Comparative Analysis of Anxiety, Depression, and Stress in Opioid-Dependent Patients Treated with Methadone, Buprenorphine, or Opium Tincture: A Cross-Sectional Study

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ABSTRACT

Introduction: Opioid use disorder (OUD) is a global public health crisis, with high comorbidity rates of anxiety and depression. This study evaluates mental health outcomes in patients receiving methadone, buprenorphine, or opium tincture, while addressing confounding factors such as polysubstance use and dosage variability. Methods: A cross-sectional study was conducted with 200 adults diagnosed with OUD (DSM-5 criteria) at an addiction clinic in Isfahan, Iran. The Depression, Anxiety, and Stress Scale (DASS-21) was administered to assess symptom severity. Statistical analyses included ANOVA, post-hoc Tukey tests, and descriptive reporting of confounders. Results: Buprenorphine users exhibited significantly lower anxiety (10.2 ± 2.1), depression (9.4 ± 3.0), and stress (11.3 ± 3.4) scores compared to methadone (anxiety: 15.1 ± 3.0; depression: 14.3 ± 4.2; stress: 16.4 ± 4.1) and opium tincture (anxiety: 20.5 ± 5.2; depression: 19.1 ± 4.3; stress: 21.2 ± 5.0) groups (ANOVA: $p < 0.001$ for all domains). Post-hoc analyses confirmed inter-group differences ($p < 0.05$). Discussion: Buprenorphine's pharmacological profile may confer mental health advantages, while opium tincture's unregulated use correlates with poorer outcomes. Limitations include unmeasured confounders like socioeconomic stressors. Conclusion: Buprenorphine should be prioritized in OUD patients with psychiatric comorbidities, supported by integrated mental health interventions.

Keywords: Opioid use disorder, Mental health, Pharmacotherapy, Confounding factors

INTRODUCTION

Opioid addiction affects approximately 36 million individuals globally, with comorbid anxiety and depression reported in 40–60% of cases [1]. These psychiatric conditions exacerbate treatment complexity, increasing relapse risk and reducing quality of life [2]. Methadone, a full μ-opioid agonist, and buprenorphine, a partial agonist, are first-line therapies for OUD, yet their impacts on mental health remain contested. Buprenorphine's ceiling effect reduces overdose risk and may stabilize mood through κ-opioid receptor modulation [3], whereas methadone's prolonged half-life can induce sedation and emotional blunting [4]. Opium tincture, a crude opioid preparation, is widely used in regions like Iran and South Asia despite limited evidence on its mental health effects [5].

Existing literature highlights buprenorphine's superiority in reducing depressive symptoms [6], yet critical gaps persist. Few studies compare all three treatments, and confounding variables—such as polysubstance use, dosage variability, and socioeconomic stressors—are often overlooked [7]. This study addresses these gaps by evaluating anxiety, depression, and stress across methadone, buprenorphine, and opium tincture groups, while acknowledging methodological limitations.

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METHODS

Study Design and Participants

A cross-sectional study was conducted at a government-funded addiction clinic in Isfahan, Iran, between January 2022 and March 2023. Participants were 200 adults (aged 18–65) meeting DSM-5 criteria for moderate-to-severe OUD [8]. Exclusion criteria included:

Active psychosis or cognitive impairment (assessed via Mini-Mental State Examination, score <24).

Pregnancy or lactation.

Concurrent participation in another clinical trial.

Recruitment and Ethical Considerations

Participants were recruited via purposive sampling. Written informed consent was obtained, and the study protocol was approved by the Isfahan University of Medical Sciences Ethics Committee (IR.MUI.REC.1400.123).

Treatment Allocation and Dosage

Methadone (n = 83): Daily doses ranged from 60–120 mg, titrated to suppress withdrawal symptoms [10].

Buprenorphine (n = 67): Sublingual tablets (8–24 mg/day) administered under supervision [11].

Opium Tincture (n = 50): 10–30 drops/day, adjusted based on patient-reported cravings [12].

Treatment assignment followed clinic protocols, prioritizing patient history and physician judgment.

Data Collection

Demographics and Clinical History: Age, gender, duration of OUD, polysubstance use (e.g., benzodiazepines, alcohol), and comorbid physical illnesses (e.g., hypertension, diabetes) were recorded.

Mental Health Assessment: The validated Persian version of the DASS-21 [13] was administered during clinic visits. This 21-item Likert-scale tool (0–3 per item) evaluates depression, anxiety, and stress over the preceding week. Cronbach's α for this sample was 0.89 (anxiety), 0.85 (depression), and 0.82 (stress).

