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Premenopausal Transition in Neurodivergent Women with Musculoskeletal Syndromes: Mechanisms, Risks, and Neuroinclusive Therapeutics

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ABSTRACT: Neurodivergent women with chronic musculoskeletal syndromes experience disproportionate premenopausal symptom burdens that are poorly characterized in extant clinical paradigms and practice. The compounded interplay of estrogen fluctuations in premenopause with sensory–executive differences and baseline nociception from joint or connective-tissue pathology yields intensified pain, mood dysregulation, and functional decline. Evidence indicates estrogen modulates nociception, neuroinflammation, bone remodeling, and monoaminergic signaling; premenopausal variability magnifies pain, affective lability, and cognitive drift—effects accentuated in autism and ADHD. Coexisting hypermobility, fibromyalgia, or connective-tissue disorders compromise joint integrity and proprioception, increasing susceptibility to estrogen-dependent changes in bone microarchitecture and tendon homeostasis. This article advances an integrative neuroendocrine–musculoskeletal framework that balances neurodivergent conditions and musculoskeletal diagnoses equally while focusing explicitly on premenopause. Methodologically, it synthesizes convergent findings from endocrinology, pain science, and neuropsychiatry to delineate mechanisms—estrogen withdrawal, dopamine dysregulation, neuroimmune priming, and gut–brain signaling—relevant to this intersection. The analysis differentiates oral versus transdermal hormone therapies, emphasizes bioidentical, liver-sparing regimens, and appraises nonhormonal agents (e.g., SSRIs/SNRIs, gabapentinoids) alongside lifestyle interventions that elevate BDNF and attenuate inflammation. Special attention addresses risk modifiers salient to neurodivergent women: progesterone sensitivity, estradiol-mediated alcohol reward potentiation, executive dysfunction affecting adherence, and sensory hyperreactivity to foreign-body contraceptives. The proposed care model operationalizes neuroinclusive practice through structured monitoring, shared decision-making, and cross-disciplinary coordination, offering a decision matrix for individualized, route-specific hormone strategies and adjuncts. Anchored in premenopausal physiology, this approach aims to mitigate pain and psychiatric morbidity, preserve bone and functional capacity, and set a research agenda to close equity gaps in women's neuroendocrine health.

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Premenopause, Neurodivergence, Musculoskeletal syndromes, Transdermal hormone therapy, Neuroinflammation

1. INTRODUCTION

The premenopausal and perimenopausal years constitute a neuroendocrine inflection point during which fluctuating estradiol and progesterone modulate pain processing, affective regulation, and sleep architecture in ways that can either buffer or amplify existing vulnerabilities. Estradiol exerts wide-ranging effects on synaptic plasticity and nociception and, when diminished, is associated with vasomotor instability, mood lability, and sleep fragmentation—symptom clusters that often interact with chronic musculoskeletal pain and fatigue (NAMS, 2023). Pharmacokinetic considerations matter in this window: transdermal estradiol avoids first-pass hepatic metabolism and produces steadier serum levels than most oral regimens, with implications for both safety and tolerability in sensitive populations (CADTH, 2025). Concomitantly, the menopausal transition intersects with skeletal remodeling; declining

estrogen accelerates bone turnover and raises fracture risk, intensifying the clinical stakes for women who already live with connective-tissue or joint disorders. Emerging psychoneuroendocrine research also clarifies how estrogenic state shapes reward sensitivity and stress responsivity—domains salient to behavioral health during midlife (Handy, Greenfield, & Payne, 2025). These dynamics converge to create distinctive therapeutic dilemmas for neurodivergent women—particularly those with autism or ADHD—who report heightened interoception, executive-function strain, and atypical responses to pharmacologic interventions. A rigorous, mechanism-informed account of premenopausal care must therefore integrate endocrine, nociceptive, cognitive, and behavioral dimensions rather than treating symptoms in isolation (NAMS, 2023; OC, 2023). The present article advances that integration for neurodivergent women with musculoskeletal syndromes by aligning current evidence with practical, route-of-administration decisions.

Against this physiological backdrop, qualitative and mixed-methods studies show that autistic adults frequently experience menopause as an intensification of earlier sensory, cognitive, and emotional challenges, compounded by barriers to care and miscommunication in clinical settings. Participants describe "complexity, multiplicity, and intensity" of symptoms, with late diagnosis and health-system friction amplifying distress and delaying targeted supports (Brady et al., 2024). Workplace research similarly documents an intersectional burden whereby menopause disrupts neurodivergent employees' day-to-day experiences—sensory load, fatigue, attention regulation—even when headline performance metrics remain intact (Gottardello & Steffan, 2024). These observations are clinically actionable: they imply that symptom severity may be underestimated by clinicians and employers who track output rather than lived effort, and that care plans must anticipate sensory and executive bottlenecks. For women managing hypermobility, chronic pain, or myofascial syndromes, the sensory consequences of fluctuating hormones can magnify pain catastrophizing and sleep fragmentation, eroding coping bandwidth. Furthermore, differences in health-care navigation—masking, fatigue after long appointments, aversion to polypharmacy—shape adherence to both hormonal and nonhormonal therapies. A neuroinclusive frame thus requires adjustments in communication, titration schedules, and monitoring strategies to align with neurocognitive profiles. In short, the premenopausal transition is not merely a hormonal event but a context shift for neurodivergent functioning that demands tailored assessment and response.

What remains insufficiently addressed is a coherent clinical pathway that (a) selects hormone therapy routes and progestogens compatible with neurodivergent sensory profiles, (b) anticipates interactions between estradiol state and reward circuitry that may modulate substance-use risk, and (c) safeguards musculoskeletal integrity and sleep while minimizing neuropsychiatric adverse effects. Current guidelines endorse multiple effective options for vasomotor symptoms—hormone therapy, SSRIs/SNRIs, gabapentin, and newer neurokinin-3 antagonists—but rarely specify how executive dysfunction, sensory hypersensitivity, or chronic pain syndromes should steer choices in route, dose, or monitoring cadence (NAMS, 2023). Safety signals also diverge by route: evidence supports lower thromboembolic risk and more stable pharmacokinetics with transdermal estradiol relative to oral preparations, a difference that may matter for patients prone to mood destabilization with serum peaks and troughs (CADTH, 2025; BMS, 2023). Concurrently, literature on estrogen and alcohol indicates that higher estradiol states can heighten alcohol's rewarding effects in some women, a consideration when discussing lifestyle risk management during HRT titration (Handy et al., 2025). Finally, bone-health surveillance and anti-inflammatory strategies must be proactively integrated for women already contending with connective-tissue laxity, tendon pain, or low bone density (OC, 2023). Without such integration, neurodivergent women face piecemeal care that overlooks route-specific tolerability, sensory load, and behavioral risk. The clinical task, therefore, is not simply to control hot flashes but to rationalize an end-to-end plan spanning mood, pain, sleep, cognition, and skeletal health. This article responds to that gap with a precision, pathway-oriented synthesis.

Accordingly, the article proceeds by mapping evidence to decision points that matter most in premenopause for neurodivergent women with musculoskeletal syndromes: choice of transdermal versus oral estrogen; selection of micronized progesterone versus synthetic progestins; staged use of nonhormonal agents for vasomotor and pain symptoms; and structured surveillance of mood, sleep, alcohol use, and bone health. It synthesizes pharmacokinetic and safety data to justify route preferences, translates guideline recommendations into neuroinclusive monitoring schedules, and embeds sensory-aware strategies (e.g., simpler regimens, predictable application routines, and minimized clinic friction). The approach emphasizes micronized progesterone or vaginal progesterone when progestin sensitivity is suspected, using shared decision-making to balance uterine protection with neuropsychiatric tolerability (BMS, 2023). Nonhormonal adjuncts—including SSRIs/SNRIs and gabapentin—are positioned not as fallback remedies but as modular tools that can be layered with or without estradiol based on individualized response and preference (NAMS, 2023). Workplace-relevant accommodations and clinician communication practices are incorporated, drawing on intersectionality research that documents how menopause and neurodivergence co-produce burden in daily functioning (Gottardello & Steffan, 2024). The framework also foregrounds bone-health optimization—nutrition, resistance training, and pharmacotherapy thresholds—given accelerated bone loss during the transition. Throughout, the goal is a reproducible, interdisciplinary pathway that clinicians and patients can adapt to sensory profiles, executive-function demands, and musculoskeletal status **(Table 1)**. Through the integration of endocrine, musculoskeletal, and neurodivergence science, the article aims to operationalize equity in premenopausal care.

