



Review

Sex representation in neurodegenerative and psychiatric disorders' preclinical and clinical studies

Mieke DuMont^{a,1}, Alyssa Agostinis^{a,1}, Kiran Singh^{a,1}, Evan Swan^a, Yvonne Buttle^a, Daniela Tropea^{b,c,d,*}^a School of Medicine, Trinity College Dublin, Dublin, Ireland^b Department of Psychiatry and Trinity Translational Medicine Institute (TTMI), Trinity College Dublin, Dublin, Ireland^c Trinity College Institute of Neuroscience, Trinity College Dublin, Lloyd Building, Dublin 2, Dublin, Ireland^d FutureNeuro, the SFI Research Centre for Chronic and Rare Neurological Diseases

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ABSTRACT

Many studies show the importance of biological sex for the onset, progression, and response to treatment in brain disorders. In line with these reports, health agencies have requested that all trials, both at the clinical and preclinical level, use a similar number of male and female subjects to correctly interpret the results. Despite these guidelines, many studies still tend to be unbalanced in the use of male and female subjects.

In this review we consider three neurodegenerative disorders: Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, and three psychiatric disorders: Depression, Attention Deficit Hyperactivity Disorder, and Schizophrenia. These disorders were chosen because of their prevalence and their recognized sex-specific differences in onset, progression, and response to treatment. Alzheimer's disease and Depression demonstrate higher prevalence in females, whereas Parkinson's Disease, Amyotrophic lateral sclerosis, Attention Deficit Hyperactivity Disorder, and schizophrenia show higher prevalence in males.

Results from preclinical and clinical studies examining each of these disorders revealed sex-specific differences in risk factors, diagnostic biomarkers, and treatment response and efficacy, suggesting a role for sex-specific therapies in neurodegenerative and neuropsychiatric disorders. However, the qualitative analysis of the percentage of males and females enrolled in clinical trials in the last two decades shows that for most of the disorders, there is still a sex bias in the patients' enrolment.

1. Introduction

Biological sex is the distinction between an individual's maleness or femaleness. We all have a sex, and it is determined by the presence of X and Y chromosomes in our cells. In the absence of the Y chromosome the embryo will develop into a female, but the presence of genes on the Y prompt the development of masculine features. The two most common sexes are female (XX) and male (XY) (Bale, 2019). In contrast, gender is the individuals' sense of their own sexuality, and is a societal concept that includes sex, and encompasses the cultural expectations and stereotypes ascribed to individuals when they identify along the

femininity-masculinity spectrum (Lips, 2020). This paper focuses solely on the biological sexes in relation to six neurological disorders—chosen on the basis of their incidence in males and females—and excludes any other external factors including, but not limited to, gender, socioeconomic status, ethnicity, geographical location, lifestyle habits, and environment. It is worth remarking that in some circumstances environmental factors interact with biological sex, i.e., in the case of exposure to inflammatory cytokines in utero, but we will not consider these interactions in this review.

Biological sex influences all the cellular processes throughout life, and in medicine it influences disease incidence, progression, phenotype

Abbreviations: AD, Alzheimer's disease; PD, Parkinson's disease; ALS, Amyotrophic lateral sclerosis; ADHD, Attention Deficit Hyperactivity Disorder; MMD, Major depressive disorder; NIH, National Institutes of Health; SRY, Sex-determining region Y; iPSC, induced pluripotent stem cells; IL, Interleukin; TNF, Tumour necrosis factor; TCA, Tricyclic antidepressant; SSRIs, Selective serotonin re-take inhibitor; MPH, methylphenidate; SHRs, spontaneously hypertensive rates.

* Corresponding author at: Trinity Translational Medicine Institute (TTMI), room 0.80, D08W9RT Dublin, Ireland.

E-mail address: tropead@tcd.ie (D. Tropea).

¹ These authors contributed equally to the manuscript.

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and response to interventions and many other aspects (Altevogt et al., 2011). The importance of the sex factor in health and disease has begun to garner more attention recently, and the number of publications in PubMed pertaining to biological sex differences has progressively increased from 1000 in the year 2000 up to 3500 in 2020.

The significance of biological sex has been highlighted in brain disorders (Duffy and Epperson, 2022), and we are progressively understanding the role of sex hormones in the development and function of brain circuits (Pinares-Garcia et al., 2018). As our knowledge of key biological differences between the male and female brain grows, it emerges that diseases' symptoms and response to treatments differ between males and females, and therefore the effect of sex should be considered in preclinical and clinical trials. In the past years there has been a clear bias to males in preclinical trials: in 1979, 70% of studies involving animal models used all males (Bale, 2019). When looking at clinical trials in brain disorders, the number of studies in male subjects are 5.5 times more numerous than studies in females (Bale, 2019). Recently, measures have been put in place to help standardise trials and to promote inclusion of both male and female participants throughout all phases of trials (Clayton and Collins, 2014). In 2014, the US National Institutes of Health (NIH) announced that researchers need to account for sex as a biological variable in NIH-funded preclinical research (Gemmati et al., 2019). However, issues of standardisation and transparency as well as lack of defined sex-specific outcomes in trials remain (Rich-Edwards et al., 2018).

In 2018, Burggraaf and colleagues (Labots et al., 2018) looked at the proportion of females and males in several drug trials run by the Food and Drug Administration and concluded that overall, females were not underrepresented (47% of participants being females). However, when the data were broken down into male and female participants in the different phases of the clinical trials, significant differences appeared: only 22% of the participants in phase I trials and 25% of participants in combined phase I/II trials were females (Labots et al., 2018).

In this review, we will consider the sex-dependent response in the treatment of three neurodegenerative disorders (Alzheimer's disease (AD), Parkinson's disease (PD), and Amyotrophic Lateral Sclerosis (ALS)) and three psychiatric disorders (Depression, Schizophrenia, and Attention-Deficit Hyperactivity Disorder (ADHD)). The disorders have been selected considering their prevalence and their sex bias: AD and Depression are epidemiologically female dominant whilst males and females report similar incidences of Schizophrenia. PD, ALS, and ADHD are most prevalent in males. We will then discuss sex representation in clinical trials in these six disorders, and we will examine whether the sex bias in clinical trials has changed over the years.

2. Materials and methods

We conducted a narrative review on biological sex in brain disorders, searching the database Pubmed for the following terms: biological sex, biological sex differences, neurodegenerative, neuropsychiatric, sex-specific difference, Depression, Attention-Deficit Hyperactivity Disorder, Schizophrenia, Alzheimer's disease, Amyotrophic Lateral Sclerosis, and Parkinson's disease.

We reported the trends in male and female participation in clinical trials over time using the database "clinical trials.gov", and focused on the trials between years 2000–2020.

We searched the terms for each disorder as well as their synonyms, and used the following inclusion criteria, "completed studies" and "with results only", to ensure that male and female participant numbers were definitive and available. We included only completed studies, including both drug trials and non-drug trials. The search with the condition "With results only" excluded trials that did not have results available. These criteria allowed access to important statistics on male and female representation necessary for our review. All available studies at this time point were included for review. No minimum sample size was set. Both observational and interventional studies were included. We did not

differentiate by trial type or phase. All trials were available in the English language.

Since we used clinicaltrials.gov, we did not consider the non-USA published trials. Furthermore, prior to 1 July 2005, clinical trials were not required to be published on clinicaltrials.gov. This examination of trials was thus limited to those trials that were registered and uploaded to clinicaltrials.gov. In addition, for most disorders, access to data on clinical trials was limited to the last 40–50 years as prior trials predated the clinicaltrials.org database.

