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Sexual Dimorphism in Levodopa-Induced Dyskinesia Following Parkinson's Disease: Uncharted Territory

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ABSTRACT

Sexual dimorphism is well-documented in Parkinson's disease (PD); however, when it comes to levodopa-induced dyskinesia (LID), epidemiological and clinical findings are scarce. This is an oversight because recent studies show significant correlations between LID risk and female sex. Estrogen strongly impacts neuronal function, affecting cognitive tasks such as movement, object recognition, and reward. In movement pathways, estrogen increases dopamine synthesis, transmission, and regulation, resulting in neuroprotection for PD in women. However, following menopause, PD prevalence, symptom severity, and LID risk increase for women. Consequently, early to mid-life estrogen state is neuroprotective, but later in life becomes a risk factor for PD and LID. This review explores estrogen's action in the brain, specifically within the dopamine system. Sexual dimorphism is described for the prevalence and onset of PD and LID. We examine the cellular basis of estrogen's role in sexual dimorphism and integrate these ideas to hypothesize why the risk for LID is higher for women, than men, with PD. Lastly, this review proposes that women with PD need their symptoms to be considered and managed differently to males. Treatment of women with PD should be based on their menopausal stage, as estrogen may be masking, exacerbating, or complicating symptoms. Importantly, we present these concepts to stimulate discussion among clinical and bench scientists so that key experiments can be conducted to examine the mechanisms underlying LID, so they can be prevented to improve the quality of life for women and men living with PD in the future.

1 | Levodopa-Induced Dyskinesia (LID)

The current gold standard treatment for Parkinson's disease (PD) is the oral administration of l-3,4-dihydroxyphenylalanine (levodopa), which decreases all motor symptoms (Bogetofte et al. 2020; Cilia et al. 2020; Fox et al. 2011; Goetz et al. 2005). However, a major paradox in PD treatment is that prolonged use results in side effects named LID (Cenci and Crossman 2018; Dauer and Przedborski 2003; Gupta et al. 2019). LID is defined as excessive, uncontrollable movements that result from large fluctuations of dopamine (DA) in the brain, which cause pathological network patterns in motor pathways (Fahn 2000; Girasole et al. 2018; Ryan et al. 2018, 2024). LID symptoms include chorea, ballism, akathisia, dystonia, or other abnormal

Abbreviations: 6-OHDA, 6-hydroxydopamine; AADC, aromatic L-amino acid decarboxylase; BG, basal ganglia; CBF, cerebral blood flow; CNS, central nervous system; D1, dopamine receptor 1; D2, dopamine receptor 2; DA, dopamine; DAT, dopamine transporter; E1, estrone; E2, estradiol; E3, estriol; ERs, estrogen receptors; ERα, estrogen receptor alpha; ERβ, estrogen receptor beta; GABA, gamma-aminobutyric acid; GDNF, glial cell line-derived neurotrophic factor; GPER1, G-coupled protein estrogen receptor 1; H:L, high:low; LID, levodopa-induced dyskinesia; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; PD, Parkinson's disease; SPN, spiny projection neuron; TH, tyrosine hydroxylase; TNFα, tumor necrosis factor alpha; VMAT, vesicular monoamine transporter.

movements (Baizabal-Carvallo and Cardoso 2020; Balint et al. 2018; Bastide et al. 2015; Fabbrini et al. 2007; Lohr et al. 2015). LID occurs in approximately 40%–50% of PD patients after 5 years (Ahlskog and Muenter 2001; Holloway et al. 2004; Rascol et al. 2000) and 50%–80% after 10 years (Hauser et al. 2007; López et al. 2010), indicating that most patients will develop LID. Following LID onset, quality of life is significantly decreased with limited treatments available to reduce this drug-induced side effect. Patients face a relentless cycle of alternating between parkinsonian symptoms and dyskinesia because discontinuing levodopa is not a viable option due to akinetic and rigid PD symptom resurgence (Yang et al. 2021). Research has focused on network (Girasole et al. 2018; Parker et al. 2018; Ryan et al. 2018, 2024) and cellular (Bove et al. 2023; Cenci 2014; Cenci et al. 2018; Hansen et al. 2022; Kwon et al. 2022; Scarduzio et al. 2022) mechanisms within brain movement networks that underlie LID. However, little research has investigated sex-based differences in the onset, progression, and severity of LID symptoms.

In today's multigendered societal structure, it is essential to use clear definitions when discussing sexual dimorphism. Whenever animal and/or human studies are mentioned, male and female will be the terms used based on the sex determined at birth, along with the corresponding circulating sex hormones. We acknowledge that this binary classification does not include all genders of individuals with PD. Further research needs to be done looking at the experiences of PD for sex and gender minorities. However, we aim to clarify sex-based PD risk factors and treatment strategies to stimulate discussion and further research.

2 | Sexual Dimorphism in PD

Significant risk factors for PD are age (Ball et al. 2019; Pang et al. 2019), pesticide use (Hubble et al. 1993; Shrestha et al. 2020), specific genetic mutations (Billingsley et al. 2018; Cherian and Divya 2020), traumatic brain injury (Ascherio and Schwarzschild 2016; Delic et al. 2020), and male sex (Cerri et al. 2019; Hayes 2019). Sexual dimorphism within PD is well-documented (for further reading, see Cerri et al. 2019; Picillo et al. 2017). Male sex is a major risk factor in developing PD, with male incidence rates 1.4 to 3.7 times female rates (Baldereschi et al. 2000; Elbaz et al. 2002; Shulman and Bhat 2006; Swerdlow et al. 2001; Taylor et al. 2007; Van Den Eeden et al. 2003; Wooten et al. 2004) across all nationalities studied. This sexual dimorphism is proposed to be due to estrogen because following menopause, and the associated decrease in endogenous estrogen production, female parkinsonian incidence increases to male levels (Ragonese et al. 2004).

There are also sex differences in the clinical presentation of PD (Cerri et al. 2019). On average, the onset of PD symptoms in males is slower than in females (Alves et al. 2009; Haaxma et al. 2007). Although women often present with milder PD symptoms in the early stages (Haaxma et al. 2007; Miller and Cronin-Golomb 2010; Shulman and Bhat 2006), women have a faster rate of disease progression, a lower quality of life with PD, and a higher mortality rate (Dahodwala et al. 2018; Georgiev et al. 2017). Women also more commonly experience tremors early (Haaxma et al. 2007), develop postural instability or rigidity (Baba et al. 2005), and have increased pain severity (Silverdale et al. 2018). In contrast, males with PD have higher rates of drooling and develop freezing of gait later (Kim et al. 2018). Males also have higher rates of camptocormia, the severe forward flexion of the trunk that occurs while upright but disappears in a supine position (Ou et al. 2018). This is important to consider as camptocormia has been linked to an increased risk of comorbidities such as deep vein thrombosis in the legs (Yamane et al. 2013). Interestingly, the higher expression of camptocormia in men could relate to greater muscle weakness in females (Phillips et al. 1993) or the higher center of gravity in males (Armenti and Adair 1992). Overall, these sex-based differences in clinical symptoms are hypothesized to relate to the different effects estrogen has in male and female brains (Bovenzi, Conti, Simonetta, et al. 2024; Jurado-Coronel et al. 2018; Lee et al. 2019; Song et al. 2020).

