Withdrawal from Long-acting-injectable buprenorphine (LAIB): Findings from a residential case series

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- **Investigators**::Nicholas Lintzeris (SESLHD, USyd), Carolyn Stubley (WHOS), Gaye Byron (WHOS), Vicky Hayes (SESLHD), Llewellyn Mills (USyd, SESLHD), Andrew Smogonyi (University Adelaide), Rick Wassing (USyd, Woolcock)
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Characterizing withdrawal from long-acting injectable buprenorphine: An observational case series

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Background: Stopping OAT

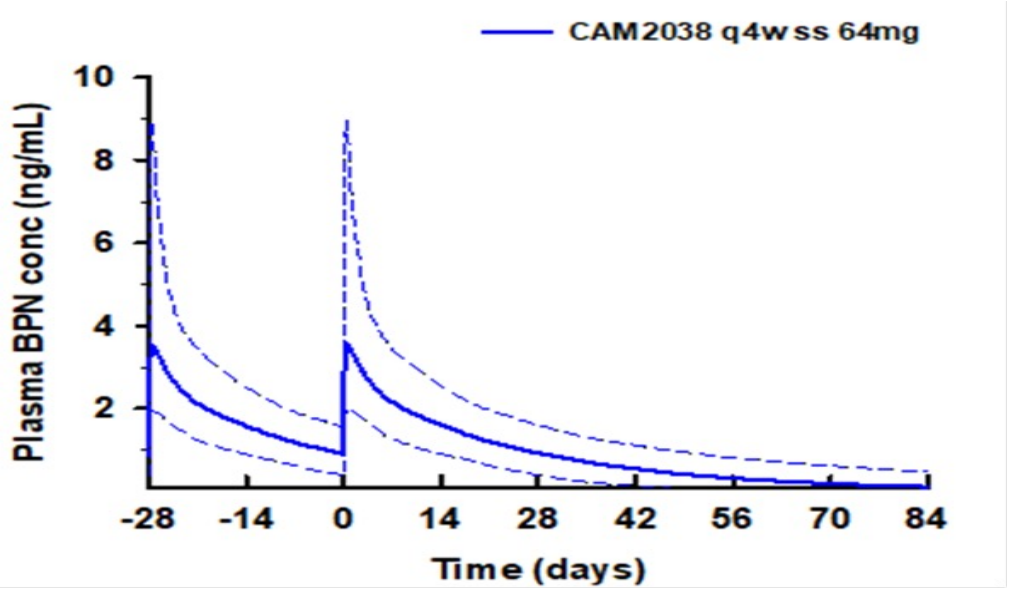
- We do not have effective ways of assisting patients to stop opioid agonist treatment
- Stopping Methadone and Sublingual Buprenorphine (SL BPN)
  - SL Buprenorphine and methadone usually involves gradual dose tapering over time – a slow process with high rates of relapse (estimated >85% within 6 months[1])
  - Withdrawal can be severe / prolonged, often peaks 1-2 weeks after last methadone / SL BPN dose
  - Expectancy important for many patients: fearful of dose reductions
  - Many patients get stuck in OAT due to "fear of withdrawal"
- Most patients have strong desire to eventually come off opioid treatment[2]
  - Poor experience of withdrawal planning: most common way of stopping treatment is "jumping off"; and most services lose contact with patients after last dose (prior to peak withdrawal)
- Little research attention to improving treatment cessation outcomes

1 Lenné M, Lintzeris N, et al. doi: 10.1111/j.1753-6405.2001.tb01832.x.

[2] Winstock, Lintzeris, Lea. doi: 10.1016/j.drugpo.2010.08.001.