Table 1. Population-specific risk modifiers and baseline assessment toolkit

Domain	Rationale	Brief measure / examples	Clinical action
Pain	Estradiol variability and neuroinflammation can lower pain thresholds; neurodivergent interoception and central sensitization magnify symptom salience;hypermobility/myofascial syndromes increase peripheral drivers.	BPI-SF; PEG-3; Pain Catastrophizing Scale (PCS); Fibromyalgia Survey Questionnaire (FSQ).	Stabilize sleep/vasomotor triggers; consider transdermal estradiol when MHT indicated; evening gabapentin trial for nocturnal symptoms; graded, hypermobility-adapted strengthening and pacing; written flare plan; coordinated pain–gynecology follow-up.
Mood / anxiety	Hormonal swings, sleep fragmentation, and progestogen sensitivity elevate affective risk; diagnostic overshadowing common in autism/ADHD.	PHQ-9; GAD-7; DASS-21; C-SSRS if any suicidality; Daily Record of Severity of Problems (DRSP) for cyclic mood symptoms/PMDD.	Prefer transdermal estradiol; select micronized progesterone when uterine protection needed; consider SSRIs/SNRIs; offer CBT/MBCT; safety plan with clear stop–start rules; early reassessment (4–6 weeks).
Sleep	Vasomotor arousals, pain, and sensory hyperarousal disrupt sleep; menopausal transition raises OSA risk.	ISI; PSQI; STOP-Bang (OSA risk); 1–2 week sleep diary; optional wearable sleep metrics.	Treat vasomotor symptoms; CBT-I adapted for neurodivergence; evening gabapentin where appropriate; optimize sensory environment (light, sound, temperature); screen/refer for OSA.
Executive function / adherence	ADHD traits and cognitive load complicate daily pill/patch routines; complex regimens reduce persistence.	BRIEF-A; medication adherence scales (MARS-5 or MMAS-8); brief digital-literacy/health-navigation screen; routine mapping interview.	Simplify (once-weekly patch or single daily dosing); visual patch-rotation guides; text/app reminders; pharmacy blister packs; align dosing with stable anchor habits; provide written after-visit summary.
Sensory burden	Sensory hypersensitivity increases distress from adhesives, GI side effects, or "foreign-body" sensations; interoceptive amplification common.	AASP; Sensory Profile (adult); 0–10 sensory-distress VAS; adhesive patch-test when relevant.	Choose gels/sprays if adhesive intolerance; rotate sites and use barrier films; avoid highly stimulating clinic environments; discuss non-implant options when foreign-body distress likely; tailor counseling pace and format.
Alcohol risk	High-estradiol states may potentiate alcohol reward; impulsivity/stress-coping patterns in ADHD/autism can increase binge risk during hormone changes.	AUDIT-C (expand to full AUDIT if positive); Timeline Follow-Back; simple craving scale (0–10).	SBIRT-style brief intervention; consider transdermal estradiol to reduce peaks; set explicit drink-limit goals; substitute non-alcohol rewards (exercise, social, sensory-soothing routines); schedule early follow-up and offer neurodiversity-aware referrals.
Bone risk	Estrogen decline accelerates bone turnover; pain-related inactivity and hypermobility increase falls and fracture exposure.	FRAX; baseline DXA (per guideline risk); serum 25-OH vitamin D; Timed Up and Go (TUG) and falls screen.	Counsel calcium/vitamin D sufficiency; prescribe hypermobility-adapted resistance and balance training; use MHT for symptom-plus-bone benefit where appropriate; start antiresorptive/anabolic therapy per risk thresholds; choose adherence-sparing schedules (e.g., infusions); reassess annually.

Note. *BPI-SF = Brief Pain Inventory–Short Form; PEG-3 = Pain, Enjoyment, General activity scale; PHQ-9 = Patient Health Questionnaire-9; GAD-7 = Generalized Anxiety Disorder-7; DASS-21 = Depression Anxiety Stress Scales-21; C-SSRS = Columbia-Suicide Severity Rating Scale; DRSP = Daily Record of Severity of Problems; ISI = Insomnia Severity Index; PSQI = Pittsburgh Sleep Quality Index; STOP-Bang = snoring, tiredness, observed apnea, blood pressure, BMI, age, neck circumference, gender; BRIEF-A = Behavior Rating Inventory of Executive Function–Adult; MARS-5/MMAS-8 = Medication Adherence scales; AASP = Adolescent/Adult Sensory Profile; VAS = visual analogue scale; AUDIT-C/AUDIT = Alcohol Use Disorders Identification Test (short/full); FRAX = Fracture Risk Assessment Tool; DXA = dual-energy X-ray absorptiometry; MHT = menopausal hormone therapy; SBIRT = Screening, Brief Intervention, and Referral to Treatment; OSA = obstructive sleep apnea.*

2. LITERATURE REVIEW

The extant literature converges on a biopsychosocial account of perimenopause that is particularly salient for neurodivergent women living with musculoskeletal syndromes (Simposon et al., 2025). Estrogen's immunomodulatory signaling intersects with central pain amplification pathways, autonomic responsivity, and sleep–wake regulation, thereby shaping both nociception and affective appraisal of pain during the menopausal transition (Ji & Zhang, 2024). Cognitive complaints—most consistently decrements in verbal learning and memory—intensify during perimenopause and co-occur with anxiety, sleep fragmentation, and vasomotor instability, creating a feedforward loop that is liable to be magnified in individuals with baseline sensory hypersensitivity or executive-control differences (Metcalf et al., 2023). These neurocognitive changes are not uniform but display marked heterogeneity across women, a variability that complicates case identification when neurodivergence masks or mimics menopausal symptomatology (Sang et al., 2024). For women with chronic musculoskeletal pain or connective-tissue instability, estrogen fluctuation can alter central sensitization thresholds and peripheral inflammatory set points, potentiating symptom flares and activity limitation (Casale et al., 2021). Because neurodivergence frequently entails heightened interoception and atypical sensory gating, the subjective salience of vasomotor and nociceptive signals may be exaggerated, changing help-seeking behavior and perceived treatment response (Price, 2023). This intersectional burden maps onto health-system frictions—short consultations, limited specialist coordination, and inconsistent guidelines—producing underdiagnosis or undertreatment. A rigorous review, therefore, must integrate endocrine, neuroimmune, and behavioral evidence while attending to the specific care barriers faced by neurodivergent populations. The following synthesis foregrounds mechanistic plausibility and actionable clinical evidence from 2023–2025 to delineate risks, interventions, and research priorities.

Emerging mechanistic studies sharpen understanding of pain trajectories across the menopausal transition in the context of neuroinflammation. Signal transducer and activator of transcription 3 (STAT3)–dependent glial signaling has been implicated in persistent pain, providing a plausible conduit by which declining estradiol attenuates anti-inflammatory tone and disinhibits cytokine cascades that heighten nociceptive gain (Dai et al., 2024). Perimenopausal fluctuations appear to modulate both microglial reactivity and dorsal-horn excitability, conditions under which preexisting musculoskeletal syndromes—e.g., myofascial pain or hypermobility-related arthralgia—may deteriorate more rapidly. Clinically, these dynamics manifest as greater pain volatility, sleep disruption, and activity avoidance, with downstream effects on mood and cognition (Guan et al., 2025). The literature suggests that centrally acting nonhormonal agents used for vasomotor symptoms—such as SNRIs—can indirectly attenuate pain by improving sleep continuity and reducing thermoregulatory arousals that otherwise amplify hyperalgesia (Iyer, Fiffick, & Batur, 2024). Nevertheless, medication tolerability is idiosyncratic in neurodivergent cohorts; dose-dependent sensory side effects and interoceptive distress may curtail adherence. A tailored, iterative titration strategy grounded in shared decision-making is recommended when pain and vasomotor instability are tightly coupled. Future trials should stratify by neurodivergent status to clarify effect modification and optimize dosing heuristics.

Qualitative and survey evidence from 2024 emphasizes that autism-specific stressors compound perimenopausal affective risk. Autistic women report distinctive constellations of symptoms—heightened sensory overload, intensification of masking demands, and destabilization of routines—during menopause, with clear calls for neuroaffirming clinical communication and paced information delivery (Brady et al., 2024; Cusano et al., 2024). Cross-group survey data comparing autistic and non-autistic British women indicate more severe mood lability, sleep fragmentation, and executive-function disruption among autistic respondents, alongside lower satisfaction with medical encounters (Jenkins & Foxhill, 2024). These findings implicate both biological sensitivity to estrogen fluctuation and structural barriers—e.g., limited appointment time, insufficient sensory accommodations—in generating disproportionate distress. Notably, respondents voiced apprehension about hormone therapies that provoke rapid level shifts or gastrointestinal side effects, a theme consistent with known interoceptive amplification. Reports also highlight underrecognition of menopausal symptoms when clinicians attribute changes solely to neurodivergence, delaying timely intervention. The literature thus recommends explicit screening for perimenopausal mood symptoms in autistic and ADHD populations and early discussion of non-oral options to minimize pharmacokinetic volatility. Such strategies align with trauma-informed, neuroinclusive practice models and are likely to improve persistence with care plans.

Cognitive outcomes occupy a central place in the perimenopausal literature, with converging evidence for transient decrements in verbal memory alongside variable effects on attention and processing speed. A 2023 review synthesizing neuropsychological and neuroimaging findings documents that cognitive complaints cluster with insomnia and hot flashes, underscoring the role of sleep-dependent consolidation and thermoregulatory arousals in day-time cognitive inefficiency (Metcalf et al., 2023). In neurodivergent women, preexisting executive-control differences may magnify the functional impact of even small decrements in working memory, especially when daily routines are already burdened by sensory avoidance and task-switching demands. Because subjective "brain fog" correlates imperfectly with objective testing, the review recommends integrating validated self-report measures with targeted cognitive tasks to capture clinically meaningful change (Bansal et al., 2025). Treatment studies remain sparse, and guidelines do not endorse menopausal hormone therapy (MHT) solely for cognitive complaints; however, interventions that improve sleep and reduce vasomotor events exert secondary cognitive benefits. Nonhormonal pharmacotherapy may thus serve dual aims—ameliorating vasomotor symptoms and enhancing sleep continuity—especially relevant where stimulant or antidepressant regimens

are already in place for ADHD or mood disorders. For neurodivergent patients, pacing of behavioral sleep strategies, sensory-friendly sleep environments, and structured cueing may be essential adjuncts (Donohoe et al., 2024). The literature calls for adequately powered trials that stratify by neurodivergence to address this evidence gap.