The full available datasets were downloaded and imported into MiniTab. Male and female participant numbers were manually collected from clinicaltrials.gov and matched to corresponding clinical trials. Each dataset was ordered by start date and percentages of males and females in each study were calculated. The complete datasets were then exported to Excel for graphical representation.

The data reported in this review reflect changes in participation ratios of males and females for a range of both neurodegenerative and neuropsychiatric disorders. Whether sex-specific outcomes were outlined within included studies was beyond the scope of this review. Specific groups wherein nature impacts on sex inclusion in our selection (war veterans, mothers, breast cancer patients, postpartum patients) were not screened for in this study.

3. The impact of sex on neurodegenerative disorders

Neurodegenerative diseases are sexually dimorphic in both the frequency and symptoms of the diseases (Gemmati et al., 2019). Yet, the exact molecular basis for sex-related differences is not fully understood (Vegeto et al., 2020). It is recognized that throughout one's life, primary sex hormone synthesis changes either due to aging or pharmacological treatment, which may act as either a risk factor or a protective factor for neurodegenerative diseases (Takahashi et al., 2000). These primary sex hormones target neuronal cells and impact the brain's sexual differentiation which contributes to the degeneration process (Vegeto et al., 2020).

These sex differences present themselves during neurodevelopment and continue throughout development and adulthood. Furthermore, sex differences in neurodegenerative diseases impact age of onset, progression, severity, and response to treatment (Loke et al., 2015). Thus, since sex differences have a vast impact on neurodegenerative diseases and their treatment, it is essential to explore the impacts of sex differences in the treatment efficacy for neurodegenerative diseases. Three major forms of neurodegenerative diseases that have varied prevalence based on sex include AD (2:1 female: male) (Mielke et al., 2014), PD (1.5:1 male: female) (Lo and Tanner, 2013) and ALS (2:1 male: female) (McCombe and Henderson, 2010).

4. The impact of sex on neuropsychiatric disorders

Neuropsychiatric disorders presumably arise due to a complex interaction of pathological genetic variation and environmental factors during critical periods of brain development (Marín, 2016). In fact, many neuropsychiatric disorders display differences in prevalence, age of onset, symptoms, or course of illness between males and females (Table 2) (Goldstein et al., 2013; Seedat et al., 2009).

In addition to prevalence differences between the sexes, expression and course of disorder differs. Females experience increased symptom severity and are diagnosed with more comorbidities in anxiety and depression disorders than males (Green et al., 2019). In ASD, females are affected less severely and have greater symptom improvement across development than do males (Szatmari et al., 2015). Males with schizophrenia exhibit a worse course of disease and poorer response to typical antipsychotic medications than females (Goldstein et al., 2013). Not all disorders exhibit expression disparities, however there are clear differences in some disease manifestations between the sexes.

Sex differences in the rate and presentation of neuropsychiatric

disorders may be due to true male-female differences, possibly involving genetic effects from sex chromosome composition or differences in thresholds for manifestation of disorders due to differential accumulation of risk factors (Middeldorp and Wray, 2018). Structural and functional differences in brain areas combined with developmental changes in sex hormone levels and their receptors are interconnected with sex differences in neuropsychiatric disorders (Bao and Swaab, 2010). However, despite robust evidence of male-female disparity in neuropsychiatric disorders, investigative research to explain and define the impact of sex is lacking. This knowledge could elucidate etiological and pathogenic mechanisms of neuropsychiatric disorders in general as well as greatly improve therapeutic approaches for affected males and females (Riecher-Rössler, 2017). Thus, this paper will explore three common neuropsychiatric disorders – depression, schizophrenia, and ADHD – that exhibit clear male-female differences in rate, disease course, and treatment response. We will focus on clinical data and research that investigated therapeutics tested based on sex differences. We will also discuss the outcomes of sex-dependent differences in treatment response and future implications of this knowledge.

5. Biological sex in individual disorders

5.1. Alzheimer's disease: Sex-dependent presentation and response to treatment

With a prevalence of 24 million individuals affected, AD is the most common neurodegenerative disorder in the world (Mayeux and Stern, 2012). Demographics, prognosis, and sex-specific differences are summarized in Table 1 (Canevelli et al., 2017; Nebel et al., 2018; Pike, 2017; Pinares-Garcia et al., 2018). Females have a more robust progression of mild cognitive impairment, followed by more severe dementia. Females also have faster hippocampal atrophy along with larger amounts of beta-amyloid plaques and neurofibrillary tangles (Ardekani et al., 2016; Barnes et al., 2005; Pike, 2017). In contrast, males typically have an accelerated disease progression, higher mortality, higher comorbidity, and later onset (Haaxma et al., 2007; Lapane et al., 2001; Van Den Eeden et al., 2003). The differences between males and females can be attributed to the differences in genetic, hormonal, and environmental factors between both males and females (Pinares-Garcia et al., 2018). (See Table 1.)

There is a sex-specific response to drugs in patients with AD. Many studies focused on the modulation of the cholinergic system in combination with other drugs or considered the contribution of genetic risk factors (Table 3). Some studies found acetylcholinesterase inhibitors to be more effective in females with mild dementia, while more effective in males when their AD progressed to more severe dementia (Ferris et al., 2009). However, there is contradicting evidence considering that multiple studies found that there was no difference between the response of

each sex to acetylcholinesterase inhibitors (Canevelli et al., 2017). Additionally, the effectiveness of insulin treatment was dose dependent. At a lower dose, both females and males showed improvement whereas at a higher dose only males showed improvement (Claxton et al., 2013). A systematic review of the response to cholinergic treatments revealed that biological sex should be considered in the interpretation of the results to specific drugs: females, but not males showed a significant response to treatment by donepezil or rivastigmine (Scacchi et al., 2014). A few years later, a meta-analysis of all the studies on acetylcholinesterase inhibitors revealed no differences between males and females (Claxton et al., 2013). It is evident that there is extremely limited data regarding the study of the impact of sex differences on drug response in patients with AD. This limited information provides a large barrier to the validity and reliability of the data presented. Furthermore, there are multiple factors that impact the effectiveness of a drug on each sex including the disease progression, the dose of a drug, and the presence or absence of the estrogen receptor 1 genotype and ApoE ϵ 4 allele (Scacchi et al., 2014). All these sex differences must be considered when designing drugs to account for the multiple confounding variables that can impact the effectiveness of each drug. Despite the need for additional studies to show the sex-dependent response to treatment, in patients with AD clinical trials show overall a balanced enrolment of patients of both sexes, although there is a significant variability between trials (Fig. 2).

5.2. Parkinson's disease: Sex-dependent presentation and response to treatment

PD is recognized as the second most common neurological disease in the world, affecting 2% of people over the age of 65 and 5% of people over 85 (Pinares-Garcia et al., 2018; Tenkorang et al., 2018). After aging, male sex is the strongest risk factor to develop PD across all ages and ethnicities (Gillies et al., 2014; Haaxma et al., 2007; Picillo et al., 2017). Additional demographics are summarized in Table 1.

Females tend to experience symptoms at a later age than males (approximately two years later) and experience a slower disease progression (Haaxma et al., 2007). Females and males also exhibit different symptoms at different rates. Females present more with tremor, depression, and constipation, whereas males present more with bradykinesia or rigidity, daytime sleepiness, dribbling, and rapid eye movement (Haaxma et al., 2007; Martinez-Martin et al., 2012).

It has been suggested that these sex-based differences are linked to the immunomodulatory effects of sex steroid hormones (Hanamsagar and Bilbo, 2016). In fact, many of the studies that focus on the sex differences within PD suggest that 17 β -estradiol (E2) is the underlying basis for this difference (Gillies et al., 2014; Tenkorang et al., 2018). E2 is thought to be neuroprotective and could help explain why females experience a less severe PD phenotype than males (Liu and Dluzen,

Table 1
Demographic for common neurodegenerative disorders.