3 | Estrogen

Estrogen is the primary female sex hormone. Estrogen is involved in numerous physiological functions, including reproduction (Uenoyama et al. 2021), vascular (Williams et al. 2020), skeletal (Ikeda et al. 2019), and cognitive functions (Brann et al. 2022; Luine and Frankfurt 2020; Russell et al. 2019) in both males and females. There are three estrogens in circulation: estrone (E1), estradiol (E2), and estriol (E3; for further reading, see Fuentes and Silveyra 2019). E2 is the most abundant naturally occurring estrogen (Gillies et al. 2014; Russell et al. 2019) and is, therefore, the focus of the current review. Estrogen is secreted from the ovaries during the female reproductive cycle. Estrogen can also be synthesized from testosterone and androgens in peripheral tissues such as the brain, muscle, liver, and adipose tissue by the enzyme aromatase (Ishikawa et al. 2006).

Estrogen acts through three identified estrogen receptors (ERs)—estrogen receptor α (ERα), estrogen receptor β (ERβ), and the G-protein coupled estrogen receptor 1 (GPER1) (Bourque et al. 2009; Chen et al. 2022; Fuentes and Silveyra 2019; Maioli et al. 2021). However, more ERs will likely be discovered in the future (Qiu et al. 2003, 2008; Smith et al. 2013). GPER1 is found in the cell membrane, while ERα/ERβ are located in the nucleus and cytoplasm (Almey et al. 2015; Rosenfeld and Cooke 2019). Due to this, estrogen has actions over both short and long (> 10 h) time courses (Fuentes and Silveyra 2019; Kelly et al. 1976, 1980; Kelly and Wagner 1999). Estrogen's short-term nongenomic effects arise by binding to the GPER1 receptor and subsequent activation of second messenger cascades (Fuentes and Silveyra 2019; Niță et al. 2021), which include protein kinase C (Marino et al. 1998), mitogen-activated protein kinase (Edwards and Boonyaratanakornkit 2003; Fu and Simoncini 2008; Watters et al. 1997; Wong and Moss 1992; Yang et al. 2008), phosphatidyl inositol 3 kinase (Marino et al. 1998, 2003), and protein kinase A pathways (Picotto et al. 1996). These second messenger cascades ultimately change membrane permeability and increase receptor expression (Fuentes and Silveyra 2019). Long-term estrogen-induced changes result from estrogen crossing the cell membrane and binding with ERα/ERβ receptors. Here, nuclear ERα/ERβ

receptors act as transcription factors (Marino et al. 2006), where estrogen binds to these receptors in the cytoplasm, the receptors dimerize, and the dimerized complex is translocated to the nucleus (Le Dily and Beato 2018). Once in the nucleus, the complex binds to specific DNA sequences called estrogen response elements (Klinge 2001) and subsequently changes gene expression (Kiess and Gallaher 1998; Kovacs et al. 2002; Varea et al. 2010; Vasconsuelo et al. 2011; Woolley 1999). ERs can also be activated in the absence of estrogen via phosphorylation of receptors or by co-regulator partner proteins (Onate et al. 1995). In addition to estrogen binding to its receptors, estrogen can also modulate functions by indirect mechanisms, such as prolactin secretion (Di Paolo, Poyet, and Labrie 1982a, 1982b; Hruska, Pitman, et al. 1982) and DA receptor sensitivity via its catecholic metabolite 2-hydroxyestrogen (Clopton and Gordon 1985), which occur hours to days after estrogen's initial effects. These multifactorial actions over short- and long-time courses, and direct or indirect actions make it difficult to investigate estrogen's effects on basal ganglia (BG) circuitry.

Estrogen secretion and ER expression are high in the first year of life, then levels decrease until puberty (Figure 1A) (Yu et al. 2022). Following puberty, estrogen secretion remains high until menopause (Figure 1A), fluctuating between 30 and 400 pg/mL throughout each menstrual cycle (Bennink 2004). Within the 28-day menstrual cycle, estrogen peaks in the follicular phase and at ovulation, then drops in the luteal and menstrual phases (Figure 1B). Progesterone peaks are similar but with delayed timing (Sherman and Korenman 1975). The corresponding cycle in adult female rodents is called the estrous cycle (Figure 1C), which has phases similar to the menstrual cycle, but over a 4–5-day period (Ajayi and Akhigbe 2020).

Preceding menopause, there is a perimenopausal period over several years where large fluctuations in circulating estrogen occur (Figure 1A). This is characterized by side effects such as hot flushes, sleep disturbances, altered mood, and irregular menstruation cycles (Delamater and Santoro 2018). Following menopause, estrogen levels fall to nonclinical circulating levels (approximately 5–20 pg/mL; Bennink 2004), and women become infertile. Menopause is associated with an increased risk of neurodegenerative disorders, heart disease, osteoporosis, and depression (Dalal and Agarwal 2015; Jamshed et al. 2014; Marras and Saunders-Pullman 2014; Nappi et al. 1999; Prabakaran et al. 2021).

Estrogen is also important for male health. Normal estrogen levels in males are significantly lower, similar to postmenopausal females (approximately 10–50 pg/mL; Hess 2003), while testosterone is high (300–1000 ng/dL; Dhindsa et al. 2010). In males, estrogen does not cycle, and the testes produce only approximately 20% of circulating estrogen. Instead, the bulk of estrogen is produced by aromatase converting testosterone to estrogen in adipose tissue, the brain, and musculoskeletal tissue (Vermeulen et al. 2002). Estrogen's function in males includes maintaining bone strength, muscle mass, metabolism, and cardiovascular function (Cooke et al. 2017; Hammes and Levin 2019; Russell and Grossmann 2019). ERs are expressed in tissues throughout the body in males, similar to females (Hutson et al. 2019). Importantly, there is a similar gross distribution of ERs in male and female brains, but subtle differences in expression levels and ER subtype exist (Almey et al. 2015) and underlie the sex-based differences in cognitive function and disease progression (Gillies and McArthur 2010) that are discussed below.