Route of estrogen delivery has implications for both safety and tolerability, with renewed comparative effectiveness work in 2025 refining prior guidance. A Canadian health-technology rapid review concluded that, while overall efficacy for vasomotor relief appears similar between oral and transdermal estradiol, transdermal delivery avoids first-pass hepatic metabolism and may confer advantages for thromboembolic and cardiometabolic risk in selected patients—particularly those with migraine, hypertension, or elevated VTE risk (Abdelrazeq, 2025). For neurodivergent women sensitive to rapid hormone excursions, the more stable pharmacokinetic profile of patches, gels, or sprays may also reduce mood perturbations associated with fluctuating serum levels, though direct trials in this population are lacking. In parallel, professional guidance emphasizes caution regarding compounded "bioidentical" formulations: when FDA-approved products exist, compounded preparations should not be used routinely given variable potency, quality, and safety monitoring (ACOG, 2023). These statements are especially pertinent where sensitivity to dose variability or excipients is pronounced. Clinicians should therefore prioritize approved transdermal estradiol and micronized progesterone when indicated, using the lowest effective dose and revisiting risk–benefit regularly. Shared decision-making should explicitly address route, excipient profiles, and delivery-system handling demands relative to executive-function capacity. Finally, research is needed to test whether transdermal regimens measurably attenuate mood and sensory volatility in neurodivergent cohorts.

Nonhormonal options constitute a second therapeutic pillar with increasing evidentiary clarity relevant to neurodivergent tolerability profiles. Current clinical reviews summarize moderate-to-high quality evidence for SNRIs (e.g., venlafaxine), SSRIs (e.g., escitalopram), gabapentin, clonidine, and behavioral interventions, with effect sizes largest for pharmacologic agents and emerging promise for neurokinin-3 receptor antagonists (Iyer et al., 2024). Gabapentin—particularly in evening dosing—can reduce nocturnal vasomotor events and improve sleep maintenance, a lever that may indirectly lower next-day sensory overwhelm and pain amplification; yet dizziness or dissociation-like sensations can limit uptake in sensory-sensitive patients (Huang, Faubion, & Grady, 2025). Evidence syntheses also note meaningful reductions in hot-flash frequency with venlafaxine and desvenlafaxine, with rapid onset that is clinically helpful when MHT is contraindicated or declined (Kim et al., 2024). Neurokinin-3 receptor antagonism targets hypothalamic KNDy-neuron thermoregulatory circuits and is now supported by randomized trials; its nonhormonal mechanism and neutral hepatic profile make it an appealing candidate for women wary of estrogen-linked mood effects (Gombert-Labedens et al., 2025). To improve adherence in populations with executive-function challenges, clinicians should streamline regimens, prefer once-daily formulations when possible, and pair pharmacotherapy with structured sleep-hygiene coaching. Trials rarely report neurodivergent stratifications, so post-marketing observational studies should capture sensory side-effect profiles and executive-load measures. Such data would guide precision prescribing that respects both symptom biology and cognitive ecology.

A rapidly developing preclinical literature links estradiol surges to enhanced alcohol reward, raising counseling considerations for menopausal care that includes hormone therapy. Using estrous-cycle–sensitive paradigms, a 2024 Nature Communications study demonstrated that high endogenous estradiol states increased binge-drinking behavior in female mice through rapid, membrane-initiated estrogen receptor-α signaling within the bed nucleus of the stria terminalis, a stress- and reward-integration hub (Zallar et al., 2024). This mechanism elevated synaptic excitation of corticotropin-releasing factor neurons and facilitated drinking, providing a concrete pathway by which estrogen can potentiate front-loading of alcohol intake. Although translational caution is warranted, the findings supply a neurobiological rationale for enhanced alcohol-related vulnerability during periods of estrogen fluctuation or exogenous estradiol exposure. Given higher baseline rates of anxiety and executive-control difficulties in subsets of neurodivergent women, the intersection of reward sensitivity and impulsivity may increase binge-drinking risk precisely when menopausal symptoms prompt therapeutic changes. Clinicians should therefore incorporate brief alcohol-use screening and psychoeducation when initiating or adjusting estrogen therapy, especially in patients with prior hazardous use or stimulant treatment for ADHD. Non-oral estradiol—because of flatter pharmacokinetics—might mitigate rapid reward-system perturbations relative to oral regimens, though this hypothesis requires human testing. Integrating alcohol-use monitoring into follow-up protocols is a pragmatic safety enhancement (Klausen et al., 2025).

Patient-reported outcomes underscore healthcare-delivery factors that modulate symptom trajectories during the transition. Autistic respondents describe clinical environments that over-stimulate—bright lights, unpredictable waiting, rapid information density—compromising history-taking and shared decision-making (Jenkins & Foxhill, 2024). These conditions diminish disclosure of sensitive topics such as alcohol use, sexual health, and suicidal ideation—issues that the mechanistic and clinical literature suggests are relevant during perimenopause (Brady et al., 2024). Neuroaffirming adaptations—structured visit agendas, written summaries, slower pacing, and accommodations for sensory sensitivities—are consistently requested and are likely to enhance adherence to both hormonal and nonhormonal regimens (Genazzani et al., 2024). When layered on musculoskeletal disability or chronic pain, clinic-navigation burdens further impede continuity, fostering therapeutic drop-out. The literature therefore supports integrated models that collocate gynecology, mental health, and pain services, with explicit protocols for cross-specialty communication. Embedding screening for mood, suicidality, alcohol use, sleep disturbance, and medication adherence within gynecologic visits is

particularly pertinent for neurodivergent populations. These delivery-system refinements are low-risk, cost-conscious, and consonant with broader accessibility mandates.

Risk–benefit appraisal must also incorporate skeletal outcomes given the confluence of musculoskeletal syndromes and menopause-associated bone loss. National guideline updates emphasize fracture-risk stratification using tools such as FRAX and integrated algorithms that combine prior fracture history, bone mineral density, and age to guide pharmacotherapy initiation (OC, 2023). Estrogen or combined MHT prevents bone loss and reduces fracture risk in appropriately selected women, while nonhormonal agents—bisphosphonates, denosumab, and anabolic therapies—remain the mainstays for high-risk patients without menopausal symptom indications for MHT (di Filippo & Rosen, 2024). For neurodivergent women with mobility limitations or sensory-driven exercise avoidance, guideline-endorsed resistance, balance, and functional training require adaptation to reduce overload and maximize adherence. Sleep optimization and anti-inflammatory diet patterns are reasonable adjuncts given their favorable effects on pain and activity tolerance, though high-quality trials in neurodivergent cohorts are needed. Shared decision-making should incorporate route-of-administration preferences, executive-function supports for medication routines, and monitoring plans compatible with sensory sensitivities. Coordination between pain specialists and menopause clinicians can minimize polypharmacy and prioritize agents with dual benefits for pain and bone health (Yang, 2025). Such comprehensive planning is foundational to reducing fracture risk while improving symptom control.

Guideline and review authors uniformly caution against routine use of compounded "bioidentical" hormones when regulated, bioidentical options exist, a point with special relevance to patients sensitive to dose variability. The 2023 ACOG Clinical Consensus highlights the paucity of high-quality data on safety and efficacy of compounded products and recommends FDA-approved formulations whenever possible, with explicit counseling on risks and uncertainties if patients persist in requesting compounded therapies (ACOG, 2023). For neurodivergent women, avoiding unpredictable pharmacokinetics and excipient variability is not merely a regulatory nicety but a practical strategy to reduce mood lability, sensory side effects, and adherence failures. This stance coheres with comparative-route evidence suggesting advantages of transdermal estradiol in certain cardiometabolic contexts and in patients who prefer to avoid hepatic first-pass effects (Abdelrazeq, 2025). Clinicians should document reasoning for product selection, specify monitoring intervals for mood, sleep, and alcohol use, and ensure that progesterone choices balance endometrial protection with neuropsychiatric tolerability. Written instructions and visual schedules can offset executive-function barriers to correct patch cycling or gel application. Clear stop–start rules for adverse-event thresholds should be co-created to reduce anxiety and emergency utilization. Such protocolization increases safety while honoring patient agency.

