

# THE \$15 BILLION SILENCE: PMDD, COMPOUND NEUROBIOLOGICAL DEFICIT, AND OCCUPATIONAL SUICIDE IN THE U.S. REGISTERED NURSE WORKFORCE

*Hormonal Vulnerability And Suicide Among Nurses And People Assigned Female At Birth In Healthcare: An Integrated Evidence Synthesis With Legal And Policy Analysis*

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This work presents an original analysis of the compound neurobiological mechanisms underlying elevated suicide risk in the U.S. registered nurse workforce, with an integrated economic burden model and institutional accountability framework.

## ABSTRACT

Female nurses die by suicide at approximately twice the rate of the general female population. A parallel literature documents that suicide attempts and deaths among people assigned female at birth (AFAB) concentrate during menstrual cycle phases of low estradiol and low progesterone, and that premenstrual dysphoric disorder (PMDD) confers approximately sevenfold elevated odds of suicide attempt and a 1.92-fold hazard of suicide death. These findings have never been studied in the same population. This manuscript establishes that intersection as a formally documented research gap, generates testable hypotheses, extends the analysis to transgender men and AFAB nonbinary individuals in healthcare, introduces a compounding neurobiological deficit model linking cholesterol substrate availability and thyroid function to the primary hormonal mechanism, and develops legal and policy frameworks governing employer and provider obligations to a workforce carrying documented, modifiable suicide risk.

Registered nurses constitute the largest professional segment of the U.S. healthcare workforce and bear a disproportionate burden of occupational psychiatric morbidity, including post-traumatic stress disorder, premenstrual dysphoric disorder (PMDD), and suicidal ideation. Despite decades of evidence linking shift work, hormonal dysregulation, and institutional moral suppression to measurable neurobiological harm, this workforce receives no standardized occupational mental health surveillance and faces diagnostic delays averaging more than a decade for PMDD alone.

This analysis establishes the aggregate economic burden of PMDD-associated occupational harm and suicide in the U.S. registered nurse workforce, maps five convergent neurobiological pathways to a common mechanistic endpoint, and positions these findings within an institutional accountability and failure-to-rescue framework. A structured

literature synthesis drew on peer-reviewed sources across psychiatry, neuroendocrinology, occupational health, and health economics, supplemented by federal workforce surveillance data from the Health Resources and Services Administration, the National Council of State Boards of Nursing, and the Bureau of Labor Statistics. Economic burden calculations applied published per-person cost estimates to a nursing-specific prevalence model. The Continuity Risk Framework (CRF), Clinical Moral Disengagement Scaffolding (CMDS), and Comprehensive Occupational Violence and Extraction Framework (COVE-F) provided the analytic architecture for institutional and systemic attribution.

An estimated 23% of ICU nurses and 18% of general medical-surgical nurses meet full diagnostic criteria for PTSD (Mealer et al., 2009), with COVID-era meta-analytic pooled prevalence reaching 29.1% across nursing populations globally (Hernandez-Bojorge et al., 2024), producing an aggregate annual economic burden of approximately \$14.0 billion. PMDD, affecting 3% to 8% of women of reproductive age and an estimated subset of AFAB individuals, is misdiagnosed at high rates as bipolar disorder or treatment-resistant depression. Five neurobiological pathways converge on mitochondrial neurosteroid synthesis: PMDD-associated GABA-A receptor hypersensitivity, statin-mediated cholesterol reduction, hypothyroid StAR protein impairment, ACE-driven HPA axis dysregulation, and PTSD-related allopregnanolone depletion. Under conditions of occupational exposure -- shift work, sleep deprivation, sustained cortisol elevation, and institutional coercion -- these pathways produce compound allopregnanolone reduction and measurable increase in suicide risk.

The economic and clinical cost of this harm is preventable. Institutional accountability, diagnostic accuracy, and occupational surveillance structured within validated escalation frameworks offer a tractable intervention pathway.

## **METHODS**

Narrative synthesis of peer-reviewed literature published 1998 through 2025 across occupational epidemiology, reproductive psychiatry, neuroendocrinology, clinical psychology, pharmacology, and legal scholarship. Primary sources include NVDRS-linked cohort studies, systematic reviews and meta-analyses, randomized controlled trials, population-based registry studies, and regulatory and statutory primary documents. Methodological limitations, contested evidence, funding conflicts in the underlying research, and historical factors shaping the evidence base are addressed inline rather than deferred to limitation sections, so that the argument is self-contained.

## **RESULTS**

Five independent and fully replicated evidence streams converge without prior integration, with an additional mechanistic pathway identified for the first time in this synthesis. Female nurses carry a relative risk of approximately 2.0 for suicide death compared to the general female population, a finding replicated across four countries with the elevation concentrated in female workers. PMDD confers a sevenfold elevation in suicide attempt odds (OR 6.97, 95% CI 2.98 to 16.29) and a population-confirmed hazard ratio of 1.92 for

suicide death (HR 1.92, 95% CI 1.43 to 2.60), with perimenstrual risk states experimentally reversed by transdermal estradiol and progesterone in a crossover randomized controlled trial. The intersection is definitively unstudied. Beyond the primary hormonal mechanism, a compounding neurobiological deficit model is proposed: statin-mediated reduction in cholesterol substrate availability, combined with hypothyroid impairment of mitochondrial cholesterol transport, reduces the precursor pool for all neurosteroid synthesis, amplifying estrogen and progesterone deficiency effects in a multi-system pattern that current psychiatric evaluation does not measure. Transgender men and AFAB nonbinary individuals in healthcare carry compound vulnerability from elevated baseline suicide risk, structural exclusion from PMDD diagnostic tools, potential persistence of ovarian cycling under testosterone therapy, and complete absence from occupational health research. The legal framework supports employer duty to screen and accommodate PMDD as an episodic disability under the ADAAA, provider liability for PMDD misdiagnosis, and regulatory action through the Dr. Lorna Breen Health Care Provider Protection Act. A fifth compounding mechanism is introduced: ACE-driven HPA axis dysregulation and PTSD-associated allopregnanolone depletion, both disproportionately prevalent in the nursing workforce, operate through the same GABA-A neurosteroid synthesis pathway as PMDD, producing a multi-source deficit state in trauma-exposed nurses that no current clinical or occupational health assessment measures. The diagnostic maze of PMDD, CPTSD, and BPD is addressed, with the single discriminating question identified: symptom timing relative to the menstrual cycle.

## CONCLUSIONS

The thesis of this manuscript is not undermined by rigorous methodological critique; it is strengthened by it. The observed relative risk of 1.99 for female nurse suicide is likely a conservative estimate because nurses who exit the workforce due to psychiatric deterioration before a suicide event are reclassified into the general female population comparison group, attenuating the true occupational signal. The wide confidence interval in the PMDD suicidality meta-analysis, even at its lower bound, establishes an approximately threefold elevation in attempt risk, comparable to or exceeding the recognized risk attributed to other psychiatric conditions that receive substantially greater research investment. The hormonal contraception literature, which appears to contradict the estrogen-deficiency model, dissolves under pharmacological specificity: synthetic progestins are not bioidentical progesterone; ethinyl estradiol is not 17-beta-estradiol; and the contraceptive literature signal is mechanistically consistent with, not contradictory to, the perimenstrual vulnerability model. The research agenda is defined, feasible, and overdue.

Keywords: nurse suicide; premenstrual dysphoric disorder; occupational suicide; nursing workforce; allopregnanolone; neurobiological convergence; failure-to-rescue; PTSD economic burden; institutional negligence; nurse mental health; GABA-A receptor dysregulation; Clinical Moral Disengagement Scaffolding; Continuity Risk Framework; perimenopause; neurodiversity; compound neurosteroid impairment; PMDD; menstrual cycle; suicide risk; hormonal vulnerability; transgender health; AFAB; occupational mental

health; cholesterol; neurosteroids; statins; statin-neurosteroid interaction; estrogen deficiency; GABA-A; borderline misdiagnosis; BPD; bipolar misdiagnosis; Americans with Disabilities Act; Dr. Lorna Breen Act; Flexner Report; research gap; healthcare worker wellbeing

## INTRODUCTION

When a nurse dies by suicide, the systems designed to document that death record a great deal. The National Violent Death Reporting System captures method, location, toxicology, the presence or absence of a recent mental health contact, and whether a crisis service had been reached. It does not record where the decedent was in her menstrual cycle.

That omission is not an oversight. It is the product of a research culture that was built, beginning in 1910, around a medical education framework that systematically excluded cyclical female biology from clinical training. The Flexner Report, published under Carnegie Foundation auspices with implementation funding from Rockefeller philanthropic institutions totaling between \$500 million and \$1 billion in early 20th-century currency, established the biomedical model as the sole legitimate form of medical education and de-funded institutions teaching plant-based medicine, midwifery, electrotherapy, and women-centered cyclical health practice. The documented institutional precommitment of the report's primary funders against competing paradigms — verifiable from primary sources including correspondence between Frederick Gates, Rockefeller's philanthropic director, and medical school representatives — produced a training infrastructure that treated menstrual variation as a confounder to be excluded from research rather than a variable to be measured. Every medical curriculum since has inherited that exclusion. The NIH Revitalization Act of 1993 mandated inclusion of women in federally funded clinical research specifically because the preceding 40-year evidence base for psychotropic and cardiovascular medications had been built on male-dominated trials and applied to female patients without sex-stratified recalibration. The research gap documented in this manuscript is a downstream consequence of these institutional decisions, not an ordinary limitation of an emerging field.

The thesis of this manuscript connects multiple independent and fully replicated evidence streams that have developed in parallel for decades without integration. Female nurses die by suicide at approximately twice the rate of the general female population, a finding consistent across the United States, United Kingdom, Australia, and Canada, with the risk concentrated entirely in female workers. A robust and growing neurobiological literature establishes that suicide attempts and deaths among AFAB individuals are significantly concentrated during menstrual cycle phases of low estradiol and low progesterone, via mechanisms now characterized at the level of specific receptor systems and confirmed in a crossover randomized controlled trial demonstrating pharmacological reversibility. Premenstrual dysphoric disorder, affecting 1.6 to 5.8 percent of cycling AFAB individuals, confers approximately sevenfold elevated odds of suicide attempt and has been associated in a Swedish national registry with a 1.92-fold hazard of suicide death. These three streams have never been examined in the same population.

This paper makes no causal claim that PMDD explains nurse suicide. It makes the more precise and defensible claim that five independently established facts have never been studied together; that the biological mechanisms connecting them are characterized, coherent, and modifiable; and that the continued failure to study the intersection constitutes preventable harm at quantifiable scale. The inference from separate literatures to a formal hypothesis is the standard epistemological structure of research-gap papers in medicine; every major clinical trial in cardiovascular, oncological, and psychiatric epidemiology was justified by exactly this type of convergent inferential reasoning before the linking study existed.

The manuscript addresses, inline throughout its sections, the methodological and interpretive challenges that rigorous peer review will raise: the comparison-population structure of the nurse-suicide literature and its implications for whether the reported relative risks are underestimates or overestimates; the evidence quality and ascertainment bias concerns in the PMDD suicidality literature; the apparent contradiction between the estrogen-deficiency model and the hormonal contraception literature, which resolves under pharmacological specificity; the distinction between suicidal ideation, suicide attempt, and completed suicide and why each level of the spectrum is addressed differently; and the institutional and funding history that generated and perpetuated the research gap. A compounding neurobiological deficit model is introduced, integrating statin-mediated cholesterol substrate reduction, thyroid hormone deficiency, and multi-system neurosteroid synthesis impairment into the primary hormonal framework. The analysis is extended to transgender men and AFAB nonbinary individuals in healthcare, who carry compound vulnerability from multiple converging sources and are entirely absent from the occupational health literature. The legal and policy framework governing action at employer, provider, and regulatory levels is analyzed. The comprehensive research agenda required to test the hypotheses generated here is specified in sufficient detail to guide funding applications, IRB submissions, and professional organization advocacy.

*Plain-language summary: Female nurses die by suicide at twice the rate of other women. There is strong evidence that women are more likely to attempt suicide when their hormone levels are lowest in their cycle. A condition called PMDD makes that risk even higher. Nobody has ever studied whether these facts are connected in nurses. This paper connects them, explains why the gap exists, describes how related factors like cholesterol-lowering medications and thyroid problems can make things worse, addresses transgender nurses and gender-diverse people, and lays out what the law requires employers and doctors to do about it.*

## **SECTION I: THE SCOPE OF WHAT HAS NOT BEEN COUNTED**

The U.S. registered nurse workforce is the largest segment of the domestic healthcare labor force, comprising approximately 3.1 million actively employed individuals as of 2024. It is also among the most psychiatrically burdened professional populations on record, with prevalence estimates for post-traumatic stress disorder, major depressive disorder, and suicidal ideation consistently exceeding general population baselines by wide margins. Despite this documented burden, no federal occupational health standard mandates

neurobiological or psychiatric surveillance for this workforce. No standardized screening protocol exists at the national level. No systematic mechanism captures the relationship between occupational exposure conditions and psychiatric deterioration in employed nurses. The omission is not technical. It is structural, and it is consequential.

### **Section Ia: Core Findings and Their Replication**

Davis et al. (2021), in a retrospective NVDRS cohort spanning 2007 through 2018, identified 2,374 nurse suicides, of whom 1,912 (80.5 percent) were female. For the 2017 to 2018 measurement period, female nurse suicide incidence was 17.1 per 100,000, compared to 10.1 per 100,000 for female physicians and 8.6 per 100,000 for the general female population aged 30 and older. The sex-standardized relative risk for female nurses versus the general female population was 1.99 (95% CI 1.82 to 2.18). The comparable figure for male nurses was 0.95, statistically non-significant and directionally inverse. Davidson et al. (2024) extended this analysis through 2021, documenting year-by-year incidence rate ratios between 1.21 and 1.41 for female nurses versus female non-nurses. Olfson et al. (2023), using an American Community Survey cohort linked to the National Death Index, reported an adjusted hazard ratio of 1.64 (95% CI 1.21 to 2.23) for registered nurses versus non-healthcare workers, with a statistically significant sex-by-occupation interaction (chi-squared = 4.83; P = .03) confirming that the healthcare worker suicide elevation is significantly stronger in female workers. The international pattern is consistent: female nurses show rate ratios of 2.65 (Australia, Milner 2016), 1.95 (Australia updated, Petrie 2023), and comparable elevations in UK and Canadian data.

### **Section Ib: The Comparison Population and the Conservative Estimate**

The relative risk of 1.99 reported by Davis et al. (2021) compares female nurses to "all females aged 30 and older," a group that includes women unemployed due to disability, chronic illness, poverty, or recent psychiatric crisis, and women who have recently exited the workforce following mental health deterioration. This is not a healthier comparison group than the nursing workforce; in many respects it carries higher baseline psychiatric burden than employed individuals. The standard healthy worker effect critique, which holds that employed populations are healthier than general populations and that occupational comparisons therefore overstate occupational risk, does not apply in the direction critics typically assume for this dataset.

More importantly, there is a classification artifact that produces underestimation rather than overestimation of the true nursing-specific risk. A female nurse who develops severe PMDD or perimenopausal psychiatric deterioration, reduces her hours, moves to non-clinical roles, and ultimately exits nursing before a suicide event is subsequently counted in the general female population comparison group, not in the nursing cohort. Her elevated psychiatric risk, partly shaped by years of nursing-specific occupational stress and hormonal disruption, is reclassified to the comparison denominator. The net effect of this dynamic movement across the "employed nurse" / "general population" boundary is to attenuate the true occupational relative risk. The published figure of 1.99 should therefore



be understood as a floor estimate of the true sex-specific occupational elevation, not a ceiling.

This classification artifact is not unique to nursing research; it affects all occupational mortality studies using point-in-time employment coding. It is noted here not as a methodological complaint but as a corrective to the assumption that the comparison population structure biases results toward overstatement. The evidence is that it biases in the opposite direction.

### **Section Ic: The Sex-Concentration Signal**

The most methodologically significant and under-analyzed feature of the nurse-suicide literature is the male-female divergence in occupational risk. Male nurses show no elevated suicide risk (RR 0.95; Olfson sex-by-occupation interaction  $P = .03$ ). Male physicians show a modestly protective pattern (IRR 0.84 vs. general male population; Makhija 2025). Female nurses and female physicians both show substantially elevated risk compared to their respective general population comparators. Healthcare occupation is simultaneously protective for males and hazardous for females.

Male and female nurses share the same occupational stressor profile: shift work, patient death exposure, moral injury, pharmacological access, and institutional help-seeking suppression. If occupational stressors were the primary driver of the female-specific elevation, some residual elevation would be expected in male nurses as well; none is observed. Moral injury shows an adjusted odds ratio of 3.38 for suicidal ideation across healthcare workers in general, but this association is not reported to be sex-differentiated in the nursing literature in a way that would account for male nurses being at population-level risk while female nurses are at twice that level.

The parsimonious explanation for a biological signal that is present in female workers and absent in male workers is a sex-linked biological variable. The most characterized such variable in relation to psychiatric vulnerability is ovarian steroid cycling: the cyclical fluctuation of estradiol and progesterone that is present in female-assigned individuals and absent in male-assigned individuals. This is not the only possible explanation; it is the most biologically coherent one, and it is the one this manuscript argues deserves empirical investigation.

### **Section Id: Method Patterns and Their Clinical Significance**

Davis et al. (2021) documented that poisoning accounted for 24.9 percent of female nurse suicides versus 16.8 percent in the general female population, with antidepressants detected in 44 percent, benzodiazepines in 42 percent, and opiates in 33.7 percent of nurse decedents. These figures reflect pharmacological access conferred by occupation. They are relevant to the compounding neurobiological deficit model: a nurse who is perimenopausal, prescribed a statin, has undiagnosed subclinical hypothyroidism, carries PMDD misdiagnosed as bipolar disorder, and is prescribed a mood stabilizer and an antidepressant, has professional-grade access to each of these agents and a biological

substrate in which their mechanisms of action interact with her underlying neurosteroid deficit in ways that standard prescribing protocols do not account for.

### **Section Ie: Help-Seeking Suppression as Amplifier**

Kelsey et al. (2021) reported that nurses with suicidal ideation were substantially less willing to seek mental health treatment than physicians or the general employed population. This occupational barrier is real, documented, and clinically important. However, it functions as an amplifier of underlying risk, not a standalone explanation for female-specific elevation. Male nurses face identical occupational help-seeking barriers and show no elevated mortality. The suppression mechanism cannot, by itself, account for the sex-differential. Its role is more precisely characterized as increasing the probability that whatever drives the female-specific risk reaches lethal severity before being addressed, rather than creating the risk in the first place.

What has not been counted is large. This paper establishes a partial count, knowing that the final number, when complete methods of accounting are applied, will be substantially larger than what appears in these pages.

The analysis proceeds from a straightforward empirical premise: when a workforce of known size is exposed to documented occupational risk factors that produce measurable neurobiological harm, and when the economic consequences of that harm have been quantified in the general population using validated methodology, an aggregate burden figure can be constructed with stated assumptions and verifiable derivation. That figure, for PTSD alone in the U.S. nursing workforce, is approximately \$14.0 billion annually. The derivation is shown explicitly in Section VII. The assumptions are stated. The uncertainty bounds are acknowledged.

The analysis then advances a compound neurobiological deficit model. PTSD does not operate in isolation in this workforce. Registered nurses -- predominantly female and AFAB, currently at a median age of 50 years per the 2024 National Council of State Boards of Nursing (NCSBN) National Nursing Workforce Survey -- bring to their occupational exposure a set of endocrine and psychiatric vulnerabilities that interact with shift work, sleep deprivation, sustained cortisol elevation, and institutional coercive conditions to produce harm at the neurobiological level. Five convergent pathways to a common mechanistic endpoint are described and documented. The endpoint is allopregnanolone depletion -- a measurable neurosteroid deficit that increases suicide risk through GABA-A receptor sensitivity disruption. Each pathway is independently documented. Their convergence in a single individual is not a theoretical extreme; it is a predictable and common presentation given the workforce demographic profile described in the literature.

The third analytic frame concerns institutional accountability. The harm described here is not individual, random, or inevitable. It is produced by occupational conditions that are known, measurable, and institutionally perpetuated. It is made substantially worse by a diagnostic failure regime that delays PMDD diagnosis by more than a decade on average and misattributes PMDD symptomatology to bipolar disorder, PTSD, or treatment-resistant depression at rates that carry their own distinct pharmacological harms. And it is made



effectively invisible by the absence of occupational health surveillance architecture that would, if it existed, make the problem legally and regulatorily actionable. The Clinical Moral Disengagement Scaffolding framework explains, in institutional-behavioral terms, how this invisibility is manufactured and maintained.

This paper does not argue that nursing is uniquely suffering in the landscape of American occupational health. It argues that the suffering is measurable, partially quantified here in integrated form for the first time, and preventable with existing clinical tools and regulatory frameworks. The economic cost of prevention is lower than the economic cost of continuation. The clinical cost of prevention is lower than the clinical cost of continuation. The human cost of continuation is unacceptable under any accountability framework this analysis applies.

The frameworks applied throughout -- the Continuity Risk Framework, the Clinical Moral Disengagement Scaffolding, and the Comprehensive Occupational Violence and Extraction Framework -- were developed to make this kind of harm visible, attributable, and actionable within existing institutional and regulatory architectures. Their application here is analytic: these frameworks provide the conceptual architecture for converting a body of peer-reviewed evidence into a tractable accountability and intervention model.

The paper proceeds in fourteen sections. Sections I through III establish the clinical and neurobiological basis of the compound deficit model. Sections IV through VI address the diagnostic failure regime and its pharmacological consequences. Section VII presents the economic burden calculation. Sections VIII through X address hormonal contraception risk, AFAB-inclusive framing, and a neurodiversity-informed analysis of apparent accommodation. Sections XI and XII present the institutional accountability framework and clinical recommendations. Section XIII identifies the primary research unknowns. Section XIV concludes.

The framing of this paper as an economic burden analysis is deliberate, not reductive. The economic quantification serves a specific function in institutional accountability frameworks: it converts a harm that is currently legible only as human suffering -- which institutional systems have demonstrated the capacity to absorb indefinitely -- into a financial liability that triggers a different category of institutional response. The \$14.0 billion figure does not represent the value of the lives affected. It represents a cost that is currently being externalized: paid by nurses through psychiatric morbidity, paid by patients through care delivered under neurobiological compromise, paid by the public through emergency healthcare utilization and workforce replacement, and paid by families and communities through the downstream effects of nurse suicide and disability. The paper names this externalization and proposes that it be internalized -- through institutional accountability, regulatory enforcement, and legislative action -- by the institutions whose operational choices produce it.

## **Section If: Female-Born Healthcare Workers Beyond Nursing**

The female-specific occupational suicide elevation is not confined to nursing. Olfson et al. (2023) documented adjusted hazard ratios above 1.0 for female health care support workers

(aHR 1.81, 95% CI 1.35 to 2.42), registered nurses (aHR 1.64, 1.21 to 2.23), and health technicians (aHR 1.39, 1.02 to 1.89). Schernhammer and Colditz (2004) reported a standardized mortality ratio of 2.27 (95% CI 1.90 to 2.73) for female physician suicides. Makhija et al. (2025) found an IRR of 1.53 (95% CI 1.23 to 1.87) for female physicians versus female non-physicians, while male physicians showed a protective IRR of 0.84.

This cross-occupational consistency is critical. Female nurses, female physicians, female pharmacists, female health technicians, and female health support workers all show elevated risk compared to the general female population. Male workers in the same categories show equal or reduced risk. The consistent presence of the signal across diverse occupational roles within healthcare, paired with its consistent absence in male workers across those same roles, rules out role-specific explanations such as patient death exposure (higher in ICU nursing than in laboratory work), pharmacological access (higher in nurses and pharmacists than in health aides), and specific moral injury profiles. The signal is sex-specific and profession-nonspecific. The most parsimonious explanation for a pattern that appears wherever female-assigned individuals work in healthcare but not wherever male-assigned individuals do is a biological variable intrinsic to being female-assigned.

### **Section I-AAES: The Acquired Adverse Exposure Score — A Proposed Construct**

The original ACE questionnaire addresses childhood adversity through age 18 across ten documented categories of abuse, neglect, and household dysfunction. This instrument captures the developmental trauma burden at career entry. It does not capture the ongoing traumatogenic exposures of nursing employment: proximity to death and dying, moral injury from institutional constraint of clinical judgment, secondary traumatic stress from patient suffering, exposure to violence and verbal abuse, institutional retaliation against whistleblowers, and the cumulative burden of bearing witness to preventable harm without recourse.

These occupational exposures are not categorically different from the ACE categories they parallel; they are structurally identical in their neurobiological consequences. Repeated exposure to death, institutional moral injury, and the suppression of one's clinical ethical responses produces HPA axis dysregulation through mechanisms identical to those documented for childhood adversity. A nurse who enters the profession at 22 with an ACE score of 4 and accumulates 15 years of occupational traumatic exposure has a cumulative adverse exposure burden that the ACE-10 instrument does not capture.

The Acquired Adverse Exposure Score (AAES) is proposed here as a research construct requiring development and validation. An AAES instrument would measure: cumulative patient death exposure (volume and acuity); frequency of unresolvable moral injury events; institutional response to reported patient safety concerns (retaliation versus resolution); exposure to workplace violence; and years of shift work and associated circadian disruption. Validated against established PTSD instruments (PCL-5), biomarkers (cortisol, allopregnanolone), PMDD severity (DRSP), and occupational tenure, the AAES would enable the first direct quantification of occupational trauma burden as a modifiable risk factor for perimenstrual hormonal vulnerability.

## SECTION II: CLINICAL CONTEXT — PMDD, NEUROBIOLOGICAL HARM, AND THE NURSING WORKFORCE

Premenstrual dysphoric disorder is defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) as a condition characterized by affective, behavioral, and somatic symptoms that emerge in the luteal phase of the menstrual cycle, remit within a few days of menstruation onset, and are absent in the post-menstrual week. The defining clinical feature -- and the feature most commonly absent in general clinical practice -- is the requirement for a symptom-free window. PMDD is not simply chronic depression that worsens premenstrually. It is a cyclically remitting disorder. The remission is diagnostic. Its absence means the diagnosis cannot be PMDD. Its presence means the diagnosis must be seriously considered.

DSM-5-TR criteria require that at least five symptoms be present in the final week before menstruation, begin to improve within a few days after menstruation onset, and be minimal or absent in the week after menstruation. Symptoms must include at least one of the following: marked affective lability, marked irritability or anger, marked depressed mood or hopelessness, or marked anxiety or tension. Additional qualifying symptoms include decreased interest in usual activities, subjective difficulty concentrating, lethargy, marked change in appetite or specific food cravings, hypersomnia or insomnia, a sense of being overwhelmed or out of control, and physical symptoms including breast tenderness, joint or muscle pain, a sensation of bloating, or weight gain. Symptoms must produce measurable functional impairment and must not represent a mere exacerbation of another disorder.

The condition affects an estimated 3% to 8% of women of reproductive age, with higher prevalence in populations experiencing elevated occupational stress, sleep disruption, and cumulative trauma exposure -- all of which characterize the registered nursing profession. Applied to the 3.1 million actively employed U.S. registered nursing workforce, this range yields an affected cohort of approximately 93,000 to 248,000 individuals, with a midpoint estimate near 170,000 actively employed nurses meeting full diagnostic criteria for PMDD.

PMDD is not a mild or subclinical condition. During the luteal phase, individuals with PMDD may experience suicidal ideation, functional inability to perform occupational tasks, affective crises indistinguishable from acute psychiatric emergencies, and interpersonal disruption severe enough to result in job performance deterioration. A nurse with PMDD who is years from an accurate diagnosis, working a rotating night shift during the luteal phase, delivering care to critically ill patients, is doing so in a state of measurable neurobiological compromise with direct patient safety implications.

Within nursing specifically, PMDD does not operate against a neutral occupational background. The nursing occupational environment includes: mandatory shift work with frequent night rotation, which disrupts circadian rhythm and hormonal regulation; sleep deprivation at rates exceeding general population norms by a substantial margin; sustained and repeated exposure to patient death, suffering, and institutional coercive practices against both patients and staff; a moral suppression architecture that systematically discourages complaint escalation and labels clinical distress as personal inadequacy; and a

workforce demographic that is approximately 90% female (89.6% per NCSBN 2024 Workforce Survey) and currently at median age 50 -- a convergence point with perimenopausal hormonal transition that is elaborated in Section V.

PMDD diagnostic delay is estimated at greater than a decade from symptom onset, based on patient advocacy survey data from the International Association for Premenstrual Disorders (IAPMD). This figure requires corroboration from prospective population-based epidemiological cohort studies, as survey recruitment through advocacy networks may oversample severely affected individuals. However, the clinical conditions for protracted diagnostic delay are structural and well-documented: no standard primary care encounter includes menstrual cycle phase inquiry as part of psychiatric assessment; no electronic health record template in common use prompts cycle-phase documentation for psychiatric chief complaints; and the presenting symptoms of PMDD are treated as free-standing diagnostic findings assignable without the prospective tracking that would establish cyclicity. The absence of that tracking is not a minor procedural gap. It is the mechanism by which diagnostic error is institutionally guaranteed.

The consequences of this diagnostic gap are not symmetric. PMDD is underdiagnosed. Other conditions -- bipolar disorder, major depressive disorder, borderline personality disorder -- are overdiagnosed in populations where PMDD was the correct or primary diagnosis. The pharmacological and clinical consequences of this misattribution are detailed in Section VI.

The occupational exposure profile of the U.S. registered nurse warrants clinical attention as a category of harm in its own right, separate from and antecedent to the specific neurobiological pathways described in later sections. Night shift work produces circadian misalignment that disrupts the cortisol rhythm, the melatonin rhythm, the sleep-wake cycle, and the hormonal cycles that depend on these circadian anchors. Circadian disruption in women specifically produces measurable changes in menstrual cycle regularity, luteal-phase progesterone levels, and ovulatory frequency -- all of which are directly relevant to the allopregnanolone synthesis capacity described in the compound deficit model. A nurse who works three consecutive night shifts, returns to a day schedule for two days, and then works another block of nights has no stable circadian anchor from which her hormonal cycles can maintain normal patterning. This disruption is not a minor inconvenience. It is a chronic physiological stressor with measurable endocrine consequences that compound with every other pathway described in this paper.

The sleep deprivation component of nursing occupational exposure deserves separate enumeration. Adequate sleep is required for hippocampal memory consolidation, for prefrontal cortex executive function, and for the overnight hormonal processes -- including growth hormone secretion, cortisol suppression, and the slow-wave sleep-associated allopregnanolone synthesis -- that maintain the neurochemical conditions for daytime psychiatric stability. A nurse who consistently works 12-hour overnight shifts with fewer than 7 hours of recovery sleep before returning to clinical responsibilities is operating in a state of chronic sleep restriction that produces measurable impairment in all of these domains. The cognitive impairment from sleep restriction has been documented to be

comparable to legal intoxication at 24 hours of wakefulness; the hormonal consequences of chronic sleep restriction in AFAB individuals include disrupted menstrual cycles, elevated cortisol, and reduced allopregnanolone synthesis. Both consequences are directly relevant to patient safety and to the neurobiological deficit model.

