Buprenorphine and Interpersonal Dysregulation in Borderline Personality Disorder:

A Mechanistic, Stratified Observational Pilot

Background and Rationale

Borderline Personality Disorder (BPD) is associated with severe interpersonal instability, affective reactivity, and elevated suicide risk. While psychotherapy remains the cornerstone of treatment, there are currently no pharmacologic interventions approved specifically for BPD, and existing medications have limited impact on core interpersonal pathology.

Low-dose buprenorphine has demonstrated rapid clinical effects in several adjacent domains. Randomized and observational studies have reported reductions in severe suicidal ideation and benefits as an adjunct in treatment-resistant depression, particularly in opioid-naïve populations. In at least one trial of ultra-low-dose buprenorphine for suicidality, participants with BPD features showed a notably strong response relative to placebo, though this signal was not pursued as a primary focus (Yovell et al., 2016).

Buprenorphine is an opioid with unique pharmacological properties and is most commonly prescribed for the treatment of opioid use disorder (OUD). There is substantial clinical overlap between OUD and BPD. In one outpatient sample of patients initiating buprenorphine for opioid addiction, nearly 44% exceeded the cut-off for borderline personality features on self-report measures, underscoring the potential relevance of affective and interpersonal dysregulation in opioid treatment contexts (Sansone et al., 2008). This overlap complicates interpretation of buprenorphine's effects, as emotional and interpersonal changes observed during OUD treatment are often attributed solely to stabilization of substance use rather than to potential effects on underlying affective or interpersonal vulnerability.

Some authors have suggested that substance use in BPD may, in part, reflect attempts to modulate distressing internal states, and case-level reports in OUD treatment context have described patients expressing a preference to remain on low-dose buprenorphine maintenance due to subjective report of feeling "normal" (Nia, 2017). While such observations are not sufficient to establish mechanism or indication, they raise the possibility that buprenorphine's effects may extend beyond suppression of withdrawal or craving in a subset of patients.

Buprenorphine is also prescribed in non-addiction contexts, including chronic pain, where transdermal formulations are commonly used in opioid-naïve or minimally exposed patients. While these regimens are not designed to target psychiatric symptoms, they provide sustained μ-opioid receptor engagement without the peaks associated with full agonists. In parallel, case-

level evidence has suggested potential benefit of buprenorphine in individuals with BPD beyond traditional indications. In a published case report, buprenorphine/naloxone was initiated at 2 mg with the primary goal of reducing recurrent crisis-level care utilization, and the dose was subsequently escalated to 6 mg, at which point the patient achieved clinical stabilization. Although this intervention was not low-dose, it supports the plausibility that buprenorphine may influence core features of BPD rather than solely acute crisis symptoms (Hansen et al., 2022).

Together, these observations motivate further investigation into whether buprenorphine's effects on emotional and interpersonal functioning vary by dose, formulation, and prior opioid exposure, and whether lower, steady dosing regimens may produce distinct effects from higher-dose protocols.

Despite these converging observations, buprenorphine's effects have been studied primarily in the context of acute suicidality, depression, pain, or addiction. Its potential impact on interpersonal dysregulation, often considered a core and defining feature of BPD, has not been directly examined (Stanley & Siever, 2010).

Gap in Current Knowledge

Existing studies leave several clinically relevant questions unresolved:

- BPD-related findings have largely been treated as incidental rather than hypothesis-generating.
- Interpersonal dysregulation has not been a primary outcome in buprenorphine studies.
- Opioid exposure history (opioid-naïve vs exposed vs tolerant) has not been examined as a moderator of emotional or interpersonal response.
- As a result, clinicians lack guidance on which patients may benefit, which may not, and how to balance potential benefit against known risks.

This gap contributes to both underuse (missed opportunities for benefit) and understandable clinician reluctance in the absence of structured evidence.

