopharmacological treatment and tailoring interventions to specific patient populations. Men and women exhibit variations throughout the entire drug journey within the body, encompassing absorption, distribution, metabolism, and excretion (ADME) processes [41]. These variations are influenced by a complex interplay of physiological, genetic, and hormonal factors, impacting both pharmacokinetics and pharmacodynamics.

Men typically have a larger body mass and higher total body water content compared to women. This can influence drug distribution, as certain medications tend to be more readily distributed into adipose tissue or water compartments. Consequently, the same dose of a medication may lead to different effective concentrations at the target site in men and women [41].

Sex chromosomes and genes located on autosomes can influence drug metabolism. For example, the activity of certain drug-metabolizing enzymes can be influenced by genetic polymorphisms, leading to differences in how quickly a medication is broken down in men and women [42–44].

Sex hormones, particularly estrogen and progesterone in women, can significantly impact drug metabolism. Estrogen can induce the activity of certain enzymes, leading to faster drug breakdown and potentially lower drug efficacy. Conversely, progesterone can inhibit some enzymes, resulting in slower metabolism and potentially higher drug levels [12,28,45,46].

Beyond drug movement, sex differences can also influence how the body responds to medications. Variations in receptor expression and sensitivity can lead to different responses to the same medication in men and women. For instance, some antidepressants may exhibit a stronger therapeutic effect in women due to differences in neurotransmitter receptor activity [28,47].

2.1. Pharmacokinetics

Pharmacokinetics studies how drugs are absorbed, distributed, metabolized and excreted in the body. This process exhibits sex-related differences that can significantly impact drug efficacy and safety.

2.1.1. Adsorption and Distribution

The first step for a drug to be processed is absorption, primarily depending on the specific drug's composition and characteristics but also on the environment encountered in the gastrointestinal tract, when considering per os administration. Men and women show some differences in physiological processes which contribute to differential drug onset and peak concentrations of medications. Compared to men, women generally have slower gastric emptying times and lower gastric acidity [48]. In addition, women tend to have longer intestinal transit times. These differences can modify drug solubility, leading to delayed gastric absorption, enhanced intestinal absorption, and increased exposure to potentially irritating substances [47]. The next step is distribution, which refers to the movement of the drug from the bloodstream to tissues and organs throughout the body. The volume of distribution (Vd) is a pharmacokinetic parameter that reflects a drug's propensity tendency to stay in the plasma or relocate to organs and tissues. Drugs with a high Vd readily leave the plasma and enter the extravascular compartment, requiring a larger dose to achieve the same plasma concentration. Conversely, drugs with lower Vd remain in the plasma, with less distribution to other tissues or organs. Vd is influenced by several factors, such as body composition, body weight, blood volume, and percentage of body fat, as well as the drug's specific properties (lipophilic or water soluble). Since women generally have a higher percentage of adipose tissue and a lower percentage of body water compared to men, special attention is required for lipophilic drugs. These drugs, such as certain psychotropic medications (e.g., benzodiazepines and antipsychotics) may have a higher Vd in women, leading to longer half-lives and potentially different clinical effects [47–50]. Clinically, this could translate into a more rapid relapse of symptoms in men compared to women upon abrupt withdrawal of a benzodiazepine or antipsychotic medication [51]. Consequently, dosing intervals for long-acting injectable forms of these drugs may need to be longer in women than in men [51]. Since only the unbound fraction of a drug crosses the blood–brain barrier and reaches the brain in an active form, the binding capacity of plasma protein to each drug must be accurately evaluated. In fact, the quantity of drug not bound to plasma protein, such as albumin and alpha-1-acid glycoprotein, can reach neuroreceptors sites and carry out its therapeutic effect. Women often exhibit lower plasma protein levels compared to men, which can lead to higher concentrations of unbound drugs and, consequently, increased drug exposure in the brain [52,53].

2.1.2. Metabolism

Following absorption and distribution, drugs undergo metabolism, a process that converts them into more polar compounds called metabolites. These metabolites are typically water-soluble, facilitating their excretion via urine or bile. The liver is the main site of metabolism, although it also occurs in the gut wall, lungs, and blood plasma. Cytochrome P450 (CYP) enzymes, particularly CYP1A2, CYP2C19, CYP2D6, and CYP3A4, catalyze these metabolic reactions. The recent literature has highlighted significant sex-based differences in the activity and distribution of CYP450 enzymes (summarized in Table 1) [54–57]. These disparities influence drug metabolism, leading to variations in drug levels, efficacy, and adverse effects between men and women. CYP1A2 activity is generally lower in women compared to men [58]. This difference is modulated by hormonal factors, particularly estrogen, which can inhibit the enzyme's activity. Antidepressants (ADs) are substrates for CYP1A2, including tricyclic ADs (TCAs) (e.g., amitriptyline, clomipramine, and imipiramine), duloxetine, fluvoxamine, and agomelatine. Some antipsychotics (APs), such as clozapine, olanzapine, and haloperidol, also fall into this category. Additionally, CYP1A2 expression is induced by various dietary compounds found in vegetables and by combustion products like those from tobacco smoking [58–61]. The lower CYP1A2 activity in women can lead to higher plasma levels of drugs metabolized by this enzyme, such as