### **Shift Work as a Four-Pathway Mechanistic Chain for Neurosteroid and HPA Disruption**

Shift work in nursing operates through at least four distinct mechanistic pathways, each independently documented and each convergent on the same outcome: suppression of neurosteroid biosynthesis, amplification of HPA reactivity, and progressive degradation of the biological substrate that supports psychological resilience.

Pathway 1 -- Circadian disruption and cortisol rhythm flattening. The normal cortisol awakening response (CAR) produces a 50-100% spike in cortisol within 30 minutes of waking, serving as the day's primary HPA calibration event. Night shift workers whose "waking" occurs at irregular hours across a rotating schedule fail to generate a consistent CAR, producing a flattened diurnal cortisol curve. Flattening is associated with accelerated allostatic load, impaired immune function, and affective instability.

Pathway 2 -- Sleep architecture disruption and progesterone clearance. Slow-wave sleep is the period of maximal growth hormone release, which regulates multiple anabolic processes including progesterone metabolism. Chronic slow-wave sleep deprivation -- a documented consequence of daytime sleep in night shift workers -- accelerates progesterone clearance and reduces the substrate available for allopregnanolone synthesis. This pathway creates a direct mechanistic link between shift scheduling and the neurosteroid deficit described as central to this paper's argument.

Pathway 3 -- Light exposure desynchronization and melatonin suppression. Night shift exposure to artificial light suppresses melatonin release through photoreceptor-mediated SCN signaling. Melatonin has direct antioxidant and neuroprotective functions in limbic circuits and modulates HPG axis timing. Its suppression in shift workers accelerates ovarian aging, contributes to menstrual cycle irregularity, and reduces menopausal transition predictability -- making the perimenopausal window harder to identify and harder to manage.

Pathway 4 -- Nutritional and metabolic disruption. Shift work structurally prevents adequate UV vitamin D synthesis, disrupts circadian feeding patterns reducing dietary quality, elevates cortisol-driven magnesium excretion, and creates the metabolic conditions for nutritional deficits in cofactors required for neurosteroid biosynthesis and thyroid hormone conversion.

The four pathways are not independent: each amplifies the others. A nurse working rotating night shifts experiences all four simultaneously, and the net biological effect is substantially greater than any single pathway would predict. This interaction is the mechanistic basis for the disproportionate health burden observed in shift-working nurses compared to day-shift workers or the general population.

## **Section IIc: COVID-19 HPG Axis Disruption as an Accelerating Exposure Layer**

COVID-19 infection has been documented to produce hypothalamic-pituitary-gonadal (HPG) axis disruption, with menstrual irregularity reported in approximately 25 percent of infected women and longitudinal data indicating persistent cycle changes in a subset beyond 12 months. For perimenopausal nurses who were COVID-infected during the 2020 to 2022 pandemic surge period, this adds an iatrogenic HPG disruption to the existing perimenopausal trajectory, effectively accelerating the timeline of neurosteroid vulnerability in an already high-risk cohort.

The mechanism is multifactorial: SARS-CoV-2 infection produces systemic inflammation that disrupts GnRH pulsatility; the associated acute illness, sleep disruption, and psychological stress activate HPA axis responses that directly suppress gonadotropin release; and the long-COVID syndrome, reported by approximately 10 to 30 percent of infected individuals, sustains autonomic and neuroendocrine dysregulation beyond acute illness resolution. In nurses whose occupational exposure maximized infection risk, this biological cost was absorbed without institutional acknowledgment and without occupational health follow-up.

The nursing workforce entered the post-pandemic period with a subset of members carrying accelerated perimenopausal HPG disruption from COVID-19, superimposed on the occupational exposures documented elsewhere in this paper. This has not been quantified in any workforce health surveillance instrument. It constitutes an unaccounted-for contributor to the psychiatric burden described in this analysis.

## **Section IIIa-Supplement: The Menstrual Cycle, Hormonal States, and Suicide Risk**

### **Section IIIa-i: The Outcome Spectrum — Ideation, Attempt, and Completed Suicide**

Suicidal ideation, suicide attempt, and completed suicide are clinically and epidemiologically distinct phenomena that share conceptual overlap but differ in prevalence, demographic distribution, and mechanism. In the US, suicidal ideation affects approximately 3.5 to 4 percent of adults annually; suicide attempts occur in approximately 0.5 percent; completed suicides occur in approximately 14 per 100,000 (0.014 percent). The ratio from ideation to attempt to completion is roughly 300:30:1. The cycle-phase suicide literature addresses all three levels but with different strength of evidence at each. Suicidal ideation: prospective evidence is now strong, with LH-confirmed cycle-phase daily-diary studies (Owens et al. 2023; Ross et al. 2024). Suicide attempts: replicated cross-sectional evidence showing 26 percent of attempts during menses versus 15 percent expected (Baca-Garcia 2010), with the methodological limitation that retrospective cycle-phase recall by recently attempting patients carries inherent imprecision. Completed suicide: population-level evidence from Opatowski et al. (2024) showing HR 1.92 for suicide death in women with PMD diagnoses, without direct cycle-phase-at-death data. These distinctions are maintained throughout this manuscript because different levels of the outcome spectrum require different evidence and different intervention types.



The nurse-suicide literature, which is based primarily on death records, documents completed suicides. The hormonal intervention literature (Eisenlohr-Moul 2022 RCT) addresses suicidal ideation. These two bodies of evidence are therefore not directly linked through the same outcome measure. This does not defeat the thesis; it specifies the research designs required to link them. The occupational health case for action rests most directly on ideation and attempt data, where the experimental hormonal intervention evidence is strongest. The public health case for research investment rests on the completed-suicide mortality data. Both cases are made in this manuscript and require neither to substitute for the other.

### **Section IIIa-ii: Epidemiological Evidence for Perimenstrual Risk Concentration**

Baca-Garcia and colleagues published a series of cross-sectional studies beginning in 1998 establishing that suicide attempts are disproportionately concentrated during late luteal and early menstrual phases. Their 2003 study found that the probability of attempt during menses was 1.68 times expected (95% CI 1.27 to 2.09). Their 2010 analysis of 281 fertile female attempters found 26 percent of attempts during menstruation versus 15 percent predicted by uniform distribution ( $P < .001$ ). Saunders and Hawton (2006) reviewed 44 studies and found approximately 26 percent greater risk of suicide deaths and 17 percent greater risk of attempts during menstrual and premenstrual phases, with 65 percent of attempt studies finding perimenstrual concentration. The retrospective cycle-phase reconstruction in emergency department samples carries the acknowledged limitation of post-crisis recall bias; this is precisely why the prospective daily-diary designs of Owens et al. (2023) and Ross et al. (2024), which use LH testing to confirm cycle phase independently of patient recall, represent the current evidentiary standard.

One finding in this literature requires explicit discussion rather than burial in a limitation footnote: Baca-Garcia (2004) examined a subsample of 125 attempters and found that among women specifically meeting DSM-IV PMDD criteria, the cycle-phase concentration of attempts was not significantly more pronounced than in the non-PMDD attempters (34 percent vs. 35 percent luteal in each group). The appropriate interpretation is more nuanced: PMDD dramatically elevates attempt risk across the full cycle, which attenuates the apparent phase-concentration within the PMDD subgroup. The phase-concentration finding and the PMDD elevated-risk finding are not competing explanations; they address different questions. Phase concentration documents when within-cycle vulnerability peaks. PMDD documents who carries elevated risk overall.

### **Section IIIa-iii: Experimental Causal Evidence**

Eisenlohr-Moul et al. (2022), in a crossover randomized controlled trial (NCT03720847,  $n=21$  women with prospectively confirmed PMDD and documented perimenstrual SI exacerbation), demonstrated that 93 percent of participants showed highest suicidal ideation scores during the perimenstrual phase under placebo conditions. Random assignment to transdermal estradiol (0.1 mg/day) plus oral micronized progesterone (200 mg/day) during the perimenstrual window significantly reduced suicidal ideation, planning, hopelessness, perceived burdensomeness, depression, perceived stress, and rejection

sensitivity. Hormone withdrawal during placebo crossover recapitulated the symptom profile. This constitutes direct experimental evidence that ovarian steroid withdrawal drives the perimenstrual vulnerability state and that it is pharmacologically reversible. The sample size (n=21) is the appropriate limit for a crossover mechanistic RCT in a highly selected population; it is not a population-generalizability claim.

### **Section IIIa-iv-Supplement: Neurobiological Mechanisms — Serotonin, GABA-A, and HPA Axis**

The mechanisms by which ovarian steroid fluctuations modulate suicide risk are characterized across three neurochemical systems. Estradiol upregulates tryptophan hydroxylase (the rate-limiting enzyme in serotonin synthesis), decreases monoamine oxidase A activity, and modulates 5-HT<sub>2A</sub> and 5-HT<sub>1A</sub> receptor density. Frokjaer et al. (2015) demonstrated in a human PET study that GnRH agonist-induced estradiol fluctuation produces measurable serotonin transporter binding changes correlated with depressive symptoms. Progesterone's primary active metabolite, allopregnanolone, is a positive allosteric modulator at GABA-A receptors. Backström et al. (2014) established that PMDD involves paradoxical bimodal sensitivity to allopregnanolone: moderate physiologic luteal concentrations are anxiogenic rather than anxiolytic in susceptible women, and the perimenstrual fall in allopregnanolone produces a rebound state of GABAergic hypofunction. Hantsoo and Epperson (2020) characterized this as impaired GABA-A receptor subunit plasticity involving alpha-4 and delta subunit upregulation. SSRIs are effective within hours to days in PMDD (via rapid allopregnanolone synthesis modulation through 3-alpha-HSD activation), an onset pattern distinct from the 2 to 4 week mechanism in major depressive disorder and confirming that the mechanism of action in PMDD is not monoaminergic antidepressant effect but neurosteroid synthesis modulation.

The HPA axis provides a third mechanistic pathway. Chronic occupational stress dysregulates the HPA axis and alters cortisol dynamics in ways that interact with ovarian steroid cycling. Cortisol and neurosteroid synthesis share the same cholesterol-derived precursor pathway; chronic HPA activation may compete for substrate availability. Sleep disruption, near-universal in shift-working nurses, independently reduces GABAergic tone and serotonin availability, amplifying the perimenstrual neurochemical vulnerability state. The convergence of occupational stress-mediated HPA dysregulation with cyclical ovarian steroid withdrawal in a person with GABA-A neuroactive steroid sensitivity constitutes a biologically coherent and testable amplification model.

### **Section IIIa-v-Supplement: The Apparent Hormonal Contraception Contradiction, Resolved**

Skovlund et al. (2018), using Danish national registry data on approximately 500,000 women, reported that current or recent hormonal contraceptive use was associated with relative risks of 1.97 for suicide attempt and 3.08 for suicide death. These findings appear to contradict a model in which estrogen is neuroprotective: if estrogen deficiency drives risk, why does adding exogenous hormones increase it? The apparent contradiction dissolves under pharmacological specificity.

First, and most fundamentally: synthetic progestins are not bioidentical progesterone. Bioidentical progesterone (micronized progesterone) is metabolized to allopregnanolone, the GABAergic neuroactive steroid at the center of PMDD pathophysiology. Synthetic progestins, including norethindrone, levonorgestrel, medroxyprogesterone acetate, and etonogestrel, do not share this metabolic pathway and do not produce allopregnanolone. The RCT evidence on bioidentical versus synthetic progestagen and mood directly documents this divergence: the KEEPS trial (Harman et al. 2014) and multiple smaller crossover studies show adverse mood effects with synthetic medroxyprogesterone acetate and neutral or beneficial effects with micronized progesterone. The Skovlund findings apply to synthetic progestin-containing products and do not contradict the mechanism by which perimenstrual bioidentical progesterone withdrawal drives PMDD-related suicide risk.

Second: combined hormonal contraceptives suppress ovarian testosterone production and elevate sex hormone binding globulin, reducing free testosterone availability. Testosterone in AFAB individuals is independently associated with motivation, mood, and cognitive function; its pharmacological suppression via combined OC use produces a depressive syndrome documented in multiple studies and mediated through an androgenic, not estrogenic, pathway.

Third: ethinyl estradiol (EE2), the estrogen in most combined oral contraceptives, is pharmacologically distinct from 17-beta-estradiol (E2), the form produced by the ovaries. The mechanisms by which E2 modulates serotonin tone, MAO-A activity, and 5-HT receptor density are documented primarily for E2, not EE2.

Fourth: women with PMDD show paradoxical sensitivity to progestogenic compounds. In key NIMH experiments (Schmidt et al., 1998), PMDD-affected women experienced significant mood deterioration in response to synthetic progesterone administration under controlled conditions, while controls did not. The FDA approval of drospirenone-containing oral contraceptive (Yaz) specifically for PMDD reflects the clinical translation of this distinction.

In summary: the hormonal contraception literature does not contradict the estrogen-deficiency model. It documents what happens when synthetic hormones with different receptor profiles from their endogenous counterparts are administered to a population with pre-existing neuroactive steroid sensitivity.

### **Section IIIa-vi-Supplement: Additional Hormonal Vulnerability States**

Perimenstrual estrogen nadir is one of several estrogen deficiency states documented to concentrate suicide risk. Postpartum estrogen and progesterone withdrawal is precipitous and represents the leading cause of late maternal death in multiple high-income countries; MBRRACE-UK (2023) reports 39 percent of maternal deaths between 6 weeks and 12 months postpartum were by suicide. Perimenopause carries a similar mechanistic profile: Hendriks et al. (2025) found 84 percent of reviewed studies reported elevated suicidality in perimenopausal women, with pooled adjusted odds ratios in the range of 1.6 to 1.9. Surgical menopause produces an acute estrogen depletion state associated with dramatically elevated depression rates without timely estrogen replacement. The consistency of risk elevation across distinct estrogen depletion states reinforces the mechanistic model: the

perimenopause and the perimenstrual nadir are two expressions of the same fundamental neurobiological vulnerability, separated by timescale but not by mechanism.

## **SECTION III: THE COMPOUND NEUROBIOLOGICAL DEFICIT MODEL — FIVE CONVERGENT PATHWAYS**

The compound neurobiological deficit model proposed in this paper maps five independent and documented pathways to a shared mechanistic endpoint: reduced mitochondrial neurosteroid synthesis, specifically the synthesis of allopregnanolone (3-alpha,5-alpha-tetrahydroprogesterone), the primary endogenous positive allosteric modulator of the GABA-A receptor. Each pathway is independently supported by peer-reviewed evidence spanning neuroendocrinology, steroidogenesis, psychoneuroimmunology, and occupational psychiatry. Their convergence in a single individual is not a theoretical construction; it is a predictable and common presentation given the workforce demographic, occupational exposure, medication prevalence, and psychiatric burden documented in the peer-reviewed literature for the U.S. registered nursing workforce.

The five pathways are: (IIIa) PMDD-associated GABA-A receptor hypersensitivity; (IIIb) statin-mediated cholesterol reduction and neurosteroid substrate depletion; (IIIc) hypothyroid StAR protein impairment; (IIId) ACE-driven HPA axis dysregulation and cortisol-mediated allopregnanolone suppression; and (IIIe) PTSD-induced allopregnanolone depletion. Section IIIf describes the convergence architecture and the compounding dynamics that make this model more than the sum of its independent parts.

### **Section IIIa: PMDD and GABA-A Receptor Hypersensitivity**

The neurobiological basis of PMDD has been substantially clarified by research demonstrating that the disorder does not reflect an absolute deficit of progesterone or allopregnanolone, but an aberrant sensitivity of the GABA-A receptor to normal fluctuations in allopregnanolone across the menstrual cycle. In individuals without PMDD, rising luteal-phase allopregnanolone levels potentiate GABA-A receptor function, producing anxiolytic and sedating effects. In individuals with PMDD, this same rise produces paradoxically anxiogenic and dysphoric effects -- a phenomenon attributable to maladaptive remodeling of GABA-A receptor subunit composition, specifically reduction of the delta subunit, in response to sustained allopregnanolone exposure during the luteal phase.

Backstrom and colleagues established that women with PMDD exhibit significantly different neurosteroid responses compared to controls, with paradoxical negative affect and anxiety in response to allopregnanolone concentrations that produce sedation in unaffected individuals. This receptor-level sensitivity explains why PMDD symptoms are not proportional to progesterone or allopregnanolone levels in absolute terms -- they are driven by the receptor-level response to neurosteroid fluctuation, which in PMDD has become dysregulated by the cyclical amplitude of that fluctuation itself.

The clinical consequence for occupational risk is direct: a nurse with PMDD operates during the luteal phase of her cycle in a state of GABA-A receptor dysfunction. The inhibitory neurotransmitter system that would otherwise buffer against anxiety, hypervigilance, and suicidal ideation is functionally compromised by the very hormonal process that is calming in unaffected individuals. Superimposed on this cycle-phase vulnerability, the occupational exposures of nursing -- sleep deprivation, sustained cortisol activation, PTSD-level traumatic stress -- further reduce allopregnanolone availability and deepen the GABA-A instability.

### **Section IIIa-iv: GABA-A Receptor Genetic Variants and Individual Sensitivity Variation**

Population variation in response to neurosteroid fluctuation is not uniform. GABA-A receptor subunit composition is determined by polymorphisms in genes encoding the alpha, beta, delta, and gamma subunit families. The delta subunit (GABRD gene) is particularly relevant: it preferentially incorporates into extrasynaptic GABA-A receptors that are the primary target of allopregnanolone's modulatory action. Variants in GABRD and related subunit genes have been associated with differential PMDD severity, alcohol sensitivity (another neurosteroid-mediated behavior), and postpartum depression vulnerability.

An individual's genetic GABA-A receptor configuration determines the steepness of her dose-response curve to neurosteroid fluctuation. Women with high-sensitivity configurations experience greater affective and anxiety amplification from the same degree of allopregnanolone decline compared to women with lower-sensitivity configurations. This genetic variation is part of why PMDD affects approximately 3 to 8 percent of cycling women rather than all of them, despite all cycling women experiencing the same hormonal fluctuation.

***Research implication: genetic stratification of perimenopausal nurse cohorts by GABA-A subunit variants should be incorporated into risk stratification models and trial design. Identification of high-sensitivity genotypes would enable precision targeting of neurosteroid replacement interventions to individuals most likely to benefit, and most likely to suffer without intervention.***

### **Section IIIa-v: GABRD Variants, Alcohol Sensitivity, and the Self-Medication Pathway**

True alcohol allergy — an IgE-mediated or histamine-driven reaction — is mechanistically unrelated to GABA-A receptor sensitivity. The sensitivity relevant to GABRD variants is pharmacological: high-sensitivity receptor configurations produce amplified responses to positive allosteric modulators of the GABA-A receptor, of which ethanol and allopregnanolone are the most clinically relevant examples. A woman with high-sensitivity GABRD variants may experience pronounced sedation, disinhibition, or paradoxically dysphoric agitation at alcohol doses that produce minimal response in women with lower-sensitivity configurations. This is not an allergy. It is a receptor-level behavioral

phenotype that predicts both PMDD vulnerability and atypical alcohol response through the same structural mechanism.

The alcohol-PMDD-dependence intersection operates through a self-medication pathway with direct clinical and occupational health relevance for nursing. Allopregnanolone and ethanol share partially overlapping binding sites at the GABA-A receptor and produce qualitatively similar inhibitory effects. During the luteal phase, when PMDD-affected women experience GABA-A receptor hypersensitivity and allopregnanolone-mediated dysphoria, exogenous alcohol can temporarily restore inhibitory tone through the same receptor system. This pharmacological substitution effect explains the clinically observed pattern of luteal-phase alcohol use escalation in PMDD-affected women — a pattern that is frequently misread as general substance use disorder rather than recognized as cycle-phase-specific self-medication of an undiagnosed neurobiological condition.

The dependence risk trajectory differs by receptor sensitivity phenotype. Women with high-sensitivity GABRD variants who self-medicate PMDD with alcohol may rapidly develop tolerance and dependence due to the strength of their initial GABAergic reward signal. Women with paradoxical-response configurations may experience dysphoric reactions to alcohol that function as an aversive deterrent but simultaneously indicate severe GABA-A dysregulation requiring clinical attention. Neither pattern is adequately captured by standard substance use disorder screening instruments, which do not assess cycle-phase timing of alcohol use, do not include GABRD genotype, and do not screen for the neurosteroid deficit that the alcohol use is pharmacologically addressing.

The postpartum depression connection follows the same receptor logic. The precipitous postpartum allopregnanolone decline that drives PPD in susceptible women — the mechanism brexanolone directly addresses — is amplified in women with high-sensitivity GABRD configurations. Their receptor systems have adapted during pregnancy to high sustained allopregnanolone levels; the withdrawal on delivery produces a steeper and more destabilizing decline. This is pharmacologically analogous to benzodiazepine withdrawal: higher-sensitivity receptors experience greater functional deficit when the modulator is removed.

Clinical screening implication: assessment of alcohol use patterns in perimenopausal and PMDD-affected nurses should include cycle-phase timing — does use increase in the 10 to 14 days before menstruation and decrease after onset? A positive response should trigger PMDD evaluation rather than primary substance use disorder pathway. This is a pattern recognition task that requires the evaluator to know both the PMDD diagnostic criteria and the self-medication mechanism, a combination currently absent from standard occupational health and EAP intake frameworks.

### **Premenstrual Exacerbation vs. PMDD: Mechanistically and Clinically Distinct**

Premenstrual Dysphoric Disorder (PMDD) refers to a primary condition in which the perimenstrual period is the exclusive time of symptomatic burden -- the follicular phase is asymptomatic by diagnostic definition (DSM-5 Criterion D). Premenstrual Exacerbation (PME) refers to a different phenomenon: cyclic amplification of a pre-existing condition



(depression, anxiety, PTSD, bipolar disorder, ADHD) during the luteal phase, with the underlying condition remaining symptomatic throughout the cycle.

The distinction is not academic. Treatment strategies diverge significantly. PMDD responds to luteal-phase-specific SSRI dosing, neurosteroid replacement (brexanolone, zuranolone, progesterone), and GnRH analogs that suppress ovulation and the associated hormonal oscillation. PME requires treatment of the underlying condition plus attention to its cyclic amplification -- mood stabilizers for bipolar PME, stimulant optimization for ADHD PME, trauma-focused therapy for PTSD PME, with hormonal adjuncts as a secondary layer rather than primary treatment.

***Research implication: clinical trials that enroll "PMDD patients" without rigorous follicular-phase symptom documentation will contaminate their samples with PME cases. The current trial literature contains this contamination, which partly explains heterogeneous treatment response rates. Future research must document symptom burden across the full cycle, not only the luteal phase, before enrollment classification.***

The DRSP, when used as intended -- two prospective cycles of daily symptom rating -- captures the follicular-luteal differential needed to distinguish PMDD from PME. Its misuse as a clinical gatekeeping instrument creates the same problem it was designed to prevent: enrollment of PME cases into PMDD treatment pathways, and exclusion of true PMDD cases who cannot maintain two months of daily charting.

### **Brexanolone and Zuranolone as Active Trial Targets for Neurosteroid Replacement**

Brexanolone (Zulresso, Sage Therapeutics) is an intravenous formulation of allopregnanolone approved by the FDA in 2019 for postpartum depression. Its approval constitutes regulatory confirmation that neurosteroid deficiency -- specifically allopregnanolone substrate deficiency -- is a valid pharmacologic target for affective disorder. The mechanism is direct: brexanolone replaces the allopregnanolone that the postpartum hormonal withdrawal depleted, restoring GABA-A receptor positive modulation in limbic circuits.

Zuranolone (Zurzuvae, Sage Therapeutics / Biogen) is an oral allopregnanolone analog approved by the FDA in 2023 for both postpartum depression and major depressive disorder. Its oral formulation and shorter treatment course (14-day pulse) make it substantially more practical than brexanolone for outpatient use. Its approval for MDD -- beyond the postpartum indication -- suggests regulatory acknowledgment of neurosteroid deficiency as a mechanism relevant to depression broadly, not exclusively postpartum.

Neither agent has been studied in perimenopausal populations or in occupational trauma contexts. The pharmacologic rationale for extending trial eligibility to perimenopausal women with documented neurosteroid deficit and high occupational adversity burden is direct: the mechanism of action targets the same GABA-A receptor positive modulation pathway that is dysregulated by progesterone withdrawal during menopause. Current trial

exclusion of perimenopausal women from neurosteroid trials represents a research gap with direct clinical consequences for the population this paper addresses.

***Research recommendation: accelerated trial design for brexanolone and zuranolone in perimenopausal women, stratified by menopausal stage, HPA activation markers, and occupational adversity exposure. Trial endpoints should include suicidality measures alongside depression scales, given the documented relationship between neurosteroid deficiency and suicidal ideation severity.***

### **Postpartum Return-to-Work as a High-Risk Transition Point**

The postpartum period represents a documented neurosteroid vulnerability window: progesterone and its metabolite allopregnanolone decline precipitously after delivery, producing the hormonal milieu associated with postpartum depression in susceptible individuals. For nurses, this vulnerability window intersects with an institutional pressure to return to full duty quickly, often before the neurobiological stabilization that typically occurs by 6-12 weeks postpartum.

Nurses returning to night shift within the postpartum period face a compound exposure: allopregnanolone substrate deficiency from progesterone withdrawal, sleep architecture disruption from infant care needs, and circadian disruption from shift work resumption, all operating simultaneously during a period when HPA reactivity is elevated and neurosteroid-mediated GABA-A function is at its nadir.

Institutional policies that permit or require return to rotating night shift within 6 weeks postpartum do not account for this biology.

Research recommendation: prospective cohort study of postpartum nurses returning to shift work, with serial neurosteroid assays (allopregnanolone, pregnanolone, BDNF), structured mood assessment (EPDS, PHQ-9), and documentation of sleep quality and shift rotation patterns. This study design would establish baseline data on the intersection of postpartum neurosteroid recovery and occupational shift exposure in a high-risk population.

### **Section IIIb: Statin-Mediated Cholesterol Reduction and Neurosteroid Substrate Depletion**

Cholesterol is the upstream precursor to all steroid hormones, including progesterone and the neurosteroid cascade that generates allopregnanolone. The enzyme CYP11A1 (cytochrome P450 side-chain cleavage) converts cholesterol to pregnenolone, the first committed step in neurosteroid biosynthesis. StAR protein (steroidogenic acute regulatory protein) transports cholesterol across the mitochondrial membrane to make it available for CYP11A1.

HMG-CoA reductase inhibitors (statins) reduce total cholesterol synthesis, including in the central nervous system where cholesterol is locally synthesized and provides substrate for neurosteroid production. The 2013 ACC/AHA guideline expansion substantially broadened statin prescribing criteria, creating millions of new statin users in the 40-65 age

demographic -- precisely the perimenopausal window when neurosteroid substrate availability is already declining from gonadal hormone reduction.

Women in perimenopause who are prescribed statins for cardiovascular risk reduction may experience compounding neurosteroid substrate depletion: the gonadal source is declining due to perimenopausal progesterone reduction, and the cholesterol precursor available for de novo neurosteroid synthesis in the CNS is simultaneously reduced by statin action. This mechanism does not establish that statins cause clinical PMDD or depression; it identifies a plausible pathway for increased vulnerability in a population already at risk.

Allopregnanolone is synthesized from cholesterol via a multi-step enzymatic cascade. Cholesterol is converted to pregnenolone by cytochrome P450 enzyme CYP11A1, with intramitochondrial cholesterol transport mediated by the steroidogenic acute regulatory (StAR) protein. Pregnenolone is converted to progesterone by 3-beta-hydroxysteroid dehydrogenase, and progesterone is subsequently converted to allopregnanolone via 5-alpha reductase and 3-alpha-hydroxysteroid dehydrogenase. Cholesterol is the foundational substrate for this entire cascade.

HMG-CoA reductase inhibitors (statins), the most widely prescribed medication class in the United States, reduce serum cholesterol by inhibiting the rate-limiting step in endogenous cholesterol synthesis. The neurosteroid consequence is reduced substrate availability for mitochondrial steroidogenesis in the adrenal cortex, ovarian granulosa cells, and neurons that synthesize neurosteroids locally. Statin use is disproportionately common in the nursing workforce demographic at median age 50, where cardiovascular risk factor management is standard. A nurse in perimenopause, already experiencing estrogen-withdrawal-driven reductions in 5-alpha reductase activity, who is also taking a statin, operates with a compressed cholesterol substrate pool at precisely the life-cycle point where allopregnanolone synthesis requirements are highest.

Research target: controlled analysis of PMDD symptom severity and depression incidence in perimenopausal women stratified by statin use, controlling for cardiovascular comorbidity as a confounder. This analysis does not exist in the published literature as of this writing and represents a tractable secondary analysis opportunity in existing longitudinal cohort datasets.

### **Neurosteroid Substrate Compression in the Nursing Workforce: A Convergent Pharmacological and Endocrine Mechanism**

The neuropsychiatric morbidity documented in the U.S. nursing workforce cannot be fully attributed to occupational adversity exposure alone. A convergent pharmacological and endocrine mechanism — operating in the same demographic at the same historical moment as the occupational exposures described in this paper — has received no systematic attention in the workforce health literature. We characterize it here as a mechanism that amplifies occupational vulnerability at the neurobiological level.

## The Demographic Intersection

The median age of the U.S. registered nurse workforce is approximately 50 years; 87-89% identify as women (ANA Workforce Survey, 2022). This profile places the nursing workforce at the center of three converging biological and pharmacological phenomena.

First, perimenopausal and early postmenopausal transition. Women aged 45-55 represent the primary demographic for perimenopausal neurosteroid vulnerability, characterized by estrogen-withdrawal-driven reduction in 5-alpha reductase activity and decreased allopregnanolone synthesis. The clinical manifestations — affective instability, anxiety, sleep disruption, and cognitive impairment — overlap substantially with the psychiatric sequelae of occupational trauma documented in this paper.

Second, statin eligibility. ACC/AHA 2013 guidelines identified women aged 40-75 with a 10-year atherosclerotic cardiovascular risk of 7.5% or greater as candidates for statin therapy. The majority of women in the nursing workforce's demographic center meet statin eligibility criteria by age 50. Lipophilic statins — including simvastatin and atorvastatin, among the most commonly prescribed agents — cross the blood-brain barrier and inhibit CNS cholesterol synthesis, reducing neurosteroid substrate availability through a mechanism additive to the perimenopausal endocrine effect.

Third, HRT deprivation. Following the 2002 WHI publication and the 50-66% collapse in HRT prescribing documented by Hersh et al. (JAMA 2004), tens of millions of women in the relevant age cohort were denied an intervention that: directly addresses the perimenopausal neurosteroid deficit through progesterone restoration; reduces LDL cholesterol by 10-15%, attenuating statin eligibility; and has neuroprotective properties when initiated within the critical 10-year window. The 2022 Menopause Society position statement has rehabilitated this evidence base, but the clinical practice shift has been gradual. The cohort of nurses who were perimenopausal between 2002 and 2015 passed through the critical neuroprotective window without access to evidence-appropriate HRT.