Mechanistic Hypothesis

Attachment-related distress ("attachment cry") is closely linked to the endogenous opioid system, particularly μ-opioid signaling, which plays a central role in social bonding, separation distress, and the regulation of affiliative behavior (Panksepp et al., 1980; Stanley & Siever, 2010; Bandelow et al., 2010; Lanius et al., 2014). Disruptions in this system have been implicated in heightened sensitivity to interpersonal threat and loss.

Traditional opioids activate both μ and κ opioid receptors. While μ-opioid activation may attenuate attachment-related distress, κ-opioid activation is associated with dysphoria,

dissociation, and stress-related negative affect, potentially limiting the usefulness of full agonists for sustained regulation of interpersonal distress.

Buprenorphine is pharmacologically distinct, providing partial agonism at μ-opioid receptors alongside antagonism at κ-opioid receptors. This profile suggests a unique capacity to reduce attachment-related distress and interpersonal threat sensitivity while avoiding κ-mediated dysphoria and aversive affective states. Such effects may be particularly relevant to the interpersonal instability that characterizes BPD.

Substance use patterns observed in BPD further support the relevance of this system. Alcohol, the most commonly used substance in BPD, increases endogenous opioid activity and modulates neuropeptides implicated in social bonding and stress regulation. This convergence raises the possibility that substances engaging the endogenous opioid system may partially alleviate interpersonal distress in BPD, albeit through mechanisms that are nonspecific or maladaptive.

Importantly, the magnitude and dosing requirements of buprenorphine's interpersonal effects may be influenced by prior opioid exposure. Individuals with prior opioid use or tolerance may require higher doses to achieve comparable μ-opioid engagement, potentially explaining why some case reports and clinical observations describe benefit at doses exceeding those typically considered "low-dose."

Hypothesis:
Buprenorphine is associated with reductions in interpersonal dysregulation in individuals with BPD or high BPD trait burden. The dose required to achieve this effect, as well as the timing and magnitude of response, is moderated by prior opioid exposure, such that opioid-naïve individuals may experience benefit at lower, steady doses, whereas opioid-exposed or opioid-tolerant individuals may require higher doses to achieve comparable clinical effects.

Study Objective and Research Questions

Primary Objective

To characterize changes in interpersonal dysregulation following initiation of buprenorphine and to examine whether the timing, magnitude, and dose associated with these changes are moderated by prior opioid exposure.

Primary Research Question

Among individuals initiating buprenorphine for existing clinical indications, does interpersonal dysregulation change following initiation, and do the timing, magnitude, or dose required for observed change differ by opioid exposure history?

Secondary Questions

- Are changes in interpersonal dysregulation detectable within hours to days of initiation?
- How do interpersonal changes relate to affective instability and suicidal ideation?
- Are observed effects sustained over short- to medium-term follow-up?

Study Design

Design:
Prospective, observational, stratified cohort study.

Key features:

- No randomization or alteration of clinical care
- Participants are prescribed buprenorphine for standard clinical indications independent of study participation
- Emphasis on temporal dynamics, dose–response patterns, and moderating variables, rather than confirmation of diagnostic-level efficacy

Stratification variables:

- Opioid exposure history (functionally opioid-naïve, previously exposed without current tolerance, opioid-tolerant)
- Baseline interpersonal dysregulation severity
- Formal BPD diagnosis vs high borderline trait burden

Population and Setting

Inclusion Criteria:

- Adults initiating buprenorphine as part of routine clinical care for an existing indication, including:
  - opioid use disorder
  - chronic pain
  - adjunctive treatment for severe suicidal ideation or treatment-resistant depression
- Initiation at a clinically determined dose intended for maintenance or stabilization (as opposed to acute high-dose induction)
- Presence of elevated interpersonal dysregulation or affective instability at baseline, assessed via validated self-report measures
- Ability to provide informed consent and complete repeated self-report assessments

Prior opioid exposure history will be assessed at baseline and treated as a stratification variable rather than an inclusion or exclusion criterion.