clozapine and olanzapine, potentially increasing the risk of adverse effects. For instance, women treated with clozapine may experience a higher incidence of side effects like sedation and weight gain due to slower drug metabolism [60]. Studies have shown significant variability in CYP2C19 enzyme activity among individuals, with sex-related differences noted. This variability is largely due to genetic polymorphisms, with women exhibiting a higher frequency of variants associated with poor metabolism. Several medications are substrates for CYP2C19, including several ADs, like TCAs, and selective serotonin reuptake inhibitors (SSRIs), such as citalopram, escitalopram, and sertraline, and bupropion, as well as many benzodiazepines (BDZs), such as diazepam, lorazepam, oxazepam, and temazepam [54,55,62,63]. Genetic polymorphisms are characterized by a wide range of activity in CYP2C19, and poor metabolizers, more prevalent in women, may require lower drug doses of commonly used psychiatric medications to avoid toxicity. This measure becomes crucial if these drugs are co-administered with strong inhibitors, like fluconazole (antifungal), ticlopidine (antiplatelet), or some SSRIs (e.g., fluvoxamine and fluoxetine [54]). Like CYP2C19, CYP2D6 activity exhibits significant polymorphism, resulting in varying metabolic rates between individuals. Women tend to be more frequently classified as extensive or ultra-rapid metabolizers, while men are more likely to be poor metabolizers. Moreover, hormonal factors have been demonstrated to modify its activity: estrogen has been shown to upregulate CYP2D6 activity, contributing to faster metabolism of drugs such as fluoxetine, paroxetine, and risperidone in women. P2D6 metabolizes a broad range of psychoactive drugs including TCAs, serotonin–norepinephrine reuptake inhibitors (SNRIs) (e.g., venlafaxine and duloxetine), mianserin, mirtazapine, numerous first- and second-generation APs (e.g., clopixol, haloperidol, zuclopenthixol, risperidone, aripiprazole, etc.), norepinephrine reuptake inhibitors (NIRs) (atomoxetine), and stimulants (e.g., amphetamine and lisdexamfetamine), as well as several class I antiarrhythmics [55,56,61,62,64]. Given the frequent co-prescription of these drugs to address multifaceted symptoms and comorbidities, personalized treatment approaches are essential. Careful dose titration and monitoring are crucial to optimize therapeutic outcomes and minimize adverse effects, especially in women who are extensive or ultra-rapid CYP2D6 metabolizers. CYP3A4 metabolizes a vast array of psychotropic medications, including BDZs (e.g., alprazolam, midazolam, triazolam, and diazepam), some hypnotics (e.g., zolpidem, zaleplon, and zopiclone), many ADs such as TCAs, SSRIs (e.g., citalopram, sertraline, and norfluoxetine), mirtazapine, trazodone, venlafaxine, many APs (e.g., haloperidol, aripiprazole, quetiapine, lurasidone, risperidone, and ziprasidone), and opioids (e.g., methadone, buprenorphine, codeine, etc.) [65–68].

Women generally have higher CYP3A4 activity than men, likely due in part to the increased activity induced by estrogen. This faster metabolism can lead to quicker clearance of these medications. Consequently, women may require higher or more frequent doses to maintain therapeutic levels [69,70].

Table 1. Sex-based differences in the activity and distribution of CYP450 enzymes in psychopharmacological treatments.

CYP Enzyme	Activity in Women	Activity in Men	Implications for Psychopharmacological Treatments	References
CYP1A2	Lower	Higher	Women may have higher plasma levels of drugs metabolized by CYP1A2, like clozapine and olanzapine, increasing the risk of side effects.	[58–61]
CYP2C19	Higher prevalence of poor metabolizers	Lower prevalence of poor metabolizers	Poor metabolizers may require lower doses of drugs like diazepam, citalopram, and escitalopram to avoid toxicity.	[55,57,62,63]

Table 1. *Cont.*

CYP Enzyme	Activity in Women	Activity in Men	Implications for Psychopharmacological Treatments	References
CYP2D6	More extensive or ultra-rapid metabolizers; estrogen upregulates activity	Fewer extensive or ultra-rapid metabolizers	Faster metabolism of drugs such as fluoxetine, paroxetine, and risperidone in women may necessitate higher doses to maintain efficacy.	[54–56,61,62,64,71]
CYP3A4	Higher	Lower	Women may clear drugs metabolized by CYP3A4 more quickly, potentially requiring higher or more frequent dosing for drugs like benzodiazepines and some antipsychotics.	[65,66,69]

2.1.3. Excretion

Excretion is the final phase of drug disposition, involving the elimination of drugs and their metabolites from the body. The kidneys are the primary organ of drug excretion, although the liver (biliary excretion) and lungs (respiratory excretion) also contribute. Excretion patterns can differ between women and men, influencing drug duration, intensity of effects, and potential side effects. Men generally have a higher glomerular filtration rate (GFR) and higher renal blood flow compared to women. This often leads to faster renal clearance and lower plasma drug concentrations in men. Hormonal factors also impact renal excretion. For instance, increased estrogen levels during pregnancy elevate renal blood flow and GFR, enhancing drug clearance. Conversely, fluid retention associated with the luteal phase of the menstrual cycle can decrease drug clearance [47–50,72].