	AD	PD	ALS
Age of onset	>65 years old Early onset <65 years old (rare)	60	58–63 sporadic 47–52 familial
Prevalence (F:M)	2:1	1:1.5–2	1:2
Symptoms	Mild cognitive impairment progressing to severe dementia; poor judgement; problems with speech and language; disturbed sleep; difficulty performing spatial tasks.	Motor symptoms: resting tremor, rigidity, bradykinesia, postural instability, shuffling gait. Non-motor symptoms: anxiety, depression, dementia, constipation.	Speech impairment; dysphagia; limb weakness and spasticity; respiratory compromise; cognitive impairment.
Prognosis	Poor. 5th leading cause of death in females. 8th leading cause of death in males.	Good prognosis if treated.	Dependent on rate of progression and respiratory involvement.
Genes/ Hormones	ApoE4 allele Estrogen receptor 1 genotype - risk factor.	SRY SNCA gene 17 β -estradiol - neuroprotective.	Estrogen - neuroprotective.

Table 2
Demographic for common neuropsychiatric disorders.

	Depression	Schizophrenia	ADHD
Age of onset	Median age of 26	M: 21–25* F: 25–30 and > 45	6–8
Prevalence (F:M)	2:1	1:1.4 overall 1:2 in <20	1:1.5 in adults 1:2.5 in children
Symptoms	Anhedonia; depressed mood; insomnia or hypersomnia; appetite or weight changes; fatigue; psychomotor impairment; worthlessness or guilt; decreased concentration; suicidal thoughts or behaviour.	Positive symptoms: delusions, hallucinations, disorganized speech and behaviour. Negative symptoms: apathy, social isolation, diminished affect. Cognitive impairment.	Hyperactivity; impulsivity; comorbid eating and anxiety disorders.
Prognosis	Good if spontaneous onset. Moderate if associated with precipitating events.	Lifelong persistent disorder. 1/5 recover; 1/5 persistent symptoms; 3/5 improvements.	Symptoms generally improve with age, but many adults continue to experience problems.
Genes/Hormones	Estrogen and progesterone - neuroprotective.	>100 genetic loci are significantly associated.	Dopamine D4 receptor gene VNTR; Dopamine D5 receptor gene microsatellite marker.

* Early-onset Schizophrenia diagnosed before age 20 demonstrates an established predilection for males. Late-onset schizophrenia diagnosed at age 45 or older is more common in females, however psychotic breakdown in females is also correlated with times of low estrogen throughout life and therefore results in a more complex statistical representation not described here.

Table 3
Treatments and imaging for neurodegenerative and neuropsychiatric disorders.

	AD	PD	ALS	Depression	Schizophrenia	ADHD
Treatment targets	Acetylcholinesterase inhibitor	Dopamine agonist	Glutamic acid inhibitor; Antioxidant	Serotonin inhibitor; Norepinephrine inhibitor	Dopamine receptor antagonist	Amphetamines
Image findings	Hippocampal atrophy; beta amyloid plaque; neurofibrillary tangles.	Decreased connectivity in basal ganglia.	Hypointensities in motor cortex; hyperintensities in corticospinal tract; brain atrophy.	Increased activity in medial prefrontal cortex and anterior cingulate cortex; decreased activity in posterior cingulate cortex and angular gyrus.	Enlarged ventricles; decreased cortical volume.	Decreased overall brain volume.

2007; Mozley et al., 2001; Shulman and Bhat, 2006). Some studies conducted on premenopausal females with PD showed that their symptoms worsened during menstruation, a time when estrogen levels are naturally lower (Quinn and Marsden, 1986). Unsurprisingly, PD symptoms also worsen in postmenopausal females, again likely linked to the decreased levels of estrogen (Tenkorang et al., 2018). Other research found that females who had a premenopausal, bilateral oophorectomy were at greater risk of developing PD (Benedetti et al., 2001). Haaxma et al. (2007) also showed that dopamine innervation in the striatum was more preserved in females with PD compared to males with PD.

When looking at male-specific biological variables, the sex-determining region Y (SRY) gene on the Y chromosome is expressed in the nigrostriatal dopaminergic system, leading to the proposition that SRY gene expression may predispose males to dopamine irregularities as seen in PD (Vegeto et al., 2020).

The differences in presentation have also been associated with differences in morphological and functional imaging studies (McCarthy, 2008; Naftolin et al., 2007; Tremblay et al., 2020). Males had lower cortical grey matter volume, higher intracerebral spinal fluid volume, and considerably more atrophy in six distinct regions of the bilateral frontal lobe. In contrast, females showed more atrophy in three regions of the left frontal lobe, right superior parietal lobe, left insular gyrus, and right medioventral occipital cortex (Tremblay et al., 2020).

The most common current pharmacological therapies for PD are levodopa in combination with a dopa decarboxylase inhibitor, non-ergot dopamine agonists, and monoamine oxidase B inhibitors (Table 3) (Beitz, 2014). However, none of these therapies considered the impact of sex when they were developed, and evidence shows that females and males react differently to them. Treatments offered should be developed with biological sex and sex hormones in mind, as the efficacy, tolerability, and pharmacokinetics of medications differ between males and

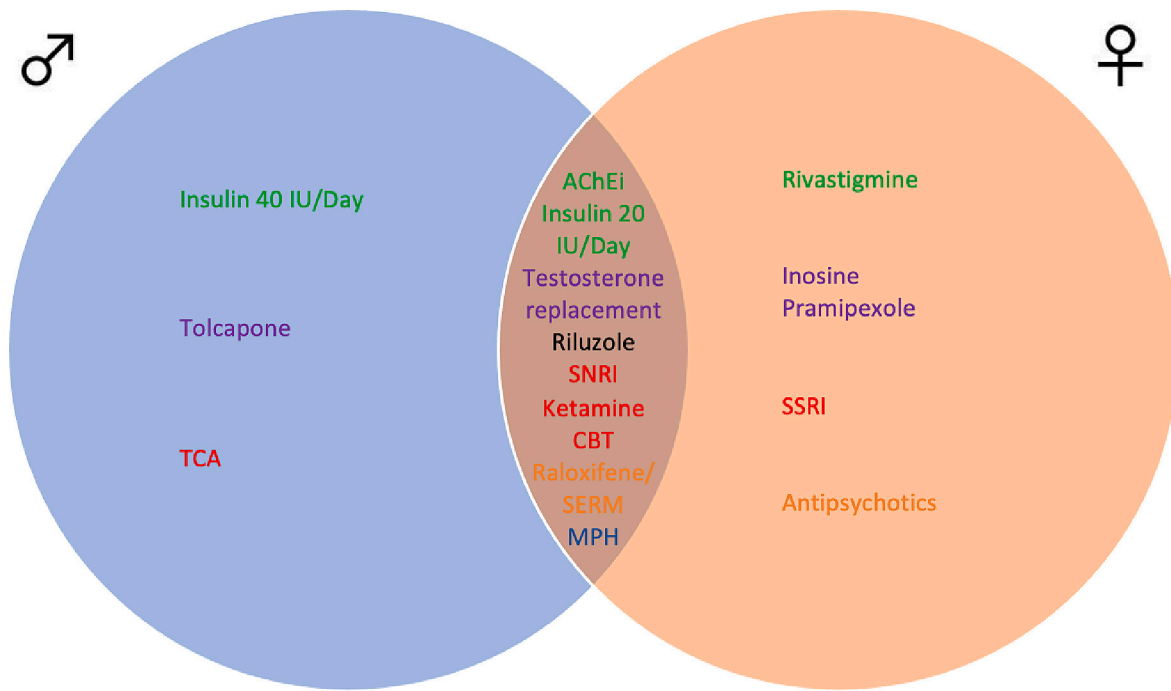
females (Gillies et al., 2014).

