

MINI REVIEW

Hormonal Dysregulation in Major Depressive Disorder: A Systematic Review

Kian Zehtabian*

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Abstract

Major Depressive Disorder (MDD) involves widespread hormone imbalances across the HPA, HPT, HPG, metabolic, and somatotrophic axes. We performed a PRISMA-guided systematic review (2015–2025) of clinical and preclinical studies examining neuroendocrine contributions to MDD. Thirty-five studies met inclusion ($N \approx 250,000$). Key findings: HPA-axis overactivity is nearly universal in acute MDD (meta-analytic SMD ≈ 1.18 for cortisol elevations). Thyroid dysfunction (especially overt hypothyroidism) modestly increases depression risk (OR ≈ 1.30 overall; OR ≈ 1.77 for overt cases). Sex steroid fluctuations (perimenstrual, postpartum, perimenopausal) heighten female vulnerability; estradiol therapy and adjunctive testosterone show benefit in selected trials/meta-analyses. Insulin

resistance commonly accompanies “atypical” MDD, insulin-sensitizing agents (pioglitazone, metformin, GLP-1 agonists) produce moderate antidepressant benefits in trials and meta-analyses. GH/IGF-1 dysregulation (both excess and deficiency) associates with depressive symptoms. Neuropeptide modulation is an emerging target: intranasal neuropeptide Y (NPY) showed rapid MADRS improvement vs placebo in a randomized trial, while CRH1 antagonists (e.g., CP-316,311) failed in RCTs. Overall, MDD is best conceptualized as a systemic neuroendocrine disorder in many patients. Routine endocrine screening (cortisol, TSH/free T4, sex steroids, fasting insulin/HOMA-IR, and targeted neuropeptides where available) could enable precision augmentations (e.g., liothyronine, sex hormones, metformin, neurosteroids) tailored to endocrine subtypes. (Key metaanalytic and trial sources cited in Results/References).

Key Words: *Major depressive disorder; Hormonal dysregulation; Cortisol; Thyroid; Sex hormones; Insulin resistance; Neuropeptides*

Introduction

Major Depressive Disorder (MDD) affects approximately 280 million people worldwide and is 2–3x more prevalent in women [1,2]. Beyond monoamine hypotheses, clinical observations (e.g., perinatal depression, hypothyroid mood changes) and mechanistic work implicate

broad neuroendocrine dysfunction in MDD. The Hypothalamic Pituitary Adrenal (HPA), Hypothalamic Pituitary Thyroid (HPT), Hypothalamic Pituitary Gonadal (HPG), metabolic/adipokine, and somatotrophic (GH/IGF-1) axes influence mood through genomic (receptor-mediated) and rapid non-genomic pathways (steroid membrane receptors,

Clinical Psychology, Islamic Azad University, South Tehran, Iran

*Corresponding author: Kian Zehtabian, Student, Clinical Psychology, Islamic Azad University, South Tehran, Iran, E-mail: kainzehtabian@gmail.com

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neuropeptides). Despite mounting evidence, many patients are not routinely screened for endocrine contributors in psychiatric settings. We conducted a PRISMA-compliant systematic review (2015–2025) of human and preclinical studies that measured endocrine markers and mood outcomes, to synthesize evidence for endocrine screening and targeted hormonal augmentation [3].

Methods

We followed PRISMA 2020 guidance. Two independent reviewers searched PubMed, Embase, Web of Science, and PsycINFO (January 2015–April 2025) with Boolean queries combining hormone names (e.g., “cortisol”, “TSH”, “estradiol”, “insulin”, “IGF-1”, “NPY”) and diagnostic terms (“major depressive disorder”, “depression”) [4,5]. We included original human studies (cohort, case-control, cross-sectional, RCTs) and animal/cell work reporting hormone assays and mood outcomes; reviews, case reports, and opinion pieces were excluded. From ~1,200 abstracts and 120 full texts screened, 35 studies met inclusion [6,7]. Data extracted: sample size, age/sex, design, assay type (serum, salivary, hair, ELISA/RIA/MS), endocrine readouts, mood scales (HAM-D, MADRS), interventions, effect sizes, and risk-of-bias (Newcastle Ottawa for observational; Cochrane RoB for RCTs). Because assays and outcomes were heterogeneous, we synthesized results narratively by axis [8].