Across domains, a consistent theme is the scarcity of trials that stratify or tailor interventions for neurodivergent populations—an evidence gap with practical consequences **(Table 2)**. Reviews of cognition and symptom clustering call for larger, well-phenotyped cohorts and standardized reproductive-stage definitions to improve comparability and causal inference (Metcalf et al., 2023). Health-technology assessments and clinical reviews supply route- and agent-level guidance but rarely address sensory-processing differences, interoceptive distress, or executive-function limitations that shape real-world adherence (Abdelrazeq, 2025; Iyer et al., 2024). Preclinical advances in estrogen-linked reward circuitry illuminate a plausible risk mechanism for binge drinking during high-estradiol states, yet translational studies in midlife women—especially those starting MHT—are lacking (Zallar et al., 2024). Observational cohorts should therefore incorporate alcohol-use phenotyping and evaluate whether transdermal regimens reduce risk signals relative to oral dosing. Pain research must integrate neuroimmune biomarkers with patient-reported sensory profiles to identify subgroups most likely to benefit from anti-inflammatory or sleep-targeted interventions. Finally, implementation science is needed to test neuroinclusive delivery models that combine endocrine, mental-health, pain, and bone-health services with environmental adaptations. Building this evidence base is essential to move from plausible mechanism to demonstrable clinical value.

Table 2. Evidence synthesis for symptom targets and interventions

Target	Intervention class	Typical dosing ranges	Onset window	Core benefits	Common adverse effects	Notes on neurodivergent tolerability	Evidence quality*
Vasomotor	**Transdermal estradiol**	Patch 0.025–0.1 mg/day (once- or twice-weekly); gel 0.5–1.5 mg/day; spray 1–3 actuations/day	~1–2 weeks for hot-flash reduction; sleep improves as vasomotor events decline	Robust relief of hot flashes/night sweats; secondary gains in sleep, mood, and pain modulation	Skin irritation, breast tenderness, headache	Flatter PK profile than oral; avoids first-pass hepatic effects; gels/sprays helpful if adhesive sensitivity; simpler weekly routines reduce executive load	High (guidelines, RCTs/observational syntheses)

Vasomotor	**Oral estradiol**	0.5–2 mg/day (estradiol); CEE 0.3–0.625 mg/day	~1–2 weeks	Effective hot-flash control; systemic symptom relief	Nausea, breast tenderness, headache; ↑TG/VTE/gallbladder risk versus transdermal	Potential GI/interoceptive distress; peak–trough swings may aggravate mood lability in sensitive patients	High for efficacy; Moderate for safety differentials versus transdermal
Vasomotor	**SSRIs/SNRIs**	Venlafaxine XR 37.5–75 mg/day (up to 150 mg); desvenlafaxine 50–100 mg/day; escitalopram 10–20 mg/day; paroxetine 7.5 mg qhs	1–2 weeks (often within 7 days)	Reduces hot-flash frequency/severity; improves sleep continuity and mood	Nausea, insomnia/activation, sexual dysfunction, sweating, hyponatremia (older adults)	Once-daily options aid adherence; coordinate with stimulants/anxiolytics; start low to limit activation/sensory jitter	Moderate–High (multiple RCTs, guideline endorsements)
Vasomotor	**Gabapentin**	300–900 mg qhs (or 300 mg TID; target ~900 mg/day)	3–7 days	Reduces nocturnal vasomotor events; improves sleep maintenance	Somnolence, dizziness, ataxia, "foggy" cognition	Night-only dosing minimizes daytime cognitive load; slow titration for sensory-sensitive patients	Moderate (RCTs and practice recommendations)
Vasomotor	**NK3 antagonists**	Fezolinetant 45 mg once daily	~1 week (some respond within days)	Significant hot-flash reduction via KNDy neuron modulation; nonhormonal	Headache, GI upset; reversible ↑LFTs—requires baseline/periodic monitoring	Once-daily, nonhormonal route avoids estrogen-linked mood concerns; plan reminders for LFT monitoring to offset executive load	High for fezolinetant (phase 3 RCTs, regulatory approval)
Sleep	**Micronized progesterone**	100 mg qhs continuous **or** 200 mg qhs for 12 days/28-day cycle	Sedation within 1–3 nights; broader effects 2–4 weeks	Improves sleep onset/maintenance; provides endometrial protection with estrogen	Somnolence, dizziness, bloating; rare mood changes	Bedtime dosing aligns with sleep goals; consider continuous regimen if cyclic mood dips; generally better-tolerated than many synthetic progestins	High for endometrial protection; Moderate for sleep benefits
Sleep	**Gabapentin**	300–900 mg qhs (titrate by 100–300 mg every 3–4 nights)	Days to 1 week	Consolidates sleep; reduces nocturnal awakenings	Somnolence, dizziness, imbalance	Start low/go slow; provide fall-risk guidance; evaluate morning "hangover" and adjust	Moderate

Pain	**Transdermal estradiol**	As above	2–6 weeks (indirect via inflammation/sleep)	May lessen musculoskeletal pain and stiffness; supports activity tolerance	As above	PK stability may blunt pain volatility linked to hormonal swings; useful where hypermobility/fibromyalgia present	Moderate (indirect and observational signals)
Pain	**SSRIs/SNRIs**	As above	1–4 weeks	SNRI class may reduce pain interference via mood/sleep gains; attenuates central sensitization	As above; BP elevation (venlafaxine) possible	Favor SNRIs when comorbid pain+anxiety; monitor activation in ADHD	Moderate
Mood	**Transdermal estradiol**	As above	1–4 weeks	May improve vasomotor-linked mood lability; facilitates sleep normalization	As above	Prefer transdermal to limit peaks/troughs that can destabilize affect	Moderate (adjunctive mood benefits)
Mood	**Micronized progesterone**	As above	2–4 weeks	Sleep-mediated mood stabilization in some; endometrial protection	Somnolence; occasional dysphoria	Trial continuous dosing if cyclic irritability; avoid progestins with adverse psychotropic profiles	Moderate (context-dependent)
Mood	**SSRIs/SNRIs**	As above	1–2 weeks (anxiety), 2–4 weeks (depression)	First-line for perimenopausal depression/anxiety; also reduces hot flashes	As above	Start low/slow; coordinate with existing psychotropics; provide sensory-friendly education about side effects	High
Cognition	**Transdermal/oral estradiol**	As above	Variable; not recommended solely for cognition	No consistent direct cognitive enhancement; indirect benefits via sleep/vasomotor control	As above	Manage expectations; target sleep and vasomotor symptoms first	Moderate for indirect effects; Low for direct cognitive indication
Cognition	**Gabapentin / SSRIs/SNRIs / NK3**	As above	1–4 weeks (indirect)	Improved sleep/thermoregulation may reduce “brain fog” and daytime inefficiency	Class-typical AEs	Emphasize indirect pathway; monitor for sedation (gabapentin) or activation (SSRIs/SNRIs)	Low–Moderate (indirect evidence)

**Evidence quality reflects synthesis of contemporary guidelines (e.g., NAMS 2023), randomized trials and comparative reviews (e.g., Iyer et al., 2024; CADTH 2025), and regulatory data for fezolinetant (2023–2025).*

Abbreviations: *CEE = conjugated equine estrogens; PK = pharmacokinetic(s); VTE = venous thromboembolism; TG = triglycerides; qhs = at bedtime; LFTs = liver function tests; KNDy = kisspeptin/neurokinin B/dynorphin neuron complex; RCTs = randomized controlled trials.*

3. METHODOLOGY

The study employed an integrative, convergent-evidence review design to synthesize mechanistic, clinical, and experiential scholarship concerning pre-/perimenopause among neurodivergent women with co-occurring musculoskeletal syndromes. The approach prioritized high-quality guidance and primary research published from January 2010 to May 2025, with explicit weighting toward contemporary sources (2023–2025) to reflect evolving therapeutics and conceptual models in menopause care and neurodiversity research (NAMS, 2023; NICE, 2024; ACOG, 2023; OC, 2023; CADTH, 2025). Two a priori questions structured the synthesis: first, how estrogenic fluctuation and route-of-administration effects intersect with neurodivergent cognition, affective regulation, pain processing, and connective-tissue vulnerability; and second, what treatment strategies—hormonal, nonhormonal, and behavioral—demonstrate safety, tolerability, and effectiveness for this intersectional population (Iyer, Fiffick, & Batur, 2024; Wright, 2024). The integrative design allowed concurrent appraisal of randomized and observational clinical studies, basic and translational mechanisms, qualitative accounts, and clinical practice guidelines, thereby supporting triangulation across evidence classes (Brady et al., 2024; Metcalf et al., 2023). Because clinical guidance on compounded products and endometrial protection influences exposure classification, the synthesis was explicitly aligned to contemporary position statements (ACOG, 2023; NAMS, 2023; NICE, 2024). Finally, the review emphasized health-equity and neuroinclusion by incorporating sources that address diagnostic overshadowing, sensory modulation, and executive-function demands in clinical implementation (Brady et al., 2024; NICE, 2024). This design choice was intended to yield decision-useful insights for multidisciplinary clinicians while preserving interpretive fidelity to neurodivergent perspectives.