There is a limited number of studies and clinical trials that look at the differences experienced between males and females undergoing treatment for PD. In the DATATOP study, both males and females were treated with levodopa and had significantly improved motor symptoms (DATATOP, 1989). However, females were more likely to experience dyskinesias when treated with levodopa compared to males, suggesting that levodopa dosages should be lower in females (DATATOP, 1989).

Tolcapone, a catechol-O-methyltransferase inhibitor, was assessed for its tolerability in females and males; it was found that females were more likely to experience gastrointestinal issues, dizziness, and orthostasis even though there were no pharmacodynamic differences found (Parashos et al., 2004). The difference in tolerability may be due to sex-specific hormonal interactions with tolcapone, where catechol estrogen (a metabolite of estrogen) competitively inhibits the activity of catechol-O-methyltransferase (Parashos et al., 2004).

Most of the studies that have looked at sex hormones and their relation to PD have focused on estrogen being neuroprotective, with the influence of testosterone on PD all but ignored. The prevalence of PD is higher in males, but the research does not reflect that. One clinical study that did examine the effects of testosterone replacement therapy in aged males with PD who were currently being treated with levodopa found that testosterone did not have an impact on either motor or non-motor symptoms (Tenkorang et al., 2018). Although this study found no benefits with testosterone replacement therapy (Fig. 1), this study administered testosterone long after PD had already been diagnosed and after the natural testosterone levels in these males had declined.

Urate, a prominent antioxidant in humans, has been looked at as a possible treatment due to its inverse relationship with the progression of PD (Ascherio et al., 2009; Schwarzschild et al., 2019). The Safety of Urate Elevation in PD (SURE-PD) clinical trial concluded that inosine



Legend: Alzheimer’s Disease, Parkinson’s Disease, ALS, Depression, Schizophrenia, ADHD

Fig. 1. Treatments for Neurodegenerative and Neuropsychiatric Disorders and Their Relative Efficacy in Either Sex. The treatments are categorized based on the research that was found using the selection criteria listed above. Those in the male-only group tend to show more benefits to males; the same for those listed in the female-only group. Those listed in the middle have either shown no significant benefit to one sex over the other or they have produced inconclusive results.

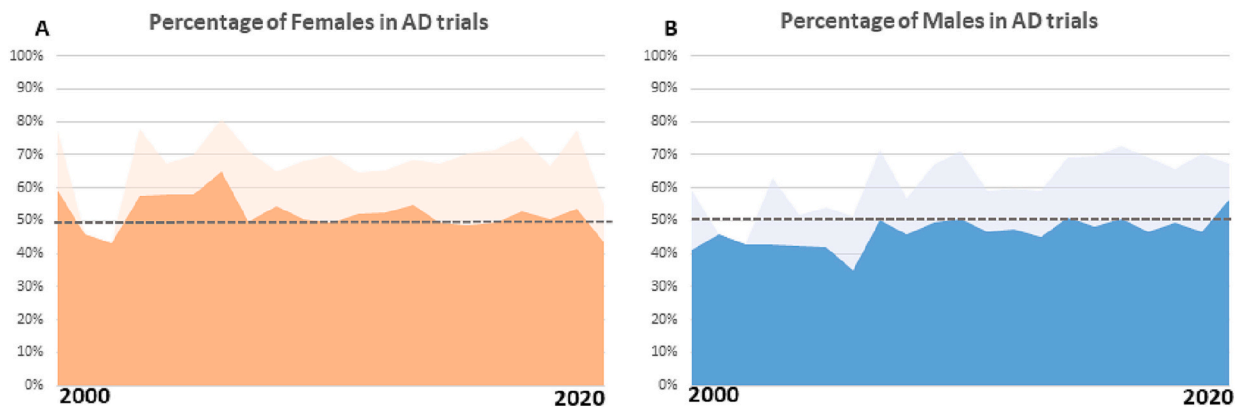


Fig. 2. Percentage of Females and Males subjects in AD Trials. Plot of average and Standard Deviation percentages of Females (A) and Males (B) subjects per year enrolled in Clinical Trials for AD between 2000 and 2020. For AD, the percentage of males and females is balanced. The dotted line shows 50% of patients enrolled for each sex.

raised average serum urate levels in both males and females, but that the increase was 50% greater in females (Fig. 1) (Schwarzschild et al., 2019). When investigating the impact on clinical outcomes long-term, only females showed a slowing of clinical progression (Schwarzschild et al., 2019). Data from clinical trials in the last 20 years show a clear prevalence of males enrolled in the studies (Fig. 3).

5.3. Amyotrophic lateral sclerosis: Sex-dependent presentation and response to treatment

ALS is a fatal, progressive neurodegenerative disease that impacts the motor system (Kiernan et al., 2011; Pape and Grose, 2020; Vegeto et al., 2020). The incidence of ALS is higher in males, impacting 3/100000 individuals per year when compared to females with 2.4/

100000 individuals per year (Logroscino et al., 2010). Males also have a higher population-based lifetime risk of ALS with 1:350 compared to females with a 1:400 population-based lifetime risk (Logroscino et al., 2010). See Table 1 for a summary of demographics.

ALS is a male-dominant disease that presents itself earlier in males than females (Pape and Grose, 2020; Vegeto et al., 2020). Females with ALS have a higher executive impairment for memory and language compared to males, causing women to be more vulnerable cognitively (Palmieri et al., 2015). Additionally, ALS presents itself in different neuronal regions in males compared to females. In males, ALS typically presents itself in the motor neurons of the lumbar tract of the spinal cord whereas, in females, ALS is typically initiated in the bulbar regions (Blasco et al., 2012).

Even though there are known differences between ALS in males and

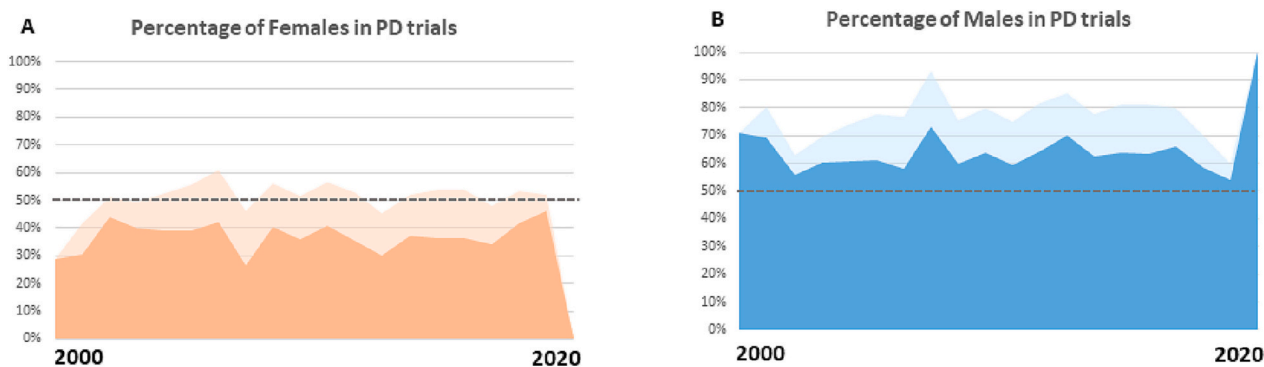


Fig. 3. Percentage of Females and Males subjects in PD Trials. Plot of average and Standard Deviation percentages of Females (A) and Males (B) subjects per year enrolled in Clinical Trials for PD between 2000 and 2020. For PD the percentage of males is higher than the percentages of females enrolled. The dotted line shows 50% of patients enrolled for each sex.