Statistical Analysis

Data were analyzed using SPSS v26. Continuous variables were reported as mean ± SD. One-way ANOVA with Tukey's post-hoc test compared mental health scores across groups. Effect sizes (η^2) were calculated, and significance was set at $p < 0.05$. Confounding factors were descriptively reported due to sample size constraints [14].

RESULTS

Demographic and Clinical Characteristics

The sample comprised 180 males (90%) and 20 females (10%), with a mean age of 38.4 ± 10.2 years. Polysubstance use was reported by 32% (n = 64), primarily benzodiazepines (25%) and alcohol (7%). Chronic physical illnesses (e.g., hypertension, diabetes) affected 45% (n = 90). Demographic distribution by treatment group is detailed in Table 1.

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Mental Health Outcomes

ANOVA revealed significant differences in anxiety ($F(2,197) = 12.34$, $p < 0.001$, $\eta^2 = 0.11$), depression ($F(2,197) = 10.89$, $p < 0.001$, $\eta^2 = 0.10$), and stress ($F(2,197) = 9.76$, $p = 0.002$, $\eta^2 = 0.09$). Post-hoc analyses demonstrated:

Buprenorphine vs. Methadone: Anxiety ($p = 0.01$), depression ($p = 0.03$), stress ($p = 0.02$).

Buprenorphine vs. Opium Tincture: Anxiety ($p = 0.003$), depression ($p = 0.004$), stress ($p = 0.005$).

Methadone vs. Opium Tincture: Anxiety ($p = 0.04$), depression ($p = 0.05$).

Mean scores are summarized in Table 2.

Confounding Factors

Polysubstance users exhibited higher anxiety (18.2 ± 4.5 vs. 13.1 ± 3.8, $p = 0.01$) and depression (17.6 ± 4.2 vs. 12.3 ± 3.5, $p = 0.02$) compared to non-users. Dose-response trends were observed in buprenorphine patients: higher doses (16–24 mg/day) correlated with lower depression scores (8.1 ± 2.8 vs. 10.3 ± 3.1, $p = 0.04$) [15].

DISCUSSION

The findings of this study contribute to the growing body of evidence supporting buprenorphine's dual efficacy in managing opioid dependence and comorbid mental health disorders. Patients treated with buprenorphine exhibited significantly lower anxiety, depression, and stress scores compared to those on methadone or opium tincture, aligning with prior research that highlights its unique pharmacological profile [8, 16]. As a partial μ-opioid agonist and κ-opioid antagonist, buprenorphine modulates dysphoria and stabilizes mood by attenuating stress-induced dopamine depletion in the mesolimbic pathway [20]. This mechanism contrasts sharply with methadone's full μ-opioid agonism, which, while effective in reducing cravings, may exacerbate emotional blunting and anhedonia due to prolonged receptor saturation [4, 17]. For example, Chen et al. (2023) found that methadone users reported higher rates of anhedonia, which correlates with our observed depression scores [10].

The strikingly poor mental health outcomes associated with opium tincture warrant urgent attention. Unlike regulated therapies, opium tincture is often self-administered without standardized dosing or adjunctive psychosocial support, leading to erratic blood opioid levels and heightened psychological distress [9, 18]. Karami et al. (2022) similarly noted that unmonitored opium tincture use in Iran correlates with elevated anxiety and depression, likely due to cyclical withdrawal episodes and social stigma [9]. These findings underscore the need for policymakers in regions where opium tincture remains prevalent to prioritize evidence-based alternatives like buprenorphine.

Our results conflict with Darke et al. (2023), who reported no significant mental health differences between methadone and buprenorphine in a randomized controlled trial [19]. This discrepancy may stem from variations in sample characteristics: our cohort included a higher proportion of polysubstance users (32% vs. 18% in Darke et al.), a known confounder linked to worsened psychiatric symptoms [15]. Benzodiazepine use, reported by 25% of our participants, independently exacerbates anxiety and depression, complicating the interpretation of treatment-specific effects [21]. Future studies should incorporate toxicology screenings to disentangle these interactions.

METHODOLOGICAL CONSIDERATIONS AND CONFOUNDING FACTORS

The cross-sectional design limits causal inference, as mental health status at baseline was not assessed. For instance, patients with preexisting anxiety might have been preferentially prescribed buprenorphine due to its perceived tolerability, introducing selection bias. Additionally, dosage variability—methadone doses ranged from 60–120 mg/day, while buprenorphine doses spanned 8–24 mg/day—was not statistically controlled.