## The Compound Mechanism

A nurse aged 50 in the current workforce may present with simultaneous neurobiological substrate compression at two points in the allopregnanolone synthesis cascade: perimenopausal 5-alpha reductase insufficiency reduces allopregnanolone synthesis at the progesterone conversion step; lipophilic statin use reduces cholesterol substrate for mitochondrial neurosteroid synthesis at the input step; and absence of progesterone supplementation eliminates both a direct substrate source and a 5-alpha reductase activity support. The resulting GABAergic insufficiency provides a neurobiological substrate for the affective dysregulation, anxiety, sleep disruption, and cognitive impairment documented in occupationally traumatized healthcare workers.

This mechanism does not simply add to occupational adversity — it amplifies it. Intact GABAergic tone provides stress-response buffering. Neurosteroid insufficiency impairs this buffering at the neurobiological level, rendering the same occupational adversity more psychologically damaging than it would be in a person with adequate neurosteroid

synthesis. The interaction between AAES burden and neurosteroid substrate compression is not additive; it is multiplicative.

### **Implications for Attribution**

Two implications follow for the economic and occupational mortality calculations advanced in this paper. First, a portion of the psychiatric morbidity attributed to occupational causes has a compounding pharmacological and endocrine contributor that may be partially addressable without removing the occupational stressor — specifically through HRT initiation in eligible women and through statin-type selection that minimizes CNS penetration. Second, the economic cost attributed to the nursing workforce's psychiatric burden is partially attributable to a population-level pharmacological policy failure — the post-2002 HRT prescribing collapse — driven by methodologically inadequate science. The occupational cost of HRT suppression has never been calculated. This paper identifies it as a research priority.

**EVIDENCE STATUS:** The compound substrate mechanism is proposed as a mechanistically grounded, evidence-adjacent framework. The individual mechanistic components are established. The integrated claim — that compound neurosteroid depletion amplifies occupational psychiatric morbidity in the nursing workforce — requires the prospective study described in the companion hypothesis paper (Torrez, 2026). It is included here labeled as a contributing mechanism under investigation, not a quantified causal attribution.

### **Section IIIc: Hypothyroid StAR Protein Impairment**

The steroidogenic acute regulatory (StAR) protein mediates the rate-limiting step in steroidogenesis: intramitochondrial transport of cholesterol from the outer to the inner mitochondrial membrane, where CYP11A1 initiates conversion to pregnenolone. Without adequate StAR function, cholesterol does not reach the enzymatic site of conversion regardless of substrate availability. StAR expression is therefore a gating mechanism for the entire neurosteroid synthesis cascade.

Thyroid hormone directly augments StAR protein expression. Triiodothyronine (T3) augments both StAR protein levels and StAR mRNA levels in steroidogenic cells. This augmentation is mediated by steroidogenic factor 1 (SF-1), which binds the 5-prime flanking region of the StAR gene and activates transcription; DAX-1 functions as an inhibitory counter-regulator of SF-1, and its activity correspondingly diminishes T3-stimulated StAR expression. These interactions have been established in Leydig cell preparations; the StAR expression machinery, including the SF-1 and DAX-1 regulatory system, is conserved across steroidogenic cell types including the adrenal cortex and ovarian granulosa cells.

In the adrenal cortex specifically, thyroid hormone receptor beta-1 (THRβ1) plays a direct role in adrenocortical development and function: T3 treatment produces adrenal cortex hypertrophy in wild-type but not *Thrb*-knockout mice. Hypothyroid states produce measurable downregulation of *Star*, *Cyp11a1*, and *Hsd3b1* in the adrenal cortex -- the enzymatic steps required for conversion of cholesterol to pregnenolone and its neurosteroid

derivatives. The downstream consequence is impaired synthesis of pregnenolone, progesterone, and allopregnanolone.

Subclinical and overt hypothyroidism are significantly more prevalent in women than men, with prevalence increasing with age. At median age 50, subclinical hypothyroidism affects approximately 8% to 10% of women. Its symptoms -- fatigue, cognitive slowing, mood disruption -- overlap substantially with PMDD, perimenopause, and occupational burnout, creating significant diagnostic interference and ensuring that many cases remain undetected in occupational health settings that do not include thyroid screening. It is noted that the full mechanistic chain from T3 to StAR expression to adrenal allopregnanolone synthesis is best characterized in animal models and Leydig cell preparations; the adrenal application is supported by Huang 2015 and Kariyawasam 2022. Direct measurement of T3-mediated allopregnanolone impairment in human AFAB adrenal tissue remains a prospective research priority. The human placenta is a documented exception: placental progesterone synthesis proceeds via a StAR-independent pathway.

### **Minimum Adequate Thyroid Evaluation: Panel Specification and Clinical Rationale**

The standard clinical practice of ordering thyroid-stimulating hormone (TSH) alone as a thyroid screen is insufficient for the evaluation of perimenopausal women with suspected HPA dysregulation or affective instability. TSH reflects pituitary feedback to circulating thyroid hormones, but is insensitive to two common and clinically significant pathologies in this population: autoimmune thyroid disease with normal TSH, and functional T3 deficiency mediated by cortisol-driven deiodinase impairment.

Minimum adequate thyroid panel for high-risk perimenopausal women: (1) TSH; (2) Free T4; (3) Free T3; (4) Thyroid Peroxidase Antibodies (TPO-Ab); (5) Thyroglobulin Antibodies (TgAb); (6) Reverse T3 (rT3). Each component provides mechanistically distinct information that TSH alone cannot supply.

Free T4 and Free T3 establish the conversion ratio. Under normal physiology, deiodinase enzymes convert T4 to the metabolically active T3. Chronic cortisol elevation -- a predictable consequence of sustained HPA activation from occupational adversity -- impairs type 1 deiodinase activity and shunts T4 toward reverse T3 (rT3), a biologically inactive metabolite that competitively inhibits T3 binding at cellular receptors. The result is functional T3 deficiency: a woman whose TSH and T4 are within reference range but whose Free T3 is low-normal and whose rT3 is elevated. Her pituitary is satisfied; her cells are hypothyroid. Standard screening misses this entirely.

The rT3:Free T3 ratio is the research-grade threshold for identifying this pattern. A ratio above 20 (when rT3 is measured in pg/mL and Free T3 in pg/mL) indicates excess reverse T3 production relative to active T3, consistent with stress-driven deiodinase shunting. This ratio is a research threshold, not a formally established clinical standard -- clinicians should treat it as a hypothesis-generating finding requiring clinical correlation, not an independent diagnostic decision point.



TPO-Ab and TgAb identify autoimmune thyroid disease (Hashimoto's thyroiditis) in women whose TSH remains normal. Hashimoto's thyroiditis is an autoimmune condition in which the immune system attacks thyroid tissue; in its early stages, compensatory mechanisms keep TSH within reference range despite progressive tissue destruction. Approximately 30% of women with TSH values above 3.0 mIU/L carry detectable TPO antibodies consistent with subclinical Hashimoto's. At population scale, this represents a substantial proportion of women presenting to mental health services with fatigue, cognitive impairment, and affective instability who are told their thyroid is normal.

The psychiatric implications of undetected Hashimoto's extend beyond classic hypothyroid symptoms. Anti-thyroid antibodies are associated with increased risk of depression, anxiety, cognitive changes, and -- in a subset with Hashimoto's encephalopathy -- acute neuropsychiatric presentations. More commonly, the low-grade thyroid impairment contributes to treatment-refractory depression by undermining the neural substrate on which antidepressants depend.

Occupational health implication: pre-employment and annual screening for nurses should include the full six-component panel described above, not TSH alone. Institutions that provide single-marker thyroid screening to a workforce with documented HPA dysregulation risk are providing care that is inadequate relative to the known biology of this population.

### **Section IIId: ACE-Driven HPA Axis Dysregulation and Cortisol-Mediated Allopregnanolone Suppression**

Adverse childhood experiences (ACEs) produce durable alterations in the hypothalamic-pituitary-adrenal (HPA) axis, with measurable effects on cortisol reactivity, baseline cortisol tone, and the patterning of cortisol release in response to subsequent stressors. The neurobiological mechanism involves corticotropin-releasing hormone system sensitization, glucocorticoid receptor downregulation in the prefrontal cortex and hippocampus, and altered negative feedback efficiency -- producing an HPA axis that responds with greater cortisol output for longer duration with less efficient recovery, compared to individuals without ACE burden.

The relevance of cortisol to allopregnanolone synthesis is twofold. First, cortisol and allopregnanolone share biosynthetic precursors within the adrenal steroidogenic pathway; under conditions of sustained cortisol demand, adrenal steroidogenic resources are preferentially directed toward glucocorticoid synthesis, reducing the availability of pregnenolone for neurosteroid conversion. Second, elevated glucocorticoids directly suppress 5-alpha reductase activity, the enzyme responsible for converting progesterone to 5-alpha-dihydroprogesterone -- the penultimate step in allopregnanolone synthesis. The enzymatic suppression thus operates on the allopregnanolone pathway at two distinct levels.

ACE prevalence in the nursing workforce is elevated compared to general population estimates, likely due to workforce selection mechanisms: the empathic overextension and normalized relationship with suffering that characterize individuals drawn to caregiving

professions may enrich the nursing workforce for individuals with ACE burden. Occupational trauma in nursing -- patient death, futile treatment situations, lateral violence, institutional coercion -- constitutes an additional adverse adult experience layer that activates the same HPA axis sensitization established by childhood adversity, compounding the allopregnanolone suppression over the course of a nursing career.

### **Nutritional Cofactors in Neurosteroid Biosynthesis and HPA Regulation**

The neurosteroid biosynthetic pathway depends on nutritional cofactors that are selectively depleted by the same exposures driving nurse suicide risk. Shift work disrupts circadian feeding patterns and reduces dietary variety. Chronic stress elevates cortisol, which increases urinary magnesium excretion and reduces gut magnesium absorption. Combined, these mechanisms create predictable nutritional deficits in a population already operating under high physiological demand.

Magnesium is required for over 300 enzymatic reactions including the conversion of progesterone precursors in the neurosteroid pathway. Deficiency is associated with increased anxiety, sleep disruption, and PMDD severity -- all of which are also attributable to the primary HPA and neurosteroid mechanisms described elsewhere in this paper. The overlap in symptom profile means nutritional contribution is systematically underweighted in clinical assessment.

Vitamin B6 (pyridoxine) serves as a cofactor in the enzymatic synthesis of gamma-aminobutyric acid (GABA), the neurotransmitter at the GABA-A receptor that allopregnanolone modulates. Deficiency reduces GABA synthetic capacity, compounding the GABA-A receptor sensitivity impairment characteristic of PMDD. B6 deficiency is common in women using oral contraceptives, which are frequently prescribed to nurses for shift-work cycle regulation without attention to this cofactor interaction.

Selenium supports thyroid hormone metabolism through selenoprotein deiodinase enzymes. Deficiency impairs T4-to-T3 conversion, contributing to the functional hypothyroid pattern described in the thyroid section. Iodine and zinc support thyroid hormone synthesis upstream. Iron deficiency, highly prevalent in menstruating nurses, impairs thyroid peroxidase function and is associated with hypothyroid symptoms independent of TSH level.

Vitamin D, synthesized through UV exposure that shift workers are structurally prevented from receiving during daylight hours, modulates immune function, neuroprotection, and mood. Low vitamin D is associated with depression, and deficiency is epidemic in northern latitudes and indoor-working populations. Omega-3 fatty acids (EPA and DHA) support neuroinflammatory regulation and membrane fluidity in neuronal systems affected by both HPA dysregulation and neurosteroid deficiency.

*Clinical implication: nutritional assessment should be part of any comprehensive workup for perimenopausal nurses presenting with affective instability. Targeted supplementation of identified deficiencies is low-risk and mechanistically supported. Research implication: trials of nutritional adjuncts in the perimenopausal nurse population are absent from the literature and represent a tractable, low-cost research target.*

**The Acquired Adverse Exposure Score (AAES): Extending ACE Methodology to Occupational Contexts**

The Adverse Childhood Experiences (ACE) instrument measures cumulative childhood trauma across ten categories (abuse, neglect, household dysfunction). Its predictive validity for adult health outcomes is well-established: a score of four or more is associated with substantially elevated risk for depression, cardiovascular disease, substance use disorder, and premature mortality. However, the ACE-10 is bounded by design to childhood exposure, creating a methodological gap for populations whose most severe adversity occurs in adulthood during occupational tenure.

Nursing provides the clearest example of this gap. A nurse who enters the profession with an ACE score of zero and spends twenty years in a critical care unit accumulating moral injury, patient loss, institutional betrayal, occupational violence, and perimenopausal HPA disruption carries a cumulative adversity burden that is unquantifiable by ACE-10. Her score remains zero despite a clinical profile of trauma exposure that would be recognizable to any treating clinician.

The Acquired Adverse Exposure Score (AAES) is proposed as a methodological extension that captures post-childhood adversity accumulation in high-exposure occupational settings. Operational criteria for the AAES should include: (1) patient death and adverse outcomes witnessed in a caretaking role; (2) workplace violence (physical, verbal, sexual) from patients, families, or supervisors; (3) moral injury events (being required to participate in care that violates clinical or ethical judgment); (4) institutional betrayal events (reporting harm and experiencing retaliation, dismissal, or no response); (5) occupational schedule disruption (mandatory overtime, rotation, on-call burden beyond normative levels); (6) workforce reduction events (downsizing, assignment expansion, role boundary erosion); (7) pandemic or mass-casualty surge exposure.

The AAES is proposed as a conceptual framework requiring empirical validation. Scale development, item weighting, and test-retest reliability have not yet been established. Its inclusion here is to identify the methodological gap and propose the construct as a research priority, not to present it as a validated instrument.

**Table 1. CMDS Neurobiological Biomarkers — Evidence Status**

Mechanism	Biomarker / Test	CMDS Layer	Evidence Status
HPA Axis Dysregulation	Cortisol awakening response; salivary cortisol	L5: Desensitization	Established (Yehuda 2016; replicated 2024)

<b>Mechanism</b>	<b>Biomarker / Test</b>	<b>CMDS Layer</b>	<b>Evidence Status</b>
Epigenetic Methylation	FKBP5 methylation assay	L5	Established — intergenerational (Yehuda 2016)
Immune Activation	IL-6, CRP, TNF-alpha; innate immune panel	L5; L2: Dehumanization	2026 preprint; requires peer-reviewed replication
Brain Network Reconfiguration	fMRI — DMN, salience, frontoparietal	L1-L5 (cumulative)	2026 preprint; requires peer-reviewed replication
Amygdala Hyperactivation	fMRI threat-response task	L3: Displacement	Established (prior moral injury literature)
Prefrontal Suppression	fMRI executive task; EEG coherence	L3; L4: Distortion	Established (prior moral injury literature)
GI Dysregulation	Patient-reported + biomarker (secretory IgA)	L5 somatic sequela	2026 preprint: 3.40x OR

### Section IIIe: PTSD-Induced Allopregnanolone Depletion

Post-traumatic stress disorder is independently associated with reduced plasma and central nervous system allopregnanolone concentrations. PTSD produces a complex neuroendocrine profile that includes CRH hypersensitivity and, in many affected individuals, disrupted cortisol dynamics that suppress 5-alpha reductase activity and reduce allopregnanolone synthesis from its progesterone substrate. The pharmacological evidence for the causal significance of allopregnanolone depletion in PTSD-associated psychiatric symptoms is direct: brexanolone (Zulresso), an intravenous formulation of allopregnanolone and the first FDA-approved treatment for postpartum depression, reverses depressive symptoms in populations characterized by allopregnanolone deficit through GABA-A receptor potentiation. This mechanism reinforces the biological plausibility of the compound deficit model.

PTSD prevalence among actively employed registered nurses is estimated at approximately 23%, yielding approximately 713,000 nurses meeting PTSD diagnostic criteria when applied to the 3.1 million actively employed workforce. This figure exceeds published PTSD prevalence estimates for combat-deployed military personnel in most studies. The conditions producing this PTSD burden are not classified hazardous conditions with regulatory oversight. They are the routine operational environment of the U.S. hospital nursing unit -- a classification failure that is itself an institutional accountability problem of the order.

### **Section IIIf: Point of Convergence -- Mitochondrial Neurosteroid Synthesis and Compound Impairment**

The five pathways described above converge on a single biological architecture: the mitochondrial neurosteroid synthesis pathway and its product, allopregnanolone. Each pathway impairs either the substrate availability for this pathway (statin-mediated cholesterol reduction), the gating mechanism for substrate entry into the mitochondria (hypothyroid StAR impairment), the enzymatic conversion of progesterone to allopregnanolone (ACE-driven cortisol elevation suppressing 5-alpha reductase), the neurosteroid reserve available to buffer GABA-A receptor function (PTSD-associated depletion), or the receptor-level capacity to respond to whatever allopregnanolone is produced (PMDD-associated GABA-A hypersensitivity and paradoxical response). None of these pathways is hypothetical. Each is documented in peer-reviewed literature. Each independently generates measurable neurobiological harm and elevated psychiatric risk.

### **Section IIIg: Ketamine, NMDA Receptor Blockade, and Convergent Neurosteroid Deficit**

A structurally distinct but mechanistically convergent pathway involves the N-methyl-D-aspartate (NMDA) glutamate receptor. Pregnanolone sulfate, an endogenous neuroactive steroid produced in the same biosynthetic cascade as allopregnanolone, functions as an NMDA receptor antagonist. Its suppression during periods of substrate depletion -- whether from chronic HPA activation, perimenopausal progesterone decline, or both -- removes a layer of glutamatergic inhibition that is independent of the GABA-A axis.

Ketamine, which produces rapid antidepressant and antisuicidal effects through NMDA blockade, pharmacologically replicates what endogenous pregnanolone sulfate provides under normal neurosteroid sufficiency. The overlapping mechanism explains why ketamine trials report particularly robust response rates in women with treatment-resistant depression and elevated suicidality: the drug fills a deficit that is neurosteroid-mediated, not merely serotonergic.

Both the GABA-A axis (via allopregnanolone substrate depletion) and the NMDA axis (via pregnanolone sulfate insufficiency) operate in parallel deficit. This dual-axis architecture means that single-receptor antidepressant strategies -- SSRIs, SNRIs -- address neither mechanism directly. A woman in perimenopause with HPA dysregulation and progesterone decline may present with treatment-refractory depression not because her serotonin system is the primary driver, but because two distinct inhibitory receptor systems are simultaneously under-resourced.

Both pathways share a downstream convergence point: upregulation of brain-derived neurotrophic factor (BDNF). Allopregnanolone restoration (via brexanolone or zuranolone) and NMDA blockade (via ketamine or esketamine) both produce BDNF-mediated synaptic repair in limbic circuits implicated in affective regulation. This convergence validates the dual-axis framework and supports the hypothesis that neurosteroid deficiency -- not

monoamine deficiency -- is the organizing mechanism for treatment-resistant suicidality in perimenopausal women with high occupational adversity.

***Clinical implication: biomarker panels for high-risk nurses should include pregnanolone sulfate and BDNF alongside allopregnanolone and standard reproductive hormones.***

***Research implication: ketamine and neurosteroid replacement trials should be run in parallel cohorts stratified by menopausal status and occupational ACE burden, not pooled in undifferentiated samples.***

### **NMDA Mechanism: Nutritional Bridge to Dual-Axis Deficit**

The NMDA antagonist function of magnesium provides a direct bridge between nutritional status and the dual-axis neurosteroid deficit described in Section IIIg. A perimenopausal nurse who is magnesium-deficient has reduced inhibitory modulation at NMDA receptors through two simultaneous mechanisms: decreased pregnanolone sulfate from neurosteroid substrate depletion, and decreased magnesium from cortisol-driven urinary wasting and shift-work-associated dietary disruption. The two deficits are additive on the same receptor system, compounding glutamatergic hyperactivation at the same site that ketamine addresses pharmacologically.

The clinical corollary is that magnesium repletion is not a supplementation footnote in this population. It is a first-line, low-cost, low-risk intervention that addresses one of the two NMDA inhibitory deficit mechanisms available without a prescription. Its absence from standard psychiatric and occupational health care for this population reflects the broader gap between available mechanism-targeted interventions and current standard practice.

The nurse who carries this compound profile -- PMDD, statin use, subclinical hypothyroidism, ACE burden, and occupational PTSD -- operates in a state of severely compromised allopregnanolone-mediated GABA-A inhibitory function. During the luteal phase of her cycle, when PMDD drives GABA-A receptor hypersensitivity and the hormonal transition produces a spike-and-withdrawal of allopregnanolone that the receptor cannot process normally, this compound deficit reaches its greatest clinical expression. The biological conditions for suicidal crisis are fully constituted. What is absent is the diagnostic framework to identify them, the occupational health surveillance to detect the individual at risk, and the institutional response to intervene before irreversible harm occurs.

The compound model is not presented as an exhaustive list. Oral contraceptive-mediated neurosteroid disruption, as documented by Skovlund and colleagues and detailed in Section VIII, constitutes a sixth pathway for AFAB nursing employees using hormonal contraception. The five pathways selected for this paper represent those with the strongest mechanistic documentation and the highest prevalence relevance to the nursing workforce demographic.

A seventh pathway merits recognition: chronic occupational violence exposure as an independent HPA axis activator. Healthcare workers who experience repetitive assault -- physical, verbal, or psychological -- sustain cortisol hypersecretion through persistent threat-state activation. Elevated cortisol suppresses 5-alpha reductase activity, directly



reducing allopregnanolone synthesis through the same enzymatic bottleneck targeted by the ACE-mediated pathway described in Section IIIId. The nurse who absorbs patient assaults without institutional response carries a neurobiological violence burden that compounds her PMDD vulnerability through an independently documented mechanism. Bureau of Labor Statistics data report healthcare worker assault rates at 14.2 incidents per 10,000 full-time equivalents -- five times the private-sector average -- with 48% of all nonfatal workplace violence across the U.S. economy concentrated in the healthcare sector. This is not a contextual stressor. It is a recurring biological insult operating through cortisol-mediated neurosteroid suppression, compounding the deficit architecture this section describes.

### **Neurosteroid Synthesis: Enzymatic Architecture and Rate-Limiting Considerations**

A more detailed account of the neurosteroid synthesis pathway clarifies why the five convergent mechanisms described in this paper each produce allopregnanolone depletion through distinct but interconnected enzymatic and receptor-level mechanisms. The synthesis of allopregnanolone from cholesterol proceeds through the following sequence. Step one: StAR-mediated intramitochondrial cholesterol transport, carrying free cholesterol from the cytoplasm-facing outer mitochondrial membrane to the matrix-facing inner mitochondrial membrane. Step two: CYP11A1-mediated oxidative cleavage of the cholesterol side chain, producing pregnenolone and isocaproaldehyde in the mitochondrial matrix. Pregnenolone exits the mitochondria into the endoplasmic reticulum. Step three: 3-beta-hydroxysteroid dehydrogenase (3-beta-HSD) converts pregnenolone to progesterone in the endoplasmic reticulum. Progesterone may exit the cell or proceed to further conversion. Step four: 5-alpha reductase (SRD5A1 or SRD5A2, depending on tissue) converts progesterone to 5-alpha-dihydroprogesterone (5-alpha-DHP). Step five: 3-alpha-hydroxysteroid dehydrogenase (3-alpha-HSD) converts 5-alpha-DHP to allopregnanolone (3-alpha,5-alpha-tetrahydroprogesterone), which is released into the cytoplasm, transported to the plasma membrane, and exerts its GABA-A modulatory effects.

Each of these five enzymatic steps can be impaired by the mechanisms described in the compound deficit model. Step one is impaired by hypothyroid StAR protein impairment (Pathway IIIc) and potentially by reduced StAR expression in settings of severe allopregnanolone depletion through feedback mechanisms. Step two is impaired by statin-mediated substrate reduction (Pathway IIIb), which reduces the cholesterol available for CYP11A1 to process even when StAR transport function is intact. Step four, the 5-alpha reductase step, is directly suppressed by elevated glucocorticoids from ACE-driven HPA dysregulation (Pathway IIId) and from PTSD-associated cortisol dynamics (Pathway IIle). The receptor-level step -- the GABA-A receptor's ability to respond appropriately to whatever allopregnanolone is produced -- is dysregulated by the PMDD-associated subunit remodeling described in Pathway IIIa. When all five mechanisms operate concurrently, every stage of the synthesis-to-effect sequence is compromised.

The clinical consequence of understanding the full enzymatic architecture is that intervention can be targeted at specific steps. Thyroid hormone optimization addresses Step one (StAR expression). Cholesterol substrate management (including reassessment of statin dosing in the context of PMDD or perimenopausal neurosteroid depletion) addresses Step two. GnRH agonist-based cycle suppression followed by add-back with bioidentical estradiol and progesterone addresses both the substrate generation at Steps three through five and the receptor-level stability at the allopregnanolone response step. 5-alpha reductase activity can be indirectly supported by cortisol normalization through trauma-informed PTSD treatment. These intervention targets are not hypothetical; they reflect the mechanism-informed clinical logic that becomes available once the compound deficit model is understood.

### **Clinical Profile of Compound Exposure: The Representative Case**

To illustrate the compound model in clinical terms, consider the following representative profile constructed from the demographic and epidemiological parameters documented in this paper. This is not a case report; it is a synthetic representation of conditions that co-occur at measurable prevalence rates in the nursing workforce demographic and are independently documented in peer-reviewed literature.

A 49-year-old AFAB registered nurse has worked rotating shifts, including a minimum of 10 night shifts per month, for 18 years in a high-acuity medical-surgical unit at a community hospital. She has been prescribed atorvastatin 20 mg daily for 4 years following a lipid panel at her annual occupational health visit indicating borderline dyslipidemia -- an expected finding at her age and shift work exposure history. Her TSH, measured at the same occupational health visit, was 3.8 mIU/L -- within the laboratory reference range, but at the upper end of the range where emerging evidence suggests subclinical impairment of thyroid-dependent steroidogenesis may begin. She was not referred for endocrine evaluation.

Her menstrual cycles have become irregular over the past 14 months, with cycle lengths ranging from 21 to 47 days. She has not connected this irregularity to her escalating premenstrual mood symptoms, because no clinician has asked about the relationship between her cycle and her mood. She presented to her primary care physician eight months ago with complaints of severe irritability, insomnia, crying spells, and transient suicidal ideation. She was assessed without cycle-phase inquiry. The physician noted a prior hospitalization for depression six years earlier -- an episode that occurred, she later recalled, in the weeks before a menstrual period that arrived 11 days late during a period of particularly heavy overtime work. She was assigned a diagnosis of recurrent major depressive disorder and started on sertraline. The sertraline has not helped with the premenstrual symptoms, which she now recognizes track within a few weeks of her cycles, though her cycles are too irregular to predict. She has not been offered cycle-phase tracking or referred to reproductive psychiatry. She is working 15-hour shifts covering for two colleagues who resigned last month.

This profile represents the convergence of: statin-mediated substrate reduction (atorvastatin); upper-range TSH suggesting reduced T3-dependent StAR expression; perimenopausal anovulatory cycles producing progressive allopregnanolone depletion; an occupational PTSD burden from 18 years of high-acuity exposure; and unrecognized PMDD now transitioning into perimenopausal mood disorder -- conditions that are indistinguishable from each other at the level of the presenting symptom and fully distinguishable only through hormonal status evaluation, cycle-phase tracking, and careful pharmacological history. None of these evaluations has been performed. The sertraline she is taking does not address any of the neurobiological mechanisms described in this paper. The institution in which she works has no mechanism to identify her risk profile. She is one of the 713,000.

**Table 2. Compound Neurobiological Deficit Model: Five Convergent Pathways to Allopregnanolone Depletion in the U.S. Registered Nurse Workforce**

Pathway	Primary Mechanism	Effect on Allopregnanolone	Nursing Workforce Prevalence Context
IIIa: PMDD / GABA-A Receptor Hypersensitivity	Aberrant GABA-A receptor subunit remodeling (delta subunit downregulation) in response to cyclic allopregnanolone fluctuation	Paradoxical anxiogenic response to allopregnanolone; receptor hypersensitivity amplifies any depletion from other pathways	3%--8% prevalence in women of reproductive age; higher prevalence estimated in high-stress occupational populations including nurses
IIIb: Statin-Mediated Cholesterol Reduction	HMG-CoA reductase inhibition reduces endogenous cholesterol synthesis and available neurosteroid substrate	Reduced cholesterol substrate for CYP11A1-mediated conversion to pregnenolone; downstream reduction in progesterone and allopregnanolone	Disproportionately common at median nurse age 50; cardiovascular risk factor management in perimenopausal workforce
IIIc: Hypothyroid StAR Protein Impairment	T3 deficiency reduces SF-1-mediated StAR transcription; Star, Cyp11a1, Hsd3b1 downregulated in adrenal cortex	Impaired intramitochondrial cholesterol transport gates entire steroidogenic cascade regardless of substrate availability	Subclinical hypothyroidism affects approximately 8%--10% of women at age 50; symptoms overlap with PMDD, perimenopause, burnout

Pathway	Primary Mechanism	Effect on Allopregnanolone	Nursing Workforce Prevalence Context
IIId: ACE/AEE-Driven HPA Dysregulation	CRH sensitization and glucocorticoid receptor downregulation from childhood adversity; occupational moral injury adds adult-exposure layer	Substrate competition: adrenal resources directed toward cortisol; 5-alpha reductase enzyme suppression by elevated glucocorticoids	ACE prevalence elevated in nursing workforce; occupational trauma adds progressive AAE burden across nursing career
IIIf: PTSD-Induced Allopregnanolone Depletion	HPA axis dysregulation and glucocorticoid disruption suppress 5-alpha reductase activity; allopregnanolone production falls	Direct reduction in available allopregnanolone; GABA-A inhibitory tone impaired; suicide risk rises proportionally	23% PTSD prevalence in actively employed RNs (~713,000 nurses); exceeds combat-deployed military prevalence estimates

Note: GABA-A = gamma-aminobutyric acid type A receptor; StAR = steroidogenic acute regulatory protein; SF-1 = steroidogenic factor 1; CYP11A1 = cholesterol side-chain cleavage enzyme; Hsd3b1 = 3-beta-hydroxysteroid dehydrogenase; HPA = hypothalamic-pituitary-adrenal; CRH = corticotropin-releasing hormone; ACE = adverse childhood experience; AAE = adverse adult experience; PTSD = post-traumatic stress disorder; RN = registered nurse.

## SECTION IV: PMDD DIAGNOSIS — STANDARDS, BARRIERS, AND THE ROLE OF PROSPECTIVE TRACKING

The clinical standard for PMDD diagnosis requires prospective daily symptom tracking over a minimum of two complete menstrual cycles. This is not an arbitrary procedural requirement. It is a scientific necessity arising from three fundamental features of the disorder: recall bias, in which individuals experiencing significant premenstrual symptoms tend to retrospectively attribute more of their month to those symptoms than prospective data support; symptom telescoping, in which the severity and duration of recalled symptoms are systematically overestimated; and intracycle mood variation that cannot be reconstructed accurately after the fact. Without prospective tracking, the diagnosis cannot be established. The DSM-5-TR is explicit on this point.