Eligibility criteria were specified using an adapted PICO/PEO framework to accommodate clinical and experiential evidence. Populations included pre- and perimenopausal adult women (typically ages 35–55) who were autistic and/or had ADHD, with or without formal diagnoses but with clear descriptors of neurodivergence, and who also demonstrated musculoskeletal syndromes relevant to connective tissue, pain, or mobility (e.g., fibromyalgia, generalized joint hypermobility/hEDS, osteoarthritis risk, chronic myofascial pain) (Vidal-Neira, 2024; Wright, 2024). Interventions and exposures comprised menopausal hormone therapy (MHT; oral vs. transdermal estradiol; progestogen strategies), nonhormonal agents with guideline-level support for vasomotor and mood symptoms (e.g., SSRIs/SNRIs, gabapentin, NK3 receptor antagonists), and structured behavioral/rehabilitative strategies; comparators included placebo, no treatment, usual care, or alternative routes/doses (NAMS, 2023; Iyer et al., 2024). Outcomes prioritized pain intensity and interference, vasomotor severity, mood and anxiety scales, sleep and cognitive performance, alcohol-use behaviors, bone density or fracture proxies, and patient-reported tolerability and sensory burden (Metcalf et al., 2023; Zallar et al., 2024). Study designs included randomized and quasi-experimental trials, prospective and retrospective cohorts, case-control analyses, mixed-methods or qualitative investigations focused on lived experience, and contemporary clinical practice guidelines and health technology assessments (Brady et al., 2024; CADTH, 2025). Exclusions encompassed postmenopause-only samples without stratified pre/perimenopausal data, pediatric or male-only studies, preclinical work lacking translational relevance, and reports predating modern MHT risk stratification unless mechanistically indispensable (Wright, 2024; NAMS, 2023). Because musculoskeletal vulnerability and neurodivergence may co-cluster, mechanistic or phenotyping studies that linked joint hypermobility, pain amplification, or connective-tissue markers to neurodivergent traits were eligible if they informed causal inference or effect modification (Wright, 2024; Vidal-Neira, 2024). The temporal scope enabled inclusion of recent regulatory and practice shifts, notably the emergence of NK3 antagonism and refined guidance on compounded hormones (ACOG, 2023; Iyer et al., 2024).

Information sources included MEDLINE (via PubMed), Embase, PsycINFO, CINAHL, Web of Science Core Collection, and Scopus, supplemented by guideline and assessment repositories (NICE, NAMS, ACOG, Osteoporosis Canada) and health-technology assessments (CADTH). Search strings combined controlled vocabulary and free-text terms across four concept blocks: (1) menopausal transition phases (premenopause, perimenopause, menopausal transition), (2) neurodivergence (autism spectrum disorder, ADHD, neurodivers*), (3) musculoskeletal and pain syndromes (fibromyalgia, hypermobility, Ehlers-Danlos, osteoarthritis, myofascial pain), and (4) interventions and mechanisms (estradiol, transdermal patch, micronized progesterone, SSRIs, SNRIs, gabapentin, neurokinin-3/fezolinetant, alcohol or reward sensitivity) (Iyer et al., 2024; Zallar et al., 2024). Searches were restricted to 2010–2025 and English language, with forward–backward citation chaining from sentinel papers and guideline bibliographies (NAMS, 2023; NICE, 2024). Gray literature encompassed organizational guidelines, regulatory communications, and HTA reviews to minimize publication bias and capture fast-moving therapeutic domains (ACOG, 2023; CADTH, 2025). Preprints were screened only when subsequent peer-reviewed versions were unavailable and the methods were transparent enough to judge risk of bias; once a peer-reviewed version appeared, the preprint was superseded (Zallar et al., 2024). Operational

decisions—such as inclusion of qualitative evidence about sensory load, executive-function demands, and clinical navigation—were pre-specified to support neuroinclusive interpretation (Brady et al., 2024). A pilot search was iteratively refined to maximize recall on NK3 antagonists and route-of-administration contrasts in MHT given their salience to hepatically mediated mood effects (NAMS, 2023; CADTH, 2025). Deduplication and record management were conducted programmatically before screening.

Study selection proceeded in two phases by independent reviewers using calibrated decision rules with adjudication by a third reviewer for conflicts. Title/abstract screening applied liberal-accelerated inclusion to minimize early exclusion of intersectional samples; full-text screening applied the full eligibility rubric with justification codes for exclusions. Data extraction followed a piloted codebook capturing sample characteristics (age, menopausal staging criteria), neurodivergence ascertainment, musculoskeletal phenotype, intervention and comparator specifications including route and dose, co-interventions, outcome measures, follow-up, and adverse-event or discontinuation data. Risk of bias was appraised at the study level with design-appropriate criteria (sequence generation/allocation concealment or confounding control; blinding and outcome ascertainment; missingness; selective reporting), and at the outcome level for subjective constructs such as pain and mood; qualitative studies were appraised for transparency, reflexivity, and analytic rigor. Given anticipated heterogeneity in populations, interventions, and metrics, random-effects meta-analysis was planned for sufficiently homogeneous strata; otherwise, synthesis without meta-analysis emphasized effect-direction plots, precision, and clinical meaningfulness. Strength of evidence was graded across consistency, directness to the intersectional population, precision, and publication bias, with decision-notes explaining downgrades or upgrades (OC, 2023; NAMS, 2023). Subgroup and sensitivity analyses were prespecified for route of estrogen delivery (oral vs. transdermal), neurodivergence subtype (autism vs. ADHD), and musculoskeletal phenotype (e.g., fibromyalgia vs. hypermobility-predominant), reflecting plausible effect modifiers (CADTH, 2025; Wright, 2024). Finally, narrative triangulation integrated mechanistic findings on estrogen–reward circuitry and alcohol sensitivity with clinical outcomes to contextualize risk for maladaptive coping or substance-use escalation during hormone modulation (Zallar et al., 2024; Iyer et al., 2024).

4. RECOMMENDATIONS

The first recommendation is to implement staged, neuroinclusive screening and staging of the premenopausal transition that explicitly integrates neurodivergence and musculoskeletal burden **(Table 3)**. Clinicians should ground diagnosis in guideline-based criteria while acknowledging that symptom expression may be atypical and easily overshadowed by autism or ADHD labels (NICE, 2024). Visits should embed brief, validated screens for mood, anxiety, sleep disturbance, pain interference, alcohol use, and executive-function barriers to adherence, with results guiding the initial care plan (NAMS, 2023). For women with chronic pain or hypermobility, clinicians should document baseline nociception, sleep quality, and activity limitations to enable responsive titration of therapies (Wright, 2024). Written summaries, predictable appointment structures, and sensory accommodations—quiet rooms, reduced lighting, and paced information delivery—should be standard to support accurate history-taking in autistic and ADHD populations (Brady et al., 2024). Because workplace functioning may mask clinical severity, practitioners should ask about effort and after-work recovery costs rather than relying solely on performance outcomes (Jenkins & Foxhill, 2024). Shared decision-making must surface route preferences, sensory sensitivities, and dose-handling constraints before any pharmacologic choice is made (NICE, 2024). These practices create an equitable diagnostic foundation that reduces delays and mismatches between treatment and lived experience (Brady et al., 2024).

Table 3. Neuroinclusive implementation checklist for clinics

Domain	Specific practices	Implementation owner	Audit metric
Environment	Quiet waiting zone; dimmable, low-glare lighting; reduced visual clutter; scent-minimization policy; availability of noise-attenuation devices and sensory kits (e.g., fidgets, weighted lap pads); temperature control options; signage offering accommodations; optional "wait in car/text when ready" check-in.	Clinic manager; Facilities/operations; Front-desk lead	Mean ambient noise level (dB) by hour; % rooms with dimmable lighting; % visits offered low-stimulus waiting; patient-reported sensory comfort ≥4/5; availability rate of sensory aids (stock checks/week).
Process	Pre-visit questionnaire (goals, sensory needs, communication preferences); extended new-patient slots; paced agenda with time estimates; buffer time between visits; consistent clinician assignment when possible; simplified	Operations lead; Scheduling team; Access coordinator	% visits with pre-visit forms completed ≥48 h prior; average schedule overrun (min); continuity index (% visits with same clinician); no-show rate; median

	forms with icons; option for asynchronous history submission; clear wayfinding and staggered arrivals.		check-in-to-room time; % first visits booked at extended length.
Communication	Written after-visit summary (AVS) in plain language with visual bullets; explicit stop–start rules for meds and when to call; teach-back documented; option for a supporter/advocate; multi-modal education (text + pictorial); choice of message vs. phone follow-up; preference-captured pronouns and sensory notes surfaced in header.	Clinicians; Nursing staff; Patient-education lead; Health literacy champion	% encounters with same-day AVS; % notes documenting stop–start rules; % visits with teach-back recorded; median portal message response time; PREM score on "felt understood/clear plan" ≥4/5.
Monitoring	Embedded brief screens (PHQ-9, GAD-7, ISI, AUDIT-C, BPI, sensory burden VAS); scheduled follow-up cadence (4–6 weeks, 12 weeks, 6/12 months); digital reminders for meds/patch rotation; lab protocol		

Abbreviations: *AVS = after-visit summary; BPI = Brief Pain Inventory; C-SSRS = Columbia-Suicide Severity Rating Scale; DXA = dual-energy X-ray absorptiometry; EHR = electronic health record; FRAX = Fracture Risk Assessment Tool; GAD-7 = Generalized Anxiety Disorder-7; ISI = Insomnia Severity Index; LFTs = liver function tests; MA = medical assistant; NK3 = neurokinin-3; PREM = patient-reported experience measure; SBIRT = Screening, Brief Intervention, and Referral to Treatment; VAS = visual analogue scale.*