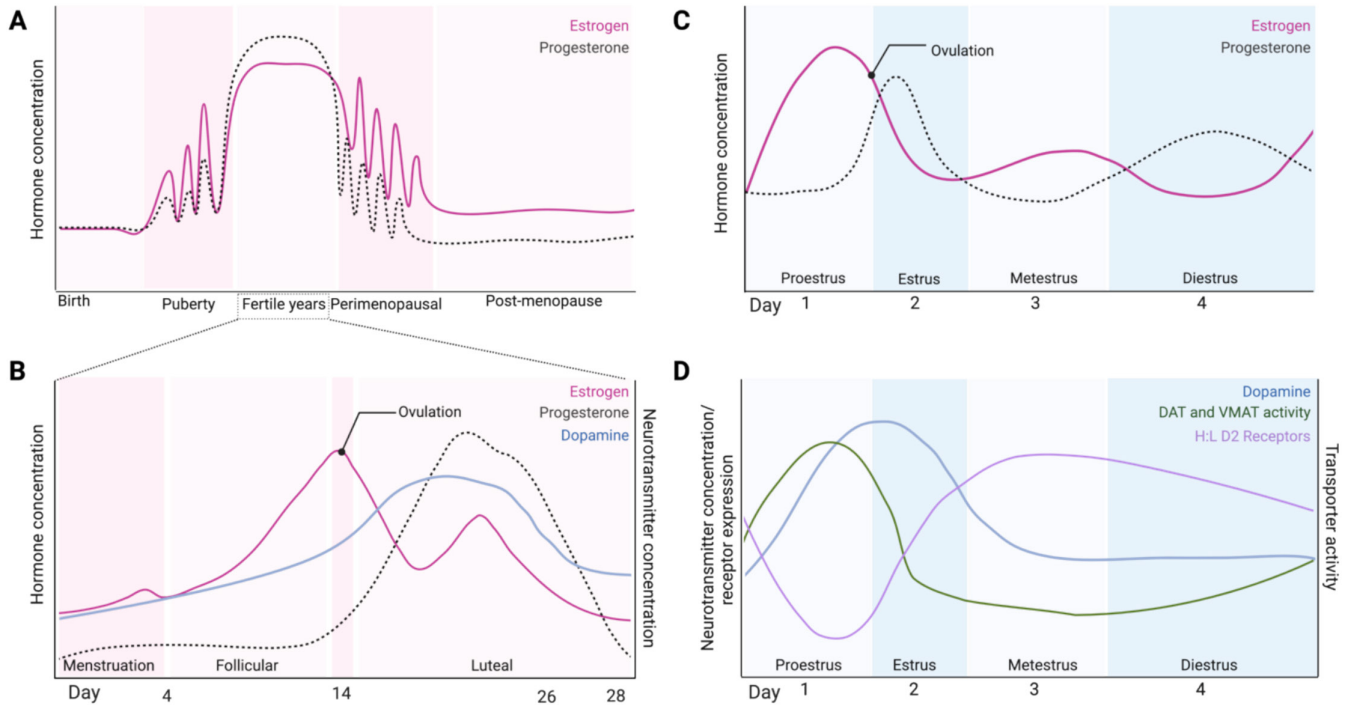

FIGURE 1 | Female hormone and neurotransmitter levels. Estrogen, progesterone and dopamine levels throughout the female lifespan (A), human menstrual (B) and rodent estrous (C) cycles, and DA transporter and receptor expression throughout the estrous cycle (D). DAT, dopamine transporter; H:L D2, high:low dopamine 2 receptor affinity ratio; VMAT, vesicular monoamine transport. Created with BioRender.com.

4 | ER Expression in the Brain

ERs were first characterized in breast and uterine tissues in 1966 (Toft and Gorski 1966). They have since been discovered in other tissues, such as the brain (Kuiper et al. 1997; Küppers and Beyer 1999; Maioli et al. 2021; Shughrue and Merchenthaler 2001; Shughrue et al. 1998), prostate (Dobbs et al. 2019; Lafront et al. 2020), testicles (Guercio et al. 2020), heart (Aryan et al. 2020; Ventura-Clapier et al. 2019), and lungs (Reyes-Garcia et al. 2021; Rollerova and Urbancikova 2000). ER expression is widespread in the brain (Kuiper et al. 1997; Küppers and Beyer 1999). High levels of expression are located in the striatum (Krentzel et al. 2021; Lewitus and Blackwell 2023), hypothalamus (Kuiper et al. 1998; Marraudino et al. 2021), hippocampus (Ma et al. 2020; Sheppard et al. 2019; Spencer et al. 2008), amygdala (Smiley et al. 2023), and the prefrontal cortex (Hill et al. 2009; Montague et al. 2008). Estrogen modulates many cognitive processes in these areas, including spatial learning (Gervais et al. 2013; Luine and Frankfurt 2020; Lymer et al. 2024; Patel et al. 2022), memory (Almey et al. 2014; Brann et al. 2021; Luine and Frankfurt 2020), and movement (Chidi-Ogbolu and Baar 2019; Lee et al. 2019). ERs are also critical for neuronal survival (Wang et al. 2001). Disrupted estrogen signalling is associated with cognitive function deficits such as object recognition, memory, and selective attention (Almey et al. 2015; Jacobs and D'Esposito 2011).

In the BG-thalamocortical motor pathway, ERs are expressed within and affect the signalling of many motor structures such as the striatum (Almey et al. 2015; Krentzel et al. 2021; Lewitus and Blackwell 2023), thalamus (Biegon 2016), and cortex (Varshney et al. 2020). Estrogen signalling deficiency affects neurotransmission within all structures and decreases movement production and quality. Due to the greater wealth of literature, the current review focuses on estrogen's effect on neurotransmission within the striatum; however, further research addressing other motor structures is warranted.

4.1 | ERs in the Striatum

Estrogen affects DA signalling in both the ventral and dorsal striatum (Figure 2A–D), resulting in sexual dimorphism in psychiatric diseases and movement disorders, respectively. The ventral striatum receives DA input from the ventral tegmental area (Edwards et al. 2017), which modulates functions such as motivation and reward (Berridge and Kringelbach 2013; Goschke and Bolte 2014). Here, DA signalling changes are linked to psychiatric diseases (Nakamura et al. 2020; Olivetti et al. 2020; Zhou et al. 2021). In the ventral striatum, all three ERs are expressed on or in DA terminals and local circuits (Almey et al. 2015; Creutz and Kritzer 2002, 2004). Estrogen directly modulates DA signalling and causes the strong sexual dimorphism of some psychiatric diseases (Figure 2C,D) (Zachry et al. 2021). Epidemiological studies agree that schizophrenia is higher in young men, while high estrogen in young women is protective (Mendrek and Stip 2011).

Conversely, in the dorsal striatum, ERs are not located on the terminals of DA neurons (Almey et al. 2012) but instead are on GABAergic spiny projection neurons (SPNs) that make up the *direct* and *indirect pathways* (Almey et al. 2012, 2015, 2016). SPNs are abundant in the striatum (~90% of all neurons) (Kawaguchi 1997) and project from the striatum to downstream motor nuclei to precisely control motor signals that underlie correct movement production (Nambu 2004; Nambu 2005, 2008). Dopaminergic neurons project to the dorsal striatum from the substantia nigra pars compacta (SNpc) (Speranza et al. 2021), where ERs have been found in the cell body of DA neurons in both male and female rats (Quesada et al. 2007; Ravizza et al. 2002). Due to the lack of ER expression on the DA terminals in the dorsal striatum, estrogen effects DA transmission by indirect mechanisms such as negative feedback from SPNs, or through changes in nuclear gene expression in SNpc DA neurons (Figure 2A,B). These direct and indirect mechanisms of estrogen actions on DA transmission will be discussed below.