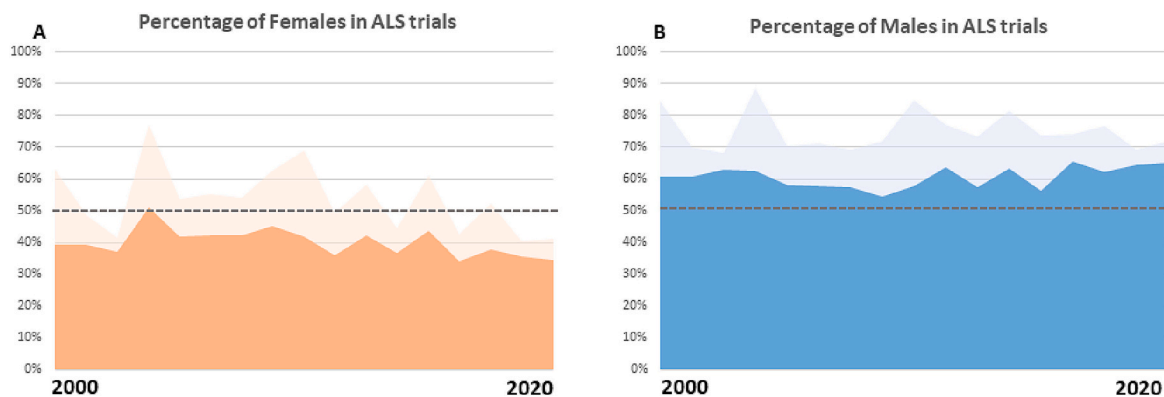


Fig. 4. Percentage of Females and Males Subjects in ALS Trials. Plot of average and Standard Deviation percentages of Females (A) and Males (B) subjects per year enrolled in Clinical Trials for ALS between 2000 and 2020. For ALS the percentage of males involved in trials is higher than the percentage of females. The dotted line shows 50% of patients enrolled for each sex.

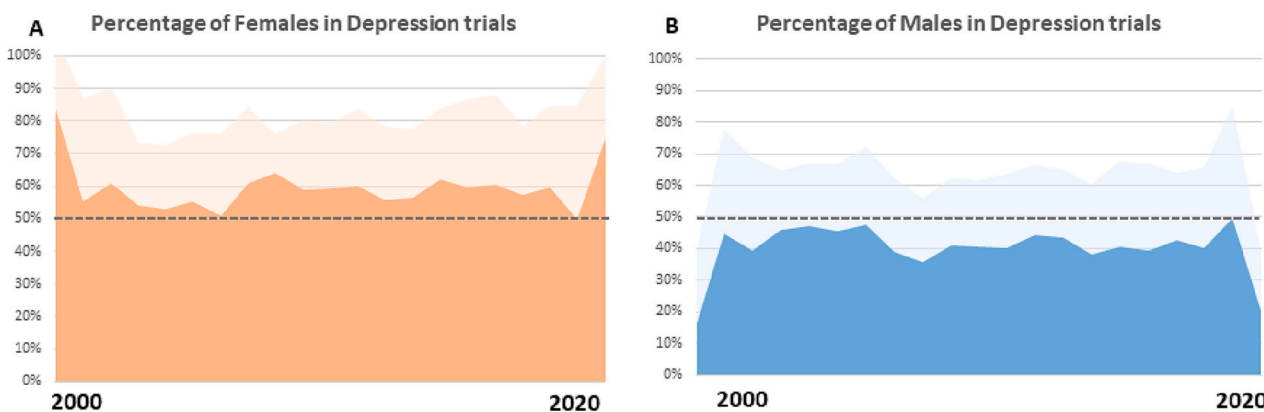


Fig. 5. Percentage of Females and Males Subjects in Depression's Trials. Plot of average and Standard Deviation percentages of Females (A) and Males (B) subjects per year enrolled in Clinical Trials for Depression between 2000 and 2020. For Depression, the percentage of females involved in trials is higher than the percentage of males. The dotted line shows 50% of patients enrolled for each sex.

females, the molecular basis of sexual dimorphism is not fully known (Vegeto et al., 2020). Sex hormones might affect ALS in either a protective or detrimental mechanism (Vegeto et al., 2020). Females that take oral contraceptives are exposed to an increased amount of estrogen which acts as a neuroprotective effect on motor neurons in ALS (de Jong et al., 2013; Trojsi et al., 2020). Postmenopausal females are more susceptible to developing ALS due to lower estrogen levels, thus decreasing estrogen levels makes females more susceptible to ALS (Rooney et al., 2017). Moreover, estrogen has protective effects on the

spinal cord motor neurons in both males and females (Ji et al., 2017; Pape and Grose, 2020). These protective effects have also been seen in mouse models where estradiol and phytoestrogens act on the spinal cord motor neurons and are neuroprotective for ALS (Trieu and Uckun, 1999). Testosterone is another sex hormone that affects ALS. Individuals with significantly decreased free testosterone levels are at a higher risk of developing ALS compared to individuals with normal testosterone levels (Militello et al., 2002). Furthermore, individuals with high levels of prenatal testosterone have an increased risk of developing sporadic

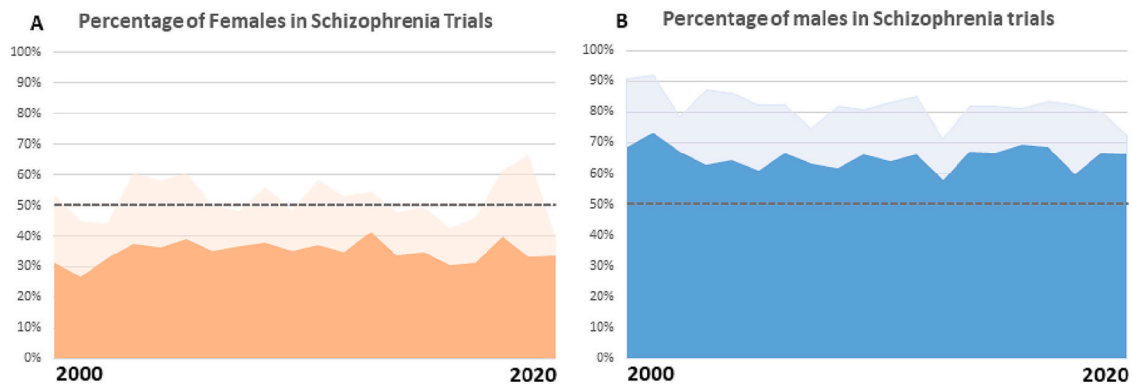


Fig. 6. Percentage of Females and Males subjects in Schizophrenia's Trials. Plot of average and Standard Deviation percentages of Females (A) and Males (B) subjects per year enrolled in Clinical Trials for Schizophrenia between 2000 and 2020. For Schizophrenia, the percentage of males involved in trials is higher than the percentage of females. The dotted line shows 50% of patients enrolled for each sex.