2.2. Pharmacodynamics

Pharmacodynamics refers to the effects of drugs on the body, specifically how they interact with cellular receptors to produce their therapeutic outcomes. Psychoactive drugs influence mood, behavior, cognition, and perception, by modulating neurotransmitter systems, including monoamines (serotonin, dopamine, and norepinephrine), amino acids (GABA and glutamate), and peptides (endorphins and substance P) [41,48,73]. The pharmacodynamic properties of these drugs are crucial determinants of their efficacy and adverse effects. Their classification as agonists or antagonists, based on receptor binding and affinity, underlies their mechanisms of action. Agonists mimic neurotransmitters, activating receptors, while antagonists block receptor activity. For example, first-generation APs primarily function as dopamine D2 receptor antagonists, reducing dopaminergic activity to alleviate positive psychotic symptoms but often exhibiting limited efficacy for negative symptoms. In contrast, third-generation APs like aripiprazole act as partial dopamine agonists, exerting a stabilizing effect by modulating dopamine activity according to baseline levels [49,73,74]. These drugs interact with G-Protein Coupled Receptors (GPCRs), producing submaximal activation compared to full agonists. Consequently, they can either enhance or diminish signal transduction pathways depending on the prevailing neurotransmitter concentration. In contrast, third-generation APs, like aripiprazole, act as partial dopamine agonists, exerting a stabilizing effect by modulating dopamine activity according to baseline levels. These drugs interact with G-protein coupled receptors (GPCRs), producing submaximal activation compared to full agonists. Consequently, they can either enhance or diminish signal transduction pathways depending on the prevailing neurotransmitter concentration [73].

Drug interactions with neurotransmitter receptors initiate signal transduction pathways, modulating neurotransmitter levels and consequently producing therapeutic effects. Bouvier et al. [75] reported sex-related differences in dopamine receptors and glucose transporters Glut1 following chronic clozapine and haloperidol treatment. Male subjects exhibited increased D2 receptor expression with both drugs, while clozapine-treated females showed decreased D2 receptor expression. Additionally, Glut1 was overexpressed in clozapine-treated females, whereas both sexes displayed elevated Glut3 levels. Human

studies have revealed higher D2-like receptor binding potentials in the left and right anterior cingulate cortex of women compared to men [76]. Furthermore, PET imaging with a radioactive ligand demonstrated that women require lower oral olanzapine doses (10 mg) than men (20 mg) to achieve therapeutic receptor occupancy [74]. Elevated levels of 5HT1A and muscarinic receptors in women may contribute to clozapine's enhanced therapeutic efficacy but also increased adverse effects. The varying hormonal milieu across the sexes and life stages creates distinct pharmacological environments, potentially influencing treatment responsiveness and outcomes. Estrogen elevates the density and activity of dopamine receptors, potentially increasing women's responsiveness to APs but also raising the risk of adverse effects [12,73]. Additionally, estrogen enhances NMDA receptor function, influencing responses to glutamate-targeting drugs like mood stabilizers and APs and potentially augmenting synaptic plasticity. D2 receptor availability fluctuates across the menstrual cycle and is influenced by contraceptives, in vitro fertilization treatment (IVF), and hormonal interventions [30]. Progesterone and its metabolites, such as allopregnanolone, enhance GABA-A receptor activity, leading to increased sensitivity to BDZs in women and consequently to more pronounced anxiolytic and sedative effects in women compared to men. Many psychotropic drugs target GPCRs, influencing intracellular signaling cascades.

Hormonal differences between the sexes can modulate these pathways. For instance, estrogen influences GPCRs, altering responses to drugs and modulating GABAergic and glutamatergic signaling. Additionally, estrogen increases serotonin receptor sensitivity, enhancing the efficacy of SSRIs in women. SSRIs work by inhibiting serotonin reuptake, affecting downstream signaling pathways involving cyclic AMP (cAMP) and protein kinases. For example, they block the serotonin transporter (SERT), leading to increased serotonin availability in the synaptic cleft and enhanced serotonergic transmission. Hormonal regulation also influences cAMP signaling: estrogen stimulates cAMP production and Protein Kinase A (PKA) activation, potentially augmenting drug efficacy [28,45,46]. BDZs act differently by enhancing GABAergic inhibition through binding to the α1 subunit of GABA-A receptors, ligand-gated ion channels that raise chloride ion influx, leading to neuronal hyperpolarization and reduced excitability. Psychostimulants, such as amphetamines and methylphenidate, increase dopamine and norepinephrine release, resulting in heightened alertness, improved concentration, and mood elevation in patients suffering from ADHD. The effects of psychoactive drugs encompass not only immediate clinical outcomes but also a long-term effect, called Long-Term Potentiation (LTP). LTP is a synaptic mechanism underlying learning and memory, dependent on glutamatergic neurotransmission and influenced by cholinergic, GABAergic, and dopaminergic systems. Multiple studies have demonstrated LTP-like activity in the dorsolateral prefrontal cortex (DLPFC), a brain region crucial for cognitive function. Abnormalities in DPFCL function and LTP are implicated in conditions such as depression, schizophrenia, and Alzheimer's disease [77–82]. ADs have been shown to promote neurogenesis and synaptic plasticity, particularly within the hippocampus. This effect is believed to be mediated by brain-derived neurotrophic factor (BDNF) and other growth factors, contributing to their delayed therapeutic effects. Additionally, psychopharmacological drugs can induce epigenetic modifications, influencing synaptic function and plasticity, and thus offering potential novel therapeutic targets. For instance, lurasidone may contribute to neuronal plasticity by modulating epigenetic pathways involved in gene transcription and increasing BDNF levels in cortical and limbic regions. Clozapine, the first developed atypical AP, has been reported to induce DNA demethylation at gene promoter sites, potentially attenuating the dysregulated GABAerginc and glutamatergic neurotransmission. Long-term clozapine treatment may mitigate epigenetic aging in male patients with psychotic spectrum disorders, potentially leading to augmented life expectancy. Although accumulating evidence supports this association, further research is imperative to elucidate potential sex-related differences in the interactions between psychoactive drugs and gene expression [58,65,66,83].