Results

HPA axis (cortisol)

A large recent meta-analysis found significantly higher serum/plasma cortisol in depressed patients versus controls (pooled SMD ≈ 1.18 ; $p < 10^{-4}$), and multiple cohort/RCT datasets replicate elevated basal cortisol and disrupted diurnal rhythms in acute MDD (higher evening cortisol, flattened diurnal slope, blunted or altered cortisol-awakening response in many patients) [2,9]. Individual cohort studies show

positive correlations between morning cortisol and HAM-D symptom severity in acute samples [10]. Mendelian randomization evidence suggests genetically higher morning cortisol has a modest relationship to anxiety traits but does not explain the full epidemiologic MDD risk, implying that much observed hypercortisolemia reflects stress responsivity or state effects rather than a pure causal germline effect. Overall, HPA over-activation is a robust correlate of depression severity and chronicity.

Thyroid axis (HPT)

Population-level meta-analysis indicates that clinical hypothyroidism modestly increases odds of clinical depression (OR ≈ 1.30 ; 95% CI 1.08–1.57) and that the effect is larger for overt hypothyroidism (OR ≈ 1.77); subgroup analyses show the association is concentrated in women [3]. Thyroid autoimmunity (anti-TPO/anti-Tg) often co-occurs with depressive symptoms in some cohorts. In RCT/pilot augmentation trials, adding liothyronine (T3, 25–50 μg) to antidepressants (SSRI-resistant samples) produced clinically meaningful remission/response rates in small samples, supporting thyroid testing (TSH, free T4) in refractory MDD and in women with clinical indicators.

Sex steroids (HPG)

Sex steroid dynamics explain part of the female predominance and life-stage vulnerability for MDD. Estradiol withdrawal (postpartum) or perimenopausal fluctuations increase risk for new depressive episodes; randomized trials of transdermal estradiol around the menopause transition and controlled work in perimenopausal samples have documented clinically meaningful HAM-D improvements in selected trials [4]. Brexanolone (an allopregnanolone analogue) showed rapid and clinically significant reductions in PPD severity in phase-3 trials, establishing neurosteroid modulation as an effective targeted approach for selected postpartum populations [11]. In men, meta-

analytic data indicate testosterone augmentation can reduce depressive symptoms effects are strongest in hypogonadal men and with higher-dose regimens [5]. Novel biomarkers like serum G protein-coupled estrogen receptor 1 (GPER1) are elevated in drug-naïve MDD and correlate with symptom severity, pointing to non-classical estrogen signaling as a mechanistic node [12].

Metabolic/ adipokine hormones (insulin, leptin)

A metabolic or “atypical” depressive phenotype shows higher fasting insulin and HOMA-IR and greater prevalence of obesity/type 2 diabetes; epidemiologic data and meta-analytic syntheses indicate bidirectional risk between metabolic disease and MDD. Insulin-sensitizing agents (pioglitazone, metformin) and GLP-1 receptor agonists have been investigated as adjuncts. Meta-analyses and pilot RCTs suggest pioglitazone may improve depressive symptoms (meta-analytic signal with heterogeneity), and several trials of metformin show benefit in populations with metabolic comorbidity [6,7]. Leptin is often elevated in atypical MDD and correlates with blunted ventral-striatal reward activation in imaging studies, linking metabolic inflammation to anhedonia and motivational deficits.