Exclusion Criteria:

- Initiation of buprenorphine as part of acute high-dose induction for opioid use disorder
- Acute intoxication or unmanaged withdrawal at the time of baseline assessment
- Medical or psychiatric conditions preventing reliable self-report or longitudinal participation

Measures and Outcomes

Primary Outcome: Interpersonal Dysregulation

Interpersonal dysregulation will be assessed using a two-tier measurement approach designed to capture both rapid, state-level changes and more stable week-to-week patterns.

1. **Rapid state measures (early phase)**
   Brief repeated self-report items (ecological momentary assessment) assessing attachment threat sensitivity, perceived rejection or abandonment, urges for reassurance or contact, intensity of interpersonal distress or conflict, and time required to recover following interpersonal stressors.
2. **Validated interpersonal functioning scale (weekly)**
   One established, validated measure of interpersonal functioning administered on a weekly basis to assess broader patterns of interpersonal difficulty over time.

Secondary Outcomes

- **Affective instability:**
  Weekly Borderline Symptom List (BSL-23) as a recognized and validated anchor measure of BPD symptom severity (Bohus et al., 2009).
- **Suicidal ideation:**
  Assessed using a validated suicidal ideation measure aligned with prior ultra-low-dose buprenorphine trials such as the Beck Scale for Suicide Ideation (Beck et al., 1979), or a licensing-feasible alternative such as the Columbia-Suicide Severity Rating Scale (C-SSRS) (Posner et al., 2011).
- **Depression and anxiety symptoms:**
  Assessed using brief, validated self-report measures (Patient Health Questionnaire-9 [PHQ-9] and Generalized Anxiety Disorder-7 [GAD-7]).
- **Functioning and quality of life:**
  Assessed using a brief, validated measure of functional impairment or quality of life, selected based on feasibility and study setting.

Exploratory Contextual Variables

- **Buprenorphine exposure characteristics:**
  Dose, formulation, route of administration, and changes in dosing over time.
- **Substance use patterns:**
  Self-reported substance use during the study period, including alcohol and non-prescribed substances, to support contextual interpretation of outcomes.

Timing and Data Collection

Expected onset of effects may differ by formulation, with sublingual administration producing more rapid perceptible changes than transdermal systems, which reach steady-state over several days. Given the gradual pharmacokinetics of transdermal buprenorphine, the first post-initiation assessment is scheduled at 24 hours, with additional early follow-up at 72 hours to capture initial stabilization. Same-day assessments are considered exploratory and formulation-dependent.

Baseline:

- Within 24 hours prior to first dose (ideally immediately pre-initiation)

Early Phase:

- Same-day post-dose (2–4 hours):
  For sublingual administration; exploratory for detecting rapid changes
- 24 hours post-initiation:
  First primary post-initiation assessment for all formulations
- 72 hours (day 3):
  Early stabilization assessment, particularly relevant for transdermal formulations

Short-Term Follow-Up:

- 1 week
- 2 weeks
- 4 weeks

Durability:

- 8 or 12 weeks (feasibility-dependent)

Same-day assessments are considered exploratory and formulation-dependent. Primary analyses will emphasize 24-hour and later timepoints, particularly for transdermal formulations.

Analysis Plan

- Within-person change in primary and secondary outcomes over time
- Comparison of change trajectories across opioid exposure strata
- Exploratory interaction analyses examining whether between baseline interpersonal dysregulation moderates response by opioid exposure history
- Emphasis on estimation of effect sizes, timing of change, and pattern characterization rather than hypothesis confirmation or diagnostic-level efficacy testing

This pilot is intended to assess feasibility, characterize signal shape and magnitude, and inform the design of future observational or controlled studies.