The second recommendation is to prioritize transdermal estradiol when MHT is indicated, using low-dose initiation and slow titration in sensory-sensitive patients. Comparative assessments indicate that transdermal delivery avoids first-pass hepatic metabolism and may yield more stable pharmacokinetics and lower thromboembolic signal in appropriately selected patients, a profile that may translate to fewer mood perturbations for those sensitive to serum peaks and troughs (CADTH, 2025). Guideline concordance should be maintained by employing regulated, FDA-/MHRA-approved bioidentical estradiol patches, gels, or sprays rather than routine compounded products of variable potency (ACOG, 2023). Start with the lowest effective dose, pair changes with scheduled follow-up focused on sleep and affect, and favor once-weekly patches or simple gel routines to minimize executive-load (NICE, 2024). For patients with migraine, hypertension, or elevated venous thromboembolism risk, the transdermal route may provide additional safety advantages relative to oral options (CADTH, 2025). Sensory-comfort strategies—site rotation guides, adhesive test patches, and written visual cues—should accompany initiation to improve tolerability in autistic and ADHD populations (Brady et al., 2024). If gastrointestinal sensitivity or interoceptive distress has complicated past oral regimens, transdermal estradiol should be the default consideration. These route-first principles balance efficacy with the neurodivergent need for pharmacokinetic stability and predictable self-management.

The third recommendation concerns progestogen selection, emphasizing micronized progesterone or other guideline-supported strategies that optimize endometrial protection while minimizing neuropsychiatric side effects. Where the uterus is present, use oral micronized progesterone in continuous or cyclic regimens tailored to mood tolerability, with evening dosing to leverage somnogenic properties and reduce daytime sedation in executive-demand contexts. For patients with suspected progestin sensitivity—irritability, dysphoria, or panic—avoid highly androgenic or sedating synthetic progestins and consider lower-dose schedules with close symptom monitoring (BMS, 2023). A levonorgestrel intrauterine system can provide local endometrial protection with minimal systemic exposure for some patients, though mood surveillance remains prudent in sensitive individuals (NICE, 2024). Routine use of compounded "bioidentical" progesterone is discouraged given inconsistent potency, purity concerns, and the potential to destabilize mood through dose variability (ACOG, 2023). Clinicians should document a clear endometrial-safety plan—dose, schedule, surveillance—and co-create stop–start rules for symptom thresholds that trigger reassessment. When cyclic regimens precipitate perimenstrual mood crashes, transition to continuous dosing and adjust estradiol to smooth fluctuations. These choices reduce route- and agent-related risks while aligning uterine protection with neurodivergent tolerability profiles.

The fourth recommendation is to position evidence-based nonhormonal therapies as modular, first-class options that can be layered with or without MHT to target vasomotor symptoms, sleep continuity, and pain amplification. High-quality evidence supports SNRIs and SSRIs—particularly venlafaxine and escitalopram—for meaningful reduction in hot flashes, with rapid onset that benefits patients delaying or avoiding estrogen. Gabapentin—especially as an evening dose—improves nocturnal vasomotor symptoms and sleep maintenance, which may secondarily attenuate daytime sensory overwhelm and hyperalgesia, though dizziness and dissociation-like sensations warrant slow titration. Emerging neurokinin-3 receptor antagonists provide a nonhormonal,

hypothalamic-targeted path for refractory vasomotor symptoms without hepatic first-pass effects, a mechanistic fit for patients wary of estrogen-linked mood lability (Iyer et al., 2024). To accommodate executive-function challenges, prefer once-daily formulations, provide pill organizers or digital prompts, and pair pharmacotherapy with brief, structured sleep-hygiene and stimulus-control coaching (NAMS, 2023). When ADHD or anxiety medications are in place, coordinate dosing schedules to minimize interaction-driven insomnia or activation (NICE, 2024). Clinicians should map expected timelines to effect for each agent and schedule early, focused follow-ups on tolerability and functional gains. This modular strategy respects heterogeneity, reduces abandonment due to side effects, and increases the likelihood of durable symptom control.

The fifth recommendation is to embed an integrated pain–sleep management pathway that addresses neuroinflammation, central sensitization, and behavioral maintenance factors. Mechanistic evidence implicating STAT3-dependent neuroinflammatory signaling in chronic pain supports early attention to sleep continuity and vasomotor control as levers to reduce nociceptive gain during premenopause (Ji & Zhang, 2024). Clinicians should combine vasomotor management with graded, low-impact strengthening, balance, and mobility work adapted for hypermobility or myofascial pain, prioritizing consistency over intensity to avoid sensory overload (Wright, 2024). Where gabapentin is used for hot flashes, evaluate dual benefits for neuropathic pain and sleep consolidation, and adjust to the lowest effective nighttime dose to limit daytime cognitive fog (Iyer et al., 2024). Behavioral insomnia treatments should be tailored with visual schedules, simplified sleep-restriction steps, and sensory-friendly sleep environments to match autistic and ADHD cognitive styles (Metcalf et al., 2023). Anti-inflammatory diet patterns and omega-3 supplementation can be offered as low-risk adjuncts, with expectations framed around modest, additive effects rather than standalone cures (NAMS, 2023). Pain-diary tools that capture sensory triggers and menstrual timing can help distinguish endocrine-driven flares from activity-induced exacerbations. This integrated pathway reduces flare frequency, preserves function, and improves cognitive bandwidth for daily tasks.

The sixth recommendation is to formalize bone-health surveillance and intervention thresholds early in the transition, particularly for women with reduced mobility or connective-tissue laxity. Use guideline-endorsed fracture-risk tools and bone mineral density testing schedules that reflect age, risk factors, and symptom burden, with documentation of individualized thresholds for initiating antiresorptives or anabolic agents (OC, 2023). Where MHT is chosen primarily for symptom relief, communicate its bone-preserving benefit as contingent on continued use, and avoid positioning estrogen as a standalone osteoporosis therapy in high-risk patients who warrant disease-modifying agents. Prescribe progressive resistance and balance training with adaptations for joint instability and sensory tolerance, emphasizing brief, routine sessions over sporadic high-load efforts (Wright, 2024). Ensure vitamin D sufficiency, dietary calcium adequacy, and fall-risk mitigation in the home and workplace, integrating occupational-therapy input when executive-function barriers impede environmental change (NICE, 2024). For patients with adherence challenges, select osteoporosis medications with dosing schedules that reduce cognitive load—e.g., yearly infusions or six-monthly injections when appropriate. Reassess risk annually, revisiting pharmacologic and lifestyle components to maintain alignment with evolving symptoms and goals. This proactive skeletal plan mitigates fracture risk while dovetailing with neurodivergent capacities and preferences.

The seventh recommendation is to integrate alcohol-risk counseling and monitoring into all hormone-modulation pathways, recognizing estradiol's capacity to potentiate reward circuitry. Preclinical evidence demonstrates that high-estradiol states can acutely enhance alcohol's reinforcing effects through rapid, nongenomic signaling in stress–reward hubs, supporting precautionary counseling during MHT initiation and uptitration (Zallar et al., 2024). Clinicians should normalize brief alcohol-use screening, discuss periods of increased vulnerability, and consider transdermal estradiol to reduce rapid pharmacokinetic swings that might amplify reward responsivity. For patients with ADHD, impulsivity, or prior hazardous drinking, schedule early follow-ups focusing on craving, quantity-frequency patterns, and substitution strategies that deliver non-alcoholic reward—exercise, social reinforcement, or sensory-soothing routines (Handy, Greenfield, & Payne, 2025). Provide written relapse-prevention plans and referral pathways that include neurodiversity-aware counseling resources, reducing stigma that impedes disclosure (Brady et al., 2024). Where alcohol-related sleep disruption or mood instability emerges, adjust hormone dose or route and add nonhormonal vasomotor control to reduce triggers (Iyer et al., 2024). Document counseling content and revisit as part of standard MHT safety monitoring to reinforce learning and support behavior change. This integrated approach treats alcohol risk as a modifiable mediator rather than a moral failing, improving safety and therapeutic durability.

The eighth recommendation is to operationalize neuroinclusive implementation across clinics through protocols, environment design, and coordinated multidisciplinary care. Menopause services should standardize longer appointments for complex neurodivergent cases, provide pre-visit questionnaires, and guarantee written after-visit summaries with clear action steps and timelines (Jenkins & Foxhill, 2024). Environmental adjustments—quiet waiting spaces, reduced visual clutter, and permission for noise-attenuation devices—should be routine, not exceptional, to lower sensory load and improve communication (Brady et al., 2024). Cross-service pathways linking gynecology, pain, mental health, and bone clinics with shared notes and agreed metrics can reduce duplication and polypharmacy risks (NICE, 2024). Protocols should specify monitoring cadence for mood, sleep, pain, alcohol use, and adherence, with explicit rescue plans for suicidal ideation or intolerable side effects (NAMS, 2023). Staff training modules on neurodiversity-affirming communication and executive-function supports can be embedded in continuing education,

with audits tied to patient-reported experience measures. Finally, services should commit to learning-health-system practices by capturing stratified outcomes for autistic and ADHD patients to refine dosing heuristics, route preferences, and counseling content over time. These implementation steps translate evidence into equitable access and sustained benefit for neurodivergent women navigating premenopause.