5 | Estrogen Control of DA Transmission in the Striatum

This section describes how estrous cycle fluctuations in estrogen concentration affect DA transmission in the ventral and dorsal striatum. Figure 2 illustrates and summarizes previously reported direct and indirect estrogen effects. However, more complex interactions will exist, especially in the human caudate and putamen.

In the ventral striatum, estrogen directly enhances DA transmission through multiple actions: increasing synthesis and transmission (Almey et al. 2012, 2016; Kawaguchi 1997; Speranza et al. 2021; Watson et al. 2006), decreasing reuptake via the DA transporter (DAT) (Watson et al. 2006), and increasing binding to (Del Río et al. 2018; Landry et al. 2002) and expression of (Di Paolo, Poyet, and Labrie 1982a, 1982b; Hruska and Nowak 1988; Landry et al. 2002) postsynaptic DA receptors. These prodopaminergic actions can be increased by endogenous fluctuations in the menstrual cycle and exogenous estrogen administration following ovariectomy (Becker and Rudick 1999; Landry et al. 2002; Le Saux et al. 2006; Thompson 1999). Extracellular DA concentrations fluctuate within the striatum, delayed, but mirroring plasma fluctuations in estrogen concentrations during the menstrual cycle (Figure 1D) (Zachry et al. 2021). During proestrus/estrus, DA release increases (Figures 1D and 2C,D) (Calipari et al. 2017; Dluzen and McDermott 2008; Morissette et al. 1990), DAT and vesicular monoamine transport (VMAT) activity increase (Figures 1D and 2C,D) (Dluzen and McDermott 2008), and D2 autoreceptor activity decreases (Calipari et al. 2017) (Figure 2). These three mechanisms result in greater re-uptake, recycling, and control of DA transmission prior to and during ovulation or estrous.

Estrogen also modulates D2 receptor sensitivity. D2 receptors exist in high- and low-affinity states, which change in ratio during the estrous cycle without changing overall expression (Figure 1D). In proestrus/estrus, the H:L-affinity D2 receptors ratio is low, while ovariectomy increases the ratio of H:L-affinity D2 compared to intact females (Bazzett and Becker 1994; Clopton and Gordon 1986; Di Paolo et al. 1988). These could be compensatory mechanisms to regulate DA release throughout the menstrual cycle; however, D2 receptors are expressed

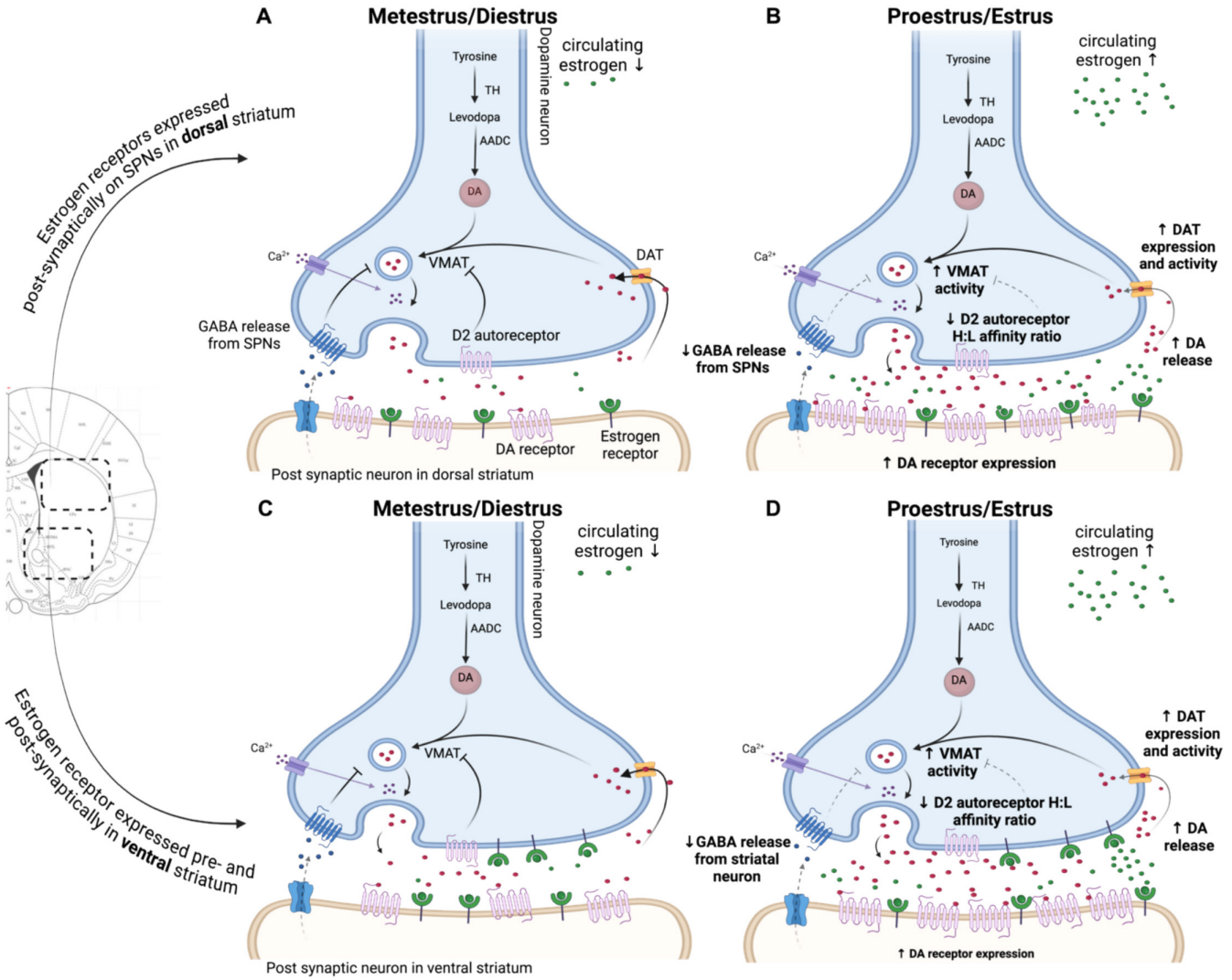

FIGURE 2 | Estrogen's modulation of DA synapses in dorsal and ventral striatum. Indirect estrogen effects in the dorsal (A, B) and ventral (C, D) striatum during metestrus/diestrus (A, C) and proestrus/estrus (B, D). (A) In the dorsal striatum, estrogen receptors are only expressed postsynaptically on spiny projection neurons (SPNs), and DA release is *indirectly* modulated by local GABA release. (B) When estrogen concentration is high in proestrus/estrus in the dorsal striatum, GABA release from SPNs decreases, and DA release increases. (C) Estrogen receptors in the ventral striatum are expressed presynaptically and postsynaptically, modulating DA release directly and indirectly. (D) During proestrus/estrus, DA release increases by increasing VMAT activity, decreasing DAT activity, decreasing DA autoreceptor activity, and decreasing local GABA release. *Note:* DA receptors are not divided into D1/D2 because that would require discussing direct or indirect pathways, respectively. Created with BioRender.com.

both postsynaptically and presynaptically as autoreceptors for negative feedback (Condon et al. 2021). Therefore, reduced D2 autoreceptor sensitivity could decrease negative feedback and increase DA release. Future research is needed to understand how estrogen-induced changes in H:L D2 receptor affinity alter DA transmission.

