Research Square

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Intravenous Buprenorphine Micro-Induction for Opioid Use Disorder in Patients Who Use Fentanyl: A Retrospective Review

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Abstract

Background:

To describe an inpatient intravenous (IV) buprenorphine micro-induction protocol and compare outcomes between two post-IV sublingual transition patterns: Pattern 1 with a 1 mg sublingual start and Pattern 2 with a 2 mg sublingual start.

Methods:

We performed a retrospective review of adult inpatients at Ventura County Medical Center who received IV buprenorphine micro-induction between April 2022 and June 2025. Patients received the same IV microdosing sequence escalated from 0.1 mg to 0.3 mg every 8 hours, followed by transition to sublingual or long-acting injectable buprenorphine. We compared withdrawal severity trends and Clinical Opiate Withdrawal Scale (COWS) improvement between patients starting sublingual buprenorphine at 1 mg versus 2 mg after the IV phase.

Results:

IV micro-induction supported transition to maintenance buprenorphine without requiring opioid abstinence before initiation. COWS scores generally improved across dose levels in both patterns. Pattern 1 (1 mg sublingual start) and Pattern 2 (2 mg sublingual start) showed similar overall improvement distributions and reduced dosing burden and workflow complexity in the Pattern 2 group.

Conclusion:

IV buprenorphine micro-induction is a practical and highly effective inpatient strategy when sublingual microdoses are difficult to operationalize. A 2 mg post-IV sublingual start may reduce dosing burden and simplify workflow without an obvious aggregate difference in withdrawal improvement.

Trial Registration

Ventura County Medical Center IRB #368 May 4, 2024

Background

Opioid use disorder (OUD) remains a devastating public health crisis in the United States, affecting millions of Americans and driving alarming rates of overdose mortality. It is estimated that over 6.1 million people aged 12 or older have an OUD[4], yet treatment accessibility and effectiveness continue to

face significant barriers. Compounding this challenge is the widespread proliferation of illicitly manufactured fentanyl, a potent synthetic opioid that has saturated the drug supply. Fentanyl's involvement in the overdose epidemic is stark: recent data indicates that synthetic opioids, primarily fentanyl, are responsible for the vast majority of opioid-related overdose deaths, with current estimates suggesting over seventy thousand overdose deaths have occurred annually since 2021.[4]

Ventura County recorded 200 fatal overdoses in 2024, down 24.5% from 2023 and 30.8% from the 2021 peak; most were accidental (183) and polysubstance (137). Opioids were involved in 143 deaths (113 fentanyl), with fentanyl deaths down 36.5% and methamphetamine deaths down 10.6% (84 deaths). Despite this improvement, potent and evolving adulterants (e.g., xylazine, bromazolam) persist, underscoring the need for low barrier, safer opioid initiation strategies, including intravenous (IV) buprenorphine micro-induction.[10]

Buprenorphine, a partial opioid agonist, is a highly effective, evidence-based medication for OUD that significantly reduces cravings, prevents relapse, and lowers mortality risk. However, the standard method for initiating buprenorphine relies on the patient being in a state of moderate to severe opioid withdrawal. For individuals whose primary substance of use is fentanyl, this standard induction protocol has proven increasingly difficult. Fentanyl’s high potency, lipid solubility, and long half-life of its metabolites can lead to prolonged and unpredictable withdrawal symptoms when compared to traditional short-acting opioids. This prolonged withdrawal window forces patients to endure severe discomfort for an extended period before buprenorphine can be safely introduced, frequently leading to premature treatment dropout or the precipitation of severe precipitated withdrawal when the medication is administered too early.