The Daily Record of Severity of Problems (DRSP) is the most widely validated prospective tracking instrument for PMDD. Developed by Endicott and colleagues and validated in multiple cohorts, it requires daily ratings of 21 symptoms on a 1 to 6 scale, with notation of menstrual bleeding and functional impact across every cycle day. Two months of DRSP data provide the cycle-phase timing documentation required to establish the diagnosis. The

DRSP is available at no cost from the International Association for Premenstrual Disorders (IAPMD; iapmd.org). The Premenstrual Symptoms Screening Tool (PSST), developed by Steiner and colleagues, provides a validated clinician-administered alternative assessing both symptom severity and functional impairment. Digital tracking applications including Me v PMDD and Clue provide accessible platforms for prospective monitoring outside clinical settings and can serve as the foundation for subsequent clinical review.

### **Section IVb: Alternative and Adjunct Cycle-Tracking Modalities**

The scientific standard for PMDD diagnosis -- two prospective cycles of the Daily Record of Severity of Problems (DRSP) -- carries a clinical gatekeeping function that its research design was never intended to serve. The DRSP was developed to ensure luteal-phase timing in research enrollment, not to adjudicate disability eligibility or insurance coverage. Its application as a mandatory diagnostic prerequisite creates systematic exclusion of patients with valid cycle-phase symptom patterns who cannot or do not maintain paper diaries with research-grade consistency.

The argument that prospective charting is the only valid evidence disregards a substantial and growing body of alternative data sources. Commercial fitness and wearable devices (Fitbit, Garmin, Apple Watch, Oura Ring) passively collect resting heart rate variability, sleep staging, and temperature data across menstrual cycles with no patient burden. Published evidence demonstrates that heart rate variability tracks luteal-phase autonomic shifts with sufficient precision to identify cycle phase retrospectively. These data sources are time-stamped, continuous, and not subject to the recall biases inherent in any self-report instrument, including the DRSP itself.

AI-assisted language analysis of digital communication logs (text messages, voice notes, AI chat transcripts) provides another adjunct modality. Cycle-phase-correlated linguistic markers -- increased negative affect, reduced response latency, altered sleep-adjacent communication patterns -- are detectable in longitudinal communication data even when the individual does not prospectively chart. This modality is particularly relevant for nurses whose shift work schedules make daily diary compliance structurally difficult.

Intermittent cycle notation -- any documented, time-stamped record of symptom onset, even if incomplete -- represents clinically meaningful longitudinal evidence. A nurse who marks "bad week" in a personal planner, texts a partner about mood crashes, or notates medication use on a shift schedule creates an evidentiary record that, when reviewed across six to twelve months, may establish a clear perimenstrual pattern. Dismissing this evidence because it was not collected on a research instrument reflects methodological literalism, not clinical rigor.

Familial and partner observer reports constitute a validated category in the psychiatric literature for conditions affecting self-monitoring capacity. Observer-rated instruments have been developed for depression, mania, and cognitive disorders; there is no principled reason to exclude observer rating from PMDD/PME evaluation, and considerable practical reason to include it for individuals who work night shifts, have high cognitive load jobs, or live with partners who can provide longitudinal behavioral observation.

***Research recommendation: the field should develop and validate a multimodal cycle-tracking composite score that integrates prospective self-report, wearable biometric data, and observer rating. Diagnostic criteria should permit any two of these three modalities to satisfy the prospective evidence requirement, with DRSP remaining one valid option rather than the exclusive one.***

#### **Section IVc: Borderline Personality Disorder and Bipolar Spectrum — Diagnoses of Exclusion Requiring Cycle Documentation: Diagnoses of Exclusion Requiring Cycle Documentation**

DSM-5 Criterion D for PMDD specifies that the symptom pattern must not represent an exacerbation of another disorder such as major depressive disorder, panic disorder, dysthymic disorder, or a personality disorder. In clinical practice, this criterion has been selectively weaponized to exclude PMDD diagnoses in women who carry borderline personality disorder (BPD) or bipolar II diagnoses, even when those women show clear cycle-phase periodicity.

BPD and PMDD are not mutually exclusive conditions. Both involve affective dysregulation and interpersonal reactivity, but BPD symptoms are longitudinally persistent and triggered by interpersonal cues, while PMDD symptoms are temporally restricted to the luteal phase and remit with menstruation. A woman with both conditions will show the BPD baseline pattern continuously and the PMDD pattern layered on top during luteal phases. Conflating the two because they share surface phenomenology is a diagnostic error with clinical consequences: the neurosteroid-mediated component of her suffering is treatable and being missed.

Bipolar II, which involves hypomanic episodes that in women often cluster premenstrually, presents a similar diagnostic challenge. Premenstrual Exacerbation (PME) of bipolar disorder -- where the luteal phase amplifies already-present mood cycling -- is categorically distinct from primary PMDD but requires the same cycle-phase documentation to identify. Without documented cycle timing, clinicians cannot distinguish primary bipolar II from PME-amplified bipolar II, and the optimal pharmacologic strategies differ. Mood stabilizers without hormonal adjuncts address one component; combined approaches are needed for PME.

Clinical mandate: any patient carrying a BPD or bipolar spectrum diagnosis who presents with cyclic mood destabilization should receive cycle-phase documentation as a required component of the workup, not an optional add-on. The diagnostic question is not "does this patient have BPD?" but "is the BPD symptom burden cycle-phase-modulated, and if so, what is the neurosteroid contribution?" Failing to ask the second question abandons a treatment-relevant mechanistic pathway.

Despite the clarity of the diagnostic standard, the operational barriers to PMDD diagnosis in clinical practice are structural and substantial. No routine clinical encounter in primary care, psychiatry, or occupational medicine includes standardized menstrual cycle phase inquiry as part of the psychiatric assessment. No electronic health record template in common use prompts clinicians to document cycle phase at the time of a psychiatric chief complaint. The



presenting symptoms of PMDD -- affective instability, suicidal ideation, irritability, anxiety, cognitive disruption, somatic complaints -- are treated as free-standing psychiatric findings and assigned DSM codes without the prospective tracking that would establish or exclude a cycle-phase pattern. The result is a clinical system that produces diagnostic error by design: it is structured to evaluate psychiatric symptoms in a way that systematically excludes the information required to diagnose PMDD.

The consequences are directional and asymmetric. PMDD is systematically underdiagnosed. Other conditions -- bipolar disorder, major depressive disorder, borderline personality disorder -- are systematically overdiagnosed in populations where PMDD was the correct or primary diagnosis. The treatment assigned on the basis of these erroneous diagnoses carries its own risk profile, which is detailed in Section VI. The nurse with unrecognized PMDD who is assigned a bipolar diagnosis and prescribed valproate is not an outlier case. She is a predictable product of a diagnostic system that is not equipped to recognize her actual condition.

### **Cycle, Occupational/life adversity, Mood pattern, Perimenopause, Adversity/trauma, Symptom severity, Safety Questionnaire (COMPASS): A Proposed Differential Diagnosis Instrument**

The existing validated instruments -- the DRSP and PSST -- were designed to confirm or exclude PMDD; neither was designed to distinguish PMDD from perimenopause, borderline personality disorder (BPD), or bipolar disorder in clinical settings where these conditions share affective symptom overlap. No validated brief instrument currently exists for this differential diagnostic purpose. The clinical need is real and unmet: a clinician seeing a patient in her late 40s who presents with cyclical affective instability, suicidal ideation, interpersonal reactivity, and insomnia requires a structured approach to distinguish PMDD, perimenopausal mood disorder, BPD, and bipolar spectrum disorder before initiating pharmacological treatment.

COMPASS (Cycle, Occupational/life adversity, Mood pattern, Perimenopause, Adversity/trauma, Symptom severity, Safety Questionnaire) is proposed here as a clinician-administered brief screening instrument to support initial differentiation across five presentations: premenstrual syndrome (PMS), premenstrual dysphoric disorder (PMDD), perimenopausal mood disorder, borderline personality disorder (BPD), and bipolar spectrum disorder.

Key distinguishing domains for COMPASS include the following eight assessment areas. Domain 1 addresses cycle-phase timing: symptom onset, offset, and the symptom-free window relative to the menstrual cycle -- the single most important discriminating feature, because PMDD and PMS have strict luteal-phase onset with follicular-phase remission, while BPD and bipolar disorder do not. Domain 2 addresses menstrual regularity and cycle changes, including irregular cycles, vasomotor symptoms, and sleep disruption as indicators of perimenopausal transition. Domain 3 addresses affective instability patterns: interpersonal trigger-driven instability in BPD versus hormonal cycle-driven instability in PMDD versus sustained episodic mood disturbance in bipolar disorder. Domain 4 addresses

suicidal ideation pattern: luteal-phase specific and cyclically remitting ideation in PMDD and perimenopause, versus chronic and relationally triggered ideation in BPD, versus episodic ideation co-occurring with mood episodes in bipolar disorder. Domain 5 addresses response to cycle manipulation: symptom resolution with GnRH agonist or oral contraceptive suppression supports PMDD; absence of response supports BPD or bipolar. Domain 6 addresses hormonal status: FSH, estradiol, progesterone, and TSH provide the endocrine context for interpretation. Domain 7 addresses pharmacological history: prior treatment with synthetic progestins versus bioidentical progesterone, and prior mood stabilizer or antipsychotic response or non-response. Domain 8 addresses ACE and occupational stress history as the modifying context within which current symptoms are occurring. Domain 8 is expanded to encompass bidirectional occupational violence assessment: (a) violence exposure history incorporating patient, visitor, and lateral peer aggression across career trajectory; and (b) occupational violence perpetration risk, assessed not as a disciplinary instrument but as a clinical screen for a trauma-exposed workforce in which the moral disengagement mechanisms documented in the CMDS framework may externalize harm under chronic organizational stressor conditions. Validated bidirectional instruments for this population constitute an identified clinical development priority (see Section XIII).

COMPASS is presented here as a proposed framework requiring prospective validation in clinical populations. It is not a validated instrument at the time of this writing. Development and validation in populations representing each of the five target presentations represents an identified research priority.

## **SECTION V: PERIMENOPAUSE, ESTROGEN WITHDRAWAL, AND ELEVATED SUICIDE RISK — A CONVERGENCE OVERLOOKED IN NURSING OCCUPATIONAL HEALTH**

Perimenopause is not a minor hormonal adjustment. It is a multi-year period of ovarian function decline characterized by erratic estradiol fluctuation, eventual sustained estrogen withdrawal, the loss of the progesterone surge accompanying ovulatory cycles, and progressive FSH elevation as the hypothalamic-pituitary axis attempts to compensate for declining ovarian responsiveness. The duration of perimenopause ranges from approximately 4 to 7 years, with onset typically between ages 45 and 55. This is not a brief transition. It is a years-long physiological reorganization that occurs during what may be the most professionally and personally demanding period of a nurse's career.

The psychiatric consequences of the perimenopausal transition are well-documented and more severe than is commonly acknowledged in clinical practice. Usall and colleagues, analyzing data from the ESEMeD epidemiological study conducted across six European countries, found that perimenopausal women were 7.0 times more likely to report suicidal ideation (7.8% prevalence) compared to premenopausal women (1.1%) and postmenopausal women (1.0%). This finding held across all six countries and was statistically independent of the presence of mood and anxiety disorders -- meaning the elevated suicide risk in perimenopause is not fully explained by comorbid depression or anxiety but reflects a risk factor associated with the perimenopausal hormonal transition itself.

A 2025 systematic review by Hendriks and colleagues, published in *Women's Health*, confirmed elevated suicide risk during perimenopause and menopause across the international literature, with perimenopause consistently representing the highest-risk window within the menopausal transition. Data from a specialist menopause clinic, reported by Hendriks and colleagues (including Newson) in *BJPsych Open* (2024), found that 16% of women attending the clinic reported suicidal ideation or self-harm thoughts in the two weeks preceding their appointment -- a figure far exceeding the general population prevalence of suicidal ideation in adult women and elicited only because hormonal status and cycle-phase context were being explicitly assessed. The clinical implication is that perimenopausal suicidal ideation is substantially undercaptured in standard psychiatric encounters that do not assess hormonal context.

The demographic intersection with the nursing workforce is direct and measurable. The median registered nurse age in 2024 is 50 years, per the NCSBN National Nursing Workforce Survey published April 2025. Perimenopause typically spans ages 45 to 55, with the highest-risk window for suicidal ideation in the active perimenopausal phase. A median age of 50 places the largest demographic cohort of the U.S. nursing workforce at the center of the highest-risk perimenopausal window for suicidal ideation. This is not a peripheral risk factor for the nursing workforce. It describes the central demographic reality of the workforce at this historical moment.

The same NCSBN 2024 data report that 39.9% of registered nurses intend to leave their current position within 5 years. Applied to the median age of 50, this departure intention places the anticipated exit window at ages 50 to 55 for the median nurse -- directly overlapping the peak perimenopause period. The workforce exit pressure that hospital systems treat as a retention and staffing problem is occurring in the same biological window as the highest-risk period for perimenopausal suicidal ideation. This convergence is not coincidental, and it is not being analyzed as such in any current occupational health or workforce surveillance framework.

Available evidence from nursing occupational suicide literature indicates that a substantial majority of nurses who died by suicide had either lost their position or were in the process of position loss in the period preceding their death. This pattern positions the moment of occupational exit -- which for the median nurse occurs in the perimenopausal window -- as a convergence point of neurobiological vulnerability, identity disruption from occupational role loss, and institutional abandonment. The conditions for a lethal crisis are structurally assembled at the intersection of a predictable biological process and a predictable workforce event, in a workforce that has no surveillance architecture designed to detect or interrupt this convergence.

The neurobiological mechanism is not speculative. Estrogen directly upregulates 5-alpha reductase expression, the enzyme that converts progesterone to 5-alpha-dihydroprogesterone and ultimately to allopregnanolone. As estrogen declines in perimenopause, 5-alpha reductase activity falls, and allopregnanolone production is correspondingly reduced. Additionally, progesterone levels decline with the anovulatory cycles of perimenopausal transition, reducing the substrate available for allopregnanolone

synthesis. The result is reduced substrate and reduced enzymatic capacity for allopregnanolone synthesis: a double mechanism for neurosteroid depletion that is intrinsic to the perimenopausal process and independent of any prior psychiatric history. A nurse who has maintained psychiatric stability throughout a 25-year career may enter perimenopause without any prior psychiatric diagnosis and develop suicidal ideation for the first time as a direct neurobiological consequence of this hormonal transition.

This convergence -- neurobiological vulnerability, occupational moral injury, workforce exit, identity disruption, and estrogen-withdrawal-driven allopregnanolone depletion -- is entirely absent from current occupational health frameworks for nursing. It is not addressed in the Dr. Lorna Breen Health Care Provider Protection Act or its 2026 reauthorization. It is not a standard component of employee assistance programming in hospital systems. It is not measured in any federal nursing workforce surveillance instrument. This is stated without rhetorical modulation because the evidence warrants directness: nurses are dying at the intersection of a predictable biological process and an institutional surveillance gap, and the gap is addressable.

The clinical framework for perimenopausal psychiatric assessment must include recognition that estrogen is not exclusively a reproductive hormone. Estrogen receptors are expressed throughout the central nervous system -- in the hypothalamus, hippocampus, amygdala, prefrontal cortex, and brainstem nuclei that regulate mood, memory, anxiety, and autonomic function. The withdrawal of estrogen in perimenopause therefore produces widespread changes in neurochemical environment, not merely the reproductive hormonal changes that conventional menopause framing emphasizes. The serotonergic system is directly sensitive to estrogen: estrogen upregulates serotonin synthesis, reduces serotonin reuptake, and modulates serotonin receptor expression. The dopaminergic reward system is similarly estrogen-sensitive, with estrogen withdrawal reducing dopamine signaling in the mesolimbic pathway. The glutamatergic system, the GABAergic system, and the noradrenergic system all show measurable changes in response to estrogen withdrawal. The psychiatric consequences of perimenopause are therefore not a single-mechanism phenomenon; they arise from the simultaneous disruption of multiple neurotransmitter systems whose stability had been maintained by estrogen-mediated modulation throughout the reproductive years.

The clinical implication is that perimenopausal depression, anxiety, and suicidal ideation may not respond to standard pharmacological approaches developed for conditions with different neurobiological profiles. A perimenopausal nurse with suicidal ideation whose crisis is driven by estrogen-withdrawal-mediated serotonin deficit, allopregnanolone depletion, and HPA axis sensitization may respond poorly to an SSRI prescribed without hormonal context -- not because SSRIs are ineffective in general, but because serotonin reuptake inhibition is a partial intervention in the context of a multi-system hormonal disruption that includes but extends beyond the serotonergic system. Hormonal stabilization -- through transdermal estradiol, progesterone supplementation using bioidentical formulations, or thyroid hormone optimization -- may be required as the primary intervention, with pharmacological adjuncts calibrated to the corrected hormonal context.

This clinical logic is not widely known or practiced among the emergency medicine and psychiatric clinicians who most frequently encounter perimenopausal suicidal crisis.

## **SECTION VI: DIAGNOSTIC FAILURES — MISDIAGNOSIS, DELAY, AND IATROGENIC HARM**

The clinical presentation of PMDD during the luteal phase can be indistinguishable, in a single cross-sectional clinical encounter, from an acute major depressive episode, a mixed affective state, or a borderline personality crisis. Suicidal ideation, affective instability, cognitive disruption, and functional impairment are all present. What is absent in the standard clinical encounter is any information about whether these symptoms were present last week, whether they will be present next week, and whether they track in a cycle-phase pattern that would establish PMDD as the diagnosis. Without that information, the diagnostic assessment is conducted without its most critical input variable, and errors are structurally inevitable.

The downstream consequences of this diagnostic gap are directional: PMDD is systematically underdiagnosed, and other conditions -- bipolar disorder, major depressive disorder, borderline personality disorder -- are systematically overdiagnosed in populations where PMDD was the correct or contributing diagnosis. Patient advocacy data from IAPMD suggest that as many as 25% of PMDD-affected individuals may receive a bipolar diagnosis before their PMDD is correctly identified; this figure requires corroboration from prospective population-representative studies, as it derives from advocacy survey data subject to selection bias toward severely affected individuals. Hirschfeld and colleagues documented the extensive experience of prior misdiagnosis among individuals with bipolar disorder, illustrating the broader pattern of diagnostic drift across mood presentations. The specific rate of PMDD-to-bipolar misdiagnosis in population-representative clinical samples has not been established in a single peer-reviewed study and constitutes a critical research gap.

The costs associated with bipolar diagnosis -- regardless of its accuracy -- are substantial. Adults assigned a diagnosis of bipolar disorder incur documented adjusted annualized direct healthcare costs of approximately \$20,846 per person per year, attributable to the diagnostic assignment and associated treatment regimens (Annals of General Psychiatry, 2023; doi:10.1186/s12991-023-00440-7; PMC10037816). Those carrying a bipolar diagnostic assignment inaccurately -- because their actual condition is PMDD, perimenopausal mood disorder, PTSD, or some combination -- will accumulate these costs from pharmacological regimens that do not address the underlying biology, from treatment-emergent adverse effects, and from the uncorrected progression of the underlying untreated condition. The use of the phrase "assigned a diagnosis of bipolar disorder" throughout this paper is deliberate and reflects a clinically meaningful distinction: the diagnostic assignment and the biological reality it purports to represent may not correspond, and the economic burden flows from the assignment regardless of its accuracy.

Valproate is among the most commonly prescribed pharmacological agents for bipolar disorder. It is prescribed to reproductive-age individuals at rates that make its teratogenic

profile a population-level concern. Children born to individuals taking valproate during pregnancy demonstrate mean full-scale IQ differences of approximately 7 to 10 points compared to children exposed to other antiseizure medications during the same gestational period. These differences are dose-dependent: at doses exceeding 800 mg per day, adjusted mean IQ differences of approximately 9.7 points have been reported, along with an approximately 8-fold increased need for educational intervention. These findings derive from the NEAD study (Meador et al., NEJM 2009; 6-9 point difference at age 3), the Norwegian controlled cohort study of Nadebaum et al. (Neurology 2015; 9.7 point difference at doses above 800mg/day, 8-fold educational intervention increase), and the EURAP neurocognitive extension protocol (Stjerna et al., Epilepsy Behav 2024). The iatrogenic harm cascade that begins with unrecognized PMDD and terminates in valproate-associated neurodevelopmental effects in the nurse's offspring is a preventable outcome of a diagnostic system failure. The harm extends beyond the nurse to the next generation.

Synthetic progestins represent a second iatrogenic pathway arising from PMDD mismanagement. Combined oral contraceptives containing synthetic progestins are frequently prescribed as empirical management for premenstrual symptoms. In individuals with PMDD, synthetic progestins can worsen clinical outcomes through the GABA-A receptor pathway: unlike endogenous progesterone and its allopregnanolone metabolite, synthetic progestins do not generate GABA-A-potentiating neurosteroids, and some synthetic progestin metabolites may produce anxiogenic rather than anxiolytic neurosteroid effects depending on the specific progestin structure and individual metabolic profile. A nurse with PMDD who is prescribed a combined oral contraceptive for premenstrual symptom management without PMDD diagnosis may experience worsening of her underlying disorder attributable to this pharmacological mismatch.

The misdiagnosis landscape for PMDD-presenting patients involves two diagnoses that merit specific quantitative documentation before the PMDD differential is addressed. Bipolar disorder is the most common incorrect diagnosis applied to women with PMDD. The IAPMD Global Survey (2018) found that approximately one in four women with prospectively confirmed PMDD had been told they had bipolar disorder before receiving the correct diagnosis, with a mean diagnostic delay of 12 years and 6 to 11 providers seen before confirmation. Wittchen et al. (2002) found 8-fold elevated odds of comorbid bipolar I and II diagnosis among women with PMDD compared to PMDD-negative women, a finding most parsimoniously explained not by true comorbidity but by the diagnostic substitution that occurs when cyclical affective states are evaluated without prospective cycle-phase documentation. The consequence of bipolar misdiagnosis in a cycling AFAB patient is not merely delay. Sodium valproate, one of the primary mood stabilizers prescribed for bipolar disorder, carries approximately 10 percent major congenital malformation risk in pregnancy and documented in utero cognitive effects. Lithium carries nephrogenic diabetes insipidus risk with chronic use and approximately 20 percent hypothyroidism incidence with long-term therapy, which is precisely the iatrogenic thyroid-function deficit that compounds neurosteroid synthesis impairment in the pathway documented throughout this manuscript. None of these agents treats PMDD.



Borderline personality disorder is a third common misdiagnosis in the PMDD-presenting population, driven by shared features of affective instability, interpersonal reactivity, emotional dysregulation, and suicidal ideation. The distinguishing feature is cycle-phase timing, which is not assessable in a single clinical encounter without prior prospective tracking. In PMDD, affective instability and suicidal ideation are luteal-phase specific and remit with menstruation; the interpersonal conflict of the luteal phase is driven by neurobiological irritability, not by attachment pattern or fear of abandonment. In BPD, affective instability is interpersonally triggered and does not remit predictably at any point in the menstrual cycle. Without prospective symptom tracking, this distinction cannot be established, and the BPD diagnosis is assigned on the basis of cross-sectional symptom presentation alone, a methodologically insufficient basis for a diagnosis with far-reaching clinical and social consequences.

The diagnostic instability of BPD as a label compounds this problem. A 20-year retrospective study of 346 patients carrying a confirmed BPD diagnosis found that prior recorded diagnoses included major depressive disorder in 44 percent, affective disorder in 33 percent, schizophrenia in 13 percent, and mania in nearly 10 percent, meaning that virtually every patient in the sample had accumulated at least one prior conflicting diagnosis across depressive, affective, and psychotic spectra before the BPD label was assigned. Ruggero et al. found that approximately 40 percent of individuals with confirmed BPD had previously been diagnosed with bipolar disorder, and NAMI characterizes BPD as one of the most commonly misdiagnosed conditions in psychiatry, noting that no accurate prevalence figure for the condition even exists because the misdiagnosis volume is too substantial to establish a clean population base. Female patients are over-diagnosed with BPD and male patients with the same presentation are systematically under-diagnosed, a sex-differentiated pattern that maps directly onto the PMDD-presenting population. What this accumulated evidence establishes is not a single misdiagnosis rate but something more significant: that BPD functions in current clinical practice less as a discrete finding and more as a label assigned to affectively dysregulated women in cross-sectional encounters where the question of cycle-phase symptom timing was not asked. In the PMDD-presenting patient, asking that question and documenting the answer prospectively across two cycles is the only methodologically adequate basis for ruling the diagnosis in or out. That question is, as documented throughout this manuscript, the one most consistently not asked.

The overall picture is one of a diagnostic system structurally unprepared to recognize PMDD and that, in its unpreparedness, produces a consistent pattern of harm: delayed diagnosis, pharmacological mismanagement, iatrogenic adverse effects, and the continuation of an unaddressed neurobiological disorder through the years during which it could most readily be treated. For the nursing workforce, this diagnostic failure occurs within an occupational context that amplifies every element of the PMDD burden and within an institutional context that discourages disclosure and suppresses escalation.

## ADHD as Unrecognized Comorbidity in the Perimenopausal Diagnostic Maze

Attention-Deficit/Hyperactivity Disorder (ADHD) in women is systematically underdiagnosed across the lifespan, with the largest diagnostic gap occurring in the perimenopausal period. Estrogen modulates dopaminergic and noradrenergic neurotransmission in prefrontal cortex circuits that govern executive function, working memory, and impulse regulation. As estrogen declines during perimenopause, women with subclinical or previously compensated ADHD may decompensate rapidly, presenting with new or dramatically worsened cognitive symptoms.

This presentation is regularly misattributed to anxiety, depression, early dementia, or "hormonal changes" without further specification. A perimenopausal nurse presenting with difficulty concentrating, task-switching impairment, emotional lability, and sleep disruption carries a differential diagnosis that includes ADHD decompensation, hypothyroid cognition, PMDD-driven luteal impairment, and sleep-deprivation cognitive effects. Each requires a different intervention; prescribing an antidepressant for what is primarily an ADHD decompensation is a treatment mismatch with predictable non-response.

***Research recommendation: adult ADHD screening should be included in any workup for perimenopausal affective instability or cognitive change. The Conners Adult ADHD Rating Scales or equivalent validated instrument should be administered with attention to sex-normed scoring and the historical underdetection of inattentive presentation in female patients.***

## The Differential Diagnosis Problem in Practice: A Clinician Training Case Example

The following hypothetical clinical vignette illustrates the diagnostic decision points at which PMDD, perimenopausal mood disorder, and bipolar disorder diverge, and demonstrates the specific information required to distinguish them -- information that is systematically absent from standard psychiatric assessments.

A 44-year-old AFAB registered nurse presents to a psychiatric urgent care clinic at 9 PM on a Tuesday reporting three days of severe depression, suicidal ideation with no plan, and inability to sleep. She has had similar episodes in the past and has previously been prescribed sertraline, which she discontinued because it made her feel "numb." She drinks three glasses of wine per week, does not smoke, and has no prior psychiatric hospitalizations. Her last menstrual period began 22 days ago.

At this point in the assessment, three diagnostic pathways are equiprobable: a major depressive episode in a patient with recurrent MDD; a mixed or depressive episode in bipolar II disorder; or a severe luteal-phase episode of PMDD. The clinician has no prior DRSP data. She cannot ask "did your symptoms begin about a week before your last period?" meaningfully, because the patient does not track her cycle and cannot accurately recall when symptoms began. The patient's own attribution -- "I just get like this sometimes" -- reflects the recall bias that makes retrospective cycle-phase assessment unreliable.

What would distinguish PMDD from the other diagnoses in this setting: First, cycle phase calculation from the last menstrual period date. Day 22 of a regular cycle places her in the

mid-to-late luteal phase -- the PMDD window. This is a three-second calculation that requires only the last menstrual period date. It does not require prospective tracking. It does not establish PMDD, but it establishes that the timing is consistent with PMDD and should prompt prospective tracking referral. Second, inquiry about prior episodes and their timing. If prior severe depressive episodes have consistently occurred in the week or two before periods and resolved within days of menstruation, the cycle-phase pattern is present -- even if imprecisely recalled. Third, inquiry about the follicular phase: "How do you feel in the week after your period starts?" If the answer is "fine" or "much better," the symptom-free window that defines PMDD is present by patient report. Fourth, FSH and estradiol to screen for perimenopausal transition at age 44. None of these steps requires a referral, a follow-up appointment, or specialized training beyond the basics proposed in Section XIIa. The entire assessment addition takes fewer than 5 minutes. It is currently not performed in any standardized way in emergency or urgent psychiatric settings.

## **Section VI-A: PMDD Misdiagnosis — Full Evidence on Consequences**

Wittchen et al. (2002), in a German longitudinal cohort, found 8-fold elevated odds of comorbid bipolar I and II diagnosis among women with PMDD compared to PMDD-negative women (OR 7.9 and 8.1 respectively). The IAPMD Global Survey (2018) found approximately 1 in 4 women with confirmed PMDD had been told they had bipolar disorder before correct diagnosis, with a mean diagnostic delay of 12 years and 6 to 11 providers seen before diagnosis. Qualitative research (Osborn et al. 2020) identifies "misdiagnosis and the lost decades" as a primary patient-reported theme.

The consequences of bipolar misdiagnosis in PMDD-affected cycling patients are substantial and documentable. Sodium valproate carries approximately 10 percent major congenital malformation risk in pregnancy and in utero cognitive effects of approximately 40 IQ points (Tomson et al. 2018), prescribed to reproductive-age AFAB patients with a missed diagnosis. Lithium carries nephrogenic diabetes insipidus risk with chronic use and approximately 20 percent hypothyroidism incidence with long-term therapy, adding an iatrogenic thyroid-function deficit to a patient who may already be developing the subclinical hypothyroidism that compounds neurosteroid synthesis impairment. Atypical antipsychotics carry metabolic syndrome risk and tardive dyskinesia at 3 to 5 percent per year with typical agents. None of these agents treats PMDD. The harm is the result of a diagnostic error generated by failure to perform the single most discriminating diagnostic step, which is to ask about symptom timing relative to the menstrual cycle and document the answer prospectively across two cycles.

SSRIs administered continuously or in luteal-phase dosing produce response rates of 60 to 70 percent in RCTs versus approximately 30 percent placebo, confirmed in the Cochrane systematic review (Marjoribanks et al., updated 2024). The mechanism is not antidepressant monoaminergic action but rapid allopregnanolone synthesis modulation through 3-alpha-HSD activation, explaining onset within hours to days. Drospirenone-containing oral contraceptive (Yaz) is FDA-approved for PMDD since 2006. GnRH analogs with add-back hormonal therapy produce approximately 73 percent response. Brexanolone and zuranolone, FDA-approved for postpartum depression via the GABA-A allopregnanolone

pathway, have mechanistic relevance for PMDD treatment under investigation. The existence of multiple effective, FDA-approved treatments is directly relevant to both the legal framework (modifiability makes non-screening less defensible) and the ethical framework (preventable harm requires prevention).

## **SECTION VII: THE ECONOMIC BURDEN MODEL**

The aggregate economic burden of PTSD in the U.S. nursing workforce is estimated at approximately \$14.0 billion annually. This figure is derived from published per-person cost data from peer-reviewed health economics research applied to a nursing-specific prevalence model. The derivation is explicit and verifiable; the assumptions are stated; the uncertainty bounds are acknowledged.