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Johnson et al. (2023) demonstrated that higher buprenorphine doses (16–24 mg/day) correlate with greater reductions in depressive symptoms [15], a trend observed in our cohort but not rigorously analyzed.

Socioeconomic stressors, such as unemployment and housing instability, were also unmeasured but likely influenced outcomes. Volkow et al. (2021) emphasize that social determinants of health account for up to 50% of variance in OUD treatment outcomes [11]. Future research should adopt mixed-methods designs to capture these factors.

Clinical and Policy Implications

Buprenorphine's safety profile and mental health benefits position it as a first-line therapy for OUD patients with psychiatric comorbidities. Integrated care models—combining pharmacotherapy with cognitive-behavioral therapy (CBT) or contingency management—are critical for this population [22]. For example, Green et al. (2022) reported a 40% reduction in depression scores when buprenorphine was paired with CBT in a real-world cohort [16].

Conversely, methadone and opium tincture programs require enhanced mental health monitoring. Clinicians should routinely screen for anhedonia in methadone users and consider dose adjustments or adjunctive antidepressants. Policymakers must accelerate the phase-out of opium tincture in favor of regulated therapies, particularly in low-resource settings where its use persists due to cost and accessibility [12].

Limitations

Cross-sectional Design: Precludes assessment of temporal relationships between treatment initiation and mental health changes.

Selection Bias: Non-randomized treatment allocation may have skewed group characteristics.

Unmeasured Confounders: Socioeconomic stressors, trauma history, and genetic factors (e.g., CYP2B6 polymorphisms affecting methadone metabolism) were not assessed [17].

Future Directions

Longitudinal studies with randomized designs are needed to establish causality. Biomarker-driven research—such as cortisol levels to assess stress response or fMRI to evaluate reward circuitry—could elucidate mechanisms underlying buprenorphine's mental health benefits [20]. Additionally, personalized dosing algorithms, informed by pharmacogenomics, may optimize outcomes for diverse patient subgroups [17].

CONCLUSION

This study provides robust evidence that buprenorphine is associated with superior mental health outcomes in opioid-dependent patients, particularly those with comorbid anxiety or depression. Its pharmacological advantages—including partial μ-opioid agonism, κ-receptor antagonism, and a favorable safety profile—position it as a cornerstone of integrated OUD care. In contrast, methadone and opium tincture regimens, while effective for craving reduction, necessitate augmented mental health support to address their association with elevated distress.

Clinicians must adopt a patient-centered approach, prioritizing buprenorphine for individuals with psychiatric comorbidities while ensuring access to psychosocial interventions. For methadone users, regular mental health screenings and dose adjustments are critical to mitigating anhedonia and emotional blunting. Policymakers should advocate for regulatory reforms to phase out opium tincture in favor of evidence-based therapies, particularly in regions where its use remains entrenched.

Future research must address this study's limitations by incorporating randomized designs, biomarker assessments, and comprehensive confounder control. By bridging the gap between addiction medicine and

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psychiatry, we can mitigate the dual burden of OUD and mental illness, ultimately improving quality of life for millions globally.

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Table 1: Demographic and Clinical Distribution by Treatment Group

Treatment Group	Gender	18–30 Years	31–45 Years	46–60 Years	Over 60 Years	Total
Methadone	Male	20	35	15	5	75
	Female	5	2	1	0	8
Buprenorphine	Male	15	31	9	5	60

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	Female	3	3	1	0	7
Opium Tincture	Male	10	18	12	5	45
	Female	1	4	0	0	5
Total		55	84	46	15	200

Table 2: DASS-21 scores (Mean ± SD) for Anxiety, Depression, and Stress Across Treatment Groups

Treatment Group	Mean Anxiety (±SD)	Mean Depression (±SD)	Mean Stress (±SD)	p-value (Anxiety)	p-value (Depression)	p-value (Stress)
Methadone	15 ± 3	14 ± 4	16 ± 4	0.02	0.03	0.02
Buprenorphine	10 ± 2	9 ± 3	11 ± 3	0.01	0.01	0.01
Opium Tincture	20 ± 5	19 ± 4	21 ± 5	0.05	0.04	0.05

p-values derived from Tukey's post-hoc test for inter-group comparisons.