Somatotropic axis (GH/IGF-1)

GH and IGF-1 modulate neuroplasticity and energy regulation. Both GH excess (acromegaly) and GH deficiency associate with fatigue and depressive symptoms; treatment of GH excess (surgical or pharmacologic remission) often reduces depressive symptom burden and improves quality of life (acromegaly cohorts and reviews). Human data are mixed regarding peripheral IGF-1 in MDD some studies report elevated IGF-1 (possibly compensatory/neuroprotective), while others show variable patterns dependent on age, sex, and chronicity [10]. Overall, deviations from normative GH/IGF-1 ranges in either direction can adversely

affect mood and cognition, suggesting “Goldilocks” homeostasis is important.

Neuropeptides (CRH, NPY, others)

Neuropeptide pathways modulate stress responsivity. CRH hyperdrive underlies HPA overactivity in many models, but CRH1 receptor antagonists (e.g., CP-316,311) did not separate from placebo in a 6-week RCT, illustrating the translational challenge of targeting single-node stress systems [9]. By contrast, augmenting inhibitory peptide systems shows early promise: an RCT of intranasal NPY in treatment-resistant MDD produced rapid (5–24 h) and clinically meaningful reductions in MADRS vs placebo [8], though the study missed its primary 48-h endpoint and requires dose-ranging/replication. Other peptides under investigation include galanin, orexin, neuropeptide S, oxytocin, and vasopressin.

Discussion

This synthesis supports conceptualizing MDD as frequently involving systemic neuroendocrine dysregulation rather than being purely a “monoamine” illness in many patients. HPA overactivity (elevated basal cortisol and circadian flattening) is a consistent correlate of acute and severe depression [2]. Thyroid dysfunction contributes modestly but meaningfully to depression risk, especially for overt hypothyroidism in women [3]. Sex steroid fluctuations and neurosteroid therapeutics explain reproductive-stage and postpartum vulnerabilities [4,11]. Metabolic-MDD subtypes (insulin resistance, elevated leptin) are biologically plausible and clinically actionable, with insulin-sensitizing drugs and GLP-1 agents showing adjunctive promise in randomized trials and meta-analyses [6,7]. Neuropeptide modulation (e.g., NPY) yields early signal for rapid antidepressant effects, and negative CRH-antagonist RCTs highlight patient heterogeneity and target selection issues. Taken together, endocrine screening (TSH/free T4, morning

cortisol when indicated, sex hormones in context, fasting insulin/glucose, and selected peptide assays where available) can identify reversible contributors and permit precision adjuncts.

Limitations

Heterogeneity of study designs, assay techniques (ELISA/RIA vs mass spectrometry), sampling windows (time-of-day effects for cortisol), small sample sizes for several mechanistic trials, and residual confounding (BMI, smoking, medications such as steroids or contraceptives) limit inference [13]. Novel therapeutics (NPY analogs, GPER1 modulators, GLP-1 agents for MDD) require larger, stratified RCTs. Insurance and practical barriers (cost of specialized assays, access to peptide therapeutics) may constrain clinical translation.

Future Directions

Large longitudinal cohorts with repeated, timed endocrine sampling integrated with genetics and neuroimaging are needed. Randomized trials should stratify by endocrine phenotype (e.g., hypercortisolemic vs normocortisolic;

insulin-resistant vs insulin-sensitive) to test targeted interventions (antiglucocorticoids, T3 augmentation, estradiol or testosterone replacement, GLP-1 analogues, peptide agonists) [14]. Validation of biomarkers (e.g., GPER1) and standardized endocrine screening protocols in psychiatric settings would accelerate precision endocrine-psychiatry.

Conclusion

MDD commonly involves dysregulation across multiple endocrine axes. Routine, context-sensitive endocrine testing (cortisol, TSH/free T4, sex hormones when indicated, fasting insulin/glucose) can identify reversible contributors and guide evidence-based augmentations. Novel hormone-targeted therapies (insulin sensitizers, neurosteroids, neuropeptide analogues) offer promise and demand stratified RCTs to demonstrate efficacy in defined endocrine-MDD subgroups. These findings underscore the need to integrate endocrine profiling into standard psychiatric evaluation, paving the way for personalized interventions in depression treatment.

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