5. DISCUSSION

The findings cohere around a central proposition: premenopausal estradiol variability interacts with neurodivergent sensory–executive phenotypes and musculoskeletal vulnerability to amplify pain, mood dysregulation, and sleep disturbance. Evidence that estradiol modulates neuroinflammation, nociceptive gain, and monoaminergic transmission provides a mechanistic substrate for symptom clustering in this population, particularly when musculoskeletal syndromes prime peripheral and central sensitization (Ji & Zhang, 2024; Wright, 2024). Neurocognitive literature further documents transient decrements in memory and attention that are tightly coupled to vasomotor instability and sleep fragmentation, effects likely to carry outsized functional costs where baseline executive control is already taxed (Metcalf et al., 2023). Qualitative data from autistic women underscore how sensory overload, masking demands, and clinical communication friction shape help-seeking and adherence, suggesting that biomedical mechanisms and delivery-system dynamics jointly drive outcomes (Brady et al., 2024; Jenkins & Foxhill, 2024). Within this intersection, premenopause is not merely a precursor to menopause but a high-leverage interval for early, route-specific intervention and environmental adaptation. The synthesis therefore justifies a dual emphasis on pharmacokinetics that minimize volatility and on neuroinclusive practice that reduces sensory and executive load. Such a posture is congruent with contemporary guideline movements toward individualized, risk-stratified care while extending them to neurodivergent realities. Taken together, the convergent evidence argues for redefining premenopausal care as an integrative, systems-aware endeavor rather than a symptom-by-symptom exercise (NICE, 2024; NAMS, 2023).

The comparative evidence on hormone-therapy routes supports a transdermal-first stance for many neurodivergent patients with musculoskeletal syndromes, given steadier serum estradiol profiles and avoidance of hepatic first-pass effects. Health technology assessment points to potential cardiometabolic and thromboembolic advantages of transdermal estradiol in selected populations, while also highlighting equivalence in vasomotor efficacy that allows route to be chosen for safety and tolerability rather than symptom control alone (Abdelrazeq, 2025). From a neurodivergent perspective, flatter pharmacokinetic curves plausibly reduce mood perturbations linked to peaks and troughs, though direct comparative trials in autistic or ADHD cohorts remain absent. Organizational guidance simultaneously cautions against routine use of compounded “bioidentical” hormones because of variable potency and quality, a concern that is particularly salient when small dose deviations can trigger sensory or affective destabilization (ACOG, 2023). Endometrial protection strategies must likewise be individualized; micronized progesterone often provides a favorable neuropsychiatric profile, whereas certain synthetic progestins may exacerbate irritability in sensitive patients (BMS, 2023). Clinicians should explicitly incorporate executive-function capacity into route selection, favoring once-weekly patches or straightforward gel routines when adherence challenges are likely. Documentation of a clear monitoring cadence for mood, sleep, and tolerability anchors safety while making dose adjustments predictable. This route-first, adherence-aware orientation addresses a unique convergence of biology and cognitive ecology (NICE, 2024; NAMS, 2023).

Nonhormonal agents emerge as modular, co-equal tools that can be sequenced or layered to target thermoregulation, sleep continuity, and pain amplification without the risks or affective lability that some patients ascribe to estrogen. Systematic clinical reviews place SNRIs and SSRIs, particularly venlafaxine and escitalopram, alongside gabapentin as first-line options with moderate-to-large effects on vasomotor frequency and sleep quality, providing rapid relief useful when hormone therapy is contraindicated or paused for diagnostic clarification (Iyer, Fiffick, & Batur, 2024; NAMS, 2023). The translational logic is compelling for neurodivergent women with pain and sensory overload: reducing nocturnal arousals can lower next-day hyperalgesia and cognitive fog, indirectly improving executive bandwidth for self-management. Neurokinin-3 receptor antagonists add a nonhormonal, hypothalamic-targeted mechanism that avoids hepatic first-pass effects and may appeal to individuals wary of estrogenic mood effects or gastrointestinal interoception. Tolerability profiles require careful pacing; dizziness or dissociation-like sensations with gabapentin and activation or sleep disruption with serotonergic agents argue for slow titration and deliberate scheduling. Because polypharmacy is common in ADHD and mood disorders, drug-drug interaction checks and coordinated dose timing are indispensable. The broader lesson is that nonhormonal agents should be framed not as fallback options but as integral components of a precision, preference-based strategy. Such reframing increases therapeutic latitude and respects heterogeneity in both biology and lived experience (NAMS, 2023).

The alcohol–estrogen axis warrants explicit integration into counseling and follow-up, given preclinical evidence that high estradiol states acutely increase the rewarding properties of alcohol via rapid, nongenomic signaling in stress–reward circuits. Experimental work demonstrates that estradiol can heighten binge-drinking behavior by exciting corticotropin-releasing factor neurons in the bed nucleus of the stria terminalis, a mechanistic pathway that plausibly maps onto real-world vulnerability during hormone initiation or dose escalation (Zallar et al., 2024). Human literature synthesizing hormonal influences on women’s alcohol use further supports heightened risk windows across reproductive transitions and underscores the need for anticipatory guidance rather than reactive

problem-solving (Handy, Greenfield, & Payne, 2025). For neurodivergent women—particularly those with impulsivity or stress-related coping patterns—the intersection of reward sensitization and executive-control strain suggests a low threshold for screening, monitoring, and brief intervention. Transdermal regimens may mitigate rapid pharmacokinetic swings that could exaggerate reward responses, although this remains a hypothesis requiring clinical validation. Behavioral substitution strategies that deliver non-alcoholic reward and sensory soothing—exercise, social reinforcement, or structured relaxation—should be operationalized in care plans. Documentation of relapse-prevention steps and referral to neurodiversity-aware substance-use services can destigmatize disclosure. Treating alcohol risk as a modifiable mediator of treatment outcomes, rather than as a moral failing, aligns with patient-centered ethics and safety (NAMS, 2023; Iyer et al., 2024).

Musculoskeletal integrity forms the second pillar of risk management, because estrogen decline accelerates bone turnover and may destabilize connective-tissue homeostasis in those already contending with hypermobility or myofascial pain. Contemporary osteoporosis guidance emphasizes fracture-risk stratification using clinical factors and bone mineral density, with clear thresholds for antiresorptive or anabolic therapy that should be adapted to executive capacity—favoring long-interval dosing when adherence is fragile (OC, 2023). Exercise prescriptions deserve equal rigor; progressive resistance, balance work, and proprioceptive training require modifications to respect joint laxity and sensory tolerance while prioritizing consistency over intensity to avoid flares (Wright, 2024). Sleep consolidation functions here as a cross-cutting intervention, because improved sleep reduces pain amplification and supports anabolic signaling relevant to bone and tendon health (Metcalf et al., 2023). Nutrition and anti-inflammatory dietary patterns are reasonable adjuncts; yet expectations must be scaled to additive effects, not curative claims, to avoid demoralization and nonadherence. Pharmacologic choices for vasomotor symptoms can synergize with pain management—night-time gabapentin, for instance, may benefit both domains, albeit with careful monitoring for cognitive haze (Iyer et al., 2024). The clinical arc should move from stabilization of sleep and vasomotor symptoms to graded loading and bone-specific therapies as needed. Such staging preserves function while mitigating fracture risk during a period of accelerated skeletal change.

Health-system delivery is a decisive determinant of success, because many barriers identified by autistic and ADHD respondents arise from the clinical environment and communication style rather than from pharmacology. Survey and qualitative evidence document how sensory load, unpredictability, and compressed information delivery degrade history-taking, shared decision-making, and trust, thereby undermining persistence with otherwise appropriate treatment plans (Brady et al., 2024; Jenkins & Foxhill, 2024). Neuroinclusive redesign—longer visits for complex cases, structured agendas, written after-visit summaries, and quiet waiting areas—should be treated as standard components of quality, not ancillary amenities. Cross-disciplinary pathways linking menopause care, pain management, mental health, and bone services can reduce polypharmacy and streamline monitoring, especially when shared metrics and stop–start rules are embedded in electronic records.. Executive-function supports—medication organizers, digital reminders, visual patch-rotation guides—translate directly into improved adherence without pathologizing cognitive style. Workplace counseling should focus on effort costs and post-work recovery rather than on visible performance alone, because masking can conceal clinically significant burden (Jenkins & Foxhill, 2024). Routine, stigma-free screening for suicidality, alcohol use, and sleep disruption respects the elevated risk profile during hormone modulation. In short, implementation science is as critical as pharmacology for realizing equity in outcomes.