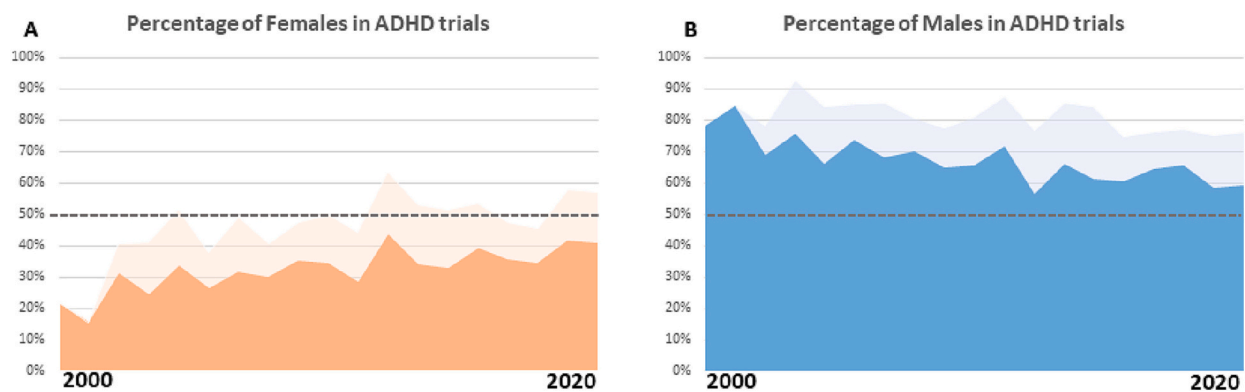


Fig. 7. Percentage of Females and Males Subjects in ADHD Trials. Plot of average and Standard Deviation percentages of Females (A) and Males (B) subjects per year enrolled in Clinical Trials for ADHD between 2000 and 2020. For ADHD, the percentage of males involved in trials is higher than the percentage of females. The dotted line shows 50% of patients enrolled for each sex.

ALS (Vivekananda et al., 2011; Trojsi et al., 2020).

A study carried out in Austria by (Cetin et al., 2015), indicated that Riluzole improved survival by 6 months in both males and females with ALS (Table 3). Edaravone is the only other mainstream pharmacological treatment used in ALS, it was approved by the Food and Drug Administration in 2017 and so far, the research into sex differences in efficacy of the drug have been limited to primarily studies on mice. Furthermore, this study was only done on females and therefore, cannot evaluate properly the effects in both males and females (Cetin et al., 2015).

As described, some sex differences have been identified in ALS, however the methodologies used in most of these studies limit the adequacy of the data. While many studies have been done over the last few decades on how sex can impact the onset, progression and treatment of ALS, a large proportion of these have only been done on mice, so do not accurately represent the condition in humans. Of the studies done in mice, most have been done on either males or females exclusively. In 2016, The NIH established sex as a biological variable for ALS (Vegeto et al., 2020). Prior to this year, most studies were performed on males as they are more susceptible to ALS, a better model to study and may develop more severe symptoms (Vegeto et al., 2020). Therefore, the sex-differences in ALS remain to be determined, however, clinical trials in the last 20 years show a clear prevalence of studies in males (Fig. 4), suggesting that the effects of treatment in females is less known (Fig. 4).

5.4. Depression: Sex-dependent presentation and response to treatment

MDD is the most prevalent psychiatric disorder and a leading cause of both mortality and morbidity worldwide (LeGates et al., 2019).

Females have an increased risk of depression due to sex hormones and sociocultural factors (Table 1). Low concentrations of estradiol stimulate the production of pro-inflammatory cytokines such as Interleukin (IL-1), IL-6, Tumour necrosis factor- α , whereas high levels inhibit their production. Progesterone and testosterone mostly have anti-inflammatory effects by reducing the amount of IL-1 β and Tumour necrosis factor production, and natural killer cell activity respectively (Slavich and Sacher, 2019).

As estrogen and progesterone levels fluctuate to a great extent such as during female puberty, postpartum, and menopause, evidence seems to suggest females are at increased risk of depressive episodes during these periods of hormonal transition (Frokjaer, 2020). Thus, before puberty, prevalence of mood and anxiety disorders is similar between male and female children, however the sex ratio diverges at adolescence with females having higher rates throughout their adult life. The increased rate of depression in females compared to males is directly proportional to the development of female reproductive function during puberty (Angold et al., 1998).

Other possible explanations for sex differences in prevalence include a female's increased likelihood to report symptoms and avail of medical services, whereas sociocultural factors possibly lead to reduced reporting of symptoms in males. For example, depressed males may mask their emotions and appear more aggressive or angry as opposed to sad, which may cause low mood to go unrecognized (Ladwig et al., 2000).

Apart from postpartum depression, which only affects females and is treated with allopregnanolone, depression is observed in both males and females. There is still very little evidence on sex-related differences in efficacy of antidepressant drug treatments, despite all the research on

the topic over the previous decades.

Sramek and colleague (Sramek et al., 2016)'s review of sex differences in the pharmacological treatment for depression concluded that the most common finding (eleven studies) found that there were no sex differences with regards to the efficacy of antidepressants. When analysing more specific treatment types, Tricyclic antidepressants (TCA) have been more effective in males, whereas females have responded better to Selective serotonin re-take inhibitor (SSRI) pharmacotherapy (Table 3) (Haykal and Akiskal, 1999; Khan et al., 2005; Kornstein et al., 2000; Sramek et al., 2016). However, Gougoulaki et al. (2021) found that there was no sex difference in response to SSRIs. Possible mechanisms underlying sex differences include differences in synaptic transmission, hippocampus, prefrontal cortex, nucleus accumbens, and pharmacokinetics. All studies which used serotonin-norepinephrine reuptake inhibitors such as venlafaxine and desvenlafaxine were shown to have no sex differences in their efficacy (Entsuah et al., 2001). Additionally, when CBT was added to the antidepressant pharmacotherapy no sex differences were detected (Cuijpers et al., 2014).

In postmenopausal females, additional hormonal replacement therapy was required to experience a favourable response from SSRIs, suggesting female sex hormones have a significant role in therapeutic response to SSRIs (Huang et al., 2008). Estrogen has been subsequently shown to influence serotonin synthesis, serotonin receptor binding, and activity. Along with this estradiol treatment, other interventions have been able to augment the effect of antidepressants when co-administered. One example of this effect is where triiodothyronine was given to patients along with TCAs. It was shown to accelerate the antidepressant effects of the drug and was particularly pronounced in females. In a separate study, folic acid supplementation was found to increase the effectiveness of fluoxetine in females, most likely explained by differences in folate concentrations in plasma in female patients (Coppen and Bailey, 2000).

Ketamine is another drug that is used in treatment-resistant forms of depression for short-term benefit, and it has been seen to quickly alleviate suicidal thoughts. Wright and Kabbaj (2018) concluded that age, sex, and history of drug use did not contribute to ketamine's efficacy. However, a larger meta-analysis analysed the effects of patients at specific time intervals. At four and twenty-four hours after administration, no differences in response were seen between sexes, however at the seven-day interval, a larger proportion of the male subjects showed a greater effect. The findings are limited though, as there is no evidence for any long-term benefit and only one ketamine dose was tried (0.5 mg/kg/40 min intravenous infusion) (Wright and Kabbaj, 2018).

In ketamine antidepressant trials on rats, the use of a common dose is especially limiting given that female rats show a heightened sensitivity to ketamine than male rats in preclinical studies. It was found that with a single intraperitoneal infusion of ketamine, females respond better to lower doses of ketamine than males depending on their estrous cycle. Upon repeated infusions, it was found that ketamine maintains some antidepressant properties in males whereas it became pro-depressive in females (Wright and Kabbaj, 2018). Data from clinical trials in the last 20 years show a clear prevalence of females enrolled in the studies (Fig. 5).

5.4.1. Schizophrenia: Sex-dependent presentation and response to treatment

Schizophrenia is a common, severe neuropsychiatric disorder affecting approximately 1% of the world's population (McCutcheon et al., 2020). Demographics are summarized in Table 1, however, it is essential to highlight that males experience a single peak age of onset from ages 21–25 while females experience two peaks: one between ages 25–30 and another smaller peak after 45 years of age (Li et al., 2016).