3. Sex Differences in Specific Psychopharmacological Treatments

3.1. Antidepressants

Major depressive disorder (MDD) exhibits notable clinical differences between men and women. Sex seems to influence the presentation, progression, and treatment outcomes of this disorder. Women have a nearly twofold higher risk of MDD diagnoses compared to men [84,85]. This sex disparity emerges after puberty and persists into adulthood. Moreover, women exhibit a higher prevalence of emotional symptoms such as sadness, guilt, and feelings of worthlessness. In contrast, men more frequently display externalizing symptoms including irritability, anger, and frustration. Additionally, women report greater somatic symptom burden, characterized by fatigue, changes in appetite, and sleep disturbances. Men, on the other hand, are more likely to present physical complaints like back pain and headache, which can potentially mask underlying depressive symptomatology. Women typically experience earlier MDD onset, often triggered by hormonal fluctuations during menstruation, pregnancy, and the menopause. Men tend to have a more chronic course with higher recurrence rates. Noticeably, social stressors related to caregiving roles, interpersonal relationships, and victimization (e.g., domestic violence and sexual assault) can exacerbate the course of MDD in women [6,85,86].

Sex differences significantly impact the pharmacokinetics, pharmacodynamics, efficacy, and side effects of antidepressant treatments [28,87,88]. To optimize treatment outcomes and minimize adverse effects, clinicians should incorporate these sex-based differences into their treatment plans. Table 2 provides an overview of how sex can influence the clinical efficacy of various antidepressant classes, highlighting the importance of personalized medicine in psychopharmacology.

Table 2. Sex differences in the efficacy of antidepressants.

Antidepressant Class	Specific Antidepressants	Sex Differences in Efficacy	Notes	References
SSRIs	Fluoxetine, Sertraline, Paroxetine, Citalopram, Escitalopram	Women tend to respond better to SSRIs than men.	Estrogen may enhance the efficacy of SSRIs by boosting serotonergic activity but with an increased risk of sexual side effects in women.	[84,89–91]
SNRIs	Venlafaxine, Duloxetine, Desvenlafaxine	Results for SNRIs are mixed, with some studies suggesting that women may have a stronger response to these medications compared to men.	Due to their dual action on serotonin and norepinephrine, SNRIs may be particularly beneficial for women, especially during hormonal fluctuations.	[86,92–95]
TCAs	Amitriptyline, Nortriptyline, Imipramine, Clomipramine	Results are mixed; some studies find no significant sex differences, while others indicate that women may experience more side effects.	Side effects like weight gain and sedation may more adversely affect women, potentially leading to decreased adherence to medication.	[90,96]
MAOIs	Phenelzine, Tranylcypromine, Isocarboxazid	Evidence is limited, but hormonal factors may play a role. Women have a statistically superior response to MAOIs.	Women may need to consider additional dietary factors and may experience a wider range of side effects.	[97,98]
Atypical Antidepressants	Bupropion, Mirtazapine, Trazodone	Bupropion generally shows similar effectiveness in both men and women. Mirtazapine might be more effective in men and is also more commonly prescribed for them.	Bupropion is often preferred by women due to its lower risk of sexual side effects; the side effect profile of Mirtazapine may limit its use in women.	[98,99]

Table 2. *Cont.*

Antidepressant Class	Specific Antidepressants	Sex Differences in Efficacy	Notes	References
Serotonin Modulators	Vortioxetine, Vilazodone	Initial studies suggest similar efficacy for both sexes, although more data are needed to confirm this.	Additional studies are needed to provide a clearer picture of sex-specific responses.	[100,101]

SSRIs: selective serotonin reuptake inhibitors; SNRIs: serotonin–norepinephrine reuptake inhibitor; TCAs: tricyclic antidepressants; MAOIs: MonoAmine Oxidase Inhibitors.

Despite extensive research, the influence of sex on antidepressant treatment effectiveness remains under debate. This ongoing discussion is partly due to methodological inconsistencies across studies. These include variations in sample size, participant demographics, baseline depression, the presence of co-occurring conditions, and differences in study design. Such factors create challenges in data interpretation and hinder the development of definitive sex-specific treatment guidelines. Further research utilizing standardized methodologies and larger, more diverse samples is crucial to definitively understand sex differences in antidepressant response.

Research on sex differences in antidepressant efficacy has yielded mixed results. For instance, some studies suggest that tricyclic antidepressants (TCAs) like imipramine may be more effective in males compared to females. This potential sex disparity could be attributed to several physiological factors such as hormonal influences, drug metabolism, or receptor sensitivity. These factors, along with pharmacokinetic and pharmacodynamic variations, can lead to different efficacy and side effect profiles for antidepressants in men and women [90,96].

Conversely, several studies suggest that women in their reproductive period may respond better to selective serotonin reuptake inhibitors (SSRIs) than men. This potential advantage might be linked to the influence of menstrual cycle fluctuations on serotonin levels, a key target of SSRIs. However, it is important to note that the results of some of these studies have been disputed, highlighting the complexity of establishing clear patterns of sex differences in antidepressant response. The evidence of greater efficacy in females remains inconsistent, with some studies reporting no significant differences between the sexes. Some studies show several limitations, such as a small sample or heterogeneous sample size, meaning that further and more consistent studies should be performed [55,91,102]. A recent study for example showed no differences in tolerability between the sexes and similar outcomes following SSRI treatment, with citalopram being equally effective for both women and men, with no differences in tolerability between the sexes and similar outcomes following SSRI treatment [103].