The ‘potential’ of LAIB in withdrawal

- Increasing use of LAIB for treatment of opioid dependence
  - Weekly or monthly SC injection
  - Most common form of BPN treatment of opioid dependence in Australia
- **Pharmacology**: Gradual reduction in plasma levels over time (a gradual slope rather than incremental steps)
- **Expectancy**: Client does not have to adjust to ‘no more daily dosing’ or fear upcoming dose reductions



Questions re: Withdrawal from LAIB:

- When will withdrawal commence?
- How severe will it be?
- When will symptoms peak and how long will they last?
- Are withdrawal outcomes better than stopping methadone / SL BPN?

Study hypothesis and objectives

Hypothesis: that cessation of LAIB treatment will result in a mild opiate withdrawal syndrome with minimal increase in cravings or deterioration in health

Study objectives:

- Primary objective: To characterize the onset, severity and duration of opiate withdrawal syndrome upon cessation of Buvidal 64mg Monthly dose in a long-term residential setting (primary endpoint)
- Secondary objectives:

1. To examine general health parameters and participant experiences of stopping LAIB treatment
2. To compare withdrawal features to patients withdrawing from SL BPN treatment in the same environment

Study Design

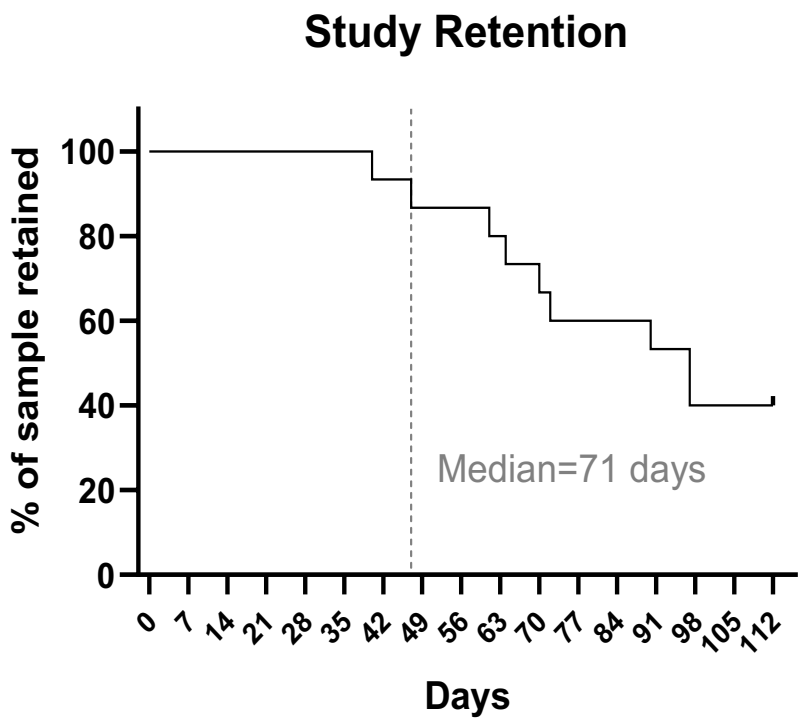
- **Open-label case series comparing withdrawal outcomes in two parallel groups of participants**: LAIB patients (n=15) and SL BPN patients (n=15)
- **Setting**: a 16-week residential rehabilitation unit specializing in assisting patients to stop opioid agonist treatment (methadone, BPN)
- **Participants**: ≥ 18 years-old; in continuous BPN treatment > 6 months (at least 2 months on LAIB or SL BPN); no severe comorbid health conditions or withdrawing from other drugs
- **Dose reductions:**
  - LAIB: 1 dose of 64mg Buvidal Monthly SC (day 1 of study)
  - SL BPN: Gradual dose taper to 'zero' over first 8 weeks
- **Rescue medications:** access to limited doses of paracetamol/ibuprofen, metoclopramide, temazepam, loperamide, hyoscine
- **Other aspects of care**: routine activities of program: daily group activities, supportive counselling, peer and professional staffing