Schizophrenia is a complex disorder with many factors contributing to its onset and progression. Estrogen has been proposed to be protective in females, offering neuroleptic effects that make females less susceptible to develop psychosis than males (Cechnicki et al., 2018). In terms of

neuroanatomy, studies have revealed greater reductions in total brain volume in males than females with schizophrenia, and consistent with this morphology, males present with more cognitive deficits than females (Mendrek and Mancini-Marie, 2016). When further considering symptomatology, females with schizophrenia present with less severe negative symptoms than males and exhibit more positive and affective symptoms, however, are assigned an overall better prognosis compared to males who experience a worse course of illness and outcome (Gogos et al., 2015).

Psychotic episodes in females with schizophrenia occur more frequently during periods of estrogen withdrawal; during the menstrual phase of the menstrual cycle, post-partum, or post-menopause (Brzezinski-Sinai and Brzezinski, 2020). Conversely, improvements in symptomatology, function and therapeutic response in female humans are seen during high-estrogen phases (Kulkarni et al., 2012). The “estrogen hypothesis” therefore denotes the neuroprotective effects of estrogen evident in schizophrenia (Kulkarni et al., 2019). In males, the earlier onset and greater severity of schizophrenia may therefore be partially explained by this estrogen hypothesis, or in other words in males, the lack thereof. Moreover, in males, testosterone is converted to estrogen in the brain and some studies have exhibited that testosterone is significantly lower in males with schizophrenia; these lower testosterone levels correlate with more severe negative symptoms (Kulkarni et al., 2013). The estrogen hypothesis therefore stands out as a clear next step to investigate in male and female schizophrenia patients—both in terms of further understanding disorder progression and for potential new treatments.

The existing body of research and data on the complete course of schizophrenia in males and females is insufficient to make clear recommendations for diagnosis and treatment in male versus female sex (Sommer et al., 2020). In general, the dimorphic nature of human schizophrenia in males and females defined thus far suggests a need to better identify differences of the disorder in *both* sexes on which to base treatment (Gogos et al., 2015). However, there is an overall lack of studies that include either males or females and those that include both sexes are underpowered (Hill, 2016).

Results from the European First Episode Schizophrenia Trial evaluated sex differences in the treatment response and decrease of psychopathology to first- and second-generation antipsychotics used in schizophrenia patients (Table 3). Of all antipsychotics tested, olanzapine (second-generation) was the only one that showed significantly greater improvement in total PANSS score in females. Moreover, it was concluded that the change of psychopathology, especially positive and total symptoms, from baseline was significantly higher in females than males at the follow-up period (Ceskova et al., 2015).

Generally, animal models of schizophrenia are highly sensitive to fluctuation of sex hormones (Kokras and Dalla, 2014). Estrogen and selective estrogen receptor modulators (SERMs) trialled in animal models demonstrate neuroprotective effects (Brzezinski-Sinai and Brzezinski, 2020; Cersosimo and Benarroch, 2015; Kulkarni et al., 2019). Estrogen, particularly 17 β -estradiol, exerts genomic and non-genomic effects in the central nervous system through estrogen receptors that influence neuronal development, dendritogenesis, synaptic plasticity and neuronal excitability, with an overall role in neuroprotection (Brzezinski-Sinai and Brzezinski, 2020). As such, the use of sex hormones and SERMs for treatment of schizophrenia presents a relevant potential therapy (Hill, 2016). Therapeutic uses of estrogen in schizophrenia are generally underexplored, even amongst females. Due to estrogen's proposed roles in neurogenesis and plasticity, and evidence of these effects within regions like the hippocampus and prefrontal cortex, estrogen may support and improve preservation of memory and attention (Weickert et al., 2015). This is especially relevant in schizophrenia because memory and attention are facets of cognition. Cognitive impairment is a highly debilitating cardinal feature of the disorder that remains largely unresponsive to current antipsychotic treatment.

The clinical application of estrogen treatment in humans with

schizophrenia is however controversial—side effects like breast and uterine cancers are hugely consequential risks for females as is feminization in males (Kulkarni et al., 2012). SERMs offer a potential route around these side effects. One such agent, raloxifene, approved for osteoporosis treatment in postmenopausal females and breast cancer treatment in females, was shown to act as an estrogen receptor agonist in the brain (Weickert et al., 2015). Weickert et al. (2015) demonstrated for the first time that both males and females receiving adjunctive raloxifene and antipsychotics showed significant improvement relative to placebo in memory and attention/processing speed. Furthermore, a meta-analysis provided an overview of the efficacy of raloxifene as augmentation therapy to antipsychotic medication in schizophrenia, finding significant positive effects on total symptom severity (de Boer et al., 2018.)

Despite the evidence that hormone levels correlate with symptoms of schizophrenia, there is still the need to clarify the differences between males and females in schizophrenia. The major lack in the studies so far being the limited number of subjects involved in the studies and the necessity of representing both sexes equally. The estrogen hypothesis surrounding schizophrenia development and progression outlines the utmost importance of considering sex in further research. Clinical trials in the last 20 years show a clear prevalence of studies in males (Fig. 6), further highlighting the need for clinical trials representing both sexes equally.

5.4.2. Attention deficit hyperactivity disorder: Sex-dependent presentation and response to treatment

ADHD is a common neurodevelopmental psychiatric disorder. Typically beginning in childhood, ADHD affects approximately 5% of children worldwide (Polanczyk et al., 2007). Overall, ADHD demonstrates a strong male-bias (Pinares-Garcia et al., 2018). A recent nationwide cohort study in Denmark reported that 5.9% of male children compared to 3.04% of female children were diagnosed with ADHD before reaching the age of 18 (Dalsgaard et al., 2020).

ADHD has primarily been studied in male children (Loyer Carbonneau et al., 2020). It is hypothesized that male children show higher levels of hyperactivity and impulsivity compared to female children who display more inattentive symptoms. Because of this, females demonstrate less disruptive behaviour, potentially leading them to be less frequently diagnosed (Merikangas & Almas, 2020). Neuroimaging research reveals that female children reach maturation in most functional regions indicated by peak cortical thickness 2–5 years earlier than male children (Lenroot et al., 2007). It is suggested that these differing patterns of cortical maturation contribute to the dimorphic manifestation of motor and executive function and differential effects of risk genes in children with ADHD (Mahone and Denckla, 2017). Overall, the sex differences in prevalence observed for ADHD are likely the result of a combination of diagnostic bias as well as true biological differences between the sexes. Differential developmental timing and trajectory derived from biological sex coinciding with individual genetic risk and environmental influences presents a much more complicated picture of disease progression. This suggests the need for improved diagnostic criteria that could potentially capture cohorts of pediatric patients based in part on sex.

The differing patterns of disorder manifestation become increasingly important when considering the psychosocial outcomes for patients. Males are more likely to have higher ADHD symptom scores and may have a tendency toward aggression, criminality, and other externalizing behaviours (Arnett et al., 2015). Conversely, females with ADHD are at an increased risk for comorbid eating and anxiety disorders (Biederman et al., 2002; Davies, 2014). Additionally, past literature presumed that female children with ADHD had better adolescent and adult outcomes than their male counterparts however large-scale longitudinal studies indicate females demonstrate persistent executive dysfunction, mood disorders and severe behavioural problems into adulthood (Mahone and Denckla, 2017).