In the dorsal striatum, estrogen modulates DA transmission through indirect mechanisms via GABAergic neurons. ERs are found on the dendritic shaft of GABAergic SPNs (Lewitus and Blackwell 2023; Meitzen et al. 2018), closely associated with the postsynaptic receptor density (Almey et al. 2012). SPNs regulate DA release by local postsynaptic GABA that binds to $GABA_A$ (Brodnik et al. 2018; Ronken et al. 1993) or $GABA_B$ (Pitman et al. 2014) receptors at the DA neuron terminal, reducing DA release (Meitzen et al. 2018). Estrogen decreases this GABA control of DA release by decreasing spine density on SPNs (Hu et al. 2006; Mermelstein et al. 1996; Schultz et al. 2009) and decreasing GABA release from dendrites (Hu et al. 2006; Schultz et al. 2009) (reviewed by Yoest et al. 2018). Consequently, impaired GABAergic function increases DA release and stimulates DA signalling-dependent functions such as latent inhibition (Nofrey et al. 2008; Quinlan et al. 2010) and object recognition memory (Gervais et al. 2013; Jacome et al. 2010) during proestrus/estrus. This estrogen-induced indirect GABAergic modulation mechanism is not unique to the striatum because it has been reported in the hippocampus (Hart et al. 2001, 2007; Wójtowicz and Mozrzymas 2010) and hypothalamus (Blaustein et al. 1992; Qiu et al. 2003; Wagner et al. 2001).

Overall, estrogen increases DA transmission in the striatum through direct and indirect mechanisms depending on striatal location. In the dorsal striatum, ERs are expressed

postsynaptically on GABAergic SPNs, which decrease GABA release and indirectly increases DA release.

6 | Estrogen's Neuroprotective Mechanisms in PD

Sex hormones are the most important determinant in PD sexual dimorphism, particularly E2. Evidence to support this comes from epidemiological and clinical studies. Firstly, males have a higher prevalence of PD than premenopausal women; however, following menopause, this disparity is lost (Mayeux et al. 1992; Ragonese et al. 2004). Secondly, women who have had a bilateral ovariectomy before menopause have an increased risk of developing PD (Benedetti et al. 2001; Pesce et al. 2023; Ragonese et al. 2006; Rocca et al. 2008). Thirdly, estrogen replacement therapy decreases the risk of developing PD (Currie et al. 2004; Liu and Dluzen 2007; Pesce et al. 2023) and reduces PD symptoms if given early in the disease progression (Benedetti et al. 2001; Saunders-Pullman et al. 1999; Tsang et al. 2000). Fourthly, premenopausal women with PD report significantly worse motor symptoms in menstrual stages where estrogen is low (Castrioto et al. 2010; Horstink et al. 2003; Jurado-Coronel et al. 2018; Quinn and Marsden 1986; Sandyk 1989). Fifthly, women develop PD later than men (Smith and Dahodwala 2014), and there is a relationship between longer fertile years/later menopause age and decreased risk of PD (Pesce et al. 2023; Ragonese et al. 2004). Lastly, women respond better to levodopa treatment when it is co-administered with transdermal E2 (Blanchet et al. 1999). Estrogen's proposed neuroprotective effects for PD include: (1) maintaining normal DA neuron density and function, (2) activation of neuroprotective downstream pathways, (3) production of neurotrophic growth factors, (4) maintaining mitochondrial function, and (5) decreasing CNS inflammation, which are discussed below.

Estrogen is hypothesized to have an impact on neuron density and function. Females have greater DA neuron density in the substantia nigra than age-matched males (Beyer et al. 1991; Vaidya et al. 2021). When estrogen is removed following ovariectomy, DA neuron numbers decrease by up to 30% in the female brain (Dean and Gogos 2021; Elnoury 2019; Leranth et al. 2000). Additionally, sexual dimorphisms have been identified in DA neuron function (Garrido-Gil et al. 2021; Kim and Park 2022; Simunovic et al. 2010). Genes involved in mitochondrial function and cellular homeostasis have different expression patterns in healthy males compared to age-matched females (Demarest and McCarthy 2015; Di Florio et al. 2020; López-Cerdán et al. 2022; Simunovic et al. 2010). These genes are associated with metabolic processes, oxidative phosphorylation, mitochondrial energy consumption, and synaptic transmission and are hypothesized to increase cellular aging and DA neuron death in males (Simunovic et al. 2010).

Estrogen activates downstream neuroprotective pathways including the mitogen-activated protein kinase (Bryant et al. 2006; Dhandapani and Brann 2002; Jankovic et al. 2024; Sheppard et al. 2022) and phosphatidyl inositol 3 kinase (Behl 2002; Dhandapani and Brann 2002; Vaidya et al. 2021) pathways. These pathways play an essential role in cell survival (Smith and Dahodwala 2014) by inhibiting pro-apoptotic proteins that mediate toxin-induced striatal neuron death (Bourque et al. 2009) such as glycogen synthase kinase 3β (Hetman et al. 2002) and BAD phosphorylation (Zhu et al. 2002). Through these pathways, estrogen also has a neuroprotective effect within 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 6-hydroxydopamine (6-OHDA) models (Bourque et al. 2009).

Another mechanism that estrogen exerts neuroprotection is the increased expression of neurotrophic growth factors such as glial cell line-derived neurotrophic factor (GDNF) (Campos et al. 2012). GDNF is a widely researched neuronal survival protein, which affects dopaminergic neuron survival in humans and animal PD models. Specifically, GDNF is neuroprotective for 6-OHDA toxicity, even if it is administered up to 4 weeks after the lesion in rats and nonhuman primates (Bowenkamp et al. 1997; Hoffer et al. 1994; Zhang et al. 1997). Evidence to support estrogen's neuroprotective effect via GDNF comes from GDNF silencing experiments, which abolished estrogen's protection of DA neurons (Campos et al. 2012).