The influence of sex on antidepressant effectiveness is not clear-cut, with some medications showing no significant differences between men and women. A large retrospective study found no sex differences in the effectiveness of TCAs, monoamine oxidase inhibitors (MAOIs), and the SSRI fluoxetine. These findings highlight the complexity of sex differences in antidepressant response, varying across different medication classes [89]. A pharmacovigilance program study observed that women were more likely to be prescribed SSRIs, particularly fluoxetine, SNRIs (duloxetine), TCAs, and trazodone, while men were more likely to receive mirtazapine and bupropion [98]. This suggests that some clinicians may consider potential sex differences when choosing medications, although more research is needed to confirm these observations.

The issue is further confounded by individual patient factors, such as genetic polymorphisms, that influence drug metabolism and response [69]. Personalized medicine approaches that consider genetic, hormonal, and psychosocial factors may hold promise in elucidating the impact of sex on antidepressant efficacy. Future research efforts should prioritize standardized diagnostic criteria and trial methodologies to minimize confounding variables and enhance the generalizability of findings. The question of sex-based differ-

ences in antidepressant efficacy remains unanswered. While some studies suggest potential variations, particularly with specific medication classes, others report no significant sex effects. Continued research, emphasizing personalized treatment approaches, is crucial to definitively understand and address these differences, ultimately leading to improved treatment outcomes for all individuals suffering from depression.

3.2. Antipsychotics

Schizophrenia is a severe mental disorder characterized by profound disruptions in thinking, language, perception, and self-awareness. It affects approximately 0.3% to 0.7% of the global population. Incidence rates vary, but typically range from 1 to 4 cases per 10,000 people annually. While schizophrenia affects both men and women, there are notable differences in clinical presentation, onset, and epidemiology [104,105]. Understanding these disparities is essential for developing sex-specific treatment and support strategies. The disorder commonly emerges during late adolescence or early adulthood, with men generally experiencing onset earlier (late teens to early twenties) than in women (mid-twenties to early thirties) [106]. Early onset is linked to a poorer prognosis and increased risk of severe symptoms. Men are more likely to exhibit negative symptoms such as social withdrawal, lack of motivation, and blunted affect. Positive symptoms, such as hallucinations and delusions, also occur but are often more prevalent in the early stages of the disease. Women tend to present more affective symptoms, including mood disturbances like depression and anxiety. They are also more likely to experience auditory hallucinations and paranoid delusions. Cognitive impairments, such as memory and attention difficulties, are often more pronounced in women [105,107]. Generally, women have a better prognosis with a more favorable response to treatment and higher levels of social functioning, while some studies show that men may have a poorer response to AP treatment compared to women [107,108]. Men are at a higher risk of suicide compared to women, as demonstrated in a 14-year follow-up study [109]. However, other studies have reported no significant sex differences in prognosis or treatment response, highlighting the need for further research to clarify these conflicting findings. Genetic predisposition, prenatal infections, and early childhood trauma are significant risk factors for both sexes. However, women are more likely to experience the influence of hormonal factors (e.g., estrogen), adverse social conditions, and life stressors [5,28,46].

Antipsychotic medications are essential in managing psychiatric disorders such as schizophrenia and bipolar disorder. However, emerging evidence suggests potential sex-based differences in treatment response and adverse effects (summarized in Table 2). A study by Usall et al. [110] found that women with schizophrenia responded better to antipsychotic treatment compared to men, particularly in symptom reduction and functional improvement. Women also demonstrated a more significant reduction in positive symptoms, potentially attributed to hormonal factors, such as the neuroprotective role of estrogen [111]. Individuals experiencing first-episode psychosis tend to show a better response to antipsychotic medications among women [112,113]. Riecher-Rössler and Butler [114] suggested that women may experience a faster and more robust treatment response, possibly due to neurobiological differences.

Despite the absence of specific guidelines for prescribing antipsychotics based on sex, clinical practice has revealed sex-related patterns in drug selection. Men are more often prescribed clozapine and olanzapine, while women are more frequently treated with aripirazole and quetiapine [115–117]. Recent research emphasizes significant sex-based differences in the efficacy and tolerability of antipsychotic medications (Table 3). These variations are attributed to diverse pharmacodynamic and pharmacokinetic factors, including drug metabolism, hormone levels, and receptor binding affinities. Studies indicate that women often exhibit higher serum concentrations of antipsychotics compared to men, even after dose adjustment [118]. For example, women demonstrate significantly higher dose-adjusted serum levels of clozapine, olanzapine, and risperidone, suggesting that lower doses may achieve therapeutic effects in women, potentially reducing the risk of side