Davis and colleagues published the most comprehensive U.S. societal cost analysis of PTSD to date in the *Journal of Clinical Psychiatry* in 2022. Using a 2018 reference year and a comprehensive societal costing methodology, they estimated the total U.S. economic burden of PTSD at \$232.2 billion. The civilian population accounted for 81.6% of total costs (\$189.5 billion), with an average excess cost per civilian with PTSD of \$18,640 per year. The military population accounted for 18.4% of costs (\$42.7 billion), with an average excess cost per military member with PTSD of \$25,684 per year. The weighted composite figure across both populations is \$19,630 per person per year. Direct healthcare costs ranged from \$12,167 to \$13,016 per person per year across civilian and military subgroups.

Nursing is a civilian occupation. The per-person figure most directly applicable is the civilian-specific figure of \$18,640 per year, representing the conservative lower bound. The composite figure of \$19,630 is applied here for the primary estimate.

PTSD prevalence in the actively employed registered nursing workforce is estimated at 23%, based on published occupational health literature. Applied to 3.1 million actively employed U.S. registered nurses, 23% yields approximately 713,000 nurses meeting PTSD diagnostic criteria. The burden calculation is as follows:

\$19,630 (composite per-person annual cost) multiplied by 713,000 (23% of 3.1 million employed RNs) equals \$13,996,190,000, rounded to \$14.0 billion per year.

Applying the civilian-specific figure: \$18,640 multiplied by 713,000 equals \$13,290,320,000, or approximately \$13.3 billion -- the conservative lower bound.

The \$14.0 billion primary estimate carries the following stated assumptions and limitations. The Davis 2022 per-person cost estimate uses 2018 reference-year pricing; healthcare cost inflation since 2018 means current costs would be materially higher. The 23% PTSD prevalence estimate is a point estimate with uncertainty bounds not consistently reported across studies. The 3.1 million employed RN figure represents projection-based estimates and may differ from actual current employed counts. Most significantly, this calculation captures PTSD economic burden only. It excludes: the additional burden of PMDD affecting an estimated 93,000 to 248,000 nurses; the psychiatric consequences of perimenopausal transition in the large cohort of nurses aged 45 to 55; costs of bipolar misdiagnosis and pharmacological mismanagement; productivity losses from presenteeism in the non-PTSD

nursing population affected by PMDD or perimenopause; costs of nursing attrition attributable to psychiatric conditions; and patient safety costs of psychiatric burden in the delivering nurse workforce.

The \$14.0 billion figure is therefore a floor, not a ceiling. It is the portion of the total burden that can be calculated from a single published study using a single well-characterized prevalence estimate. The full burden -- which would require an integrated costing model incorporating all conditions described in this paper -- is substantially larger.

## **Section VIIb: The Economic Argument — Davidson Career Value Framework and Aggregate Loss Estimation**

The full economic case for intervening in nurse suicide risk extends substantially beyond the direct costs of a single departure or death. Davidson and colleagues (DOI: 10.1111/nuf.12380) established a career value framework in which the full productive value of a mid-career nurse -- incorporating recruitment, onboarding, training, skill accumulation, and mentorship capacity -- ranges from \$1.1 million to \$1.85 million per nurse, compared to institutional replacement cost estimates of \$56,300 to \$72,000. The replacement cost figure captures only the direct transaction of filling a vacancy; it excludes the loss of institutional knowledge, the mentorship deficit passed to newer nurses, and the productivity reduction in units operating with unfamiliar staff.

Applying the Davidson career value range to the documented annual nurse suicide toll produces a conservative aggregate figure. If approximately 400-730 nurses die by suicide annually in the United States (range dependent on methodology and identification completeness), and if even the lower Davidson career value estimate of \$1.1 million is applied, the annual aggregate economic loss from nurse suicides alone falls between \$440 million and \$803 million. When attrition driven by untreated perimenopausal mental health burden -- nurses who leave the profession rather than die -- is included at proportional career value, the aggregate figure approaches or exceeds \$15 billion annually.

*[Methodology note on the nurse suicide mortality range: The 400 to 730 deaths figure is derived from multiplying the documented elevated proportional mortality ratio (PMR) for nurse suicide (approximately 1.58 to 1.65 relative to the general population, depending on the study cited) against the baseline female occupational death rate, applied to the estimated nursing workforce of 4.3 million. This calculation uses Milner et al. (2017) as the primary PMR source. The figure is a range estimate at the center of published methodology; the lower bound using conservative PMR inputs approaches 400 annually, and the upper bound using occupational health attribution methods may exceed 1,000. Users of this figure should represent it as a range estimate with stated methodology, not as a census count.]*

Assumption disclosure (required for integrity): the \$15 billion figure integrates multiple epidemiologic and economic estimates that each carry their own uncertainty ranges. The nurse suicide toll depends on identification completeness; the Davidson career value depends on institutional context and specialty; the attrition multiplier depends on assumptions about what proportion of early nursing departures are driven by untreated

perimenopausal mental health burden rather than other factors. Users of this figure in policy or litigation contexts should represent it as an order-of-magnitude estimate derived from documented components, not as a precisely calculated total. The individual components -- suicide toll, career value per nurse, attrition fraction -- should each be cited independently with their respective uncertainty ranges.

The economic framing serves a specific strategic function: it translates a public health and human rights argument into the language of institutional risk and fiduciary obligation. Boards and health system executives who are unresponsive to suffering may be responsive to documented financial exposure. The argument is not that economic loss is more important than human loss; it is that economic loss is a consequence of human loss that falls within institutional governance responsibility.

### **Section VIIc: Economic Burden Model — Sensitivity Analysis and Alternative Calculations**

Several alternative calculations are presented here to establish the range within which the \$14.0 billion primary estimate sits, and to demonstrate that the figure holds across reasonable variation in the key input parameters.

Scenario A: Conservative estimate using civilian-specific per-person cost and lower-bound PTSD prevalence. If the civilian-specific per-person cost of \$18,640 is used and PTSD prevalence is estimated at 20% rather than 23% -- the low end of published estimates for nursing -- the affected cohort is 620,000 nurses and the burden is  $\$18,640 \times 620,000 = \$11,556,800,000$ , or approximately \$11.6 billion. This represents the conservative floor of the estimate.

Scenario B: Current-dollar estimate using inflation adjustment. The Davis 2022 analysis used 2018 reference-year pricing. Healthcare cost inflation from 2018 to 2025 (the most recent full year available) has been approximately 20% to 25% by CPI-Medical deflator, which would imply a current-dollar per-person cost of approximately \$22,556 to \$24,538 using the composite figure. At the 2025-dollar midpoint of \$23,547 and the 23% prevalence estimate, the burden calculates to  $\$23,547 \times 713,000 = \$16,789,011,000$ , or approximately \$16.8 billion. This represents the current-dollar upper bound using the composite per-person cost.

Scenario C: Prevalence escalation scenario. Published PTSD prevalence estimates for nursing have ranged from 22% to 32% across studies depending on the clinical setting (ICU versus general medical-surgical), the PTSD assessment instrument, and the calendar period (with post-COVID studies generally reporting higher prevalence). At the upper-bound prevalence estimate of 32%, the affected cohort is 992,000 nurses, and the burden at the primary per-person cost is  $\$19,630 \times 992,000 = \$19,473,000,000$ , or approximately \$19.5 billion. This scenario is not implausible: the COVID-19 pandemic produced documented spikes in nursing PTSD prevalence, and the workforce has not fully returned to pre-pandemic psychiatric baselines.



The range across all three scenarios, from conservative to current-dollar high-prevalence, is \$11.6 billion to \$19.5 billion, with the primary estimate of \$14.0 billion sitting in the lower-middle of this range. The \$14.0 billion figure is therefore not an outlier or an overestimate; it is a methodologically conservative estimate that understates the current-dollar burden by a margin that healthcare cost inflation alone would place above \$16 billion.

## **Section VII-A: Economic Analysis of Misdiagnosis — PMDD and CPTSD**

### **Section VIIa-i: The Cost of PMDD Misdiagnosis as Bipolar Disorder**

The economic burden of PMDD misdiagnosis is computable from established bipolar disorder cost literature. Adjusted annualized direct healthcare costs for adults with bipolar disorder average \$20,846 per year versus \$11,391 for the general population, an excess of \$9,455 per year in direct costs alone (Rajagopalan et al., 2023). Indirect costs add \$5,521 per year in excess. Over the documented mean diagnostic delay of 12 years, the per-patient excess economic burden is approximately \$113,460 in direct costs and \$66,252 in indirect costs, totaling approximately \$179,712 per misdiagnosed patient — compared to correct first-line PMDD treatment with generic sertraline costing \$200 to \$600 per year.

At population scale: with approximately 260,000 US AFAB individuals currently carrying a bipolar disorder misdiagnosis attributable to undiagnosed PMDD (per IAPMD survey data), aggregate annual excess direct healthcare costs exceed \$2.46 billion per year. The iatrogenic consequences of inappropriate pharmacotherapy — valproate-associated congenital malformations, lithium-induced hypothyroidism that compounds neurosteroid synthesis impairment, atypical antipsychotic-associated metabolic syndrome — generate additional costs not included in this estimate.

### **Section VIIa-ii: The Cost of CPTSD Misdiagnosis as Borderline Personality Disorder**

The total excess economic burden of PTSD in the United States was estimated at \$232.2 billion for 2018, corresponding to \$19,630 per individual with PTSD (Davis et al., 2022). CPTSD generates higher per-capita costs than standard PTSD by virtue of greater functional impairment, longer treatment duration, and substantially higher rates of misdiagnosis that extend the period of inappropriate treatment. Correct first-line CPTSD treatment — trauma-focused CBT or EMDR — typically produces remission in 8 to 16 weeks at approximately \$6,000 total cost. BPD-pathway treatment via dialectical behavior therapy costs \$7,800 to \$15,600 annually for 1 to 3 years before reassessment, generating \$9,600 to \$25,200 in excess treatment costs over the first two years alone.

### **Section VIIa-iii: Nursing-Workforce-Specific Economic Burden**

Nurse replacement costs \$56,300 to \$72,000 per departure. Nationwide, RN turnover alone costs an estimated \$6.5 billion annually (NurseRegistry, 2025). PTSD prevalence of 23 percent in nurses, applied to 3.1 million US RNs, suggests approximately 713,000 nurses carry PTSD with an aggregate excess economic burden approaching \$13.3 billion per year — largely invisible to the healthcare economic system because the majority do not access

treatment. Female nurse suicides (approximately 729 per year, Davis 2021) generate direct replacement costs of approximately \$46.7 million and secondary turnover cascade costs (5 to 10 colleagues affected per suicide event) of \$140 million to \$233 million annually.

The investment case for prevention is computable and positive. PMDD screening using validated self-report instruments costs \$0 per administration. Treatment of confirmed PMDD cases (estimated 43,000 to 157,000 nurses at 1.6 to 5.8 percent prevalence) with generic sertraline costs \$8.6 million to \$63 million annually. If effective PMDD treatment prevents 10 percent of nursing departures attributable to untreated psychiatric disability, and if 400 annual departures are prevented at \$64,000 per replacement, the healthcare system recovers \$25.6 million in year one against a treatment investment of \$17.3 million to \$63 million. Return on investment is positive within 12 to 36 months by conservative modeling.

## **SECTION VIII: SKOVLUND 2018 AND HORMONAL CONTRACEPTION AS OCCUPATIONAL RISK MODIFIER**

Hormonal contraceptives are among the most widely prescribed medications to women of reproductive age in the United States and constitute a standard element of reproductive healthcare for the predominantly female nursing workforce. The work of Skovlund and colleagues, published in the *American Journal of Psychiatry* in 2018, establishes hormonal contraception as an independent and measurable modifier of suicide risk with direct relevance to occupational health planning for the nursing workforce.

Skovlund and colleagues conducted a prospective cohort study using the Danish national registry system, following more than 450,000 women over a study period of up to 17 years with complete medication dispensing records and linked cause-of-death data. Current or recent hormonal contraceptive users demonstrated a relative risk of 1.97 (95% confidence interval 1.85 to 2.10) for suicide attempt compared to women who had never used hormonal contraception. The relative risk for completed suicide was 3.08 (95% CI 1.34 to 7.08). These findings held across combined oral contraceptive formulations and progestin-only formulations, and were most pronounced in adolescent users (ages 15 to 19), for whom the RR for suicide attempt approached 3.0. The study is the largest and most methodologically rigorous investigation of this association published at the time of this writing.

The neurosteroid mechanism most consistent with these findings is the compound deficit model described in Section III. Synthetic progestins in hormonal contraceptives do not generate allopregnanolone via the same enzymatic pathway as endogenous progesterone; some synthetic progestin metabolites may produce anxiogenic rather than anxiolytic neurosteroid effects; and hormonal contraceptive suppression of the hypothalamic-pituitary-ovarian axis eliminates the endogenous progesterone and allopregnanolone surge of the luteal phase, potentially creating a sustained state of allopregnanolone relative deficit in susceptible individuals. For a nurse with PMDD -- who already operates with GABA-A receptor hypersensitivity -- the addition of hormonal contraceptive-mediated allopregnanolone disruption constitutes an additional pharmacological mechanism along the compound deficit pathway.

From an occupational health perspective, the Skovlund findings establish that the pharmacological regimen of a significant proportion of the nursing workforce is an independent modifier of their suicide risk -- a risk factor that is currently assessed in no occupational health framework in nursing. Hormonal contraceptive use is not recorded in occupational health intake instruments. The interaction between hormonal contraceptive use, PMDD status, PTSD burden, and perimenopausal transition has not been systematically evaluated in the nursing workforce. This represents both an analytic gap and a surveillance failure with preventable mortality consequences.

Whether the elevated suicide risk from hormonal contraception represents a direct neurosteroid biological effect, a mood regulatory effect through other mechanisms, a selection effect of women with existing vulnerability being prescribed hormonal contraception, or some combination remains an unresolved question. What is established is the statistical association and its magnitude. What is not established is whether modifying hormonal contraceptive prescribing in high-risk occupational populations would reduce the observed risk. This is a prospective research question with direct clinical and occupational health policy implications.

### **Hormonal Contraception and PTSD: A Compound Risk Interaction Not Yet Evaluated**

The Skovlund findings document an elevated suicide risk in current or recent hormonal contraceptive users at the population level. In the nursing workforce, the interaction between hormonal contraceptive use and occupational PTSD -- both of which independently reduce allopregnanolone and impair GABA-A inhibitory function -- has not been examined. A nurse with occupational PTSD who is also using hormonal contraception is potentially subject to a compound allopregnanolone depletion that combines the PTSD-associated reduction in 5-alpha reductase activity with the hormonal contraceptive-associated elimination of the endogenous luteal-phase allopregnanolone surge. The additive or synergistic nature of this interaction at the neurosteroid level is unknown, and the clinical implications for suicide risk assessment in this double-exposed population have not been studied.

This interaction is clinically relevant in the nursing workforce because hormonal contraceptive use and occupational PTSD co-occur at measurable rates: approximately 23% of employed nurses meet PTSD criteria, and hormonal contraceptive use in women of reproductive age in the U.S. is estimated at approximately 65% at any given time. Even modest overlap between these populations produces a substantial cohort of nurses carrying both risk factors simultaneously -- a cohort that no current occupational health framework identifies, monitors, or supports. The COMPASS framework proposed in Section IV includes hormonal contraceptive type and duration as Domain 7 assessment elements precisely because this pharmacological history modifies the neurosteroid risk profile in ways that are clinically actionable.

## SECTION IX: AFAB-INCLUSIVE FRAMING AND THE LIMITS OF THE EXISTING EVIDENCE BASE

The occupational signal in female nurses represents amplification of a biological baseline risk present in the general AFAB population. In the United States, the cycling AFAB population aged 15 to 50 numbers approximately 65 million. At a conservative prospective PMDD prevalence of 1.6 percent, approximately 1.04 million people carry confirmed PMDD. At 5.8 percent, approximately 3.77 million. Globally, the cycling AFAB population numbers approximately 1.8 to 2 billion; PMDD affects an estimated 29 to 116 million people worldwide. PTSD prevalence in AFAB individuals in the United States is approximately 10 to 12 percent, compared to 3 to 5 percent in male-assigned individuals; approximately 14 to 17 million US AFAB individuals carry PTSD. The intersection of PTSD and PMDD, at even conservative overlap estimates, exceeds 2 million people in the United States alone.

The analysis presented in this paper applies to female and AFAB (assigned female at birth) individuals because the neurobiological mechanisms described -- PMDD, allopregnanolone synthesis via ovarian and adrenal steroidogenesis, perimenopausal estrogen withdrawal -- are biological processes whose occurrence is linked to having been assigned female at birth and to the hormonal architecture associated with that assignment at the reproductive life cycle stages described. The nursing workforce is approximately 90% female (89.6% per NCSBN 2024 Workforce Survey) per NCSBN 2024 data; the remaining 10% includes male, nonbinary, and gender-diverse individuals whose hormonal profiles may or may not include AFAB-typical neurosteroid dynamics depending on current and prior hormone status.

For transgender women and transfeminine individuals currently using feminizing hormone therapy, the relevant neurosteroid considerations differ from those of cisgender women: exogenous estradiol may influence 5-alpha reductase activity and allopregnanolone synthesis capacity; synthetic progestins used in some feminizing regimens carry the same GABA-A interaction considerations as for cisgender women; and the interaction between gender-affirming hormone therapy and PTSD-associated allopregnanolone depletion in the nursing occupational context has not been studied. This represents a research gap with direct clinical relevance for a population facing both occupational stressors and the compounding burden of gender-identity-based discrimination in healthcare workplace environments.

For nonbinary and gender-diverse AFAB individuals who do not use gender-affirming hormones, the biological mechanisms described in this paper apply at the same level as for cisgender women, while the occupational stressors may be compounded by identity-based discrimination and the absence of gender-affirming occupational health frameworks. The compound neurobiological deficit model operates with the same mechanistic logic; the social and psychological accelerants of the trajectory toward psychiatric crisis may be greater.

The majority of primary literature cited in this paper studied cisgender women. This reflects the composition of the research base rather than the actual scope of populations affected. As gender-inclusive research designs become more common in endocrinology, psychiatry,

and occupational health, the evidence base for non-cisgender AFAB individuals will expand. In the interim, clinical application of the compound neurobiological deficit model should include explicit hormone status assessment, gender-affirming medication use documentation, and individual neurosteroid pathway evaluation rather than demographic assumption.

**The Endocrine Evaluation Protocol: What Is Currently Missing**

The neurobiological deficit model described in this paper has clear diagnostic implications: an individual presenting with psychiatric symptoms in the perimenopausal age window requires endocrine evaluation as part of the differential diagnostic workup, not as an optional add-on to psychiatric assessment. The standard endocrine evaluation relevant to the compound deficit model includes: serum FSH and estradiol measured on cycle day 3 (or at any time in an irregular or anovulatory cycle) to establish ovarian reserve and menopausal status; serum progesterone at the mid-luteal phase (day 21 of a 28-day cycle, or approximately one week before anticipated menstruation in irregular cycles) to confirm ovulation and assess luteal adequacy; serum TSH to screen for hypothyroidism as a contributor to impaired StAR expression; and a fasting lipid panel to assess the cholesterol substrate pool in the context of statin use.

These are not novel, expensive, or inaccessible laboratory tests. They are standard components of the clinical endocrine evaluation. They are not, however, standard components of the psychiatric assessment, the occupational health intake, or the emergency psychiatric evaluation -- which are the three clinical settings where perimenopausal suicidal ideation in nurses is most likely to present. Adding these evaluations to the standard assessment protocol for psychiatric presentations in reproductive-age and perimenopausal patients costs less than a single emergency department visit. It provides the endocrine context without which the differential diagnosis of PMDD, perimenopause, BPD, and bipolar disorder cannot be accurately completed.

The argument that endocrine evaluation is outside the scope of psychiatric practice or occupational medicine is not a clinical argument. It is a jurisdictional one, and it is costing lives. The most appropriate response to a jurisdictional boundary that prevents accurate diagnosis of a lethal condition is to revise the jurisdictional boundary -- through training standards, electronic health record template design, and occupational health protocol development -- not to maintain it while nurses suffer and die from conditions that basic laboratory testing would have helped identify.

**Table 3. Conservative Annual Economic Burden Estimates: PMDD and CPTSD Misdiagnosis, U.S. Nursing and General Population**

Cost Category	Annual Estimate	Source Basis
PMDD misdiagnosis as bipolar: excess direct costs (U.S. nursing workforce)	\$102 million	Rajagopalan 2023; IAPMD 2018

<b>Cost Category</b>	<b>Annual Estimate</b>	<b>Source Basis</b>
PMDD misdiagnosis as bipolar: excess direct costs (U.S. general population)	\$2.46 billion	Rajagopalan 2023; IAPMD 2018
PTSD/CPTSD excess economic burden: nursing workforce	\$13.3 billion	Davis 2022; Stelnicki 2020
Nurse turnover attributable to unmanaged hormonal/trauma illness (partial)	\$1.73 billion	NSI 2021; NurseRegistry 2025
Female nurse suicides: direct replacement + secondary cascade	\$280 million/yr	Davis 2021; occupational psychology lit.
PMDD screening + treatment program (all screen-positive nurses)	\$8.6 -- \$63 million	ROI positive yr 1-3 by replacement cost alone
NET: conservative annual floor burden from misdiagnosis and inaction	>\$15.9 billion/year	Floor estimate only

## **Section IXb: CMDS and AFAB Gender-Diverse Patients — The Double Suppression Mechanism**

Trans men and AFAB nonbinary individuals in healthcare face a specific additional CMDS risk: healthcare systems that fail to affirm their gender identity apply an additional diagnostic overshadowing mechanism, in which the trans identity itself becomes the explanatory frame for any psychiatric presentation. A trans man presenting with perimenstrual suicidal ideation may find his presentation attributed to gender dysphoria, transition-related distress, or psychological instability rather than the hormonal mechanism generating the acute risk state. The interaction of psychiatric-label CMDS and trans-identity CMDS produces a particularly hazardous clinical environment in which the correct diagnosis has two independent pathways of institutional suppression. No national clinical guideline from ACOG, APA, or ISPMD includes specific PMDD management guidance for trans men or AFAB nonbinary individuals.

## **Section IXc: Institutional and Regulatory Obligations Specific to AFAB Healthcare Workers**

The biological mechanisms documented in this paper affect AFAB individuals as a function of reproductive physiology, and the nursing workforce is 90 percent female. The failure to address these mechanisms in occupational health frameworks is therefore not a neutral omission — it is a sex-specific failure with a specific legal and ethical profile.



Title VII of the Civil Rights Act prohibits employment discrimination on the basis of sex. The Pregnant Workers Fairness Act (enacted June 2023) requires reasonable accommodation for conditions related to pregnancy, childbirth, and related medical conditions. The ADA Amendments Act broadened the definition of disability to include episodic conditions that substantially limit a major life activity when active. Taken together, these frameworks create a legal architecture that, properly applied, reaches PMDD, perimenopausal psychiatric conditions, and postpartum neurosteroid disorders as conditions for which employers have affirmative accommodation and non-discrimination obligations.

The gap is in application, not in law. Healthcare employers have not been required to treat PMDD or perimenopausal psychiatric burden as occupational health matters subject to these frameworks, because no regulatory body has formally interpreted these conditions as qualifying under existing protections in the occupational context. The result is that AFAB nurses carry a biologically-driven occupational health burden that their male counterparts do not carry, in a workforce that is predominantly AFAB, with no institutional or regulatory mechanism acknowledging or addressing the disparity.

***What the institutional obligations are, stated directly: Healthcare employers have an obligation under Title VII and the PWFA to provide reasonable accommodation for PMDD-related functional impairment when disclosed. This includes scheduling accommodations that account for predictable luteal-phase symptom severity, modification of mandatory overtime requirements during high-severity cycle phases, and access to occupational health evaluation without adverse employment consequences. Healthcare employers have an obligation under OSHA's general duty clause to maintain a work environment free from recognized hazards causing or likely to cause serious harm. The documented neurobiological harm from the combination of shift work, sleep deprivation, and perimenopausal hormonal transition constitutes a recognized hazard by the standards of this paper's evidence base.***

State nursing boards have an obligation to separate mental health treatment access from adverse licensure action, to remove interrogatory language on license applications and renewal forms that functions as a deterrent to treatment-seeking, and to affirmatively communicate to nurses that mental health treatment does not constitute a reportable condition in the majority of jurisdictions that have reformed their language. The persistence of punitive or ambiguous licensing language in states that have not reformed constitutes a structural barrier to care that disproportionately harms AFAB nursing professionals whose conditions require psychiatric management.

The explicit naming of these obligations in occupational health policy literature is not present in the existing literature on nurse mental health. This paper names them as a required element of the accountability architecture — not as advocacy, but as an accurate mapping of the legal landscape as it applies to this specific population.

## **SECTION X: ENVIRONMENTAL MISMATCH, ADAPTIVE COMPLIANCE, AND THE LIMITS OF APPARENT ACCOMMODATION — A NEURODIVERSITY-INFORMED FRAMEWORK FOR OCCUPATIONAL HARM**

The occupational conditions documented in this analysis are harmful for all nursing employees. Apparent accommodation -- meaning the absence of overt protest or visible clinical deterioration in some individuals exposed to the same conditions -- does not indicate the absence of harm. It indicates a different trajectory of harm, a different relationship to the institutional mechanisms that label suffering as personal failure, or a different set of biological and psychological mediators that delay the expression of harm without preventing its accumulation.

Within nursing, two patterns are observable: workers who manifest visible deterioration in the form of burnout, psychiatric crisis, resignation, or death, and workers who appear to adapt to the same conditions without overt protest. The distinction between these groups is not a measure of individual resilience or professional fitness. It is a research question that has not been adequately studied. Factors that may mediate the apparent divergence include: adverse childhood experience (ACE) scores and adverse adult experience (AAE) accumulation; neurodivergent status and access to neurodiversity-affirming frameworks; differential access to collective voice and institutional validation; biological mediators including baseline allopregnanolone tone, cortisol reactivity, and HPA axis variability; and sociocultural programming regarding what constitutes acceptable suffering in a professional context.

The social model of disability provides the appropriate analytic frame for this analysis. Disability is understood to arise from the interaction between an individual and an environment that fails to accommodate natural human variation -- not from the individual. Neurodivergence is variation, not pathology. The occupational environment of U.S. hospital nursing was not designed to accommodate neurological variation; it was designed for a single mode of function with narrow tolerances for behavioral and emotional expression, and it punishes deviation from that mode through informal mechanisms (social exclusion, reputational damage, supervisory retaliation) and formal mechanisms (performance management, documentation, termination) that are well-documented in the nursing workplace culture literature and captured structurally in the CMDS framework.

The analogy to interpersonal violence survivor work is analytically appropriate. A victim of sustained intimate partner violence who does not leave, and who presents without overt symptomatology, is not less harmed. They have adapted to survive within a harmful environment. The adaptation requires study and intervention, not admiration. The same framework applies to nurses who appear to tolerate institutional coercive conditions without protest: their accommodation is a coping mechanism shaped by environmental pressure, not evidence that the environment is safe.

The occupational neurodiversity question this analysis opens is the following: does the neurodivergent worker's access to collective frameworks of environmental attribution -- the cognitive framework that locates the problem in the environment rather than in the self -- confer protective function against the internalization of harm? And conversely, does the neurotypical worker's conditioning within systems that frame institutional suffering as individual inadequacy accelerate the trajectory from harm to crisis? These are empirical questions. They require study.

Proposed research design: a longitudinal cohort of nursing employees stratified by neurodivergent status (self-reported using validated neurodiversity-affirming assessment instruments), ACE score, and institutional environment score (derived from the CMDS Leadership Accountability Rubric), with prospective tracking of biological stress markers (plasma cortisol, allopregnanolone, inflammatory cytokines), psychiatric symptomatology (using validated PTSD, depression, and suicidal ideation instruments), and occupational outcomes (retention, involuntary separation, psychiatric hospitalization, completed suicide). This design would provide the first population-level data on whether neurodivergent status modifies the trajectory from occupational harm to occupational crisis in the nursing workforce, and would directly inform the development of neurodiversity-affirming occupational health frameworks for healthcare employers.

## **Section Xb: Neurodivergence and the PMDD Intersection — A Specific Research Priority**

The intersection of PMDD and neurodivergence represents a specific and under-studied clinical population that is disproportionately represented in the nursing workforce and disproportionately harmed by current diagnostic and occupational health frameworks. Autistic AFAB individuals have significantly higher rates of PMDD and premenstrual exacerbation of autistic traits compared to non-autistic women, with some studies reporting rates of clinically significant premenstrual symptoms in this population approaching 90%. The neurobiological basis for this intersection likely involves both the GABA-A sensitivity differences documented in autism spectrum presentations and the hormonal sensitivity mechanisms described in the PMDD compound deficit model. The resulting clinical picture -- autistic trait amplification in the luteal phase, with sensory sensitivity, emotional dysregulation, and social communication difficulties that are significantly worse in the premenstrual week -- is frequently misread as deteriorating psychiatric condition rather than recognized as a PMDD-autism interaction requiring cycle-phase-aware management.

ADHD in AFAB individuals presents a parallel intersection with PMDD: estrogen modulates dopamine signaling, and the estrogen fluctuation of the menstrual cycle produces corresponding fluctuations in dopamine-mediated executive function, attention regulation, and impulse control. AFAB individuals with ADHD frequently report that their ADHD symptoms worsen substantially in the premenstrual phase, in a pattern that tracks precisely with the allopregnanolone withdrawal and estrogen decline of the late luteal phase. This ADHD-PMDD interaction is not a minor clinical nuance; it can produce a degree of executive dysfunction in the luteal phase that constitutes a patient safety risk in clinical nursing

practice. The nurse with ADHD and unrecognized PMDD who is 10 days from a correct diagnosis, working the night shift in the late luteal phase of her cycle, may be operating with a degree of attentional impairment that exceeds the threshold of safe clinical practice -- a threshold that no current occupational health framework measures, monitors, or addresses.

The research priority at this intersection is clear: longitudinal study of PMDD symptom severity and ADHD symptom expression across menstrual cycle phases in AFAB nursing employees, with hormonal status tracking, occupational outcome documentation, and assessment of medication interactions (including the interaction between ADHD stimulant medications, which are dopaminergic, and the estrogen-dependent dopamine dynamics of the menstrual cycle). This study would have direct patient safety implications and would inform cycle-phase-aware occupational accommodation protocols for neurodivergent nursing employees.

### **Section Xc: Comparison With Other High-ACE Professions — What Nursing-Specific Factors Require New Models**

Elevated suicide risk among high-adversity occupations — law enforcement, fire service, emergency medical services, military — is documented and has generated institutional suicide prevention programs with dedicated federal funding, peer support infrastructure, and injury classification frameworks. Nursing is categorically comparable in occupational adversity exposure but systematically underserved by equivalent prevention infrastructure. Understanding what nursing-specific factors exceed or differ from these comparison populations clarifies where adaptation of existing models is insufficient and where new frameworks are required.

First responders encounter traumatic events episodically; nurses encounter them continuously across every shift, often in higher exposure density per shift hour. A firefighter may manage several fatalities per month; an ICU nurse may manage multiple deaths per week across a career spanning decades. The cumulative exposure density differs in kind, not only degree.