Current strategies for initiating buprenorphine are diverse, tailored to balance patient comfort, safety, and the pharmacological challenges of potent opioids like fentanyl. The standard induction remains a common approach, requiring patients to abstain from opioids until they enter moderate withdrawal before receiving a first dose to avoid precipitated withdrawal. To circumvent the need for uncomfortable withdrawal, micro-induction involves administering very small, repetitive doses of sublingual buprenorphine (starting as low as 0.5 mg or less) while the patient continues their full-agonist opioid, gradually displacing the full agonist over several days.[9] A similar low-dose strategy uses transdermal patches to deliver a steady, micro-level infusion of buprenorphine during the transition.[2] Conversely, macro-dosing represents a rapid-start approach, often utilized in emergency departments or inpatient units with Addiction Medicine Consultants, where high doses (e.g., up to 72 mg or more) are administered immediately upon the onset of withdrawal to saturate mu-opioid receptors and suppress symptoms rapidly.[1,6,8] An emerging method, Direct to Inject (DTI), allows patients to bypass the typical sublingual stabilization period by transitioning directly to long-acting injectable (LAI) buprenorphine, sometimes after a single test dose.[3,7] Finally, some traditional protocols may still rely on a "cold turkey" detoxification or extended abstinence period prior to induction, though this is increasingly disfavored due to high dropout rates compared to the newer, more patient-centered approaches.

This paper describes a less commonly reported approach: IV buprenorphine micro-induction, which allows precise microdosing (e.g., 0.1–0.3 mg) that is difficult to achieve with available sublingual formulations. In this study, patients received the same IV micro-dosing sequence and were then transitioned to sublingual buprenorphine beginning at either 1 mg or 2 mg. We compare these two post-IV sublingual transition patterns and assess withdrawal trajectories using Clinical Opiate Withdrawal Scale (COWS) scores.

A previous case report also explored the potential benefit of a shortened induction course using this method compared to methadone.[5] The IV route allows for precise, micro-dosing strategies and controlled administration in a medically supervised setting, potentially minimizing the arduous withdrawal period and mitigating the risk of precipitated withdrawal that plagues standard induction methods. By examining the pharmacokinetics of fentanyl and the challenges it poses to conventional OUD treatment entry, this research aims to highlight how the controlled, inpatient administration of IV buprenorphine may offer a safer, more tolerable, and ultimately more successful pathway to initiating life-saving OUD treatment for this vulnerable population.

Methods

Study design and setting

We conducted a retrospective observational study of adult inpatients (18 years and older) admitted to Ventura County Medical Center for opioid withdrawal management who received IV buprenorphine micro-induction. The study focused on comparing two post-IV sublingual transition patterns (1 mg vs 2 mg sublingual start) (Figure 1) and evaluating withdrawal response using serial COWS scores.

Independent and dependent variables

The primary independent variable was post-IV sublingual buprenorphine starting dose pattern: Pattern 1 (1 mg sublingual start) versus Pattern 2 (2 mg sublingual start). The primary outcome was change in withdrawal severity measured by COWS scores across the induction sequence and by calculated COWS improvement (pre-dose minus post-dose COWS, where positive values indicate symptom improvement).

COWS scores were also summarized by dose level and treatment pattern for descriptive comparison. Age group, sex, housing status, and selected clinical characteristics were treated as covariates for subgroup analyses, and length of stay was treated as a continuous descriptive variable.

Data source and extraction

The analytic sample included hospitalized patients who received the IV buprenorphine micro-induction protocol and had medication administration data with corresponding documented COWS scores. Data was abstracted from the electronic medical record, including demographics, medication administration timing and dose, COWS scores, and transition to sublingual or LAI buprenorphine.

Unit of analysis and analytic sample

The unit of analysis was the individual dose administration event linked to associated COWS measurements. Patients received a standardized IV micro-induction sequence before transition to sublingual buprenorphine, beginning at either 1 mg (Pattern 1) or 2 mg (Pattern 2). Additional supportive medications (for example clonidine, hydroxyzine, gabapentin, ondansetron, or full-agonist opioids) were recorded when used for symptom management.

Because patients contributed multiple dose events during a single admission, repeated observations were summarized descriptively by treatment pattern and dose level. COWS improvement distributions were compared across patterns, and age group distributions were examined using Pearson chi-square testing.

Bias

Selection bias was addressed by including all inpatients who received the IV buprenorphine micro-induction protocol during the study period. Lastly, measurement bias was addressed by using previously recorded data such as COWS scores and medication administration records.