effects [73,119,120]. Hormones such as estrogen can influence the efficacy of antipsychotic medications. Hormonal augmentation therapy, including the use of estrogen or raloxifene, has been explored to enhance antipsychotic efficacy in women with schizophrenia spectrum disorders [121–123]. Additionally, strategies to manage antipsychotic-induced hyperprolactinemia, which is more prevalent in women, have been investigated to improve treatment outcomes [73]. Women generally require lower antipsychotic doses to achieve the same receptor occupancy as men, particularly at the D2 receptor, crucial for antipsychotic efficacy. This difference can lead to higher rates of adverse effects in women when prescribed similar doses as men. Women may experience more pronounced extrapyramidal symptoms (movement disorders) and elevated prolactin levels, resulting in side effects such as menstrual irregularities and bone density loss [70,115]. Overall, while women may respond well to lower antipsychotic doses, they are also more susceptible to certain side effects due to higher drug concentrations and hormonal interactions. Therefore, personalized treatment plans considering sex differences are crucial for optimizing therapeutic outcomes and minimizing adverse effects in antipsychotic treatment [73,119,124]. Women require lower doses to achieve similar therapeutic effects due to higher D2 receptor occupancy [41,124]. However, this increased sensitivity also elevates the risk of side effects such as weight gain and metabolic disturbances [70,104,125]. For risperidone, while efficacy appears similar between the sexes, women are more susceptible to side effects like hyperprolactinemia and weight gain [119,126]. Clozapine has shown higher efficacy at lower doses in women but also carries a greater risk of adverse effects such as agranulocytosis and seizures [75,127]. Despite these sex-based differences, clinical dosing frequently lacks sex-specific recommendations, potentially leading to overdosing in women and increased adverse event risk. Tailoring antipsychotic dosages based on sex-specific pharmacokinetic and pharmacodynamic data could improve efficacy and reduce side effects [88]. A study comparing dose-adjusted aripiprazole concentrations found no significant efficacy differences between the sexes, although women tended to have slightly higher serum levels [25]. Another analysis confirmed similar aripiprazole response rates in terms of symptom reduction and side effects for both men and women, indicating no substantial sex-based efficacy differences [128]. Research on long-acting injectable (LAI) paliperidone revealed higher dose-adjusted serum concentrations in women compared to men, potentially influencing efficacy and side effects profiles. Additionally, LAI antipsychotic prescription rates are lower in women than in men. Notably, older women exhibit significantly higher concentrations than younger women and men of all ages [129,130]. In terms of efficacy, paliperidone is generally effective in symptom control for both sexes, but women might experience more pronounced therapeutic benefits due to their higher drug concentrations [130]. Research indicates that the effectiveness of quetiapine, a medication for schizophrenia and bipolar disorder, may vary between men and women [118,131,132]. According to the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), while both genders respond to quetiapine, women tend to experience greater reductions in symptoms, particularly positive and depressive symptoms [133]. Additionally, studies on dose-adjusted serum concentrations of quetiapine have revealed age-related sex differences. While no significant differences were observed between younger men and women, older women exhibited higher dose-adjusted quetiapine concentrations compared to older men [76]. Even if current guidelines do not take sex differences into account and recommend the same antipsychotic drug doses for men and women, this might not be the most appropriate treatment strategy in many clinical situations. Research is warranted evaluating data on sex-specific treatment, including sex-specific dosing, blood levels, efficacy, tolerability, and the side effects of different antipsychotics.

Table 3. Sex-based differences in the efficacy and side effects of antipsychotics.

Antipsychotic	Efficacy	Side Effects	Sex Differences	References
Aripiprazole	- Effective for both men and women. - Slightly higher serum concentrations in women.	- Generally well tolerated. - Lower risk of weight gain and metabolic side effects. - Common side effects include akathisia and insomnia.	- No significant differences in overall efficacy between the sexes. Women may have slightly higher serum concentrations, possibly leading to more pronounced therapeutic effects at lower doses.	[25,73,124,134]
Paliperidone	- Effective for symptom control in both men and women. Higher dose-adjusted serum concentrations in women, especially older women.	- Weight gain, hyperprolactinemia, and metabolic side effects are common. - Potential for extrapyramidal symptoms (movement disorders).	- Higher serum concentrations in women can lead to more pronounced therapeutic effects but also a higher risk of side effects. - Women are more susceptible to hyperprolactinemia.	[25,110,124]
Quetiapine	- Effective for treating schizophrenia and bipolar disorder in both sexes. - Women may show better response in reducing positive and depressive symptoms.	- Common side effects include sedation, weight gain, and metabolic disturbances. - Less risk of extrapyramidal symptoms compared to other antipsychotics.	- Higher dose-adjusted serum concentrations in older women. Men are more likely to experience weight gain and metabolic side effects. - Women may have more prolactin-related issues and hormonal imbalances.	[25,33,135]
Olanzapine	- Effective for both men and women in treating schizophrenia and bipolar disorder. - Women might achieve therapeutic effects at lower doses.	- Significant risk of weight gain and metabolic side effects. - Sedation and anticholinergic effects.	- Women often achieve therapeutic effects at lower doses due to higher serum concentrations. - Higher risk of weight gain and metabolic issues in women.	[60,74]
Risperidone	- Effective for both men and women. - Women might require lower doses for efficacy.	- Common side effects include weight gain, hyperprolactinemia, and metabolic disturbances. - Risk of extrapyramidal symptoms at higher doses.	- Women may experience more significant side effects such as hyperprolactinemia and weight gain. - Higher serum concentrations in women.	[25,56,71]
Clozapine	- Highly effective for treatment-resistant schizophrenia in both sexes.	- Risk of agranulocytosis, weight gain, metabolic issues, and sedation. - Seizure risk and myocarditis.	- Women tend to have higher serum concentrations and may require lower doses. - Higher risk of agranulocytosis and other side effects in women.	[25,119,127]