The gender composition of nursing — approximately 90 percent female in the United States — creates an overlay of sex-specific biology that has no parallel in male-dominated first responder populations. The perimenopausal mechanism described in this paper has no equivalent in law enforcement or fire service occupational mortality literature because the epidemiologic composition of those workforces has not generated the research question. Nursing's demographic profile requires nursing-specific biology, not adaptations of male-normed frameworks.

The caretaker role creates a moral-authority barrier to help-seeking that differs structurally from the stoicism barrier in first responder cultures. Nurses are trained in and evaluated on the competence to manage others' crises. Presenting as someone who cannot manage their own is a professional identity threat of a specific type. Intervention models developed for first responder cultures address stoicism and stigma; those developed for nursing must

additionally address competence-identity conflict and the institutional accountability suppression architecture documented in the CMDS framework.

Finally, the regulatory environment differs. First responders have union representation, workers' compensation frameworks with injury classification for psychological harm, and in many jurisdictions presumptive coverage for PTSD. Nurses in most U.S. states have none of these. The structural protection gap amplifies the harm gap.

### **Section Xd: Adolescent Onset and Career Entry as Compound Vulnerability Windows**

PMDD onset frequently coincides with the initiation of regular ovulatory cycles in adolescence. A young woman who enters nursing school at 18 to 22 while already experiencing undiagnosed PMDD faces a compounding exposure: the biological vulnerability is present from career entry and will be amplified by every layer of occupational adversity she accumulates over subsequent decades.

The diagnostic gap for adolescent PMDD is substantial. Menstrual symptoms are normalized in adolescent clinical encounters; affective instability during the luteal phase is attributed to "teenage hormones," academic stress, or personality factors. A 19-year-old nursing student with severe luteal-phase depression and suicidal ideation is unlikely to receive a PMDD diagnosis in current clinical practice; she is more likely to receive an antidepressant and a referral, neither of which addresses the neurosteroid mechanism driving her symptoms.

Career entry into nursing simultaneously with undiagnosed PMDD creates a trajectory risk: the individual is learning to suppress help-seeking through professional socialization at exactly the same time she most needs clinical support. Twenty years later, she is a perimenopausal nurse with a long history of undiagnosed PMDD now transitioning into the highest-risk window of her neurobiological vulnerability, with decades of conditioned help-seeking suppression behind her and no institutional awareness of the trajectory she represents.

The intervention implication is early detection: PMDD screening in nursing school curricula, with prospective cycle tracking as a health literacy component rather than a clinical gatekeeping requirement, would capture the trajectory at its origin point rather than at its crisis expression. This is a low-cost educational intervention with potential to alter a decades-long harm trajectory before it compounds.

## **SECTION XI: INSTITUTIONAL ACCOUNTABILITY — CMDS, CRF, AND COVE-F APPLIED**

The neurobiological and economic harm documented in this paper is not produced by individual clinical failure. It is produced by institutional conditions that are known, measurable, and actively perpetuated by systems that benefit -- in the short term -- from the suppression of escalation, the normalization of harm, and the attribution of institutional failure to individual inadequacy. Three frameworks provide the analytic architecture for

attributing this harm to its institutional sources with specificity sufficient to support regulatory and legal accountability: the Clinical Moral Disengagement Scaffolding (CMDS), the Continuity Risk Framework (CRF), and the Comprehensive Occupational Violence and Extraction Framework (COVE-F).

The Clinical Moral Disengagement Scaffolding (CMDS) describes the five-layer architecture through which healthcare institutions suppress nurse escalation of safety concerns. The five layers are: social justification of harm (reframing institutional failures as systemic necessities, often using patient-care mission as the justification for workforce harm); advantageous comparison (normalizing harm by reference to worse conditions elsewhere); displacement of responsibility (locating accountability with regulatory bodies, accreditation agencies, or staffing market forces rather than with institutional leadership); diffusion of responsibility (distributing culpability across so many actors that no single actor bears identifiable accountability); and dehumanization (institutional language and process that abstracts nurses from their status as human beings with biological needs, rendering psychiatric deterioration invisible in quality metrics). The CMDS framework maps each layer to specific institutional behaviors and provides the Leadership Accountability Rubric as a measurement instrument for their identification and quantification.

The five-layer framing above represents the original CMDS architecture as published. An expanded seven-mechanism elaboration of the framework, developed in subsequent clinical application, is presented below. The two formulations are not contradictory; the seven mechanisms are a granular operational specification of what the five layers describe at the structural level.

### **Section XIa-expanded: CMDS — The Seven Mechanisms in Institutional Operation**

Author positionality disclosure: The CMDS framework was developed by Jennifer Torrez, RN, the corresponding author of this paper. Its inclusion constitutes the author's own theoretical contribution, not an independently replicated finding. It is presented as a proposed explanatory framework supported by the mechanisms described throughout this paper, not as established empirical theory. This disclosure is required by research integrity standards when authors publish original conceptual frameworks in work they have also authored.

***Mechanism 1. Harm minimization through administrative language. Adverse events, near-misses, and clinician distress are translated into bureaucratic categories that reduce their moral salience. A nurse who reports systemic understaffing produces a "staffing concern," not a patient safety crisis. The linguistic transformation is not accidental; it is structurally necessary to prevent individual harm from becoming a documented institutional liability.***

***Mechanism 2. Diffusion of responsibility through hierarchical distance. Clinical harm that occurs at the bedside is attributable to the bedside nurse, not to the staffing model, the budget decision, or the administrator who approved both. Each layer of hierarchy between the site of harm and the decision-makers diffuses individual responsibility until no identifiable actor carries it. Bandura's displacement of responsibility maps directly: the harm is acknowledged in aggregate but owned by no one in particular.***



***Mechanism 3. Dehumanization through productivity metrics. When nurses are evaluated primarily through throughput data — patient volume, discharge timing, documentation completion rates — the evaluation system implicitly reduces them to productivity units rather than clinical professionals with moral and biological limits. The dehumanization is not explicit; it operates through the metrics institutions choose to measure and reward.***

***Mechanism 4. Institutional betrayal as trust architecture exploitation. Jonathan Shay's concept of moral injury requires that the betrayal come from a legitimate authority. Institutions hold legitimate authority over nurses' professional survival through licensure, employment, and reference access. When those institutions betray clinician trust through retaliation after reporting, dismissal of documented concerns, or active suppression of safety data, they commit a specific form of moral injury that exploits the power asymmetry of the employment relationship.***

***Mechanism 5. Normalization of the abnormal. When understaffing, mandatory overtime, and patient deaths under preventable circumstances become routine features of the clinical environment, individual clinicians lose the reference point against which abnormality would be recognized. The harm becomes the baseline. Deviations upward toward adequacy appear exceptional rather than standard.***

***Mechanism 6. Suppression of escalation pathways. Formal channels for escalating clinical or ethical concerns — incident reports, chain-of-command protocols, regulatory complaints — are present in institutional policy but functionally ineffective in practice. The nurse who files a report learns through experience that reports produce documentation but not change, and that visible reporters are associated with administrative attention that functions punitively rather than protectively.***

***Mechanism 7. Harm chain documentation gap. The systematic absence of documentation connecting individual adverse events, clinician departures, staffing decisions, and patient outcomes is not passive neglect; it is structural. Institutions that do not connect these data points cannot be held accountable for the chain of decisions producing a specific harm. The documentation gap is the gap in accountability.***

CMDS and nurse suicide risk. CMDS suppresses help-seeking through a convergent mechanism: it simultaneously invalidates the nurse's perception that something is wrong (normalization through Mechanism 5), removes the expectation that reporting produces change (Mechanism 6), and threatens professional consequences for visible distress (Mechanism 3). A nurse operating within a CMDS-structured institution has been conditioned, through institutional experience, to suppress the same cognitive and behavioral responses that constitute mental health help-seeking. The pathway from CMDS exposure to elevated suicide risk operates through this suppression at the neurobiological level, compounding the allopregnanolone depletion documented in Section III.

Applied to the compound neurobiological deficit described in this paper, CMDS explains the institutional mechanism by which nurses carrying a preventable and identifiable psychiatric burden are simultaneously denied diagnostic support and institutionally discouraged from disclosing that burden. The nurse with unrecognized PMDD who experiences suicidal

ideation during the luteal phase of her cycle, who works the following night shift because staffing is inadequate, who does not disclose her distress because institutional conditioning has taught her that disclosure results in investigation rather than support -- this nurse is a product of the CMDS suppression architecture. The institution that employs her has created the conditions for her deterioration and installed the mechanisms that prevent its detection and treatment.

The Continuity Risk Framework (CRF) models organizational deterioration through nine sequential stages, from early signal suppression through escalating institutional failure to terminal failure event. Applied to the nursing workforce as the analytic patient of the institutional system, the CRF provides a structured escalation model for identifying the stage of institutional failure producing occupational psychiatric harm in nursing at any given institution. The CRF ninth stage -- the failure event that finally becomes visible -- corresponds in nursing occupational health to completed suicide, mass psychiatric break, or catastrophic staff attrition producing patient harm cascade. The preceding eight stages are present in the institutional record of any hospital system with high nurse psychiatric burden; they are not currently being read as stages of institutional failure requiring escalating intervention. The CRF provides the reading framework.

The Comprehensive Occupational Violence and Extraction Framework (COVE-F) provides the structural violence taxonomy for the harm described in this paper. Occupational extraction -- the systematic drawing of labor, cognitive capacity, biological health, and psychological reserve from a workforce without commensurate return in the form of safety, support, compensation, or institutional recognition of the cost being borne -- is the operating mechanism of the current U.S. hospital nursing employment model. COVE-F maps this extraction pattern across its multiple dimensions: physical (mandatory overtime, shift structures that violate circadian physiology, insufficient recovery time); psychological (moral suppression, mandatory positivity culture, institutional reframing of distress as weakness, identity erosion through dehumanizing institutional language); economic (wage suppression techniques and structures that do not compensate for the biological and psychological risks documented in this paper); and relational (normalization of lateral violence, absence of peer support infrastructure in high-mortality environments).

Together, these three frameworks convert the neurobiological and economic findings of this paper into an institutional accountability architecture that is analytically rigorous and operationally deployable. The CMDS identifies who is suppressing escalation and by what mechanism. The CRF identifies what stage of institutional deterioration has been reached and what intervention is indicated at that stage. The COVE-F quantifies what is being extracted from the workforce and maps the extraction to its institutional sources. The intersection of these three analyses points directly to the institutional actors, systemic processes, and regulatory gaps that are producing the \$14.0 billion annual burden documented here and the preventable deaths that accompany it.

## **Institutional Accountability in Practice: The Audit as Clinical Tool**

The CMDS Leadership Accountability Rubric provides a structured instrument for auditing the five-layer suppression architecture at the institutional level. Application of this rubric to a hospital system with documented high nurse psychiatric burden produces a quantitative assessment of each suppression layer: what social justifications are being deployed to normalize workforce harm; what advantageous comparisons are institutionally embedded in leadership communication; where responsibility is being displaced and how diffusion of accountability is structured across the organizational chart; and what dehumanizing language and process elements are embedded in the documentation and performance management systems that handle nursing staff.

This audit is not a theoretical exercise. It produces actionable findings: specific language in institutional communications that frames workforce harm as systemic necessity; specific documentation practices that record nurse distress as performance failure rather than occupational injury; specific scheduling and staffing practices that systematically produce the sleep deprivation, cortisol dysregulation, and moral injury documented in the neurobiological harm model. Each of these findings corresponds to a correctable institutional behavior. The audit creates the accountability record that regulatory action, legal action, or board-level governance correction requires.

The CRF nine-stage deterioration model, applied to the same institutional dataset, identifies which stage of institutional failure the organization has reached. An institution at Stage 3 (escalating signal suppression with beginning-level staff psychiatric symptom expression) requires different interventions than an institution at Stage 7 (mass symptom expression with early catastrophic event signals). The CRF provides the staging framework; the CMDS provides the mechanism identification; the COVE-F provides the extraction quantification. Together, the three frameworks produce a comprehensive institutional accountability assessment that can be presented to governing boards, regulatory agencies, or legal counsel with the same confidence that a clinical diagnostic workup supports a treatment recommendation.

## **Section XIb: Acuity Built on Faulty Diagnostic Data — Cascading System Corruption**

Patient acuity scoring — the systematic measurement of nursing care intensity per patient — is the foundational input for evidence-based nurse-to-patient staffing ratios. Acuity data drive staffing grid decisions, float pool allocation, charge nurse assignments, and in some systems real-time bed capacity management. When the diagnostic data underlying acuity classification are inaccurate, the corruption propagates through every downstream system that depends on them.

The diagnostic pathways described earlier in this paper — PMDD/PME misclassification, the thyroid assessment gap, ADHD decompensation classified as anxiety, IPV-mediated PTSD classified as depression — are not only clinical errors with consequences for individual patients. Each misdiagnosis produces an incorrect acuity classification. A patient whose PMDD is misclassified as major depression may be assigned a lower acuity score than her

clinical complexity warrants. A patient with undetected Hashimoto's thyroiditis presenting with fatigue and cognitive impairment may be routed to a dementia workup path rather than an endocrine path, with different acuity and resource implications.

When faulty diagnostic data systematically produce lower acuity classifications than clinical reality warrants, the staffing model built on those classifications is wrong — not by random error, but by systematic underestimation of care need. Nurses assigned to those patients carry an undocumented care burden: they are providing care for the actual acuity of the patient while being measured and resourced against the documented acuity. The gap is invisible in staffing data and visible only in nurse experience of overwhelm that administrators can attribute to individual performance rather than systemic underdocumentation.

This acuity corruption cascades into quality metrics, regulatory reporting, and CRF staging data. Quality metrics derived from acuity-adjusted outcome comparisons are comparing unadjusted apples. Regulatory reporting of staffing adequacy uses acuity data that understate actual care demand. CRF stage assignments that use acuity as a variable are misclassifying risk. Every layer of analysis built on corrupted acuity data inherits the corruption.

***Discovery target: institutions with documented nurse suicides should provide complete acuity data for the units involved, with independent clinical review of whether documented acuity matched clinical complexity for patients on those units in the 90 days before the event. Systematic underacuity documentation in units associated with nurse adverse events would constitute evidence of the acuity corruption mechanism described here.***

## **Section XIb-ii: Provider Accountability for Diagnostic Failure, Overshadowing, and Career Consequences to the HCW**

The diagnostic failure regime documented in Section VI is not a passive gap. It is a pattern of clinical action — diagnosis assignment, medication initiation, treatment selection — performed by licensed providers in the absence of information that the standard of care, properly applied, requires. Naming this as accountability-generating is not a litigation-specific claim; it is a clinical quality and patient safety assertion with specific professional, regulatory, and legal implications.

The standard of care for psychiatric assessment of reproductive-age and perimenopausal patients includes cycle-phase inquiry as a component of the differential diagnosis of affective symptoms. This standard is derivable from the DSM-5-TR criteria for PMDD — which require prospective cycle-phase documentation — and from the general principle that the differential diagnosis must be pursued before a diagnosis is assigned. A provider who assigns a bipolar disorder diagnosis to a 44-year-old female patient presenting in suicidal crisis without documenting the patient's cycle phase, without ordering FSH and estradiol, and without initiating prospective symptom tracking has deviated from the standard of care in a way that is both documentable and consequential.

Diagnostic overshadowing — the attribution of all presenting symptoms to a pre-existing diagnosis without evaluation of new or alternative explanations — is a recognized source of diagnostic error with its own literature in disability medicine, emergency psychiatry, and primary care. In the PMDD-affected population, overshadowing operates predictably: a prior bipolar diagnosis suppresses PMDD evaluation because the clinician attributes affective instability to the documented condition, regardless of its applicability, rather than investigating the cycle-phase pattern. A prior borderline personality disorder diagnosis suppresses PMDD evaluation for the same reason. The overshadowing is not neutral; it carries the same standard-of-care analysis as any other failure to pursue a differential diagnosis in the presence of clinical information suggesting an alternative etiology.

The consequences to the patient when overshadowing produces prolonged misdiagnosis include: years of pharmacological treatment for a condition the patient does not have, with attendant side effect burden; absence of treatment for the condition the patient does have, with attendant functional deterioration; and in the case of valproate prescribed to a reproductive-age patient on a false bipolar diagnosis, potential teratogenic harm to offspring. Each of these consequences is attributable to an identifiable clinical decision made without the information the standard of care required.

The consequences to the healthcare worker as patient are distinct in kind, not only degree. The population this paper primarily concerns — registered nurses — is the same population most likely to experience PMDD misdiagnosis in a clinical encounter, because the occupational factors driving PMDD severity in nurses are the same factors that drive under-disclosure of mental health conditions. A nurse who presents to her own employer's occupational health service with luteal-phase suicidal ideation and receives a bipolar disorder diagnosis without cycle-phase evaluation has received inadequate care. She has also received care with potential career consequences: the bipolar diagnosis enters her medical record, may affect her workers' compensation claims, may be discoverable in licensing board proceedings, and may follow her through background checks for future positions. The inadequate care produces a documentation injury layered on top of the clinical injury.

This dual harm — clinical mismanagement producing both untreated condition and damaging documentation — is a specific failure mode that occupational health frameworks for nursing must address. The nurse who is afraid to seek care because inadequate care will produce a permanent diagnostic label that threatens her license is not being irrational. She is correctly identifying a risk the system has not resolved. The policy response is not to tell her the risk is overstated; it is to remove the risk through reformed licensing language (Section IXc), protections for disclosed occupational psychiatric conditions from adverse employment action, and clinical training that reduces the probability of the misdiagnosis occurring in the first place.

***Provider documentation obligations, stated directly: Any clinician evaluating a perimenopausal or reproductive-age patient presenting with affective instability, suicidal ideation, or psychiatric crisis has an obligation, derivable from the standard of care, to: document the patient's menstrual cycle phase or menopausal status at the time of presentation; order FSH, estradiol, and TSH as part of the initial laboratory workup; initiate or refer for prospective cycle-phase symptom tracking before assigning a primary psychiatric diagnosis; and document explicitly why PMDD and perimenopausal mood disorder were considered and on what basis they were included or excluded from the differential. These are not extraordinary interventions. They add minutes to an assessment and tens of dollars to a laboratory order. Their current absence from standard practice is the mechanism by which the diagnostic failure regime described in this paper operates. Their inclusion in training requirements, electronic health record templates, and accreditation standards is the mechanism by which it stops.***

## **Existing Policy Frameworks And The Causal Gap**

The professional policy landscape for nurse mental health and suicide prevention has generated measurable legislative activity. The American Academy of Nursing has signed onto the STOP Suicide Act (H.R. 8124), which would create SAMHSA grant programs for outpatient and virtual stabilization services, and the Barriers to Suicide Act of 2025 (H.R. 3505), which would fund physical barriers on bridges and other high-risk structures. The Dr. Lorna Breen Health Care Provider Protection Act (P.L. 117-105, signed March 18, 2022) established grant programs supporting healthcare worker mental health programs, with emphasis on EAP access, peer support, and removal of stigmatizing licensure questions at the state level. The Academy's September 2025 policy dialogue resource outputs include the 988 Lifeline, personal safety planning templates, and organizational guidance on anonymous mental health screening. The 2023 AAN Expert Panel Consensus Statement acknowledged that heightened conditions exacerbate the epidemic of nurse suicide and called for urgent action.

These interventions operate downstream of the causal architecture this paper documents. Physical barrier legislation addresses method restriction without addressing suicidal ideation generation. EAP promotion addresses help-seeking access without addressing the institutional conditions that create the need for help while simultaneously suppressing the capacity to seek it. Stigma reduction through licensure question reform addresses one disclosure barrier without addressing the documented reality that nurses who disclose mental health conditions face retaliation mechanisms operating through board of nursing complaint processes, institutional performance documentation, and informal scheduling consequences. The causal pathway from CMDS-documented moral injury to psychological collapse to occupational suicide risk does not pass through stigma as its primary mechanism. It passes through institutional escalation suppression, blame transfer, failure-to-rescue environments in which clinicians absorb the psychological cost of preventable patient harm, and the systematic unavailability of institutional remediation. The 2023 Expert Panel recommendations remained routed through CDC suicide prevention strategies and trauma-informed care guidance rather than through any mechanism of



institutional accountability or structural cause-removal. This is a precise and identifiable gap.

*[Qualification on state licensing notification: Claims regarding mandatory reporting obligations for mental health treatment to state nursing boards vary substantially by state and have changed in several jurisdictions in response to advocacy from nursing organizations. The statement that mental health treatment triggers mandatory licensing notification is not accurate as a categorical claim across all U.S. states. Users should verify current state-specific board rules before citing this as a general barrier; some states have moved toward decoupling mental health treatment history from licensure adverse action.]*

The surveillance denominator problem is foundational. As of 2025, published literature is still calling for movement toward standardized surveillance of nurse suicide mortality, meaning the field has not yet achieved a baseline measurement standard. Without standardized mortality surveillance, there is no denominator. Without a denominator, every intervention is unmeasurable, every claim of improvement is unverifiable, and every policy ask lacks quantified urgency. The frameworks developed in this body of work address the institutional causal layer the existing policy framework does not reach. The CMDS describes the suppression architecture that converts moral injury into psychological collapse. The CRF models institutional deterioration through nine stages from early signal suppression to terminal failure. The COMPASS provides clinical screening for the neurobiological and occupational conditions that precede psychological collapse. These are not wellness interventions. They are causal architecture mapping tools, and the policy instrument that attaches liability to institutional conditions rather than individual clinicians is the structural lever that does not yet exist.

## **Section XI-A: CMDS and the Labeled Nurse-Patient — The Suppressed Care Chain**

The CMDS suppression architecture documented above applies not only to nurses as workers but to nurses as patients seeking care for their own psychiatric conditions. Once a patient carries a BPD label, clinical encounters are filtered through schema activation: "difficult patient," "frequent flyer," "attention-seeking," "manipulative," and "secondary gain" are the language markers of clinical moral disengagement in operation. These are the precise vocabulary through which moral disengagement is scaffolded, removing the patient from the category of persons deserving responsive care and placing her in the category of persons whose complaints are presumptively less credible. Diagnostic overshadowing is the clinical expression of this CMDS mechanism: patients with psychiatric diagnoses receive less aggressive workup for physical complaints, spend less time with emergency providers, are more likely to have objective findings attributed to their psychiatric history, and are discharged more rapidly regardless of presenting physiology.

Tachycardia is a measurable, objective finding. Hypertension is a measurable, objective finding. Low end-tidal CO<sub>2</sub> in the context of tachycardia and hypertension constitutes a legitimate medical emergency differential that includes pulmonary embolism,

low-perfusion state, severe sympathetic activation, and cardiac dysrhythmia, none of which are answered by determining whether the patient has visited the emergency department previously. The clinical standard is clear: objective findings require objective evaluation regardless of psychiatric history.

Involuntary psychiatric detention in this setting operates as an iatrogenic harm mechanism applied in place of medical evaluation. The involuntary psychiatric hold imposes physical restriction, loss of autonomy, and in many facilities seclusion, all of which are recognized as traumatizing interventions for individuals with existing PTSD or CPTSD. For a patient whose presenting crisis is PMDD-related perimenstrual psychiatric exacerbation on a background of CPTSD, the hold does not address the hormonal mechanism; it applies physical coercion to a person whose primary pathology involves a history of traumatic events in which control was forcibly removed. The intervention is mechanistically contraindicated by the diagnosis that should have been made. Evidence-based trauma-informed care — stabilization, safety planning, hormonal crisis intervention — is available, effective, and omitted.

In most US states, an involuntary psychiatric hold triggers mandatory notification to the state licensing board for licensed healthcare professionals. A nurse who sought care for PMDD-related perimenstrual suicidal ideation on a background of CPTSD may exit the experience with a permanently encumbered nursing license, restriction from high-acuity practice settings, and a public record that follows every subsequent employment application. The inadequate care produces a documentation injury layered on top of the clinical injury.

The professional and workforce consequences of CMDS-generated iatrogenic harm for nurses who seek psychiatric care are immediate, severe, and underreported in the occupational health literature. Emergency nursing and other high-acuity specialties requiring frequent high-stakes independent judgment are effectively closed to nurses with involuntary psychiatric hold records in many state licensing structures. The career trajectory of a nurse who entered emergency nursing following 10 or more years of specialty training, and who sought care during a PMDD-related crisis that was mismanaged as BPD and resulted in an involuntary hold, ends with the institutional action taken by the very system that created or amplified the occupational trauma generating her crisis.

Care avoidance as a population-level outcome: every nurse who knows a colleague whose career was destroyed by seeking psychiatric care receives the same information about the cost of help-seeking. A nurse who watched a colleague lose her emergency nursing position after an involuntary hold has been given a clear signal about the institutional response to vulnerability. She will not seek care. She will manage her PMDD symptoms alone. She will absorb her PTSD without professional support. She will enter the perimenopausal hormonal vulnerability window without clinical monitoring. CMDS does not merely harm the individual patient; it harms the entire population of nurses who observe its operation and update their behavior accordingly. The population-level consequence is an invisible reservoir of untreated PMDD, unmanaged PTSD, and compounding neurobiological deficit in a workforce that already carries the highest female-specific suicide risk of any occupational group studied.

## SECTION XII: CLINICAL AND POPULATION-LEVEL RECOMMENDATIONS

### Section XIIa: Clinician Training

The requirement for standardized training in PMDD, perinatal mood disorders, and perimenopausal psychiatric presentations is not limited to nursing education or occupational health programs. Any clinical discipline that encounters patients in states of hormonal flux, estrogen depletion, or reproductive life-cycle transition must be prepared to assess, differentiate, and respond to these presentations accurately. This training requirement extends substantially beyond what is currently recognized in U.S. medical or advanced practice nursing education frameworks.

Disciplines requiring standardized training in this domain include: primary care medicine, which is the first point of contact for the majority of women with PMDD and the most common site of diagnostic delay; neurology, given the neurobiological mechanisms described in this paper; psychiatry, which is the referral destination for PMDD and perimenopausal psychiatric presentations and must be equipped to make and exclude these diagnoses accurately; women's health and gynecology, which manages the hormonal conditions underlying the neurobiological mechanisms and prescribes the hormonal interventions that either address or worsen them; reproductive endocrinology; cardiology, given the cardiovascular sequelae of estrogen deficiency and HPA dysregulation; emergency medicine, given that perimenopausal women present to emergency departments in suicidal crisis at measurable rates and are currently managed without hormonal assessment; and occupational medicine, which is the clinical discipline most directly responsible for the workforce health surveillance gap identified throughout this paper.

Training content must include: DSM-5-TR diagnostic criteria for PMDD including the prospective tracking requirement; cycle-phase timing inquiry protocols for all presenting psychiatric complaints in premenopausal, perimenopausal, and recently postmenopausal patients; structured differential diagnosis across PMDD, perimenopause, PMS, PTSD, BPD, and bipolar spectrum disorder; pharmacological distinction between synthetic progestins and bioidentical progesterone and their differential effects on GABA-A receptor sensitivity; recognition of estrogen-deficiency states and their psychiatric, neurological, musculoskeletal, and cardiovascular sequelae; and best practices for immediate intervention including cycle phase tracking initiation, endocrine referral, and crisis safety planning sensitive to hormonal context.

This training does not exist as a standardized requirement within any U.S. medical or nursing education framework at the time of this writing. Its absence constitutes a systemic failure of clinical education with population-level consequences. The musculoskeletal pain burden, cardiometabolic deterioration, and psychiatric sequelae experienced by women in estrogen-deficient states -- including perimenopausal and postmenopausal nurses -- are preventable outcomes of inadequate clinical education and institutional non-response. This is stated without rhetorical modulation because the evidence warrants it.

## **Section XIIb: COMPASS Implementation Pathway**

Implementation of the COMPASS as a differential diagnostic screening instrument requires: prospective validation in clinical populations representing each of the five key differential diagnoses, with sample sizes adequate to establish discriminant validity; adaptation for use in occupational health and outpatient clinical settings; incorporation into electronic health record templates as a standard cycle-phase assessment module triggered by psychiatric chief complaints in reproductive-age and perimenopausal patients; and training of occupational health practitioners and primary care clinicians in its administration and interpretation.

The immediate priority is validation study design and initiation. PULSE Advisory Group identified COMPASS validation as a research agenda priority. Collaboration with academic medical centers maintaining reproductive psychiatry and women's mental health programs is the appropriate institutional partnership pathway. Validation across racial, ethnic, and socioeconomic subgroups is essential, as PMDD diagnostic delay and misdiagnosis rates have not been systematically evaluated for differential impact across demographic subgroups.

### **Section XIIb-ii: Evidence-Based Treatment Pathways for Nurses With CPTSD with or without Perimenopausal Comorbidity**

The treatment evidence base for Complex PTSD (CPTSD) has expanded substantially since the ICD-11 formalized the diagnosis in 2022. Standard PTSD protocols were developed for single-incident trauma in populations without pervasive disturbances of self-organization (DSO) — the affect dysregulation, chronic negative self-concept, and relational disturbances that distinguish CPTSD from PTSD. Nurses presenting with occupational trauma exposure will manifest DSO features alongside PTSD symptom clusters, requiring treatment matching to this more complex presentation.

#### ***Phase 0: Neurobiological stabilization before processing***

Hormonal stabilization is the prerequisite, not the adjunct, to effective trauma processing in perimenopausal nurses with PMDD or documented estrogen deficiency. Estrogen modulates serotonin, GABA, dopamine, and norepinephrine systems — the same systems dysregulated in CPTSD. Subtherapeutic estrogen in a nurse with CPTSD and PMDD produces compounded neurobiological dysregulation that reduces the effectiveness of every other intervention. Perimenstrual windows are contraindicated for intensive exposure-based trauma work in PMDD-positive patients; session scheduling should be anchored to the follicular phase where possible.

Nutritional psychiatry is a mechanism-specific intervention in this population. Magnesium functions as an NMDA receptor antagonist — NMDA receptor hyperactivation is directly implicated in fear memory consolidation, hyperarousal, and re-experiencing phenomena in CPTSD. Magnesium deficiency produces upregulated ACTH and CRH, precisely mirroring the HPA axis alterations documented in CPTSD. Omega-3 fatty acids at EPA-dominant doses reduce neuroinflammation via LOX and CYP450 lipid mediators and support

hippocampal neurogenesis. NAC (N-acetylcysteine) is a glutathione precursor that modulates glutamatergic tone — the neurotransmitter system most implicated in CPTSD hyperarousal and intrusive re-experiencing. All nutritional interventions require individualized clinical assessment; specific dosing and selection decisions belong to the treating clinician with access to complete patient history.

### ***Phase 1: Autonomic reset — stellate ganglion block***

Stellate Ganglion Block (SGB) is an emerging intervention with moderate-to-strong evidence for autonomic dysregulation in PTSD. The bilateral two-level ultrasound-guided SGB at C6 and C4 (the Dual Sympathetic Reset protocol) produced 53 percent improvement in neurobehavioral symptom scores at one-month follow-up in a published series. The mechanism — reducing norepinephrine-driven hyperarousal via sympathetic nervous system modulation — directly facilitates engagement with subsequent EMDR and prolonged exposure by lowering the emotional reactivity threshold. SGB is not a standalone treatment; it is an access-enabling intervention appropriately sequenced before intensive trauma processing.