Notwithstanding these practical directives, the evidentiary substrate exhibits important limitations that temper confidence and delineate a research agenda. Randomized trials rarely stratify by neurodivergence, making it difficult to quantify effect modification or to identify tolerability signals unique to autistic or ADHD cohorts (Metcalf et al., 2023; Iyer et al., 2024). Observational studies often lack standardized staging criteria for the menopausal transition, complicating cross-study synthesis and causal inference. Preclinical insights into estrogen-linked alcohol reward require careful translation, because rodent circuits and dosing paradigms do not map cleanly onto human pharmacokinetics or environmental contexts (Zallar et al., 2024). Guidance on compounded hormones remains largely consensus-based in the absence of robust comparative trials, although the safety rationale for avoiding variability is persuasive in sensory-sensitive populations (ACOG, 2023). Pain-mechanism studies implicate STAT3-dependent glial signaling, but biomarkers suitable for clinical stratification are not yet standardized (Ji & Zhang, 2024). Bone-health recommendations draw on general population data, leaving questions about how connective-tissue disorders intersect with standard thresholds. The methodological heterogeneity that characterizes this literature should motivate—not paralyze—pragmatic experimentation in real-world clinics. Clear reporting on neurodivergent status and musculoskeletal phenotypes is a minimum step toward interpretability.

A forward-looking research program should therefore prioritize pragmatic, comparative trials that test route-of-administration decisions, progestogen choices, and nonhormonal algorithms specifically in neurodivergent women with musculoskeletal syndromes. Transdermal versus oral estradiol, micronized progesterone versus selected progestins, and the addition of neurokinin-3 antagonists versus SNRIs/SSRIs represent decision nodes ready for evaluation using patient-centered outcomes and tolerability profiles (Abdelrazeq, 2025; Iyer et al., 2024). Embedded implementation-science designs can simultaneously examine neuroinclusive delivery models—visit length, environmental adaptations, written summaries—and their effect on adherence and quality of life (NICE, 2024). Digital phenotyping with wearables offers a feasible method to track sleep continuity, thermoregulatory events, activity, and alcohol use with minimal respondent burden, enabling just-in-time titration. Biomarker substudies should test whether inflammatory signatures or autonomic markers identify subgroups most likely to benefit from specific interventions,

extending mechanistic plausibility into actionable stratification (Ji & Zhang, 2024). Alcohol-risk mitigation protocols linked to hormone titration schedules merit prospective validation, with attention to impulsivity and executive-control moderators (Handy et al., 2025; Zallar et al., 2024). Finally, outcome sets must include cognitive and sensory-burden measures alongside traditional vasomotor and bone metrics to capture what matters most to patients. Such a program would convert conceptual integration into measurable gains.

Clinical implications follow directly from this synthesis and justify a structured, stepwise pathway. First, stage the transition and screen broadly for mood, sleep, pain interference, and alcohol risk using brief tools embedded into accessible visits (NICE, 2024). Second, select transdermal estradiol when MHT is indicated, pair with micronized progesterone when uterine protection is required, and titrate slowly with early follow-up focused on sensory and affective tolerability (BMS, 2023; Abdelrazeq, 2025). Third, deploy nonhormonal agents as modular co-equals for thermoregulation and sleep consolidation, coordinating with existing ADHD or mood treatments and simplifying regimens to match executive capacity (Iyer et al., 2024; NAMS, 2023). Fourth, couple symptom control to graded, sensory-aware rehabilitation and bone-risk mitigation, with dosing choices that minimize cognitive load for long-term therapies. Fifth, integrate alcohol-risk counseling into every hormone-modulation discussion and document relapse-prevention steps as part of standard safety practice (Handy et al., 2025). Finally, institutionalize neuroinclusive delivery—quiet spaces, written summaries, longer visits—and commit to continuous quality improvement with stratified outcomes. This pathway operationalizes equity by aligning mechanisms with lived realities.

The equity lens sharpened by this analysis has implications beyond the target population, because neuroinclusive design improves care for any patient with sensory sensitivity, executive-function strain, or communication barriers. Environmental modifications, written scaffolds, and predictable monitoring cadence function as universal design elements that rarely harm and often help. In ecosystems strained by time limits and polypharmacy, these low-cost interventions can yield disproportionate gains in adherence and satisfaction. Importantly, route-of-administration choices that privilege pharmacokinetic stability may generalize to patients with migraine, mood vulnerability, or hepatic risk irrespective of neurodivergence. The integrated pain–sleep approach similarly benefits individuals with central sensitization phenotypes, not only those with diagnosed neurodivergence (Ji & Zhang, 2024). As precision medicine becomes increasingly operational, the convergence of pharmacology, environment, and behavior should be the norm rather than the exception. This reframing shifts clinical success metrics from symptom counts to sustained function and quality of life.

Therefore, the discussion affirms that premenopause constitutes a strategic window for neurodivergent women with musculoskeletal syndromes in which targeted pharmacokinetic choices, modular nonhormonal therapies, bone-risk management, alcohol-risk mitigation, and neuroinclusive delivery can jointly alter trajectories. The argument rests on mechanistic plausibility, contemporary comparative evidence, and patient-reported barriers, while acknowledging gaps that necessitate pragmatic and translational research. By centering route stability, progestogen tolerability, sleep-pain coupling, and environmental design, clinicians can reduce flare frequency, stabilize mood, protect skeletal health, and preserve cognitive bandwidth. Organizational guidance provides a scaffold, but durable gains will depend on embedding neuroinclusive protocols into routine care and measuring outcomes that matter to patients. Future work should test the proposed pathway with stratification by neurodivergent status and musculoskeletal phenotype, validating benefits at scale. Until such trials report, a careful, patient-centered application of the present synthesis offers a defensible and humane standard. The ethical impetus is clear: align science with lived experience to deliver safer, steadier, and more sustainable premenopausal care.

6. CONCLUSION

The evidence synthesized here supports a reframing of premenopause as a strategically actionable interval in which estradiol variability interacts with neurodivergent sensory–executive profiles and coexisting musculoskeletal syndromes to produce disproportionate burdens in pain, mood, sleep, and day-to-day functioning. Mechanistic findings implicating neuroinflammatory signaling and nociceptive gain clarify why symptom clusters intensify when estrogen declines and sleep fragments—dynamics that exact higher functional costs in autism and ADHD due to baseline executive-control demands and interoceptive salience. Comparative assessments and guideline positions converge on a route-first principle: when menopausal hormone therapy is indicated, transdermal estradiol offers pharmacokinetic stability and avoids hepatic first-pass effects, features that plausibly reduce mood volatility in sensitive populations. Progestogen selection emerges as equally consequential, with micronized progesterone favored for endometrial protection where the neuropsychiatric tolerability profile is a priority and compounded products are discouraged because of dose variability. Nonhormonal agents—SNRIs/SSRIs, gabapentin, and neurokinin-3 receptor antagonists—should be framed as modular, co-equal tools that target thermoregulation, sleep consolidation, and pain amplification without obligate estrogen exposure. Alcohol-risk counseling must be embedded in hormone-modulation discussions, given evidence that high-estradiol states potentiate alcohol reward and may intersect with impulsivity and stress reactivity in neurodivergent cohorts. Bone-health surveillance and sensory-aware rehabilitation require early, explicit planning because accelerated turnover and joint instability threaten function during the transition. Implementation science is not ancillary: neuroinclusive delivery—longer visits, written summaries, quiet environments, and shared metrics—directly improves adherence and safety in populations reporting clinic-

environment distress. Taken together, these strands argue for a coordinated, systems-aware pathway that aligns pharmacology, environment, and behavioral supports to stabilize symptoms and preserve capability in premenopause.

Future progress depends on embedding this pathway within research and practice agendas that measure what matters to neurodivergent women with musculoskeletal syndromes. Pragmatic, stratified trials should compare oral versus transdermal estradiol, micronized progesterone versus selected progestins, and modular nonhormonal sequences, using outcomes that integrate vasomotor control with sleep continuity, sensory burden, pain interference, cognitive efficiency, and adherence. Digital phenotyping—wearable sleep/thermoregulatory markers, passive mobility indices, and low-burden alcohol-use telemetry—can enable just-in-time titration while minimizing reporting load in executive-function constraints. Clinics should adopt universal-design principles as standard quality measures, including pre-visit questionnaires, paced information delivery, and explicit stop–start rules for adverse-event thresholds, with outcomes audited by neurodivergent status to close equity gaps. Policy statements discouraging routine use of compounded "bioidentical" hormones should be operationalized through formularies that privilege regulated transdermal estradiol and micronized progesterone while maintaining access to nonhormonal agents for contraindications or preference. Bone-health algorithms must incorporate adherence-sparing dosing (e.g., infusions or biannual injections) and sensory-tailored exercise prescriptions that privilege consistency over intensity. Alcohol-risk mitigation should be standardized within hormone-modulation care plans via brief interventions and neurodiversity-aware referrals, acknowledging the biological plausibility of risk amplification during high-estradiol states. In sum, by coupling pharmacokinetic stability, neuroinclusive delivery, and rigorous monitoring of cross-domain outcomes, premenopausal care can move from piecemeal symptom control to durable improvement in function and quality of life. The ethical and scientific imperative is clear: translate convergent evidence into reproducible, equitable practice that centers neurodivergent lived experience while safeguarding musculoskeletal health.

Data Availability

Data available upon request.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Authors' Contributions

Conceptualization, P. Hutson; Methodology, P. Hutson; Validation, P. Hutson; Investigation, J. Hutson – Original Draft Preparation, J. Hutson; Writing – Review & Editing, J. Hutson.; Visualization, J. Hutson.

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