3.3. Mood Stabilizers

While the overall prevalence of BD is similar between men and women, there are notable differences in age of onset, clinical presentation, and comorbidities. BP type I affects women and men equally, whereas BP type II, including mixed episodes, bipolar depression, and rapid cycles (defined as four or more mood episodes in a year). is more common in women. Women typically experience a later onset of BD, with an average age of the mid-20s to early 30s, compared to men's late teens to early 20s [136,137]. Men are more likely to present with an initial manic episode, while women often experience an initial depressive episode [136]. While the severity of episodes can vary, men potentially experience more severe manic episodes and women experience more severe depressive episodes. No significant differences have been found in psychotic features of BP type I. The onset and course of the illness are often triggered or influenced by hormonal fluctuation during a woman's reproductive lifetime [138,139]. Women may face mood exacerbation and relapse premenstrually or during the menstrual cycle, leading to premenstrual depressive syndrome in approximately 25% of cases. Pregnancy represents another critical period for women: the postpartum period is associated with an increased risk of mood

episode recurrence, particularly postpartum psychosis, which may be exacerbated by the discontinuation of mood stabilizers which are more common during this time [138,140]. Indeed, women who discontinue psychotropic medication during pregnancy have a higher risk of mood recurrence compared to those who discontinue medication but not during pregnancy [140,141]. Women are more likely to discontinue medication due to perceived side effects [99]. Comorbidities also differ between the sexes: men with BD are more prone to substance use disorder, while women are more likely to experience anxiety disorders, panic disorder, PTSD, and a history of sexual abuse or domestic violence [142–144]. Early exposure to extreme stressors, such as violence, abuse, and neglect is strongly associated with rapid cycling, increased suicide attempts, and PTSD [142]. Women are at a higher risk of developing eating disorders compared to men. Physical health issues also show sex differences, with women more likely to develop hypothyroidism, thyroid failure, metabolic syndrome, diabetes, obesity, and migraine [144–146]. Studies generally show no sex-based differences in lithium response, a first-line treatment in BD, both in preventing recurrence and managing acute episodes, in conjunction with other medications (e.g., other mood stabilizers and APs). However, women tend to receive a later bipolar disorder diagnosis and delayed lithium treatment compared to men [31,141,147,148]. Men are more prone to lithium-induced tremors [147], which can impact quality of life and necessitate dose adjustments or additional medications. Antiepileptic drugs, such as valproate (VPA), lamotrigine, and carbamazepine, are commonly used as mood stabilizers in BD. VPA is effective in treating manic episodes and rapid cycling. While women may exhibit an optimal response to VPA treatment, particularly in managing rapid cycling, its use is contraindicated in women of childbearing age without strict contraceptive measures due to its high teratogenic risk [149,150]. Women also tend to have a higher risk of VPA-related side effects, such as weight gain, metabolic disorders, and polycystic ovary syndrome (PCOS) [151,152]. Lamotrigine is particularly effective as a maintenance treatment in preventing depressive episodes and delaying mood episode recurrence. Both men and women with BD benefit from lamotrigine's mood-stabilizing properties, but some studies suggest that women may experience a slightly better response, including robust antidepressant effects [138,153]. Given the predominance of depressive polarity in women with BD, preventing depressive episodes is crucial for effective treatment [154]. Lamotrigine exhibits fewer side effects compared to other antiepileptics, particularly VPA, with no associated weight gain and a lower risk of PCOS, hyperandrogenism, and ovulatory dysfunction [151,152,155,156]. Carbamazepine (CBZ) has demonstrated significant efficacy in reducing the frequency of mood episodes and hospitalizations in BD patients [157,158]. Both men and women benefit from CBZ treatment, particularly in maintaining rapid cycling. Given the higher prevalence of rapid cycling and mixed episodes in women with BD, studies have demonstrated the efficacy of CBZ in reducing rehospitalization rates in this specific population [159–161]. It has been highlighted that women, compared to men, might experience different side effects and adherence issues with CBZ. In fact, women are more likely to report side effects such as dizziness, gastrointestinal disturbances, and skin rashes, which can impact treatment adherence and perceived efficacy [161,162]. In women of childbearing age, CBZ prescription is cautioned due to its potential teratogenic effects, even if lower compared to VPA [161]. Sex-based differences in the efficacy and side effects of mood stabilizers are summarized in Table 4. There is still limited research on sex differences in mood stabilizer response and it seems that the female population is underrepresented in clinical trials and has not received enough attention to guide treatment recommendations. In many studies, it is difficult to explain if the observed sex differences were due to potentially predictable pharmacokinetic variances or to pharmacodynamic sex differences. Moreover, the influence of age on sex-related variations in treatment outcomes, specifically before and after the periods of adolescence and the menopause, or the effect of oral contraceptives and other hormonal treatments on the response and tolerability to these medications should be better elucidated.

Table 4. Sex-based differences in efficacy and side effects of mood stabilizers.

Mood Stabilizer	Efficacy in Men	Efficacy in Women	Side Effects in Men	Side Effects in Women	References
Lithium	Effective in treating manic episodes.	Effective in preventing depressive episodes.	More likely to experience tremor.	Higher risk of thyroid dysfunction, weight gain, and edema.	[25,31,141]
Valproate	Effective for manic episodes and rapid cycling.	Effective for rapid cycling and mood stabilization.	Lower incidence of weight gain and metabolic effects.	Higher risk of weight gain, metabolic syndrome, and PCOS. Contraindicated in women of childbearing age due to teratogenic risk.	[25,31,156]
Lamotrigine	Effective in preventing depressive episodes.	Effective, potentially more robust antidepressant effects.	Lower risk of severe skin reactions.	Higher risk of severe skin reactions (e.g., Stevens–Johnson syndrome).	[153,156]
Carbamazepine	Effective in reducing mood episodes and hospitalizations.	Effective, particularly in rapid cycling and mixed episodes.	Lower incidence of side effects impacting adherence.	Higher incidence of dizziness, gastrointestinal disturbances, and skin rashes. Higher risk during pregnancy.	[25,162]

4. Conclusions

Sex-based disparities in psychopharmacological treatment represent a complex and multifaceted area of investigation, with profound implications for both clinical practice and research. While there has been a growing recognition of the significance of sex as a biological variable in recent years, a substantial knowledge gap persists regarding the nuanced differences between men and women in their responses to psychotropic medications. Biological factors, including the intricate interplay of hormones, genetics, and neurobiological substrates, contribute significantly to differential drug responses between the sexes. Hormonal fluctuations throughout a woman's lifespan, such as those associated with menstruation, pregnancy, and the menopause, can markedly influence drug pharmacokinetics and pharmacodynamics. Conversely, the relatively stable hormonal milieu in men may lead to distinct patterns of drug metabolism and response. Furthermore, genetic variations between the sexes can modulate drug efficacy and tolerability, underscoring the importance of considering genetic factors in personalized treatment approaches.