Results

Sample Selection and Data Processing

Of 1,213 observations read from the dataset, 1,082 observations (89.2%) were retained for data processing after applying exclusion criteria. A total of 131 observations (10.8%) were excluded, including 3 unique patient encounters from patients who received both dosage patterns within the same admission, as assignment to multiple patterns would violate the assumption of mutually exclusive treatment groups. The 1,082 dose-level observations were aggregated by unique encounter identifier to create a patient-level analytical dataset, yielding 106 unique patient encounters for final analysis. Of these, 57 patients (53.8%) were classified as Pattern 1 and 49 patients (46.2%) as Pattern 2 based on the distinct sequence of dose levels received during their admission. Analyses and visualizations were performed using SAS version 9.4. Missing data were handled via complete-case analysis (i.e., observations with missing values for a given variable were excluded from analyses involving that variable).

Descriptive Statistics of COWS Scores by Dosage Pattern

For the Pattern 1 group, COWS average scores demonstrated a dose-response relationship, with mean scores declining as dose levels increased. Mean COWS scores ranged from 5.29 (SD = 3.52, n = 108) at the lowest dose value (0.1 mg) to 3.51 (SD = 2.71, n = 181) at the highest dose value (2.0 mg) (Figure 2). This pattern was consistent across all intermediate dose levels, with progressive reductions in mean COWS scores observed at 0.15 mg (M = 4.46, SD = 3.13, n = 108), 0.3 mg (M = 5.17, SD = 3.87, n = 109),

and 1.0 mg (M = 3.97, SD = 2.79, n = 200). The overall range of individual COWS scores spanned from 0 to 17.0 across all dose values. Notably, the minimum COWS score of 0 was observed at all dose levels.

For the Pattern 2 group, mean COWS average scores similarly declined with increasing dose levels, ranging from 5.34 (SD = 4.52, n = 76) at 0.1 mg to 4.29 (SD = 3.43, n = 146) at 2.0 mg. Intermediate dose levels showed mean scores of 4.85 (SD = 3.32, n = 78) at 0.15 mg and 5.03 (SD = 4.05, n = 76) at 0.3 mg. Compared to Pattern 1, Pattern 2 exhibited notably higher standard deviations at comparable dose levels, indicating greater variability in treatment response. The range of individual COWS scores was wider for Pattern 2 (0 to 19.5) compared to Pattern 1 (0 to 17.0), with the maximum score of 19.5 representing more severe withdrawal symptoms. As with Pattern 1, minimum scores of 0 were documented across all dose values.

COWS Improvement Analysis

COWS improvement scores were calculated as the difference between first and last COWS assessments (first COWS − last COWS), with positive values indicating symptom reduction and negative values indicating worsening symptoms.

Pattern 1 demonstrated a median improvement score of approximately 2 points, with an interquartile range (IQR) spanning from 0 to 5 points (Figure 3). The distribution of improvement scores ranged from a minimum of approximately −4 (worsening) to a maximum of approximately 10 (substantial improvement). Two outliers were identified at improvement scores of approximately 13 and 15 points, representing exceptional treatment responses. The presence of negative values indicated that some patients (approximately 25% based on the lower quartile of 0) experienced no improvement or worsening of withdrawal symptoms despite treatment.

Pattern 2 showed a similar median improvement score of approximately 2 points, with an IQR ranging from approximately −2 to 4 points. The overall distribution spanned from approximately −8 (substantial worsening) to approximately 11 (marked improvement). Two outliers were observed with improved scores of approximately 14 and 16 points. Notably, Pattern 2 demonstrated a lower first quartile (−2 vs. 0), suggesting that a larger proportion of patients in this group experienced worsening symptoms or minimal improvement. The broader range of negative values (minimum of −8 vs. −4) indicated greater potential for treatment failure in the Pattern 2 group.

Visual inspection of box plots revealed similar distributions between the two dosage patterns, with overlapping interquartile ranges and comparable median values. Both patterns exhibited negative minimum values, confirming that worsening of withdrawal symptoms occurred in a subset of patients regardless of dosing strategy. The visual similarity of the distributions suggests no substantial difference in overall COWS improvement between Pattern 1 and Pattern 2 at the aggregate level, though Pattern 2 showed greater variability and a longer tail toward negative outcomes.

Age Group Distribution by Dosage Pattern

Of the 57 patients assigned to Pattern 1, 53 had complete age group data (4 with missing data excluded from age-specific analyses). The distribution across age categories excluding missing age data was as follows: 18-29 years (n = 7, 13.2%), 30-39 years (n = 20, 37.7%), 40-49 years (n = 15, 28.3%), 50-59 years (n = 7, 13.2%), and 60+ years (n = 4, 7.6%) (Table 1). The 30-39 age group constituted the largest proportion of Pattern 1 patients, while the oldest (60+) age groups had the smallest representation.