Estrogen also has a role in maintaining mitochondrial function and influences a cell's response to oxidative stress. Following the application of 3-nitroprionic acid, resulting in the accumulation of reactive oxygen species, exogenous estrogen treatment restores ATP levels to 80% of nontreated control neurons (Wang et al. 2001). Therefore, mitochondrial activity was substantially enhanced through estrogen's action. In addition, estrogen significantly reduces toxicity from glutamate, hydrogen peroxide, and superoxide anions (Sawada et al. 1998). Interestingly, this effect was independent of the ER and was hypothesized to be through reduced cytosolic calcium levels, perhaps a secondary mechanism that is redundant except during times of stress. Enhancing mitochondrial energy production prevents aging and PD-associated neuron degeneration (Cunnane et al. 2016, 2020; Norwitz et al. 2019).

Estrogen also protects neurons by decreasing central nervous system (CNS) inflammation. Increased inflammation has been linked to various pathogeneses of PD in recent literature (Devos et al. 2013; Kip and Parr-Brownlie 2022, 2023; Tufekci et al. 2012). Some women are diagnosed with PD postpartum: a time when estrogen levels decrease and the body moves from an anti-inflammatory state to a pro-inflammatory state (Maltête et al. 2017; Olivola et al. 2020). However, there is no evidence that postpartum estrogen levels are lower in women with PD than other new mothers. Estrogen reduces cytokine levels, leukocyte CNS entry, and microglia activation in vivo and in vitro (Pozzi et al. 2006). Additionally, after 6-OHDA lesion in rats, a selective nonsteroidal ERβ agonist prevented the increase of TNFα in blood monocytes and brain homogenate (McFarland et al. 2013).

Overall, estrogen's neuroprotective effect in PD is multifactorial, resulting in clear sexual dimorphism in PD onset and symptoms. However, following menopause, this neuroprotection is decreased in women, and the risk of PD becomes similar to men.

7 | Sexual Dimorphism in LID

Although much is known about sexual dimorphism in PD, significantly less is known about sexual dimorphism in LID. This is

an oversight in the field, considering that studies have shown that women are more likely to develop LID (Bjornestad et al. 2016; Bovenzi, Schirinzi, Conti, et al. 2024; Chandran et al. 2014; Colombo et al. 2015; Group 1996; Hassin-Baer et al. 2011; Hely et al. 1995; Iwaki et al. 2021; Jurado-Coronel et al. 2018; Lyons et al. 1998; Meoni et al. 2020; Sato et al. 2006; Sharma et al. 2010; Zappia et al. 2005). Females also develop LID faster than males (Bovenzi, Conti, et al. 2023), with the median time to LID appearance after treatment was started being 4 years compared to 6 years, respectively (Hassin-Baer et al. 2011). Sex differences are also seen in the response to levodopa dosing (Kaasinen et al. 2001). Women have greater levodopa bioavailability, higher plasma concentrations, and a greater area under the plasma concentration-time curve for a given weight-adjusted dose (Kaasinen et al. 2001). Women are typically given a lower levodopa dose than men, even when adjusting for body weight. Epidemiological studies report sex to be a risk factor in LID incidence (Bjornestad et al. 2016; Bovenzi, Schirinzi, Conti, et al. 2024; Chandran et al. 2014; Colombo et al. 2015; Group 1996; Hassin-Baer et al. 2011; Hely et al. 1995; Iwaki et al. 2021; Jurado-Coronel et al. 2018; Lyons et al. 1998; Meoni et al. 2020; Sato et al. 2006; Sharma et al. 2010; Zappia et al. 2005), with some studies finding sex to be the greatest risk factor (Bjornestad et al. 2016; Zappia et al. 2005). In contrast, some epidemiological studies found other risk factors to be stronger such as dose rate (Fahn 1999; Olanow et al. 2013; Schrag et al. 1998; Zhang et al. 2013) and treatment duration (Rajput et al. 2002; Sharma et al. 2010). Overall, epidemiological studies support sexual dimorphism in LID, and more research is needed to understand the underlying mechanisms.

Consistent with PD generally, estrogen is hypothesized to have a neuroprotective effect on LID (Bovenzi, Conti, Degoli, et al. 2024; Bovenzi, Conti, Simonetta, et al. 2024; Cerri et al. 2019). This was first postulated in the 1970s when it was clinically described that dyskinesia was more frequent in older females following menopause (Bedard et al. 1977). To date, no study has compared LID incidence in premenopausal and postmenopausal women; therefore, future epidemiological studies need to examine this relationship. However, Bedard et al. (1977) described two women's experiences. The first was a premenopausal woman who experienced greater dyskinesia symptoms during menstruation. The second woman's symptoms worsened following administration of a drug that blocked estrogen's action. Since then, studies have found strong correlations between higher estrogen levels and decreased LID motor complications (Bovenzi, Schirinzi, Conti, et al. 2024) in women (Bovenzi, Conti, Degoli, et al. 2024) and men (Bovenzi, Sancesario, et al. 2023). Furthermore, estrogen replacement therapies can decrease LID/PD symptoms (Nicoletti et al. 2007; Pesce et al. 2023).

8 | Mechanism of Estrogen Effects on LID

We predict these clinical findings describing increased LID symptoms with decreased estrogen concentrations, and the reverse relationship, relate to estrogen's action on DA metabolism. We hypothesize that increased estrogen results in greater control of extracellular DA concentrations and, therefore, prevents LIDs by reducing large fluctuations of DA that are not associated with movement (Figure 3A). Evidence for this hypothesis primarily comes from animal research. DA concentrations in the striatum decreased in ovariectomized rats treated with estrogen (Dupont et al. 1981). However, women with greater exposure to estrogen had higher DAT bioavailability (Lee et al. 2019), consistent with enhanced control over DA concentrations. Although the link between estrogen, cellular mechanisms, DA concentration, and LID has not been rigorously investigated in human cohorts, we propose that once menopause occurs, and estrogen levels decline, extracellular DA concentrations fluctuate to nonphysiological levels, causing pathological activity in motor pathways and LID symptoms (Figure 3B). In this section, we will discuss three possible cellular mechanisms that may underlie the increased LID risk in women. It is important to note that these mechanisms are hypothesized and are posed with caution. Further research is needed to better understand the precise mechanisms of estrogen's effect on DA release and how this relates to LID incidence in women.

The first hypothesis is that estrogen affects extracellular DA concentrations by modulating DAT activity. DAT uptakes excess DA, thereby controlling extracellular DA concentrations and recycling excess DA (Watson et al. 2006). DAT bioavailability is decreased in postmenopausal women (Lee et al. 2019), which would reduce control of DA extracellular concentration when estrogen levels decline. In addition, experiments in animal models of PD show that DAT expression is reduced following ovariectomy, but rescued following estrogen treatment (Chavez et al. 2010). Together, these experiments support estrogen concentrations and DAT activity being linked. We hypothesize that once estrogen declines in menopause and DAT activity is decreased, control over extracellular DA is reduced, resulting in larger nonphysiological fluctuations and a greater risk of developing LID.

