Pilot Study Comparing Traditional to Low-Dose Initiation with Buprenorphine

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Research Objective

- Buprenorphine is one of three FDA-approved medications for treatment of opioid use disorder (OUD)
- In traditional initiation, patients must abstain from opioids until withdrawal is experienced prior to starting buprenorphine, but barriers to this method exist (withdrawal)
- Low-dose initiation is an alternative approach that uses small but escalating doses of buprenorphine with continuation of full agonist opioid.
- First description in 2016 “Bernese Method”
- To date, no study has compared low-dose vs. traditional in a prospective randomized trial.

Study Design

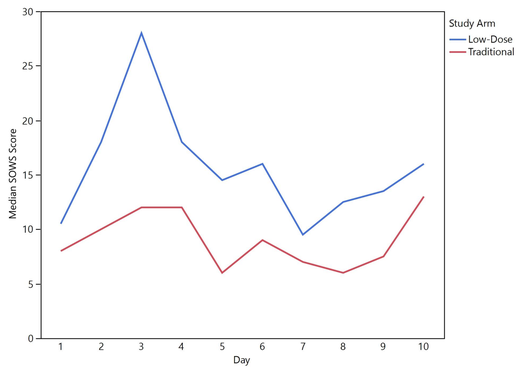
- Quasi-experimental randomized trial evaluating patients entering treatment with a telehealth OUD provider.
- Setting: U.S.’s largest telehealth OUD provider, treating >13,000 patients in ~30 states.
- After consent during 1st visit, newly enrolled or reenrolling patients randomized to either traditional initiation or low-dose initiation.
- Patients asked to complete daily survey for 10 days that included Subjective Opiate Withdrawal Scale (SOWS) score
- Clinical outcomes followed prospectively through day 30

Traditional Initiation Protocol:

- Patient to wait until significant withdrawal symptoms, typically SOWS score ≥17
- Wait at least 12 hours after last short-acting opioid use, or up to 72 hours for longer-acting opioids and fentanyl
- Doses start at 2 mg and can reach maximum of 16 mg on Day 1 depending on response, followed by steady dosing (typically 8-24 mg) on following days

Low-Dose Initiation Protocol (Manitoba Protocol):

	Dose	Instructions	Daily total
Day 1	0.5 mg (¼ film/tab)	Take 0.5 mg in the morning and at night	1 mg
Day 2	1 mg (½ film/tab)	Take 1 mg in the morning and at night	2 mg
Day 3	2 mg (1 film/tab)	Take 2 mg in the morning and at night	4 mg
Day 4	3 mg (1 ½ films/tabs)	Take 3 mg in the morning and at night	6 mg
Day 5	4 mg (2 films/tabs)	Take 4 mg in the morning and at night	8 mg
Day 6	4 mg (2 films/tabs)	Take 4 mg in the morning, at noon, and at night	12 mg
Day 7	12 mg (6 films/tabs)	Take 12 mg in the morning	12 mg



Cohort Characteristics:

	Traditional (n=13)	Low-Dose (n=13)	
Age	40.3 (SD 12.6) years	36.1 (SD 5.9) years	p=0.14
Gender	Female 23.1%	Female 53.9%	p=0.11
Insurance	Self-pay 46.2% Medicaid 15.4% Commercial 38.5%	Self-pay 15.4% Medicaid 38.5% Commercial 46.2%	p=0.18
Primary opioid	Fentanyl/Heroin 23.1% Prescription Opioids 76.9%	Fentanyl/Heroin 84.6% Prescription Opioids 15.4%	**p=0.001**
Prior experience with buprenorphine	Yes 46.2%	Yes 38.5%	p=0.69
History of precipitated withdrawal	Yes 15.4%	Yes 46.2%	p=0.09
History of unsuccessful induction	Yes 7.7%	Yes 38.5%	p=0.06

Subjective Opiate Withdrawal Scale (SOWS) Daily Scores:

Study Arm	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
Low-Dose			63	25	64					
Low-Dose		18	14	18	14	13	8	13	20	28
Low-Dose		17	20	12	20					16
Low-Dose				5	1		1		8	
Low-Dose	6	23	28	18	8	20	12	15	10	7
Low-Dose			30	23	20	16	8	12	6	15
Low-Dose	15	20	29	14	15	36	22	12		64
Low-Dose		7								32
Low-Dose									52	
Low-Dose					7					
Low-Dose		11							17	
Low-Dose			5				11			5
Low-Dose		23				3				
Traditional	9	5	17	13			23	29		17
Traditional						26				
Traditional		18	6	7	5	8	5	3		3
Traditional	3									
Traditional				17	6	10	7	3	9	14
Traditional		33								
Traditional	7	4							1	
Traditional		8	3	1	1					
Traditional		10	12	7	8	7	7	8	6	
Traditional	29	15		11		10	6	9		7
Traditional	60	64	38	52	41		18	23	19	19
Traditional			34	17	10	9	9	4	13	13
Traditional	4	2	4		2	2	1	0	0	2

Aggregate Subjective Opiate Withdrawal Scale (SOWS) Scores:

For patients reporting SOWS at least twice on days 1-5	Traditional (n=10), mean **14.2** (SD 14.1) Low-Dose (n=7), mean **21.1** (SD 14.6)	p=0.18
For patients reporting SOWS at least twice on days 6-10	Traditional (n=8), mean **10.2** (SD 7.4) Low-Dose (n=6), mean **14.4** (SD 10.2)	p=0.21
Maximum SOWS score reported	Traditional (n=13), mean **21.7** (SD 16.9) Low-Dose (n=13), mean **27.4** (SD 16.6)	p=0.20

Key Outcome Measures

	Traditional	Low-Dose	
Opioid Use at 30 Days	Yes: 23.1%	Yes: 53.9%	p=0.11
Still in Treatment with our Group	Yes: 85.6%	Yes: 38.5%	**p=0.02**
Evidence of Return to Use or Ongoing Use	Yes: 23.1%	Yes: 84.6%	**p=0.001**

Principal Findings

- 33 patients consented between March & November 2023.
- Seven patients withdrew from the study:
  1 returned to use, 1 changed arms due to precipitated withdrawal, 1 requested to withdraw from study, 2 left the program for financial reasons, 2 did not attend follow-up visits
- Study ended early due to low enrollment.
- Final cohort included 26 patients: 13 (50%) in the traditional arm and 13 (50%) in the low-dose arm.
- For patients who reported on days 9-10 (n=20), patients in the **low-dose arm were more likely to still have cravings for opioids** (90.0% vs, 30.0%, p=0.004) and were **more likely to still be using full-agonist opioids** (70.0% vs. 10.0%, p=0.004).
- **Low-dose patients less likely to be in treatment at 30 days** (38.5% vs. 85.6%), and **more likely to have evidence of return to use/ongoing use at 30 days** (84.6% vs. 23.1%).

Conclusions

- This was a pilot study. There was an imbalance between the two arms in use of fentanyl/heroin vs. prescription opioid use. There was a high study drop-out rate and low compliance with daily withdrawal reporting. **Results must be interpreted with caution!**
- However, the results suggest that traditional initiation is associated with less cravings and use of opioids at 9-10 days, less rate of return to use/ongoing use at 30 days, and greater retention in treatment.

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