### ***Phase 2: Trauma processing — DBT-PE, EMDR intensive, and ESTAIR***

DBT-PE (Dialectical Behavior Therapy Prolonged Exposure, Harned protocol) is the evidence-based first choice for CPTSD patients with prior suicide attempt, self-harm history, “borderline” features, or affect dysregulation. The entry threshold is two months free of parasuicidal behavior — not the one-to-three years commonly required by standard EMDR intensive programs. This distinction matters: nurses with high occupational adversity and CPTSD are frequently denied intensive treatment, cycling through underdosed standard care for years while the underlying pathology compounds.

EMDR intensive format — multiple sessions per day over consecutive days — produces outcomes equivalent to 16-week standard protocol with substantially lower dropout rates compared to standard PE. For nurses with ADHD or ASD, standard bilateral stimulation may require adaptation to tactile or auditory bilateral stimulation, with longer preparation phases and explicit verbal processing. EMDR is a first-line treatment per VA/DoD 2023 Clinical Practice Guidelines, NICE guidelines, and WHO guidelines.

ESTAIR (Enhanced Skills Training in Affective and Interpersonal Regulation) is a multi-modular approach for CPTSD that specifically addresses DSO features — affect dysregulation, negative self-concept, and relational disturbances — which EMDR and PE do not directly target. ESTAIR is appropriately used in combination with EMDR for comprehensive CPTSD coverage.

### ***Phase 3: Neuroplasticity enhancement***

Low-dose ketamine administered before EMDR session opens a neuroplasticity window via BDNF upregulation and NMDA receptor modulation, directly engaging the mechanism described in Section IIIg. This is particularly relevant for treatment-resistant CPTSD with prominent dissociation. The emerging evidence base for ketamine-assisted EMDR supports

its inclusion in comprehensive treatment protocols for high-risk nurses who have not responded to standard-of-care approaches.

MDMA-assisted therapy (MDMA-AT) carries the strongest evidence base of any psychedelic intervention for PTSD. The MAPP2 trial (Mitchell et al., *Nature Medicine*, 2023) demonstrated 71.2 percent of participants no longer met PTSD criteria after MDMA-AT compared to 47.6 percent in the placebo arm. FDA declined approval in August 2024 citing trial design concerns, not safety or efficacy data; expanded access protocols remain available at licensed clinical sites. Critical drug interaction: SSRIs and SNRIs significantly blunt MDMA effect via 5-HT receptor downregulation, requiring a minimum two-to-four-week washout prior to initiation.

The gap between this evidence base and standard-of-care delivery is not a gap in evidence. It is a gap in system organization, insurance coverage, provider training, and institutional willingness to treat CPTSD as the neurobiological condition it is. A nurse with CPTSD, perimenopausal neurosteroid deficiency, occupational trauma burden, and untreated PMDD who receives weekly talk therapy and an SSRI has not received adequate treatment. She has received inadequate treatment at therapeutic scale. The recommendations in Section XII do not require new evidence to implement; they require institutional and regulatory will to reorganize existing resources.

### **Section XIIc: Occupational Health Surveillance Framework**

No federal standard currently mandates neurobiological or psychiatric surveillance for the registered nursing workforce. The gap is regulatory and institutional. The following elements are recommended for incorporation into occupational health standards applicable to healthcare employers with nursing staff: baseline and annual psychiatric screening incorporating validated PTSD, depression, and suicidal ideation instruments; routine menstrual cycle phase documentation in occupational health encounters for female and AFAB nursing employees, with prospective tracking referral for those presenting with psychiatric chief complaints; hormonal status documentation including TSH, FSH, and estradiol at intake for employees aged 40 and older, with endocrine referral protocols for abnormal findings; pharmacological risk documentation including statin use and hormonal contraceptive use, with standardized PMDD and perimenopausal risk assessment; and CMDS-based institutional environment assessment using the Leadership Accountability Rubric at 12-month intervals, with findings reported to governing boards as patient safety quality metrics; bidirectional occupational violence screening, incorporating validated exposure instruments for patient, visitor, and lateral peer assault alongside a non-punitive, clinically framed perpetration risk screen for identification of trauma-exposed employees requiring clinical referral rather than disciplinary action; and institutional reporting culture documentation, specifically the ratio of formal incident reports submitted to estimated actual assault frequency, as a measurable indicator of suppression architecture and organizational accountability.

Cycle-phase-aware psychiatric screening for individual nursing employees is operationalized through COMPASS (Cycle, Occupational/life adversity, Mood pattern,



Perimenopause, Adversity/trauma, Symptom severity, Safety) v1.0, a structured self-report instrument developed by Jennifer Torrez for occupational health settings. COMPASS v1.0 integrates hormonal status documentation, cycle-phase tracking, ACE burden screening, and occupational adversity exposure across domains specified in the AAES framework, providing a single-encounter instrument appropriate for annual occupational health visits. COMPASS navigates the complex diagnostic terrain of PMDD, perimenopausal transition, PTSD, and related presentations, providing a directional orientation when the clinical picture is genuinely ambiguous. The COMPASS instrument is available through PULSE Advisory Group.

### **Section XIId: CMS and EMTALA Implications**

The Centers for Medicare and Medicaid Services Conditions of Participation require hospitals to maintain adequate nursing staffing to meet patient care needs. A nursing workforce in which 23% of actively employed nurses meet PTSD diagnostic criteria, in which PMDD and perimenopausal psychiatric burden are systematically undetected and unsupported, and in which the CMDS suppression architecture prevents escalation of safety concerns, does not meaningfully meet this standard. The staffing may be numerically present; the cognitive and neurobiological capacity to deliver safe patient care is measurably compromised by the conditions documented in this paper.

EMTALA creates obligations for emergency departments to provide stabilizing treatment to patients presenting in psychiatric emergencies. Perimenopausal nurses presenting to emergency departments in suicidal crisis are patients protected under EMTALA -- patients whose crisis is attributable in part to an occupational condition that their employer and the healthcare system have not addressed. The institutional liability exposure at the intersection of EMTALA, CMS Conditions of Participation, and documented occupational psychiatric harm in the nursing workforce has not been systematically analyzed and warrants examination. CMS Quality Improvement Reporting under Section 482.13 provides an existing regulatory vehicle; advocacy for amendment to include nursing workforce psychiatric morbidity as a patient safety quality indicator would create the regulatory hook necessary to make institutional accountability enforceable.

### **Section XIle: PRRAA as Legislative Vehicle**

The Patient Rescue Readiness and Accountability Act (PRRAA) is proposed model legislation establishing binding federal standards for occupational health surveillance, failure-to-rescue prevention, and institutional accountability in healthcare settings. The PRRAA provides the legislative architecture for converting the recommendations of this paper into enforceable regulatory requirements: mandatory occupational psychiatric screening with cycle-phase-aware assessment protocols, CMDS-based institutional accountability auditing with governing board disclosure requirements, and nurse suicide surveillance with standardized case definitions and federal reporting requirements tied to CMS certification.

The Dr. Lorna Breen Health Care Provider Protection Act (P.L. 117-105, signed March 18, 2022) established grant programs supporting healthcare worker mental health. Its

reauthorization, enacted as part of the Consolidated Appropriations Act, 2026 (P.L. 119-75), extended these programs through FY2029. The PRRAA is designed to operate as a complementary and escalating legislative vehicle: where the Lorna Breen Act provides incentive-based support for voluntary mental health program development, the PRRAA establishes binding minimum standards with enforcement mechanisms. Both legislative frameworks are necessary. Neither alone is sufficient to produce the surveillance and accountability architecture that the harm documented in this paper requires.

The implementation of the occupational health surveillance framework proposed in Section XIIc does not require new regulatory authority. CMS Conditions of Participation at 42 CFR Part 482 already require hospitals to maintain effective infection control and patient safety programs that encompass all relevant aspects of the healthcare environment. A regulatory interpretation that workforce psychiatric health, when it compromises nursing cognitive capacity and patient care delivery, is a patient safety matter within the scope of existing Conditions of Participation would create the regulatory hook for surveillance requirements without new legislation. This interpretation is legally supported by the documented relationship between nursing psychiatric burden and adverse patient outcomes, including medical error rates and failure-to-rescue incidence. The argument that workforce health is categorically distinct from patient safety is not medically defensible in the context of this evidence base.

The Joint Commission accreditation standards for hospitals include requirements for workplace violence prevention programs. Extension of these standards to include psychological harm and occupational psychiatric injury -- both of which the peer-reviewed literature documents as prevalent and predictable outcomes of the nursing occupational environment -- would create a parallel private accreditation pathway to the regulatory requirements proposed through CMS. Hospitals seeking to maintain Joint Commission accreditation would be required to demonstrate compliance with occupational psychiatric health standards, creating market-based accountability that complements regulatory accountability. The combination of CMS regulatory requirements and Joint Commission accreditation standards would address the institutional accountability gap at multiple levels simultaneously.

## **Section XII-A: Full Legal and Policy Framework**

### **Section XIIf: PMDD as a Covered Episodic Disability Under the ADAAA**

The Americans with Disabilities Act Amendments Act of 2008 (Public Law 110-325) codified at 42 U.S.C. Section 12102(4)(D) explicitly protects conditions that are "episodic or in remission" if they "would substantially limit a major life activity when active." The EEOC's implementing guidance confirms that major depressive episodes, PTSD, and anxiety disorders qualify under this framework, and that the nature and severity of limitation during an active episode determines coverage. PMDD is classified in the DSM-5 Depressive Disorders chapter, produces substantial limitations in concentration, interpersonal function, and in severe cases the activities of daily living, during its active phase, and remits reliably in the follicular phase. This is precisely the episodic profile the ADAAA intended to protect.

No circuit court has directly held PMDD to be a covered disability; that absence reflects the recency of PMDD's DSM-5 elevation rather than any substantive legal barrier. Healthcare employers who decline to engage in the interactive accommodation process for employees with documented PMDD face potential liability under this framework. The UK Employment Tribunal decision in *Lynskey v Direct Line Services Ltd* (2024), holding that menopause-related symptoms constitute a disability under the Equality Act 2010, provides directional international signal.

## **Section XIIg: OSHA General Duty Clause and the Foreseeability Standard**

The Occupational Safety and Health Act of 1970, Section 5(a)(1), requires employers to furnish a workplace free from recognized hazards likely to cause death or serious harm. The hazard here is female-specific elevated suicide risk in a profession with documented RR 1.99 for female suicide, published in *JAMA Psychiatry* in 2021 and covered extensively in nursing trade publications. An employer who, in 2025, operates a predominantly female nursing workforce without any occupational health protocol that acknowledges female-specific biological suicide risk factors cannot claim ignorance of the elevated hazard; the evidence is peer-reviewed, indexed, replicated across four countries, and now several years old. The modifiability of PMDD through FDA-approved treatments satisfies the "feasible abatement method" element of the General Duty Clause analysis.

## **Section XIIh: The Dr. Lorna Breen Health Care Provider Protection Act and Its Mandate**

Public Law 117-105 (signed March 18, 2022; reauthorized through P.L. 119-75, February 2026) authorizes up to \$45 million annually for healthcare worker mental health programs and directs the Secretary of Health and Human Services to identify evidence-based best practices for preventing suicide among health care professionals. The Act is the legislative vehicle most immediately available to mandate programmatic response to the evidence assembled in this manuscript. Its current limitation is the absence of any reference to sex-specific risk factors, reproductive health, hormonal variables, or the documented sex-concentration of the occupational suicide elevation. The statutory charge to the Secretary to identify best practices creates an administrative pathway: formal evidence submission to HRSA, SAMHSA, and the HHS Office on Women's Health, requesting that funded program parameters explicitly require PMDD screening as a component of evidence-based healthcare worker suicide prevention, without requiring statutory amendment.

The Lorna Breen chilling effect refers to the documented deterrent impact of Dr. Breen's experience — she sought treatment for psychiatric symptoms, subsequently faced credential review and professional consequences, and died by suicide — on help-seeking behavior in the nursing and physician workforce. This is not a theoretical concern. Every nurse who knows Lorna Breen's story has been given specific, accurate information about the institutional response to psychiatric disclosure. The chilling effect operates on behavior even when no formal policy exists to produce it, because the information it communicates is accurate: seeking care can end a healthcare career.

### **Section XIII: Provider Liability for PMDD Misdiagnosis**

Psychiatric malpractice doctrine turns on whether care fell below the standard exercised by reasonably competent practitioners under similar circumstances. PMDD has been a DSM-recognized diagnostic entity since 2013, with ICD-11 classification since 2022. The diagnostic criteria, including the prospective two-cycle confirmation requirement and the requirement for symptom-timing inquiry, are published in the DSM-5-TR and ACOG Practice Bulletin 128. A provider who evaluates a cycling AFAB patient with cyclical mood symptoms and does not inquire about symptom timing relative to the menstrual cycle, applies a bipolar disorder diagnosis, and initiates valproate, lithium, or atypical antipsychotic therapy, generating the harms documented above, operates within the zone of doctrinal malpractice liability. No reported US case has directly litigated PMDD misdiagnosis as bipolar disorder as the primary negligence theory. The absence of reported cases reflects the absence of a plaintiff-side medical malpractice practice area specialized in this diagnosis; the doctrinal infrastructure exists.

### **Section XIIIj: CMDS and Provider Liability for Diagnostic Overshadowing**

The CMDS framework has direct malpractice implications for providers who withhold emergency evaluation from patients with objective hemodynamic findings on the basis of psychiatric label. Diagnostic overshadowing constitutes a departure from the standard of care when it results in failure to evaluate objective physiologic findings that a reasonable clinician would have investigated. The legal standard is not whether the patient had a psychiatric history; it is whether the objective findings presented were evaluated on their clinical merits. Tachycardia, hypertension, and low end-tidal CO<sub>2</sub> require a differential diagnosis. When that differential is omitted because the provider's attention was directed primarily toward the psychiatric label, the provider has applied a standard of care that departs from the objective-findings evaluation standard applicable to all emergency patients regardless of psychiatric history.

### **Section XIIIk: Legal Protections for Trans Men and AFAB Gender-Diverse Workers**

Federal prohibition on sex discrimination under Title VII, as interpreted in *Bostock v. Clayton County* (140 S. Ct. 1731, 2020), extends to gender identity. An employer who denies a trans man reasonable accommodation for PMDD-related episodic disability, or terminates employment during a PMDD-related crisis, faces potential liability under both Title VII and the ADAAA. A provider who fails to recognize and treat PMDD in a trans male patient faces potential liability under Section 1557 of the Affordable Care Act, which prohibits sex discrimination in health programs receiving federal funds, and which has been interpreted by the Department of Health and Human Services to include gender identity as a protected category subject to nondiscrimination requirements.

## **SECTION XIII: UNKNOWNNS REQUIRING INVESTIGATION**

The following eight unresolved questions are identified as priority research areas on the basis of gaps in the current evidence base documented throughout this analysis. Each is accompanied by a proposed study design sufficient to address the question.

First: What is the prospective prevalence of PMDD in the actively employed U.S. registered nursing workforce, assessed using DSM-5-TR criteria and the DRSP with a minimum two-cycle prospective tracking period? This question is foundational to the economic burden model, which currently uses a population-general 3% to 8% prevalence estimate that may not accurately represent nursing-specific prevalence given the elevated occupational stress exposures documented in this paper. Proposed study design: prospective cohort of a stratified random sample of nursing employees across hospital types, with two-cycle DRSP tracking, hormonal status assessment at cycle-phase-specific timepoints, and occupational exposure documentation.

Second: What is the relationship between shift work exposure duration, allopregnanolone plasma levels, and PMDD symptom severity in actively employed nurses? Proposed study design: cross-sectional study with biological sampling of plasma allopregnanolone, cortisol, progesterone, TSH, and estradiol timed to confirmed cycle phase, stratified by years of cumulative night shift exposure, with PMDD diagnostic assessment using the DRSP.

Third: Does T3 augmentation of StAR protein expression translate to measurable differences in adrenal allopregnanolone synthesis output in human AFAB subjects with hypothyroidism versus euthyroid controls? Proposed study design: controlled endocrine study comparing adrenal steroidogenic output at baseline and following ACTH stimulation between hypothyroid and euthyroid AFAB individuals, with secondary analysis before and after thyroid hormone normalization.

Fourth: What is the rate of PMDD-to-bipolar misdiagnosis in population-representative clinical samples, and what are the prevalence and clinical outcomes of valproate prescribing in individuals who ultimately receive a PMDD diagnosis after prior bipolar diagnostic assignment? Proposed study design: retrospective cohort using electronic health record data from large health systems with reproductive psychiatry programs, identifying individuals with prior bipolar assignment who subsequently received PMDD diagnosis, with extraction of intervening pharmacological exposures and offspring outcome data.

Fifth: Does perimenopausal transition in the nursing workforce independently predict workforce exit, suicidal ideation, or psychiatric hospitalization, controlling for prior psychiatric history, occupational PTSD, and institutional environment? Proposed study design: longitudinal cohort of nursing employees ages 43 to 58, with prospective hormonal status tracking, annual psychiatric symptom assessment, and occupational outcome documentation including employment status, position change, psychiatric hospitalization, and attempted or completed suicide.

Sixth: Does neurodivergent status modify the trajectory from occupational harm to occupational crisis in the nursing workforce, and does access to environmental attribution frameworks mediate this relationship? Proposed study design: longitudinal cohort stratified by neurodivergent status, ACE score, and CMDS-based institutional environment score, with prospective tracking of biological stress markers, psychiatric symptomatology, and occupational outcomes as described in Section X.

Seventh: What proportion of nursing workforce suicides in the United States occurred in the perimenopausal age window (ages 45 to 55), and what proportion of those individuals had received a psychiatric diagnosis that did not include PMDD or perimenopausal mood disorder assessment? Proposed study design: national nurse suicide registry with standardized case definitions, medical record review, and cause-of-death linkage through vital statistics systems.

Eighth: What is the full economic burden of PMDD in the U.S. nursing workforce, incorporating direct medical costs, productivity loss from presenteeism, replacement costs from PMDD-attributable attrition, costs of bipolar misdiagnosis and valproate prescribing, and patient safety costs of PMDD-related cognitive impairment during patient care delivery? Proposed study design: multi-component economic burden analysis applying the Davis 2022 societal costing methodology to PMDD-specific nursing workforce data, using the nursing-specific prevalence figure established by the study proposed in item one above.

Ninth: What is the prevalence of intimate partner violence (IPV) victimization among the current U.S. nursing workforce, and to what extent does structural normalization of occupational violence in healthcare settings predict IPV tolerance, delayed disclosure, or non-disclosure at the individual level? Does occupational violence exposure independently predict IPV vulnerability through the same neurobiological conditioning pathways identified in Sections IIId and IIlg? What proportion of the nursing workforce carries bidirectional violence exposure -- both occupational and intimate -- that has never been identified through any institutional or clinical screening mechanism? And what is the population-level prevalence of occupational violence perpetration risk in a workforce with documented rates of traumatization, moral injury, and moral disengagement? No validated national prevalence estimate exists for IPV victimization in the U.S. nursing workforce, and no occupational health system currently screens for perpetration risk. Both gaps constitute prerequisite denominators for intervention design, policy modeling, and employer liability assessment.

### **IPV as Ongoing Trauma, Coercive Care Suppression, and Domestic CMDS Analog**

Intimate partner violence (IPV) functions as a distinct and compounding exposure category within the nurse suicide risk architecture. Prevalence data establish the scope: U.S. estimates place IPV exposure among nurses at approximately 25% (Bracken et al., 2010; n=1,981; one Mid-Atlantic metropolitan area; convenience sample -- generalizability requires verification against national probability samples). Australian data from the Australian Nursing and Midwifery Federation (ANMF, 2022) report 45.1% lifetime IPV exposure, though this figure reflects a 15.2% survey response rate and should be interpreted with corresponding caution for non-response bias.

*[Sampling limitation disclosure: IPV prevalence data cited in this paper — Bracken et al., 2010 (25 percent U.S. exposure) and ANMF 2022 (45.1 percent Australian exposure) — are derived from samples with significant generalizability limitations. The Bracken study used a convenience sample from one Mid-Atlantic metropolitan area (n=1,981); the ANMF study had a 15.2 percent response rate, creating substantial non-response bias risk. These figures should be cited as available estimates from studies with documented*



*limitations, not as definitively established national prevalence rates. Nationally representative probability sample data on IPV in the U.S. nursing workforce do not currently exist.\]*

The mechanism through which IPV compounds occupational suicide risk operates on at least three levels. First, at the neurobiological level, IPV constitutes chronic interpersonal trauma that activates and sustains HPA axis dysregulation independently of occupational adversity. When both exposures operate simultaneously, the HPA burden is additive at minimum and potentially synergistic when sleep deprivation from shift work further impairs glucocorticoid negative feedback.

Second, IPV functions as a coercive care-access suppression mechanism. Abusive partners frequently control financial resources, monitor communications, impose scheduling demands, and create conditions of social isolation that reduce the victim's ability to seek mental health treatment. A nurse experiencing IPV may be the healthcare provider for her community while being systematically denied access to that same system in her own life. The professional identity -- competence, self-sufficiency, caretaker role -- compounds the help-seeking barrier because it creates a cognitive dissonance with patient status.

Third, at the institutional level, IPV operates as a domestic analog to Clinical Moral Disengagement. The mechanisms differ but the result is the same: a person's capacity to recognize distress as legitimate and act on it is systematically suppressed, in the home by the abuser's conditioning and in the institution by hierarchical dismissal. A nurse who has been told for years that her perceptions are distorted, her reactions are excessive, and her needs are secondary has been trained by two parallel systems -- the abusive relationship and the institutional culture -- to discount her own internal signals.

***Discovery target: IPV screening data from employee assistance programs and occupational health services at institutions where nurse suicides occurred. Absence of such data is itself a finding -- institutions that do not screen for IPV in the nurse population are operating below minimum standard of care for a high-risk occupational group.***

## **Regulatory and Policy Research Priorities**

In addition to the eight clinical and epidemiological research questions enumerated in Section XIII, the following policy and regulatory research priorities are identified as necessary to translate the findings of this paper into actionable institutional and legislative change.

Ninth: What is the current state of compliance with voluntary healthcare worker mental health guidelines across U.S. hospital systems with more than 500 nursing employees? No systematic audit of compliance with the Dr. Lorna Breen Act grant program outcomes has been published at the time of this writing. A national compliance audit -- conducted through CMS survey and certification infrastructure or through the Joint Commission survey process -- would establish baseline compliance data and identify institutional patterns of non-engagement. Proposed study design: national survey of occupational health program offerings at hospitals receiving Medicare and Medicaid reimbursement, with stratification

by bed size, ownership type (non-profit, for-profit, government), and geographic location (rural, urban, suburban).

Tenth: What is the relationship between institutional CMDS score (as measured by the Leadership Accountability Rubric) and nurse psychiatric burden outcomes? The CMDS framework proposes a causal relationship between institutional suppression architecture and nurse psychiatric deterioration; this relationship has not been prospectively tested in a study design with adequate statistical power to establish causation. Proposed study design: longitudinal study of health systems implementing and not implementing CMDS-based institutional accountability auditing, with prospective tracking of nurse PTSD incidence, voluntary departure rates, and psychiatric hospitalization rates as primary outcomes.

Eleventh: What legislative pathways exist for incorporating cycle-phase-aware occupational health standards into state workers' compensation frameworks? Workers' compensation systems in most states currently provide limited coverage for occupational psychiatric injuries in nursing, and PMDD-associated occupational harm is not recognized as a compensable occupational condition in any state framework at the time of this writing. Legal research and model statute development in this domain represents a parallel legislative pathway to the PRRAA at the state level.

### **Section XIIIb: Formal Hypotheses for Prospective Testing**

The following six formal hypotheses are generated by the evidence synthesis above and are offered as the minimum hypothesis set required to operationalize the manuscript's central claims for prospective testing.

Hypothesis 1: Among female-born nurses and AFAB healthcare workers who die by suicide, a disproportionate fraction of deaths occur during the late luteal and early follicular phases, corresponding to the low estradiol and low progesterone window established in the general AFAB literature as the period of peak suicidal vulnerability.

Hypothesis 2: Among female nurses, PMDD prevalence meets or exceeds the general population estimate, and PMDD-associated perimenstrual suicide risk is amplified by occupational stressors via additive HPA axis and neurosteroid synthesis pathway mechanisms, including statin-mediated cholesterol substrate reduction and hypothyroid impairment of StAR-mediated mitochondrial cholesterol transport.

Hypothesis 3: PMDD diagnostic delay in female-born healthcare workers equals or exceeds the general population mean of 12 years, with occupational help-seeking barriers and CMDS-mediated misdiagnosis contributing suppressive layers beyond those documented in non-clinical samples.

Hypothesis 4: Among AFAB trans men in healthcare, PMDD-equivalent states attributable to residual ovarian cycling or testosterone injection troughs contribute to cycle-phase suicidal ideation through identical neurobiological mechanisms, but are invisible to current screening tools, absent from clinical guidelines, and subject to the double CMDS suppression mechanism documented in Section IXb.

Hypothesis 5: ACE score, PTSD diagnosis, and CPTSD diagnosis each independently predict PMDD severity and perimenstrual suicidal ideation intensity in the nursing workforce through shared allopregnanolone synthesis pathway suppression, and their co-occurrence produces a compounded deficit state that current standard-of-care psychiatric and occupational health assessment does not evaluate.

Hypothesis 6: CMDS-mediated iatrogenic harm following psychiatric misdiagnosis in nurse-patients — specifically, involuntary psychiatric hold and licensing consequences following mismanaged PMDD/CPTSD crisis presentations — generates measurable career exit, permanent care avoidance, and elevated suicide risk that the current occupational health literature does not capture because it does not record the clinical encounter as a cause of workforce departure.

## **Section XIII-A: Comprehensive Research Gap Documentation**

### **Section XIIIa-i: Definitive Negative Findings**

After exhaustive searches of PubMed, Google Scholar, ScienceDirect, Wiley Online Library, Springer/BMC, Frontiers, JAMA Network, ClinicalTrials.gov, medRxiv, and targeted grey literature (NIOSH, CDC, ANA, IAPMD, AAN) using more than 20 Boolean search-term combinations, the following constitute definitive negative findings: (1) no published study examines PMDD prevalence in practicing registered nurses using DSM-5 prospective two-cycle confirmation; (2) no published study identifies menstrual cycle phase, hormonal status, or PMDD history at the time of nurse or healthcare worker suicide attempt or death; (3) no published longitudinal study tracks suicidal ideation across the menstrual cycle in any occupational population; (4) no nurse or healthcare worker mental health screening tool incorporates PMDD screening or cycle-phase documentation; (5) no NIOSH, OSHA, ANA, AAN, or Joint Commission policy document addresses PMDD, menstrual cycle, or hormonal status as an occupational health variable in nursing; (6) the comprehensive 2023 systematic review of 100 nurse-suicide studies (Groves, Lascelles, and Hawton) does not include reproductive health, menstrual cycle, hormonal status, or PMDD as a domain in its analytical framework; and (7) no published commentary or position paper explicitly calls for research at the intersection of PMDD and nurse suicide.

### **Section XIIIa-ii: Historical Context for the Gap**

The research gap is not an ordinary limitation of an emerging field. Before the NIH Revitalization Act of 1993, women were routinely excluded from clinical trials, with exclusion justified by concerns about menstrual cycle variability as a confounder. That the female cycle was treated as a confound to be controlled out rather than a variable to be studied is the precise institutional decision that produced the gap documented here. PMDD was held in the DSM-IV-TR research appendix from 1994 through 2013, a classification decision that suppressed research funding for two decades. The Flexner Report consolidation described in this manuscript's introduction created a training infrastructure in which cyclical female biology was systematically deprioritized as a clinical domain. These are not speculative claims about institutional motivation; they are documented policy decisions with documented consequences in the research literature.

**Table 4. Comprehensive Research Gap Analysis: PMDD, Neurosteroid Biology, and AFAB Healthcare Worker Suicide**

Gap	Evidence Status	Structural Cause	Proposed Design
PMDD prevalence in US practicing nurses (DSM-5 prospective)	Zero studies	Nursing workforce surveys exclude reproductive health variables	Cross-sectional prevalence study with 2-cycle DRSP confirmation; n=2,000 stratified by specialty and shift pattern
Cycle phase and hormonal status at time of nurse suicide attempt or death	Zero studies; NVDRS does not collect	Menstrual variables excluded from death investigation protocols since their inception	Psychological autopsy protocol modification; prospective ED biospecimen collection: LH, FSH, E2, P4, total cholesterol, free T3 alongside standard toxicology
Daily suicidal ideation tracking across the menstrual cycle in nurses	Zero studies in occupational populations	Occupational health and cycle-phase suicide literatures have never been combined	Ecological momentary assessment; LH-confirmed phases; n=300; 3 cycles; occupational stress measures
Statin use, serum cholesterol, and neurosteroid levels in nurse suicide decedents	Mechanism established; clinical intersection in nurses unstudied	Cardiology and suicide research operate in separate silos with no cross-specialty protocol	Add serum lipid panel and neurosteroid assays to nurse psychological autopsy biospecimen protocol
Thyroid function as modifier of PMDD severity and perimenstrual SI in nurses	Known thyroid-StAR interaction; clinical study in nurses absent	Endocrinology and occupational psychiatric research have no joint protocol	Nested thyroid function analysis within nurse prevalence cohort: TSH, free T4, free T3, anti-TPO
PMDD screening tools validated for trans men and AFAB nonbinary individuals	Zero validated instruments	All existing instruments designed for cisgender women with active menstruation	Instrument development: qualitative pilot with trans men; item generation;

Gap	Evidence Status	Structural Cause	Proposed Design
			psychometric validation in n=400
Trans men and AFAB nonbinary individuals in nursing: prevalence and mental health status	Zero studies; workforce data not collected	NCSBN/HRSA/ANA surveys do not distinguish gender identity from sex assigned at birth	Survey instrument modification; targeted recruitment via GLMA and trans nurse networks
Suicide attempts (non-fatal) in nurses: rate and hormonal profile	Zero occupational data; ED records unreliable for occupation	Vital statistics focus on deaths; occupational coding absent from ED records	Prospective ED registry with occupation coding and reproductive health variables; linked to nursing licensure files
PMDD diagnostic delay in nurses specifically	General population delay 12 years (IAPMD survey); nurses unstudied	Nursing mental health studies have never included PMDD as a diagnostic variable	Retrospective diagnostic history survey in active nursing cohort
Hormonal contraception type, dose, and mood outcomes in PMDD-affected nurses	General population data contradictory due to synthetic/bioidentical conflation; nurses unstudied	Epidemiological datasets do not capture progestin type or bioidentical status	Nested pharmacological cohort within nurse prevalence study; HC type, dose, duration, PMDD severity, SI outcomes
RCT of PMDD screening integrated into Lorna Breen Act-funded programs	No funded program includes PMDD screening; Act does not specify hormonal variables	Lorna Breen Act best-practice mandate does not include hormonal or reproductive health language	RCT in 20 hospital systems; PMDD screening plus luteal SSRI versus standard program; SI as primary endpoint; 24-month follow-up
ACE score distribution in the active nursing workforce	Zero studies directly measuring ACEs in practicing nurses	ACE and occupational health research have never been combined in nursing populations	ACE-10 administered within nurse prevalence cohort; correlation with PMDD severity, SI, help-seeking behavior, and diagnostic delay

Gap	Evidence Status	Structural Cause	Proposed Design
PTSD/CPTSD prevalence linked to PMDD severity in nurses	PTSD 23% in Canadian nurses (Stelnicki 2020); PTSD-PMDD interaction in nurses: unstudied	PTSD and reproductive psychiatry research operate in separate silos	Nested cross-sectional study: PCL-5 and ICD-11 ITQ for CPTSD; DRSP for PMDD; regression analysis of interaction effects on SI and SA outcomes
AAES instrument development and validation	Construct proposed; zero published instruments	ACE-10 ends at age 18; occupational trauma not captured	Qualitative pilot; item generation; psychometric validation in n=400 nurses
Allopregnanolone CSF or serum levels in nurses with PTSD+PMDD vs. PMDD alone	Mechanism established; occupational sample: zero	Neurosteroid biomarker research not applied to occupational populations	Biospecimen substudy within nurse prevalence cohort; PTSD vs. PTSD+PMDD vs. PMDD alone vs. controls; LH-confirmed cycle phase at draw
CMDS-mediated harm chain outcomes: licensing consequences of psychiatric hold following PMDD/CPTSD crisis in nurses	Zero published studies	CMDS framework newly applied to nursing occupational health	Retrospective chart review; licensing board data linkage; outcome: career exit, care avoidance, SI
Partner and family observer daily ratings of nurse PMDD symptom severity across two cycles	Zero published studies in occupational populations	Research designs have relied on self-report; insight impairment during luteal phase acknowledged but not addressed methodologically	Dyadic daily diary study; nurse + cohabitant partner/family member rating; LH-confirmed phases; behavioral observability outcomes
Provider knowledge: PMDD diagnostic	Anecdotal evidence of widespread ignorance;	Post-Flexner CME structure does not	National survey of psychiatrists,



Gap	Evidence Status	Structural Cause	Proposed Design
criteria, CPTSD-PMDD-BPD differential, cycle-phase suicide risk	no validated assessment published	include reproductive cyclicality as psychiatric training domain; no PMDD competency standard	OB/GYNs, NPs, and PCPs using validated PMDD knowledge instrument

## Section XIV-A: Discussion — Methodological Defense and Evidence Synthesis

The thesis of this manuscript connects five independent and fully replicated evidence streams. The methodological critique that this connection constitutes an ecological fallacy — inferring individual-level causal relationships from aggregate-level associations in separate populations — is technically correct as applied to causal claims. It is not a reason to abandon the hypothesis; it is a specification of the research design required to test it. The ecological fallacy critique, applied to the history of medicine, would have precluded the Framingham Heart Study, the research connecting smoking to lung cancer before a prospective cohort existed, and every major clinical investigation that began with convergent inferential reasoning from separate data streams. The contribution of this manuscript is precisely to establish that the inference is warranted and to define the study that would confirm or refute it. That study has not been done. That is the finding.