Psychological factors, such as stress and coping mechanisms, can also differ between the sexes and influence treatment outcomes. Women, for instance, may experience higher levels of stress and anxiety, which can affect their response to psychotropic medications. Social and cultural influences are critical in shaping individuals' attitudes toward mental health and treatment adherence. In many cultures, mental health stigma is more pronounced among men, leading to underreporting of symptoms and reluctance to seek treatment. On the other hand, women may face social pressures related to caregiving roles, impacting their ability to prioritize their mental health. Addressing these social and cultural factors through education and supportive interventions can improve treatment adherence and outcomes.

Incorporating sex as a fundamental variable in personalized treatment plans holds the promise of optimizing therapeutic outcomes and minimizing adverse effects. By tailoring treatment regimens to the unique biological and sociocultural characteristics of individual patients, clinicians can enhance treatment efficacy, improve patient quality of life, and reduce healthcare costs. This paradigm shift necessitates a concerted effort to bridge the existing research gap and to develop sex-specific guidelines and treatment protocols. By doing so, the field of psychopharmacology can move toward a more equitable and effective approach to mental healthcare.

5. Future Directions

Future psychopharmacological research should focus on clear and robust sex-based differentiation. Large-scale, sex-specific studies are essential to understand how biological variations between men and women influence drug absorption, distribution, metabolism, and excretion. Such studies could inform more precise dosing guidelines and the development of sex-specific treatment protocols.

It has been noticed that pharmacological preclinical research is still characterized by a sex bias that mostly concentrates on male animals, even when the disease of interest is a disorder that is more common in women. This risks leading to a worse understanding of the pathophysiological, physiological, and biochemical pathways in females than in males, with a consequent drawback to the expanding knowledge of the significance of sex differences in pharmacology. To improve the translation of the observed results to humans, create novel and more effective therapeutic approaches, and therefore advance customized therapy, sex must be taken into account as a variable starting in the preclinical stage [163].

Personalized medicine, which tailors therapy to individual patient characteristics including genetics, lifestyle, and environment, has demonstrated promise in various medical fields. Incorporating sex as a key variable in personalized psychopharmacological treatment plans could enhance efficacy and reduce adverse effects.

To advance the field of sex-aware drug repurposing, several critical avenues warrant exploration. Multi-omics integration holds immense promise by providing a comprehensive understanding of sex-specific molecular variations underlying drug responses. Incorporating genomic, transcriptomic, and proteomic data will enable the identification of key sex-specific biomarkers and pathways, facilitating the development of more precise treatment strategies. Furthermore, rigorous clinical trial design is essential to address the historical underrepresentation of women in clinical research. By ensuring balanced sex distribution in trial populations, ongoing research will be able to generate robust evidence on sex-based differences in drug efficacy and safety. Consequently, this will enhance the development of sex-specific predictive models and algorithms. Phenotypic characterization of sex-specific drug responses is another crucial area of focus. By establishing standardized phenotypic profiles, it could be possible to identify consistent patterns of drug effects between the sexes, leading to more accurate drug repurposing decisions. Additionally, patient stratification based on sex-related factors, such as hormonal status and genetic variants, offers the potential to tailor drug treatments to specific patient subgroups, maximizing therapeutic benefits and minimizing adverse events.

In clinical practice, women are shown to experience adverse drug reactions from approved drug products more often than men and often receive suboptimal drug therapy. Continuous fluctuations in endogenous steroid sex hormones occurring throughout the menstrual cycle, during pregnancy, and in the perimenopausal period alter drug efficacy, so males and females appear to respond differently to the same drug [164]. Sex as a biological variable should be skilfully addressed and powered both in experimental pharmacological designs and analyses and in the precise choice of specific medicine with adequate dose adjustments for each patient.

The future of psychopharmacological treatment necessitates a comprehensive understanding of sex differences to achieve more effective and personalized care. By investing in research that explores these differences, the medical community can develop tailored treatment approaches that improve mental health outcomes for both men and women. This requires a concerted effort to bridge the research gap, incorporate sex-specific considerations into clinical practice, and address the limitations of current knowledge to ultimately deliver more equitable and effective mental healthcare.

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List of Abbreviations

ADHD	Attention-deficit and hyperactivity disorders
ADs	Antidepressants
ADME	Drug absorption, distribution, metabolism, and excretion
APs	Antipsychotics
BDZs	Benzodiazepines
CYP	Cytochromes
GABA	γ-aminobutyric acid
GFR	Glomerular filtration rate
DALYs	Disability-adjusted life-years
NRIs	Norepinephrine reuptake inhibitors
PTSD	Post-traumatic stress disorder
SSRIs	Selective serotonin reuptake inhibitor
SNRIs	Serotonin–norepinephrine reuptake inhibitor
SUDs	Substance use disorder
YLDs	Years lived with disability
TCAs	Tricyclic antidepressants
Vd	Volume of distribution

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