Of the 49 patients in Pattern 2, 29 had complete age group data (20 with missing data excluded). The age distribution excluding missing age data differed notably from Pattern 1: 18-29 years (n = 6, 20.7%), 30-39 years (n = 6, 20.7%), 40-49 years (n = 9, 31.0%), 50-59 years (n = 6, 20.7%), and 60+ years (n = 2, 6.9%). In contrast to Pattern 1, the 40-49 age group predominated Pattern 2, accounting for more than one-thirds of patients with complete age data. The 18-29, 30-39, and 50-59 age group constituted the second-largest category in Pattern 2, whereas 60+ represented the smallest group.

A Pearson chi-square test of independence revealed there is a statistically significant association between dosage pattern assignment and age group ($p = 0.001$).

Discussion

IV buprenorphine micro-induction is a highly effective inpatient approach for patients with fentanyl exposure who may not tolerate traditional abstinence-based induction. In our cohort, withdrawal severity generally improved over the course of induction in both treatment patterns, and overall COWS improvement distributions were similar whether the post-IV sublingual transition began at 1 mg or 2 mg.

The 2 mg sublingual-start pattern appears operationally attractive because it can reduce dosing complexity and nursing workflow burden after the IV phase. At the same time, the broader spread of COWS improvement values in this group suggests some patients may benefit from a more gradual transition, supporting protocol flexibility based on clinical response.

Although this study did not directly measure precipitated withdrawal rates, the overall stability and improvement of COWS scores across the induction sequence provide indirect clinical support that this IV first strategy can facilitate safe induction onto buprenorphine in a monitored setting.

Limitations

This study has several limitations. As a retrospective single-center review, it is subject to missing data, documentation variability, and confounding by clinical decision-making. Treatment pattern selection was not randomized, so differences between groups may reflect patient complexity rather than dose pattern alone. We also did not directly measure precipitated withdrawal, long-term retention, or outpatient follow-up outcomes.

Conclusions

Intravenous buprenorphine micro-induction enables a gradual, monitored transition onto buprenorphine without requiring prolonged opioid abstinence and is a practical strategy for hospitalized patients with high opioid tolerance or fentanyl exposure. In this cohort, patients transitioned to sublingual buprenorphine starting at either 1 mg or 2 mg after the same IV microdosing sequence had similar overall COWS improvement distributions. The 2 mg start may offer workflow advantages by reducing dosing steps, while the 1 mg start may remain useful for patients who need a slower transition.

Overall, these findings support IV buprenorphine micro-induction as a safe and highly effective strategy to improve induction onto buprenorphine in the inpatient setting. Prospective studies should evaluate precipitated withdrawal, and longer-term treatment outcomes. In conclusion, IV buprenorphine micro-induction using a standardized IV phase followed by individualized sublingual transition (1 mg or 2 mg start) is a practical inpatient protocol for initiating buprenorphine in patients with high opioid tolerance and fentanyl exposure.

Abbreviations

COWS – Clinical Opiate Withdrawal Scale

DTI – direct-to-inject

IQR – interquartile range

IV – intravenous

LAI – long-acting injectable

OUD – opioid use disorder

Declarations

Ethics approval and consent to participate: This retrospective study was reviewed and approved by the Ventura County Medical Center Institutional Review Board, which granted a waiver of informed consent due to the retrospective nature of the study. All procedures were performed in accordance with the ethical standards of the institutional research committee and the 1964 Declaration of Helsinki and its later amendments.

Clinical Trial Number: not applicable

Consent for publication: not applicable

Availability of data and materials: The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: VR analyzed and interpreted the patient data. MK and LC were major contributors in writing the manuscript. TK and ML organized data collection and provided draft edits. All authors read and approved the final manuscript.

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Table

Table 1: Demographic and Socioeconomic Characteristics of Study Participants (N=106)

Note: Pregnancy status was assessed only for female participants (n=34). Unknown category includes missing, declined, or undocumented responses.