Outcomes and measures

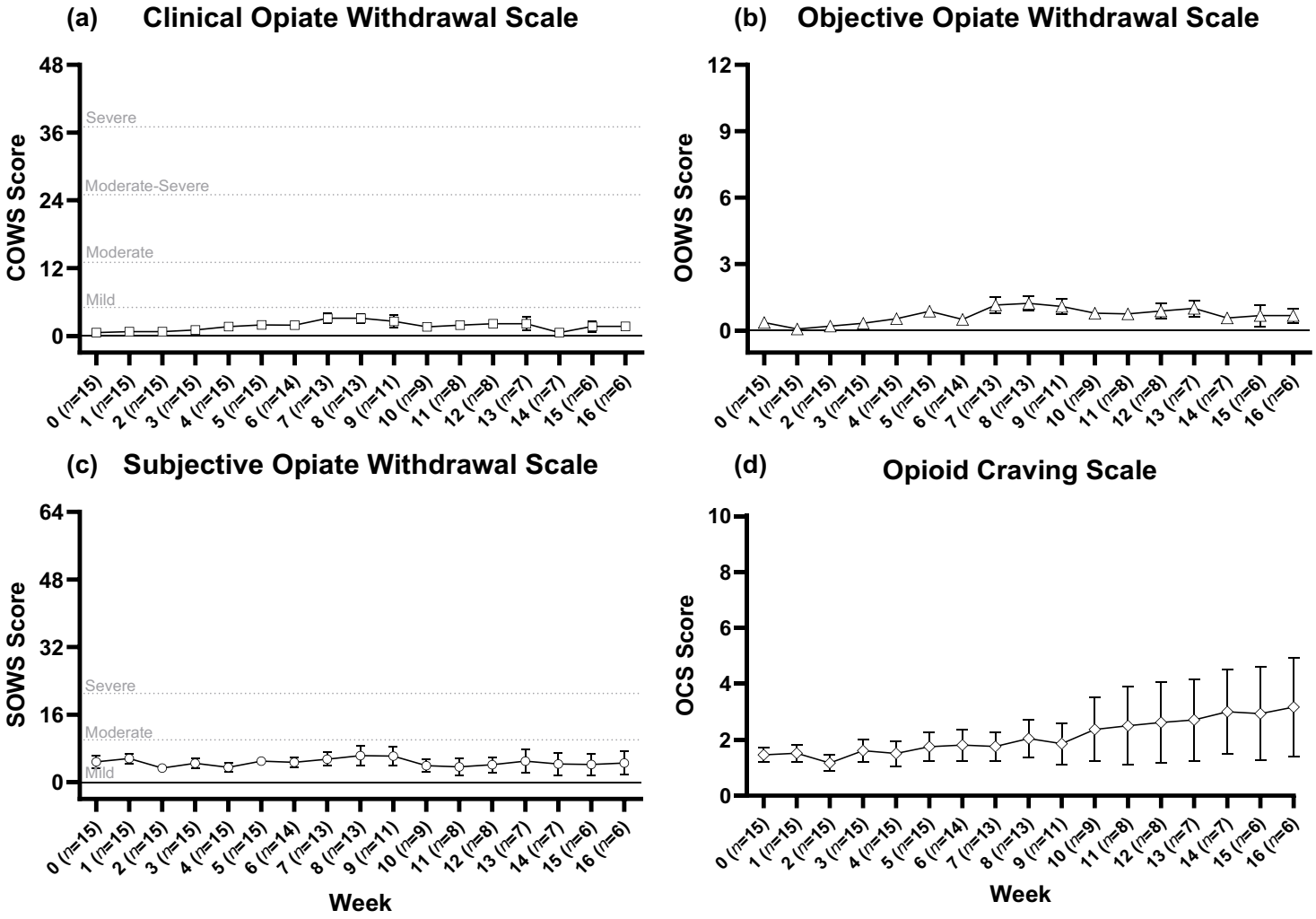
- **Withdrawal severity**: Clinical Opioid Withdrawal Scale (COWS), Subjective Opioid Withdrawal Scale (SOWS), Objective Opioid Withdrawal Scale (OOWS)
- **Cravings**: Opioid Cravings Scale
- **General health**: PROMIS-29 (physical function, anxiety, depression, pain, fatigue, sleep subscales)
- **Sleep**: Objective (actigraphy) and subjective (ISI; sleep diary)
- **Client satisfaction**: TSQM and ratings of client preference
- **Biological measures**: urine and blood samples for BPN levels