Given the suggested diagnostic bias for ADHD, the sex-based differences in individual risk and brain development, and the different early- and later-life disorder manifestations between males and females with ADHD, investigative research and treatment regimens should consider sexual dimorphism within ADHD. Currently, pediatric patients treated with first-line medication show improvement in inattention, hyperactivity, and impulsivity (Southammakosane and Schmitz, 2015). However, generally females are not well represented in clinical trials to begin with (Bale, 2019). More robust evidence directed toward both disease progression and treatment response amongst males and females should be investigated given the indisputable differences in males and females with ADHD.

At present, there is limited research on how the treatments that are currently available affect males and females differently in ADHD. However, the data that is available indicates that there is little difference, if any, in the response of males and females to the most common treatments for ADHD.

The most frequently used drug in the treatment of ADHD is methylphenidate (MPH), a stimulant medication (Table 3) (Sonuga-Barke et al., 2007). A study by Sonuga-Barke et al. (2007) on children aged 6–12 years old with a confirmed diagnosis of ADHD found that the only significant difference in response to MPH between males and females was an increase in comorbid anxiety disorder. It was observed however, that in comparison to males, females had a superior response at 1.5 h post-dose, but an inferior response at 12 h post-dose. These results led the authors to conclude that the dose titration of MPH administered once a day should consider these differing responses (Sonuga-Barke et al., 2007). To date this study has not been replicated. Further studies need to be done to determine a more accurate optimal dose for females to avoid the up and down response hours after dosing.

Another study from Rucklidge and colleagues also showed no significant difference between males and females in response to MPH (Rucklidge, 2008). In addition, they also did not find a difference in response between children and adults, a significant and interesting finding considering the change in hormone levels during puberty and during menopause in females. Interestingly, a study by Justice and de Wit (2000) showed that a response to stimulants is enhanced by estragon, but oppositely is dampened by progesterone (Justice and de Wit, 2000).

Although pharmacological management strategies and parental psychoeducation (Thapar and Cooper, 2016) can be useful to control the symptoms of ADHD, a one-size-fits-all approach to treatment does not exist and this caveat becomes critically evident when considering the sexual dimorphism that exists in the clinical manifestation of ADHD.

Animal models are quite common when studying human diseases and disorders, especially mice and rats. They offer a large sample size and are biologically similar enough to provide some insight into how a method of diagnosis or treatment might translate into human studies. Rucklidge reviewed a study examining rat models of ADHD that were spontaneously hypertensive rates (SHRs) (Rucklidge, 2008). The authors indicated that, if it's assumed that male SHR rats are equivalent to human males with the hyperactive/impulsive subtype of ADHD, and the female SHR rats are equivalent to human females with the inattentive subtype of ADHD, then their results could be extrapolated to humans. When examining behavioural characteristics, the study indicated that the male SHR behaviour could be due to a shorter than normal delay-of-reinforcement gradient or altered reinforcement mechanism. In contrast, they suggested the behaviour of female SHRs correlates more with attention-deficit. Linking these results to humans, the suggestion is that males with ADHD may benefit more with immediate rewards, increased reinforcement, and a higher emphasis placed on behavioural modification. Data from clinical trials in the last 20 years show a clear prevalence of males enrolled in the studies (Fig. 7) with ADHD having the largest disparity between sex prevalence in trials out of all the neurodegenerative and neuropsychiatric disorders that are highlighted in this review.

5.4.3. Looking ahead: How to assure a proper sex-dependent stratification in future studies

Considering sex as biological variable is central to the efforts made by the scientific community in defining quantifiable parameters to better understand and classify brain disorders, and in particular psychiatric conditions (Morris et al., 2022). Indeed, the quest for a new approach to diagnosis and classification of psychiatric disorders includes the dissection of the heterogeneity present in these disorders, and the quantification of the biological parameters that influence the processes regulating the mind-body connection. In this context, the pillars described by Morris and colleagues suggest that to advance the research in neurological and psychiatric disorders the biological sex should be considered in both preclinical and clinical trials, and in the most recent approaches, such as data science, AI, and computational psychiatry.

However, to date, studies report a higher percentage of male animals used in the preclinical trials (Bale, 2019), and this imbalance in sexes hinders our understanding of any sex specific differences in the efficacy of the drugs. Future preclinical trials must include both male and female animals so that sex specific differences can be accounted for at the beginning of drug trials. Additionally, sex-specific factors such as hormone concentration, and phases of sexual development (menstruation or menopause) should be considered in the analysis of the results.

In pre-clinical studies, scientists can now use Induced Pluripotent Stem Cells (iPSCs), a model where cells derived from patients are modified to generate brain cells with the same genetic background of the patients of origin. iPSCs promise to uncover endophenotypes related to disease presentation (Vadodaria et al., 2020) and have applications in personalized medicine and translational research. Probably because of its cellular nature, the effects of the sex variable has not been explored for this model, although it cannot be excluded that cellular-based phenomena dependent on sex may influence the preparation (Dandulakis et al., 2016).

Regarding clinical studies, policies and regulations to incorporate sex-based and gender-based analysis into scientific research are in place in Canada (Health Canada, 2023), USA (NIH website, 2015) and Europe (European Union website, 2020). Despite these recommendations, for the majority of the disorders the number of individuals of each sex is unbalanced, and there has been an unchanging male-female ratio for patients recruited since 2014 (Moore et al., 2023). Apart from AD, for the other disorders considered in this review, there is a tendency to reinforce the trend of the predominant sex orientation when recruiting participants in clinical trials. This tendency is true in both neurodegenerative and psychiatric disorders. While it is natural to enrol more patients in the predominant sex, there is a need to oversample the underrepresented gender in clinical trials for disorders that have sex bias, to ensure that the studies are adequately powered to conduct sex stratified analysis.

Another aspect that should be considered in planning the studies is the symptoms presentation over time and the long-term effect of medication in different sexes. The diseases discussed in this review all display different time courses, symptoms, and prevalence depending on sex and age. Thus, it is essential that future studies analyse patients over a long period of time to fully understand disease development and progression. A longitudinal study will be important to determine if drugs are more effective at different stages in disease, or in different sexes. Furthermore, a longitudinal study will allow for potential risk factors that contribute to disease progression and severity to be accounted for. Differences between sexes must be considered, as sensitivity to sex will likely reveal more about a disease already understood to be dimorphic.

Research must consider sex-specific differences, such as differences in the size of specific brain regions. This could be the case of brain imaging techniques measuring rates of atrophy and degeneration in the brain. Identifying the specific brain regions affected would allow for the treatment to be more specific and personalized for the patient and, thus, result in better treatment outcomes.

Furthermore, it is essential to understand the underlying

mechanisms that cause males and females to respond differently to clinical interventions. Studies need to determine if it is either the drug's pharmacodynamics or pharmacokinetics that is the source for differing treatment efficacy. These effects could be due to change in metabolic rates between males and females, or to differences in primary sex hormones.

Overall, understanding the impact that sexual dimorphism presents on clinical trials and drug treatment may contribute to more successful and personalized treatment options.

Authors' contributions

AA - Introduction, Results, Parkinson's Disease, Attention Deficit Hyperactivity Disorder, Depression, Conclusion, Tables.

MD - Introduction, Results, Alzheimer's Disease, Amyotrophic Lateral Sclerosis, Depression, Conclusion, Graphs, Tables.

KS - Introduction, Results, Schizophrenia, Attention Deficit Hyperactivity Disorder, Depression, Conclusion.

ES - Data search and part of Results.

YB - Data Search and part of Methods.

DT - Ideation of the manuscript, general supervision, contribution to manuscript preparation and editing (all sessions), figures.

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Declaration of Competing Interest

The authors declare no conflict of interest and no use of AI in the generation of this manuscript.

Data availability

Data will be made available on request.

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