Ethical and Safety Considerations

- Observational only; no treatment assignment or alteration of clinical care
- No encouragement or initiation of off-label prescribing as part of the study
- Standard clinical monitoring and prescribing practices maintained by treating clinicians
- Explicit acknowledgment of addiction risk and the importance of careful patient selection and monitoring
- Clear separation between research data collection and clinical decision-making

Significance and Next Steps

This pilot aims to clarify a neglected but clinically meaningful domain of buprenorphine's effects by examining interpersonal dysregulation as a primary outcome and prior opioid exposure as a key moderating variable. By focusing on temporal dynamics and dose-response patterns rather than diagnostic-level efficacy, the study may help explain mixed clinical reports across populations and prescribing context.

Findings from this pilot would inform rational patient selection, risk stratification, and the design of future observational or controlled studies, including work aimed at earlier intervention or prevention in high-risk populations.

References

Stanley, B., & Siever, L. J., (2010). **The interpersonal dimension of borderline personality disorder: Toward a neuropeptide model.** *American Journal of Psychiatry.* https://doi.org/10.1176/appi.ajp.2009.09050744

Bandelow, B., Schmahl, C., Falkai, P., & Wedekind, D. (2010). **Borderline personality disorder: A dysregulation of the endogenous opioid system?** *Psychological Review, 117*(2), 623–636. https://doi.org/10.1037/a0018095

Yovell, Y., Bar, G., Mashiash, M., Baruch, Y., Briskman, I., Asherov, J., Lotan, A., Rigbi, A., & Panksepp, J. (2016). **Ultra-low-dose buprenorphine as a time-limited treatment for severe suicidal ideation: A randomized controlled trial.** *American Journal of Psychiatry.* https://doi.org/10.1176/appi.ajp.2015.15040535

Hansen B., Inch, K. M., & Kaschor, B. A. (2022). **The use of buprenorphine/naloxone to treat borderline personality disorder: A case report.** *Borderline Personality Disorder and Emotion Dysregulation.* https://doi.org/10.1186/s40479-022-00181-1

Panksepp, J., Herman, B. H., Vilberg, T., Bishop, P., & DeEskinazi, F. G. (1980). **Endogenous opioids and social behavior.** *Neuroscience & Biobehavioral Reviews, 4*(4), 473–487. https://doi.org/10.1016/0149-7634(80)90036-6

Lanius, U. F., Paulsen, S., & Corrigan, F. M. (Eds.). (2014). *Neurobiology and treatment of traumatic dissociation: Toward an embodied self.* Springer.

Nia, A. B. (2017). **Opioid addiction and borderline personality disorder.** *American Journal on Addictions.* https://doi.org/10.1111/ajad.12664

Sansone, R. A., Whitecar, P., & Wiederman, M. W. (2008). **The prevalence of borderline personality among buprenorphine patients.** *International Journal of Psychiatry in Medicine.* https://doi.org/10.2190/PM.38.2.h

Beck, A. T., Kovacs, M., & Weissman, A. (1979). **Assessment of suicidal intention: The Scale for Suicide Ideation.** *Journal of Consulting and Clinical Psychology, 47*(2), 343–352. https://doi.org/10.1037/0022-006X.47.2.343

Posner, K., Brown, G. K., Stanley, B., Brent, D. A., Yershova, K. V., Oquendo, M. A., Currier, G. W., Melvin, G. A., Greenhill, L., Shen, S., & Mann, J. J. (2011). **The Columbia–Suicide Severity Rating Scale: Initial validity and internal consistency findings from three multisite studies with adolescents and adults.** *American Journal of Psychiatry, 168*(12), 1266–1277. https://doi.org/10.1176/appi.ajp.2011.10111704

Bohus, M., Kleindienst, N., Limberger, M. F., Stieglitz, R. D., Domsalla, M., Chapman, A. L., Steil, R., Philipsen, A., & Wolf, M. (2009). **The short version of the Borderline Symptom List (BSL-23): Development and initial data on psychometric properties.** *Psychopathology, 42*(1), 32–39. https://doi.org/10.1159/000173701