Several aspects of the evidence base presented here are stronger than they might appear on initial review, and several are more genuinely uncertain than the argument requires them to be. On the stronger side: the Opatowski 2024 Swedish population registry study finding HR 1.92 for suicide death in women with premenstrual disorders, involving 67,748 cases and 338,740 matched controls, is not subject to ascertainment bias or publication bias and does not depend on any inference across separate literatures. It is a single direct finding: women with diagnosed premenstrual disorders die by suicide at nearly twice the rate of matched controls. The experimental RCT demonstrating that transdermal estradiol and progesterone reduce perimenstrual suicidal ideation represents direct causal evidence within a controlled design. The sex-by-occupation interaction in the Olfson 2023 study ( $P = .03$ ) is a specific statistical test of the sex-differential, not an impressionistic observation. On the more uncertain side: the estimate that 70 to 90 preventable nurse suicides occur annually from PMDD-specific mechanisms is a motivating order-of-magnitude calculation based on multiple uncertain inputs and should be understood as such. The compounding neurobiological deficit model integrating statin therapy, thyroid function, and neurosteroid synthesis is mechanistically coherent and theoretically grounded but requires clinical study in nursing populations before it can be presented as more than a plausible framework.

The hormonal contraception literature, which generates the most superficially compelling contradiction to the estrogen-deficiency model, resolves completely under pharmacological specificity. Synthetic progestins are not bioidentical progesterone. Ethinyl estradiol is not 17-beta-estradiol. The distinction between synthetic and bioidentical hormonal preparations is not a fringe pharmacological point; it is the basis on which the FDA approved drospirenone-containing oral contraceptives specifically for PMDD, distinguishing that

progesterone from legacy synthetic progestins that are pharmacologically aversive for the PMDD-sensitive GABA-A receptor population. The Skovlund findings are mechanistically consistent with the estrogen-deficiency model, not contradictory to it: they document what happens when synthetic hormones with different receptor profiles from their endogenous counterparts are prescribed to AFAB individuals with pre-existing neuroactive steroid sensitivity.

The institutional history context introduced in this manuscript's Introduction is not decorative. The Flexner Report (1910), the Carnegie-Rockefeller medical education consolidation, and the two-decade suppression of PMDD in a DSM appendix are documented historical events with direct consequences for the research gap this paper describes. Acknowledging them is not conspiratorial; it is accurate. The NIH Revitalization Act of 1993 was enacted in direct response to documented exclusion of women from clinical trials. The Howard et al. (2025) characterization of reproductive health neglect as arising from "historic gender bias in mental health research" appears in *World Psychiatry*. These are institutional characterizations from mainstream sources, not outlier critiques. They explain why, in 2025, no nurse suicide investigation has ever asked where the decedent was in her menstrual cycle. That explanation does not accept the gap as legitimate; it identifies what produced it, which is the prerequisite for changing it.

The trans men and AFAB nonbinary section of this manuscript is the most evidence-limited, and is explicitly framed as such. Three distinct risk components are identified and evidenced separately rather than collapsed into a single additive estimate: elevated baseline transgender suicide risk (primarily attributable to minority stress), potential PMDD-equivalent hormonal vulnerability in those with retained ovarian function (hypothesis level, partially supported), and occupational amplification via shared healthcare worker stressors (plausible by analogy, not directly measured in trans men). The NCSBN gender identity data gap is a standalone policy finding requiring immediate correction.

The research agenda proposed in Section XIII is not aspirational. It is the minimum work required to confirm or refute the central thesis. Each study is methodologically feasible with existing tools. The coordination barrier, specifically the absence of multi-specialty and cross-disciplinary research infrastructure connecting occupational health, reproductive psychiatry, and neuroendocrinology in a single investigation, is the practical obstacle. That obstacle is remediable through NIOSH Total Worker Health program infrastructure, HRSA nursing workforce research programs, NIH Office of Research on Women's Health, and the administrative pathway created by the Lorna Breen Act's best-practices mandate. The evidence to justify action is assembled. The mechanisms to fund that action exist. What is absent is the institutional recognition that these two facts belong in the same sentence.

## **SECTION XIV: CONCLUSION**

The compound neurobiological deficit model described in this paper is not a theoretical construction assembled from speculative connections. It is built from documented mechanisms in peer-reviewed endocrinology, neuroendocrinology, psychiatry, and occupational health literature, applied to a workforce whose demographic characteristics,

occupational exposures, medication prevalence, and psychiatric burden make the convergence of these mechanisms not a rare clinical edge case but a predictable and common presentation.

An estimated 713,000 actively employed U.S. registered nurses currently meet diagnostic criteria for PTSD. The annual economic burden of that PTSD, calculated using the published composite per-person cost of \$19,630 from Davis and colleagues, is approximately \$14.0 billion. That figure does not include PMDD, which affects an estimated 93,000 to 248,000 additional members of the same workforce. It does not include the psychiatric consequences of perimenopausal transition in the largest demographic cohort of the nursing workforce, currently at median age 50 -- the midpoint of the highest-risk window for perimenopausal suicidal ideation per Usall and colleagues. It does not include the cascading patient safety costs of a workforce delivering care under these neurobiological conditions without surveillance, support, or institutional recognition of the risk.

The diagnostic system that would identify and address this harm does not currently function in any organized sense. PMDD is diagnosed years to decades after onset. Bipolar or borderline disorder is assigned to patients whose presenting symptoms are trauma related with PMDD with cycle-phase timing that was never evaluated. Perimenopausal suicidal crisis is managed in emergency departments without hormonal evaluation, without cycle-phase history, and without clinical frameworks that connect the presenting crisis to the hormonal biology driving it. Nurses exit the workforce at the peak of perimenopausal neurobiological vulnerability, at the moment of occupational identity loss, without any institutional mechanism that recognizes this convergence as a medical event requiring a medical response.

The institutional framework that would prevent this harm does not exist at the regulatory level. No federal standard mandates psychiatric surveillance for nurses. No CMS Condition of Participation connects nursing workforce psychiatric burden to patient safety compliance in an enforceable way. No occupational health intake instrument in standard use asks about menstrual cycle phase, hormonal contraceptive or statin use, or perimenopausal status. The CMDS suppression architecture ensures that nurses who are deteriorating do not disclose it, and that institutions producing harm do not record it in ways that would trigger external accountability.

None of this is inevitable. Every element of the harm documented here is addressable with existing clinical tools, validated instruments, regulatory frameworks, and legislative vehicles that are currently available. The DRSP and PSST can be implemented in occupational health settings today. The COMPASS can be developed and validated within an existing reproductive psychiatry research infrastructure. The CRF escalation model can be applied to nursing workforce deterioration within any health system that chooses to read its workforce health data as a patient safety metric. The CMDS accountability rubric can be used by governing boards to audit institutional suppression architecture. The PRRAA provides the legislative framework for making these tools mandatory rather than optional.

What is required is the institutional and regulatory will to use these tools, and the recognition that the workforce delivering patient care is itself a patient safety system that, when it fails, produces patient harm. The \$14.0 billion figure in the economic burden section of this paper is the cost of the system as it currently operates. The cost of the system as it should operate -- with diagnostic accuracy, occupational surveillance, hormonal-context-aware mental health support, and institutional accountability -- is substantially lower. The human cost of the current system, measured not in dollars but in nurses who died by suicide during the perimenopausal exit from a profession, is not quantifiable in these pages. It is, however, attributable. Attribution is the beginning of accountability.

The silence referenced in this paper's title is the institutional silence that allows this harm to continue without counting, without attribution, and without intervention. This analysis proposes to end that silence with the most durable instrument available: peer-reviewed evidence, stated methodology, and a call to regulatory and clinical action that is grounded in both.

### **A Note on Methodology: What This Analysis Is and Is Not**

This paper is a structured literature synthesis combined with an applied economic burden calculation and a framework-based institutional analysis. It is not a systematic review meeting PRISMA or Cochrane criteria: no pre-registered search protocol was implemented, no formal quality assessment of individual studies was performed, and no meta-analytic pooling was conducted. The analysis is transparent about this methodological classification and presents its contribution accordingly.

What this analysis offers that a systematic review of individual studies cannot is integrative architecture: the synthesis of independently documented mechanisms into a compound model that no single study could establish, and the application of validated accountability frameworks to that compound model in a way that produces actionable institutional and regulatory recommendations. This is the analytic work that the evidence base for nursing occupational psychiatric harm currently lacks. The individual mechanisms are documented. The diagnostic failure regime is documented. The economic burden methodology is validated. The institutional accountability frameworks are published. The integration of these elements into a single coherent analysis -- with stated assumptions, cited derivations, and explicit identification of unknowns -- is the original contribution of this paper.

Future work should include: prospective validation of the compound deficit model through biological sampling studies in the nursing workforce; randomized or quasi-experimental evaluation of institutional accountability interventions based on the CMDS and CRF frameworks; and formal systematic reviews of PMDD prevalence and diagnostic accuracy in occupational health populations. The analytic architecture presented here provides the conceptual scaffolding for that future work. The eight research questions in Section XIII translate that scaffolding into study designs. The twelve recommendations in Section XII translate the evidence base into actionable institutional and regulatory responses that do not require waiting for additional research to begin.

The burden of proof for inaction in occupational health is different from the burden of proof in clinical research. In clinical research, we require strong evidence before adopting an intervention. In occupational health, the standard is: when a plausible mechanism exists, a large workforce is exposed, and measurable harm is documented, the burden falls on those who choose not to intervene to demonstrate that the cost of non-intervention is acceptable. By any measure applied in this paper -- economic, clinical, or ethical -- the cost of non-intervention in the nursing occupational psychiatric crisis is not acceptable. The evidence presented here is sufficient to justify action. The action is specified. The delay is the choice.

This paper is submitted as a contribution to the literature at a specific historical moment: the U.S. nursing workforce is at median age 50, approaching the most concentrated period of perimenopausal transition it has ever collectively experienced; 39.9% of that workforce intends to leave within 5 years; the neurobiological conditions for psychiatric crisis are fully assembled in a large and quantifiable subset of actively employed nurses; and the institutional and regulatory infrastructure to detect and respond to that crisis does not exist. The coincidence of these conditions is not permanent. The median age of the workforce will change. The perimenopausal window will pass. The opportunity to intervene before the preventable deaths that statistical certainty indicates will occur in this demographic window -- is bounded in time. This paper is written in that window, with the intention of reducing the number of nurses who leave it by suicide.

Disclosure: The Continuity Risk Framework (CRF), Clinical Moral Disengagement Scaffolding (CMDs), Comprehensive Occupational Violence and Extraction Framework (COVE-F), and Patient Rescue Readiness and Accountability Act (PRRAA) are frameworks and model legislation authored by Jennifer Torrez and published through PULSE Advisory Group. The COMPASS is proposed model work authored by Jennifer Torrez. No external funding was received for this analysis. The author has no financial conflicts of interest with respect to any pharmaceutical products, laboratory tests, or medical devices referenced in this paper. The frameworks cited are published under open-access terms at Zenodo and are available for academic and clinical use with attribution.

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The author may be contacted for peer review correspondence, collaborative research inquiries, and policy consultation. Requests for the COMPASS validation protocol, the CMDs Leadership Accountability Rubric, or the CRF nine-stage deterioration assessment tool should be directed to [jen@prismqd.ai](mailto:jen@prismqd.ai)

## **SECTION XV: THE SUBSTRATE-DEFICIT SPINE APPLIED TO THE INPATIENT POPULATION — EVIDENCE-BASED PRACTICE IMPLICATIONS, SURVEILLANCE GAPS BY ADMISSION TIER, AND GLYCEMIC REGULATION IN ESTROGEN-DEFICIENT PATIENTS**

### **Overview and Analytic Rationale**

This paper has documented a compound neurobiological deficit model producing measurable harm in the nurse workforce. The mechanisms are not exclusive to clinicians. The same substrate-deficit architecture — estrogen deficiency, cholesterol substrate compression, HPA dysregulation, neurosteroid synthesis impairment — operates in patients admitted to acute care settings. What changes is the care environment: the nurse carries this deficit while delivering care to others; the patient carries it while depending on care from others. The failure geometry that makes the nurse invisible in occupational health frameworks makes the same patient invisible in standard diagnostic and monitoring frameworks.

This section extends the substrate-deficit spine from workforce harm to bedside harm. It addresses three questions:

1. How does evidence-based practice (EBP) for conditions involving hormonal substrate deficiency operate, or fail to operate, across inpatient admission tiers?
2. What specific surveillance gaps emerge when an estrogen-deficient, substrate-compromised patient is admitted below ICU level?
3. What are the glycemic implications of estrogen deficiency for diabetic and post-surgical patients on tight glycemic control protocols, and how does the current evidence base translate to nursing plan of care and medical management?

**EVIDENCE STATUS:** The clinical mechanisms described in this section are supported by peer-reviewed literature in endocrinology, cardiac surgery outcomes, and glycemic physiology. The bedside care implications and nursing plan-of-care recommendations are derived from those mechanisms and from established EBP principles; they are framed as clinical reasoning to be evaluated by treating clinicians, not as institutional protocols or individualized treatment directives.

### **Section XVa: EBP and Admission-Tier Mismatch in the Estrogen-Deficient Patient**

Evidence-based practice standards for postoperative and medically complex patients assume a monitoring substrate proportional to clinical risk. The core EBP principle is: documented risk drives surveillance intensity. Where risk is underdocumented, surveillance intensity defaults to the acuity-assigned tier, and the gap between documented and actual risk becomes a failure-to-rescue geometry.

The estrogen-deficient inpatient — whether post-menopausal, perimenopausal, or in acute estrogen withdrawal — carries a documented substrate deficit with measurable consequences for wound healing, autonomic stability, immune function, and glycemic



regulation. Current EBP frameworks do not include hormonal substrate status as a standard risk stratification input for medical-surgical or step-down patients. Hormonal status is assessed in reproductive medicine, not in standard acute care admission protocols.

**The practical consequence of this gap is tiered and predictable.**

ICU tier: The ICU patient receives continuous telemetry, q1 to q2 hour nursing assessment, a low threshold for escalation, and multi-system monitoring including serial glucose, hemodynamic parameters, and wound assessment at defined intervals. An estrogen-deficient patient in the ICU is observed with sufficient granularity that substrate-deficit-mediated deterioration — delayed wound healing, glucose instability, autonomic dysregulation — has a reasonable chance of being detected before it crosses into a crisis event.

Step-down and medical-surgical tiers: The step-down patient receives q4-hour vitals and a once-a-shift nursing assessment at the institutional standard. The medical-surgical patient receives equivalent monitoring at a longer interval in many facilities. A substrate-deficit-mediated deterioration that would be detected in the ICU environment accumulates silently at these tiers, surfacing as a rapid-response event, an unexpected readmission, or a wound complication attributed in documentation to the acute presentation rather than to the unassessed hormonal substrate.

This is the acuity corruption mechanism described in Section XIb operating on the patient instead of the nurse. The patient's true clinical complexity exceeds the documented acuity. The monitoring tier assigned underestimates the surveillance required. The result is a predictable failure geometry, not a random adverse event.

EBP implication: The admission-tier decision for estrogen-deficient patients with complex medical or surgical presentations should include hormonal substrate status as a risk stratification input. This does not require new technology. It requires including estrogen status, progesterone level, and thyroid function in the pre-admission or admission-day laboratory panel and applying clinical judgment about whether the substrate deficit changes the surveillance requirement for that patient's condition.

## **Section XVb: ICU-Level Considerations — Monitoring Architecture for the Substrate-Compromised Patient**

When a patient with known or suspected estrogen deficiency does reach ICU-level care, the monitoring framework should explicitly include substrate-deficit-aware surveillance domains that are currently absent from standard ICU documentation.

Hormonal context on admission: The ICU admission assessment should include estrogen status, cycle phase or menopausal status, progesterone or neurosteroid substrate indicators, and thyroid function (free T3, free T4, TSH with TPO-Ab if autoimmune thyroiditis is suspected). These are standard laboratory tests. Their absence from ICU admission documentation means that clinical deterioration attributable to substrate deficit will be classified under the acute diagnosis, perpetuating the diagnostic void.

Wound surveillance in estrogen-deficient post-surgical patients: Estrogen deficiency impairs endothelial nitric-oxide signaling, reduces fibroblast activity, and slows epithelial repair. In post-cardiac-surgery patients specifically — post-CABG, post-valve, post-thoracic vascular — sternal and saphenous graft-site healing occurs against this substrate background. ICU nursing assessment of incisions and surgical sites should document healing trajectory with explicit attention to estrogen status as a context variable. A wound that appears adequate on post-operative day three but is healing slower than expected is not an independent clinical finding in an estrogen-deficient patient; it is a substrate-deficit expression requiring clinical integration.

Autonomic instability framing: Post-operative delirium workup in estrogen-deficient patients should include hormonal context in the differential. Estrogen withdrawal produces measurable changes in noradrenergic signaling, serotonergic tone, and GABAergic function — the same neurotransmitter systems implicated in delirium. The standard delirium workup (age, anesthesia type, opioid use, electrolytes, sleep disruption) does not include hormonal status. Defaulting to age and anesthesia as the primary explanatory variables in a perimenopausal or surgically menopausal patient with post-operative agitation misses a potentially addressable hormonal contributor.

ICU nursing plan of care: ICU nursing assessments should include a standard entry for hormonal status in the systems review for female and AFAB patients aged 40 and older. This is a documentation standard change, not a clinical protocol change. The clinical consequences of the documentation becoming standard — endocrine consult when indicated, hormonal context flagged in surgical handoffs, wound surveillance elevated when substrate deficit is documented — are significant.

### **Section XVc: Non-ICU Trajectory — The Failure Geometry of Under-Surveilled Substrate Deficit**

The non-ICU patient with estrogen deficiency admitted to a medical-surgical or step-down unit follows a predictable trajectory under current standard practice. The trajectory has four phases.

***Phase 1: Adequate-appearing presentation. On admission, the patient meets criteria for the assigned tier. Vital signs are stable. The acute condition — post-surgical recovery, medical diagnosis, procedural care — appears managed. There is no apparent clinical urgency beyond the acute presentation. Hormonal status is not assessed. The substrate deficit is present but not visible at the monitoring density of the assigned tier.***

***Phase 2: Accumulation below the detection threshold. Over 24 to 72 hours, substrate-deficit-mediated processes accumulate: healing progresses more slowly than expected; glucose regulation is less stable than the care team anticipates; autonomic tone shows subtle irregularities that fall below the threshold for the nursing assessment interval to capture. Each individual finding, assessed at q4 or q8 hours, is within the range of acceptable variation for the acute condition. The aggregate trajectory is not assessed because the monitoring interval does not support trajectory assessment.***

***Phase 3: Threshold crossing. A threshold event — wound dehiscence, glucose crisis, arrhythmia, altered mental status — brings the patient to medical attention as an acute event. The event is documented as a complication of the acute condition. The substrate context is not part of the documented clinical reasoning because it was never assessed.***

**Phase 4: Attribution failure. The adverse event is attributed to the acute diagnosis, patient comorbidities, or individual physiologic variation. The hormonal substrate deficit that contributed to the trajectory is absent from the record. The readmission, if it occurs, carries the same diagnostic attribution. The pattern is not visible in quality metrics because the substrate deficit was never documented as a variable.**

This is the same failure-to-rescue geometry that characterizes the nurse occupational harm described in the main body of this paper: the causal factor is present, measurable, and undocumented, and the outcome is attributed to the surface-level presentation.

Nursing plan of care implication — non-ICU setting: Four specific nursing care changes at the bedside are supported by this analysis and require no new technology or institutional infrastructure.

1. Capture estrogen and menopausal status in the nursing admission assessment for female and AFAB patients aged 40 and older, explicitly, as a field distinct from last menstrual period checkbox documentation. Menstrual period date alone does not communicate menopausal status, current HRT use, or surgical menopause history.
2. For estrogen-deficient post-surgical patients on medical-surgical tiers, treat wound assessment frequency and documentation detail as a higher-acuity task than the standing institutional protocol assigns. The nurse who recognizes that the documented acuity understates the substrate risk and adjusts her surveillance frequency accordingly is practicing at the appropriate level of clinical reasoning. Document the rationale for increased surveillance frequency.
3. Watch for affective and autonomic instability in the estrogen-deficient or acutely estrogen-withdrawn patient as clinical signs requiring assessment, not behavioral events requiring management. Post-operative irritability, sleep disruption, and cognitive change in a perimenopausal patient are not inevitably behavioral; they may reflect hormonal substrate change that warrants endocrine clinical inquiry. Flag and document.
4. Elevate glycemic surveillance frequency in estrogen-deficient patients on tight glycemic control protocols, particularly in the immediate post-surgical period. The rationale is detailed in Section XVd below.

## **Section XVd: Estrogen, Glycemic Regulation, and the Implications for DM2 Patients and Tight Glycemic Control in Cardiac Surgery**

The relationship between estrogen and glucose metabolism is mechanistically established and clinically consequential. Estrogen functions as a direct regulator of insulin sensitivity through multiple pathways: estrogen receptor beta (ERbeta) signaling in pancreatic beta cells supports insulin secretion; estrogen receptor alpha (ERalpha) signaling in skeletal

muscle and adipose tissue modulates glucose uptake and insulin sensitivity; and estrogen's anti-inflammatory effects reduce cytokine-driven insulin resistance in peripheral tissues. As estrogen declines in perimenopause and following surgical menopause, these regulatory functions are reduced, and glucose metabolism becomes progressively less stable.

The clinical expression in the non-diabetic perimenopausal patient includes: increased post-meal glucose excursions, reduced first-phase insulin response, and elevated fasting glucose that may not yet meet diagnostic criteria for type 2 diabetes but represents measurable insulin resistance. In the patient who already carries a type 2 diabetes diagnosis, estrogen deficiency compounds existing insulin resistance through the same mechanisms, reducing the effectiveness of standard glycemic management and making tight glycemic control protocols less predictable in their response.

### **Implications For Cabg And Cardiac Surgical Patients On Tight Glycemic Control**

The cardiac surgery literature has established that hyperglycemia in the perioperative period is independently associated with increased sternal wound infection, mediastinitis, atrial fibrillation, and mortality. Tight glycemic control protocols — typically targeting glucose 140 to 180 mg/dL in the post-surgical ICU — were developed to reduce these outcomes. The majority of the trials establishing these protocols did not stratify by estrogen status. For estrogen-deficient patients on tight glycemic control following cardiac surgery, the following clinical considerations apply and are currently absent from standard post-cardiac surgical nursing protocols.

Glycemic variability is greater in estrogen-deficient patients. Estrogen-deficient physiology produces wider glucose excursions in response to the same clinical inputs — surgical stress response, corticosteroid exposure, nutritional support transitions, catecholamine infusions — compared to estrogen-sufficient physiology. A tight glycemic control protocol calibrated to average post-cardiac-surgery glucose response will underperform in estrogen-deficient patients. More frequent glucose checks, or a narrower initial target window, may be warranted until the individual patient's response pattern is established.

Corticosteroids and HPA dysregulation compound estrogen-deficient glucose instability. Post-cardiac-surgical patients frequently receive corticosteroids for inflammatory response management. In an estrogen-deficient patient with pre-existing HPA dysregulation, exogenous corticosteroids produce a more pronounced and prolonged hyperglycemic response. The cortisol-driven insulin resistance of surgical stress superimposed on estrogen-deficient baseline insulin resistance creates a compound hyperglycemia mechanism. Standard sliding-scale insulin protocols may be inadequate; earlier transition to continuous insulin infusion titration may be required.

Statin use modifies both neurosteroid substrate and glycemic response. Statins are independently associated with a modest increase in new-onset diabetes risk and with impaired glycemic control in existing diabetics, through mechanisms including reduced mitochondrial coenzyme Q10 availability affecting insulin secretory capacity, and potential direct effects on pancreatic beta-cell function. In the estrogen-deficient post-cardiac-surgery patient on a statin, the glycemic management challenge represents at

least three compounding mechanisms: estrogen-deficient insulin resistance, surgical stress hyperglycemia, and statin-associated glycemic impairment.

### **Medical Plan Of Care Implications**

1. Endocrine context — specifically estrogen status, menopausal status, and current HRT — should appear in the post-cardiac-surgery problem list and be reviewed in the context of glycemic management planning. This is the single documentation change with the highest downstream leverage: endocrine status visible in the problem list prompts consult and calibrated management rather than defaulting to standard protocol.
2. For estrogen-deficient post-cardiac-surgery patients with pre-existing DM2 or intraoperative hyperglycemia, consider earlier endocrine consultation for glycemic management rather than defaulting to nursing-administered sliding-scale protocol alone.
3. Statin type selection is not glycemically neutral in this population. Lipophilic statins (simvastatin, atorvastatin) carry greater glycemic impairment signal compared to hydrophilic statins (rosuvastatin, pravastatin). In a high-risk estrogen-deficient post-cardiac-surgery DM2 patient, statin type review is a tractable intervention within the cardiac team's purview.
4. Progesterone and bioidentical estrogen, when used as part of a menopausal hormone therapy regimen, have independent glycemic effects that should be considered in post-surgical glycemic management planning. Bioidentical progesterone has a more favorable metabolic profile than synthetic progestins; transdermal estradiol avoids first-pass hepatic metabolism and its associated glycemic effects.

### **Nursing Plan Of Care — Glycemic Specifics For Estrogen-Deficient Patients**

Post-CABG tight glycemic control, patient estrogen-deficient: Document estrogen status on care plan; flag for endocrine if glucose variance exceeds protocol target range more than twice within 8 hours. DM2 patient on insulin, post-surgical, perimenopausal: Assess cycle phase or menopausal status; note whether patient is on HRT and what type; communicate to prescriber if HRT was recently discontinued. Post-op patient on corticosteroids, estrogen-deficient: Anticipate prolonged hyperglycemic response; notify prescriber at first evidence of sustained glucose above protocol target rather than waiting for second-tier escalation threshold. Step-down patient, post-cardiac-surgery, estrogen-deficient DM2 on statin: Consider advocating for higher-frequency glucose checks based on documented substrate deficit; document rationale in nursing notes. Patient with unrecognized perimenopause, presenting with glucose instability not explained by current DM2 management: Include menopausal status inquiry in nursing assessment; flag for primary team if cycle changes or vasomotor symptoms are concurrent.

### **Section XVe: The Parallel Structure — Workforce and Patient Harm Sharing a Substrate-Deficit Spine**

The argument advanced throughout this paper is that the nursing workforce carries a compound substrate deficit that is institutionally invisible, diagnostically uncaptured, and

systematically producing physical and psychiatric harm. The argument in this section is its mirror: patients admitted to acute care settings carry equivalent substrate deficits that are institutionally invisible for the same reasons — no documentation standard, no surveillance architecture, no clinical training to recognize hormonal substrate status as a risk variable for non-reproductive medical conditions.

The structural cause is identical in both cases: clinical training and institutional frameworks that treat hormonal status as relevant only in reproductive contexts. A perimenopausal patient admitted for CABG is not a reproductive patient; she is a cardiac patient. The institutional and educational systems that trained every clinician who will touch her care therefore have no mechanism for incorporating her perimenopausal estrogen deficiency into the cardiac surgical risk assessment, the post-operative monitoring protocol, or the glycemic management plan.

This is not a failure of individual clinicians. It is a failure of the frameworks within which clinicians operate — the same framework failure this paper documents for the nursing workforce. The intervention architecture is also parallel: documentation standards that capture hormonal status as a clinical variable; surveillance protocols calibrated to substrate-deficit risk rather than only to acute diagnosis; and training in the neurobiological and metabolic implications of hormonal substrate deficiency across clinical specialties, not only in reproductive medicine.

The substrate-deficit spine connects workforce harm and patient harm through a shared mechanism: when the hormonal and neurosteroid substrate that supports healing, metabolic stability, autonomic resilience, and psychiatric function is depleted — whether in the nurse delivering care or the patient receiving it — the consequences are predictable, measurable, and currently untracked in institutional quality systems.

Naming this connection is the analytic contribution of this section. The clinical and policy interventions it implies extend the accountability framework of this paper beyond the workforce into the patient population for whom that workforce is responsible. The economic consequences of unaddressed substrate deficit in the inpatient population — prolonged surgical recovery, increased readmissions, suboptimal glycemic control, wound complication costs, increased delirium incidence — represent a parallel economic burden to the workforce burden quantified in Section VII. That burden has not been calculated. This section proposes the conceptual framework for calculating it, and identifies it as a research priority for the health economics literature.

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