Variable	Characteristic	Frequency	Percent (%)
Age Group	18-29	13	15.9
	30-39	26	31.7
	40-49	24	29.3
	50-59	13	15.9
	60+	6	7.3
Housing Status	Stable Housing	62	58.5
	Non-stable/ Homeless	19	17.9
	Unknown	25	23.6
Pregnancy Status	No	34	100
Primary Insurance	Medicare HMO	1	0.9
	Medicare Other	5	4.7
	Self-Pay	1	0.9
	Blue Cross Plans	1	0.9
	Kaiser Plans	1	0.9
	Other Insurance	74	69.8
	Unknown	23	21.7
Race	Hispanic/Latino	34	32.1
	White	48	45.3
	Unknown	23	21.7
	Other/Unknown/Declined	1	0.9
Sex	Female	34	32.1
	Male	49	46.2
	Unknown	23	21.7

Figures

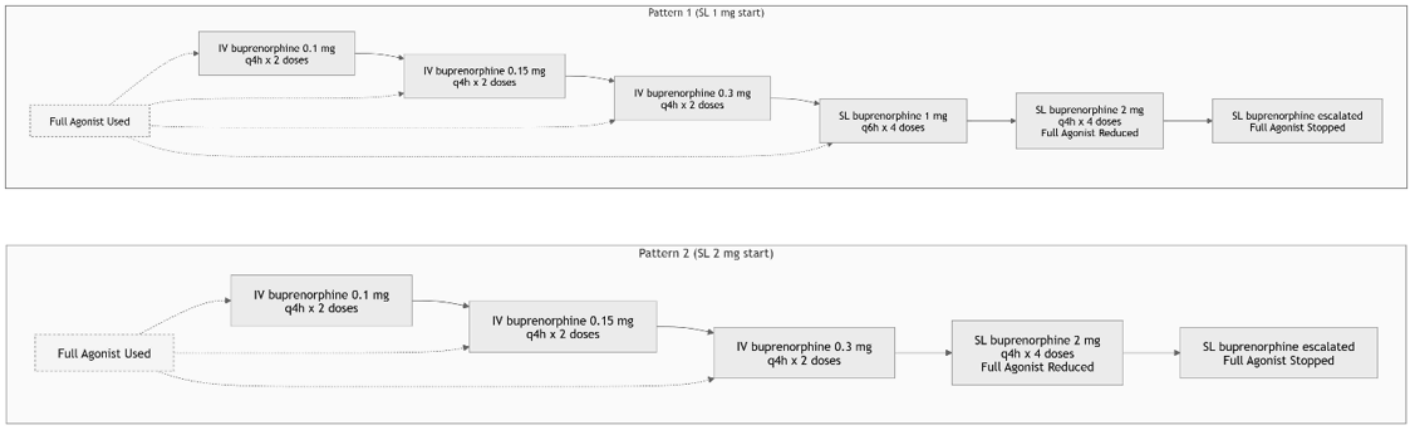
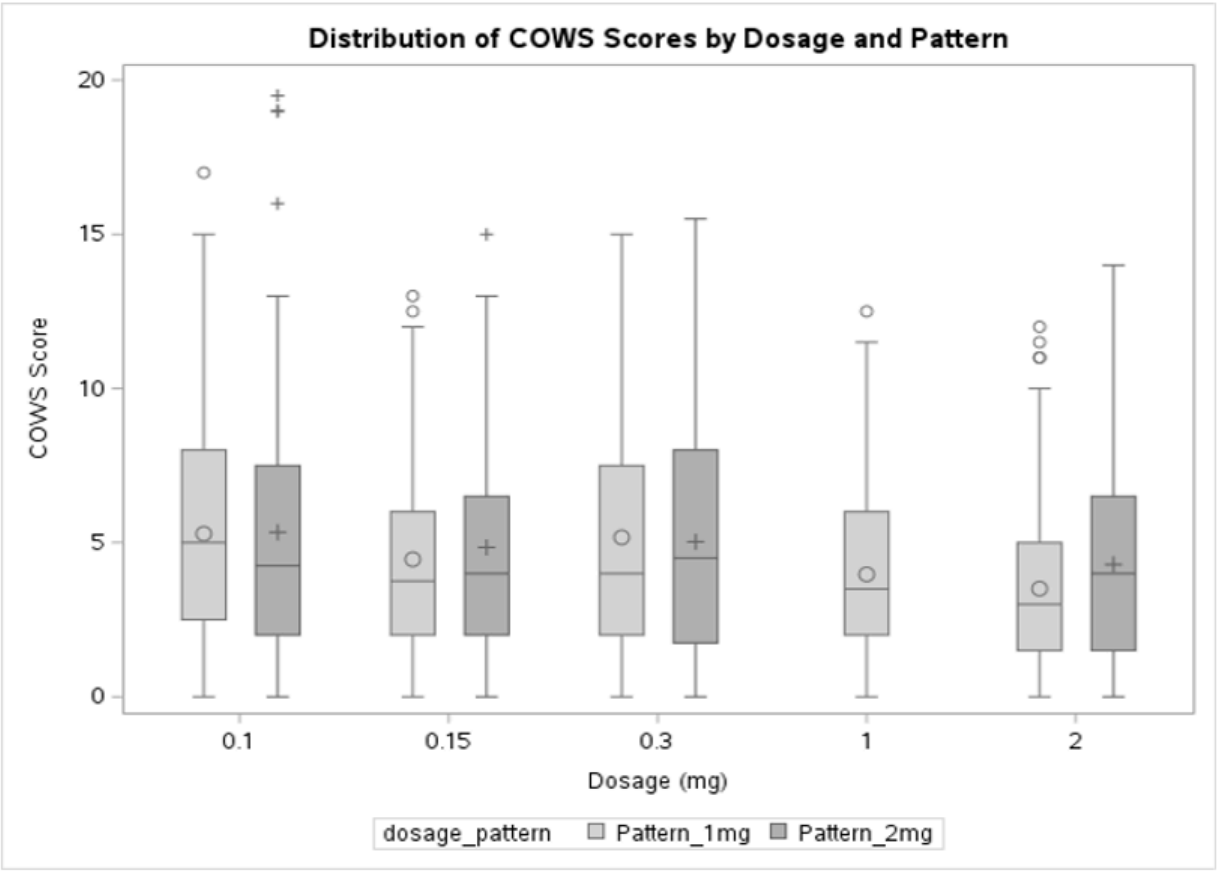