The second hypothesis is that estrogen affects extracellular DA concentrations by modulating postsynaptic DA receptors. Estrogen increases the expression of postsynaptic DA receptors (Aubert et al. 2005; Del Río et al. 2018; Di Paolo, Poyet, and Labrie 1982a, 1982b; Goetz et al. 1983; Hruska and Nowak 1988; Landry et al. 2002). Specifically, D1 receptor expression increased by 30%–40% following estrogen treatment in males (Di Paolo, Poyet, and Labrie 1982a) or ovariectomized females (Di Paolo, Poyet, and Labrie 1982b; Fuxe et al. 1979), while D2 receptor expression increased by 20% (Hruska and Nowak 1988). In addition, chronic estrogen treatment in ovariectomized 6-OHDA lesioned rats has been shown to increase postsynaptic DA binding and decrease DA concentration while not affecting DA turnover in the striatum in intact and lesioned hemispheres (Di Paolo, Bedard, et al. 1982). This study shows that estrogen increased the population of postsynaptic DA receptors, resulting in changes to DA metabolism and greater control of extracellular DA. Other studies report similar results in non-ovariectomized female (Goetz et al. 1983) and male rats (Hruska 1986; Hruska, Ludmer, et al. 1982). Based on these studies, we hypothesize that once estrogen declines following menopause, DA receptor expression decreases, resulting in decreased postsynaptic binding of DA, increased extracellular DA concentration, and greater DA spillover, ultimately increasing the risk of developing LID.

Thirdly, estrogen also controls D2 autoreceptor action by influencing its affinity (Figure 3). D2 autoreceptors negatively

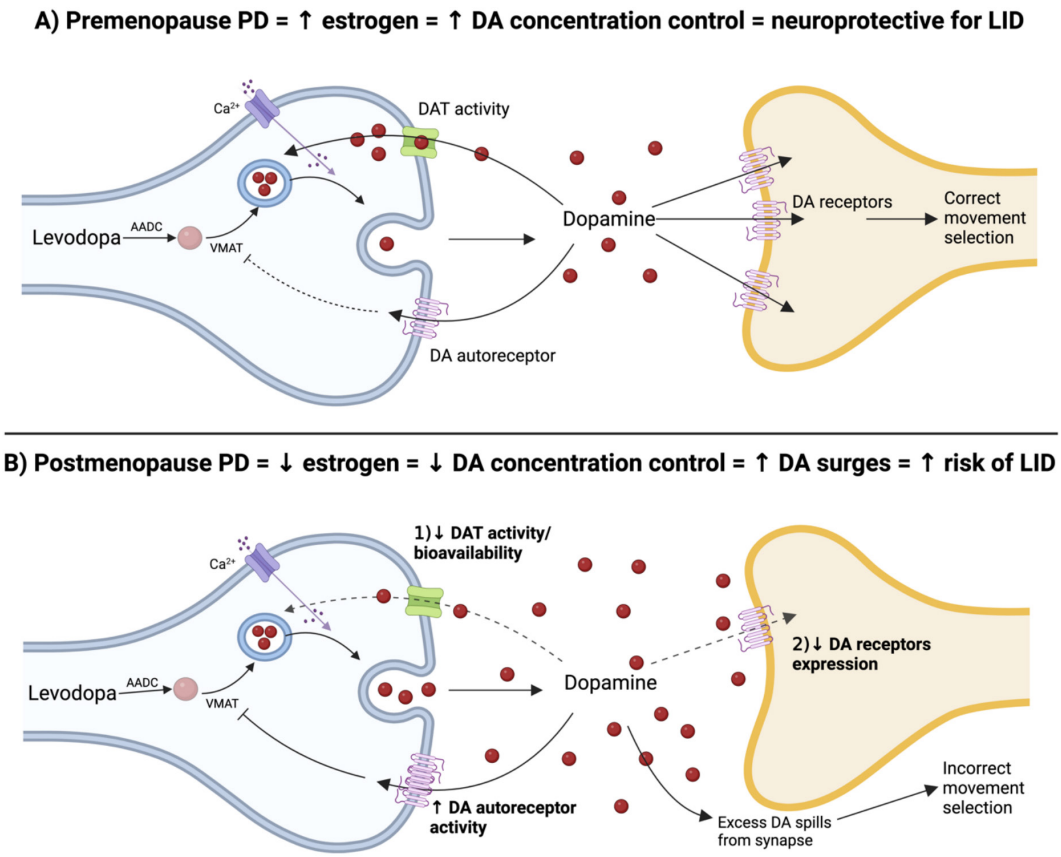

FIGURE 3 | Proposed mechanism of increased LID in postmenopausal women. (A) In premenopausal women, estrogen controls DA surges generated by levodopa administration via increased DAT activity, decreased D2 autoreceptor activity, and increased postsynaptic binding. (B) Following menopause, when estrogen levels have declined, extracellular DA concentration surges and LID symptoms occur because DA spillover activates receptors on other spiny projection neurons. *Note:* Synapses are related to Figure 2 but have been simplified for clarity. Created with BioRender.com.

feedback to control DA release at DA-SPN synapses, maintaining physiological DA levels and action, which are then modulated by estrogen. For example, in proestrus/estrus when the plasma level of estrogen is high, H:L-affinity D2 receptor ratio is low (Figure 1D) (Di Paolo et al. 1988), resulting in decreased negative feedback and increasing DA release and extracellular concentration. Conversely, when the H:L-affinity D2 receptor ratio is high in diestrus, this results in greater negative feedback and decreased extracellular DA levels (Di Paolo et al. 1988). Ovariectomy increases the H:L-affinity D2 receptor ratio (Bazzett and Becker 1994; Clopton and Gordon 1986; Di Paolo et al. 1988; Lévesque and Di Paolo 1988), and within 30 min of acute estrogen treatment, D2 binding was dominated by low-affinity receptors (Lévesque and Di Paolo 1988). One study hypothesized that estrogen desensitizes these DA autoreceptors (Calipari et al. 2017), as DA release remained high after applying a D2 receptor agonist. One interpretation of this result is that the DA system is primed to respond maximally when estrogen levels are high, resulting in enhanced movement selection. In contrast, when estrogen levels decrease during menopause, this enhanced movement selection is impaired, and selection of the correct motor pathway is reduced, increasing the risk of LID. Significant future research is needed to understand how estrogen-induced changes in H:L D2 receptor affinity alter DA transmission throughout the estrous cycle and following menopause.

In addition to these cellular mechanisms, there are several other mechanisms that may play a role to increase LID risk in women. Other mechanisms that may influence increased LID incidence in women include sex differences in the metabolism of levodopa, cerebral blood flow (CBF), and glial or immune responses. Women have greater levodopa bioavailability, meaning the same dose has a greater effect compared to men (Shulman 2007). Due to this, women are typically given a lower levodopa dose, but the increased bioavailability could also result in excessive extracellular DA concentration and increase the risk of LID onset. Secondly, CBF is higher in women compared to age-matched males (Gur and Gur 1990; Muer et al. 2024), including in the caudate and putamen (Gur and Gur 1990). Levodopa also increases CBF in PD patients (Jourdain et al. 2016) and rodent models of PD (Ohlin et al. 2012), and was further enhanced in PD patients with LID compared to non-dyskinetic PD patients (Hirano et al. 2008). Consequently, an increase in CBF results in stronger levodopa responses, higher DA concentration fluctuations, and greater LID risk, which may be further exacerbated in women by greater increases in CBF. Lastly, levodopa administration also results in increased blood brain–barrier leakage (Lerner et al. 2017; Ohlin et al. 2012), and immune response effects also show sexual dimorphism. Specifically, women have increased glial reactivity (O'Connor and Nissen 2023; Rubtsova et al. 2015) as demonstrated in

neurodegenerative (Vila-Castelar et al. 2024), neuropsychiatric (Sirkis et al. 2024), and autoimmune diseases (McCombe et al. 2009; Rubtsova et al. 2015). This finding is important because LID is associated with maladaptive gliovascular reactivity (Elabi et al. 2023) and elevated levels of pro-inflammatory cytokines in the striatum may contribute to the development of LID (dos Santos Pereira et al. 2022).

9 | Parkinsonian Presentation Along a Woman's Lifespan

Here, we discuss how estrogen production during a woman's lifespan may impact her PD diagnosis and symptom progression. This aims to raise awareness that women should be considered differently from their male counterparts in PD progression, depending on their life stage and estrogen production, as estrogen significantly affects DA metabolism and transmission.

Firstly, the prodromal presentation of PD occurs decades before PD diagnosis (Gonera et al. 1997; Hustad and Aasly 2020), possibly when women are still menstruating. Prodromal symptoms present at the early stages of midbrain DA degeneration (Hustad and Aasly 2020) and include a decreased sense of smell, sleep disturbances, and digestive disorders (Heinzel et al. 2019; Hustad and Aasly 2020). In menstruating women, previously described prodopaminergic actions may maintain high DA levels for approximately half of the menstrual cycle. Under these circumstances, estrogen-triggered high DA levels in the striatum may maintain SPN function, and prodromal symptom presentation is likely to be attenuated. However, prodromal PD symptoms may be increased during menstruation/diestrus when estrogen is low and DA levels fall below physiological levels. During the prodromal stage, motor and nonmotor symptoms will fluctuate, making it difficult for future patients and their clinicians to recognize that small changes in function are not life-induced variations but rather a cluster of prodromal PD symptoms.

PD diagnosis will occur when about 70% of DA neurons have degenerated, and motor symptoms are present (Gonera et al. 1997). Depending on a woman's age at which this occurs, she may still be menstruating, undergoing perimenopause or postmenopausal. Since the average age of PD onset is over 60 years of age (Pagano et al. 2016) and the average age of menopause is 51 years of age (Greendale et al. 1999), the majority of women will be postmenopausal; however, all possible stages should be considered to account for human variation in PD diagnosis and menopausal age (Hirsch et al. 2016). Firstly, in menstruating women, symptoms may be masked by estrogen's prodopaminergic actions in the estrous stage of the cycle (Bovenzi, Conti, Degoli, et al. 2024). Conversely, women report significantly worse PD motor symptoms where estrogen is low (Castrioto et al. 2010; Horstink et al. 2003; Jurado-Coronel et al. 2018; Quinn and Marsden 1986; Sandyk 1989). These effects may be difficult for clinicians to recognize due to the compounding effects of DA replacement medications. PD symptoms are reported to increase in severity in pregnancy and postpartum (Bovenzi, Conti, et al. 2023; Maltête et al. 2017; Olivola et al. 2020; Seier and Hiller 2017) when estrogen levels fluctuate greatly. This is an important treatment consideration for clinicians to manage with PD patients wanting to conceive. In perimenopausal women, it is likely that large fluctuations of estrogen that are associated with perimenopausal symptoms (Greendale et al. 1999) will also cause significant fluctuations in PD symptoms. Lastly, postmenopausal women diagnosed with PD will likely have increased symptom severity and faster symptom progression (Baba et al. 2005; Georgiev et al. 2017) than their male counterparts.

Lastly, after years of PD diagnosis, decreased estrogen in postmenopausal women may impact DA replacement therapies, decrease the therapeutic window, increase the risk, and decrease the onset time of LID (Bovenzi, Schirinzi, Conti, et al. 2024). These symptom complications relate to the previously described impaired DAT activity, decreased DA receptor activity and/or decreased D2 autoreceptor activity (Figure 3B). Ultimately, when estrogen levels are low, the female brain is in a state that increases the risk of LID onset or triggers a shorter LID latency once levodopa medication has started.

Studies describing these phenomena are limited; therefore, some of the previous statements are speculative. To date, no epidemiological study has compared LID rates, clinical symptoms, or time to LID onset in premenopausal vs. postmenopausal women. Other questions still need to be answered, such as do women have greater LID prevalence and severity following menopause or in perimenopausal low estrogen stages? We recommend that clinicians ask premenopausal female PD patients if symptoms change during their menstrual cycle, so the levodopa dose could be refined depending on estrogen levels to control DA swings and decrease the risk of LID.

10 | Conclusion

Many questions still need to be answered regarding estrogen's effect on BG circuitry and how this affects sexual dimorphism in PD and LID. We hypothesize that estrogen increases the release of DA and enhances control of extracellular DA concentrations. However, once circulating estrogen decreases following menopause, this results in a greater risk of LID symptom emergence and severity. Further research will be critical in understanding this association to improve clinical outcomes for women and men with LID worldwide. Women's PD progression must be considered different to that of their male counterparts, as estrogen's strong interactions with DA metabolism and transmission will likely affect all stages of symptom progression. Lastly, we hope this review stimulates discussion among clinicians and bench researchers to consider estrogen's important role in DA metabolism, movement selection, and movement disorders. Collaborative effort will be essential to conduct the experiments and clinical studies needed to improve outcomes for women with PD and LID.

Author Contributions

The manuscript was co-written and co-edited by the authors. Figure concepts were developed by L.M.B. and L.C.P.-B. and created by L.M.B. Financial disclosure: L.C.P.-B. is employed by the University of Otago and is seconded to the Ministry of Business, Innovation and Employment in New Zealand as a Science Advisor. She is a member of the Board for Te Whai Ao—Dodd Walls Center, and a member of the Mātauranga Science Insights Panel for the Ministry for the Environment in New Zealand.

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Conflicts of Interest

The authors declare no conflicts of interest.

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