Figure 1

IV buprenorphine microinduction dosing patterns used in the study. Both patterns used the same IV escalation sequence (0.1 mg, 0.15 mg, 0.3 mg; each q4h × 2 doses), followed by sublingual buprenorphine with either a 1 mg start (Pattern 1) or 2 mg start (Pattern 2). Full agonist opioids were continued during the early IV and SL dosing steps, reduced at the SL buprenorphine 2 mg q4h phase, and stopped after subsequent SL buprenorphine escalation.

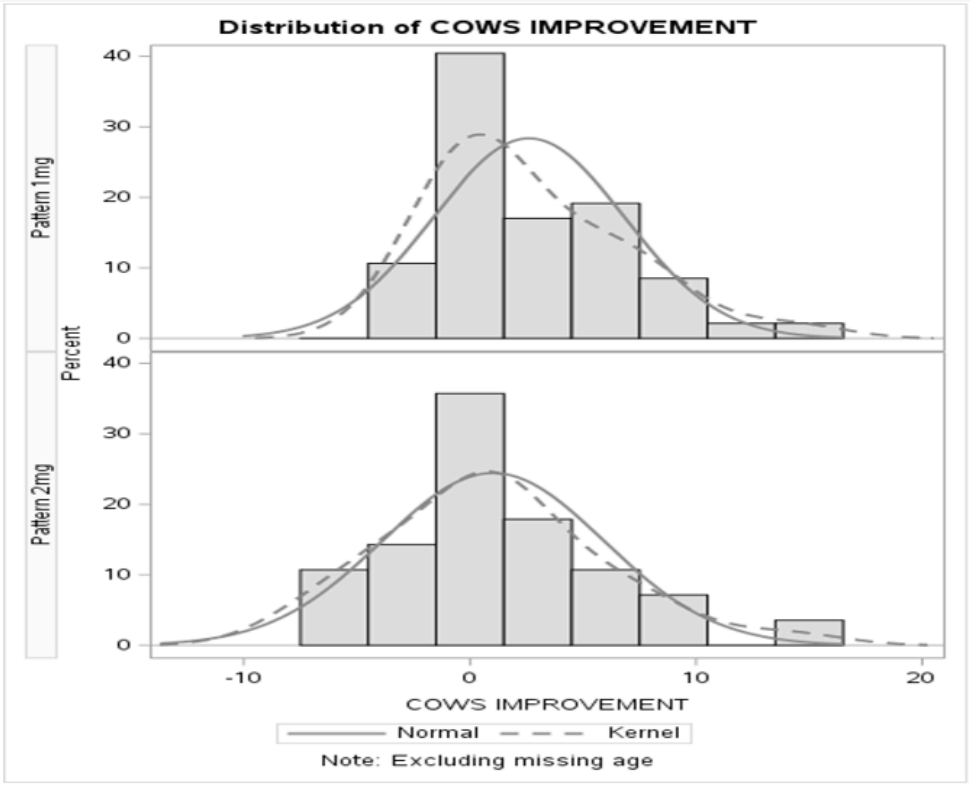


Pattern 1mg: 0.1, 0.15, 0.3, 1, 2
Pattern 2mg: 0.1, 0.15, 0.3, 2

Figure 2

Distribution of COWS Scores by Dose Level and Treatment Pattern (N=106)

Box plots comparing Clinical Opiate Withdrawal Scale (COWS) scores across dose levels by treatment pattern: Pattern 1 (1 mg sublingual start after IV phase; n=57) and Pattern 2 (2 mg sublingual start after IV phase; n=49). Box plots display the median (center line), interquartile range (box), whiskers (most extreme data points within 1.5 x IQR), and outliers (points beyond whiskers).



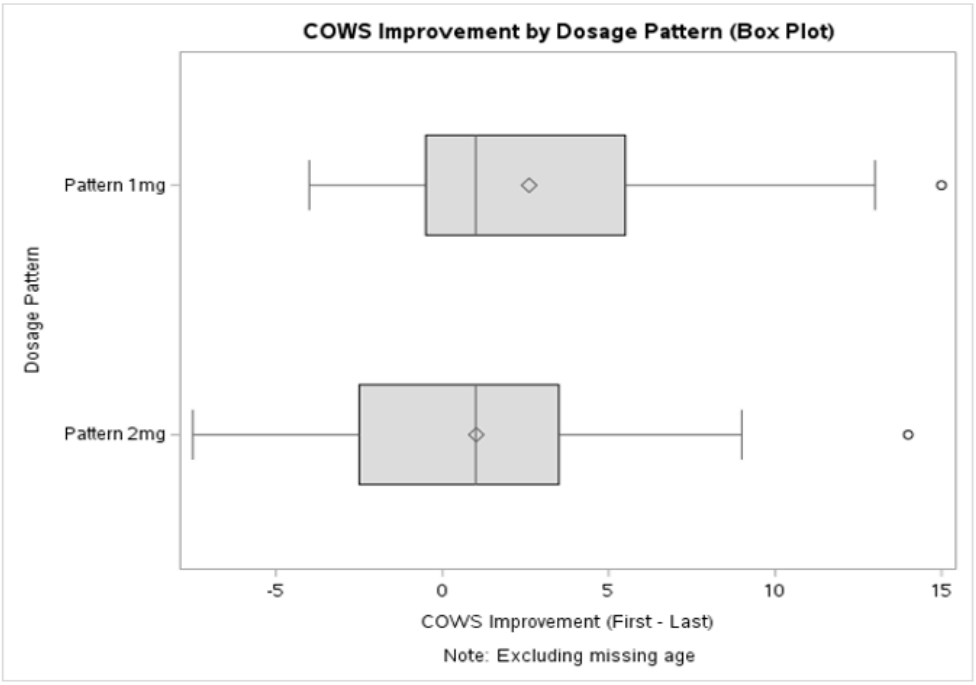


Figure 3

COWS Improvement by Treatment Pattern

Distribution plots showing COWS improvement scores (pre-dose COWS minus post-dose COWS) by treatment pattern: Pattern 1 (1 mg sublingual start) and Pattern 2 (2 mg sublingual start). Positive values indicate reduction in withdrawal symptoms.