Results: recruitment and retention

- Only 2 participants recruited on SL BPN arm: both participants discharged against medical advice on reaching 0mg BPN (weeks 8, 9)
- 25 participants enrolled on Buvidal arm and administered 64mg dose
  - N=10 withdrew from study prior to reaching week 4 after last dose (n=4 administrative discharge, n=6 self-discharge)
  - **N=15 continued beyond week 4 after last dose and included in data analysis**

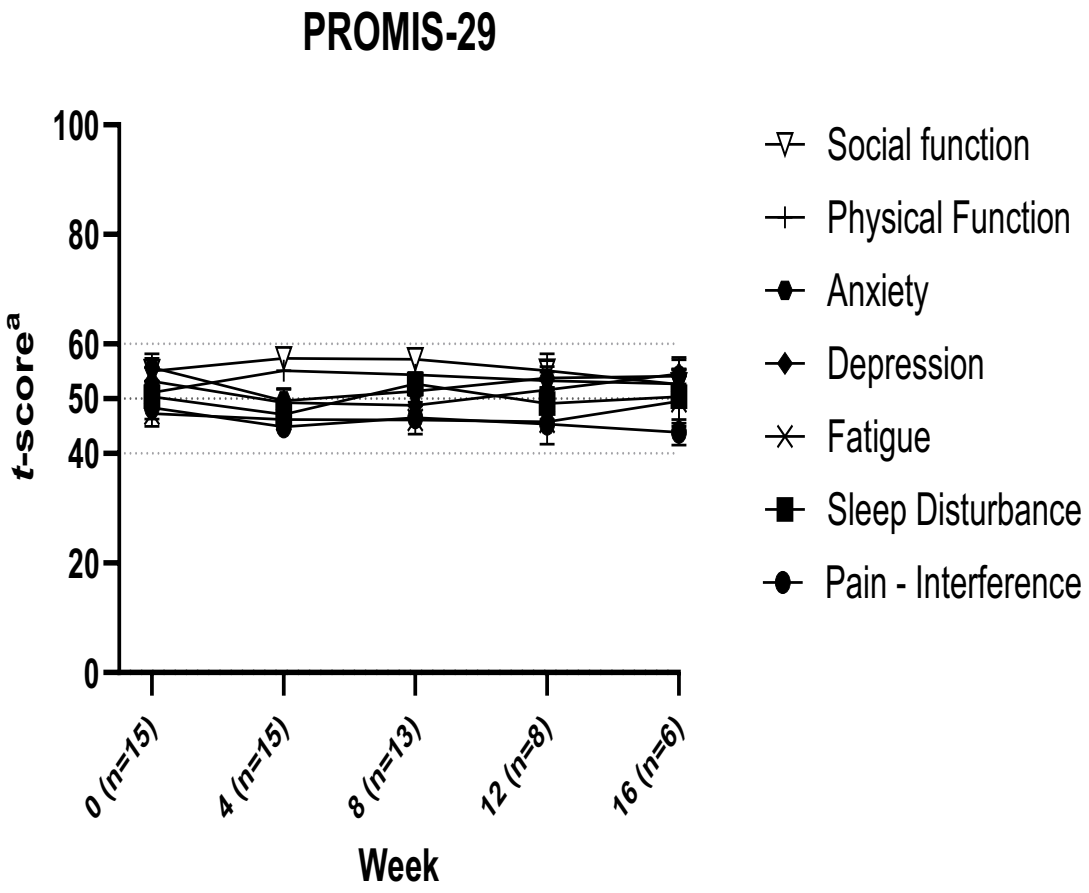


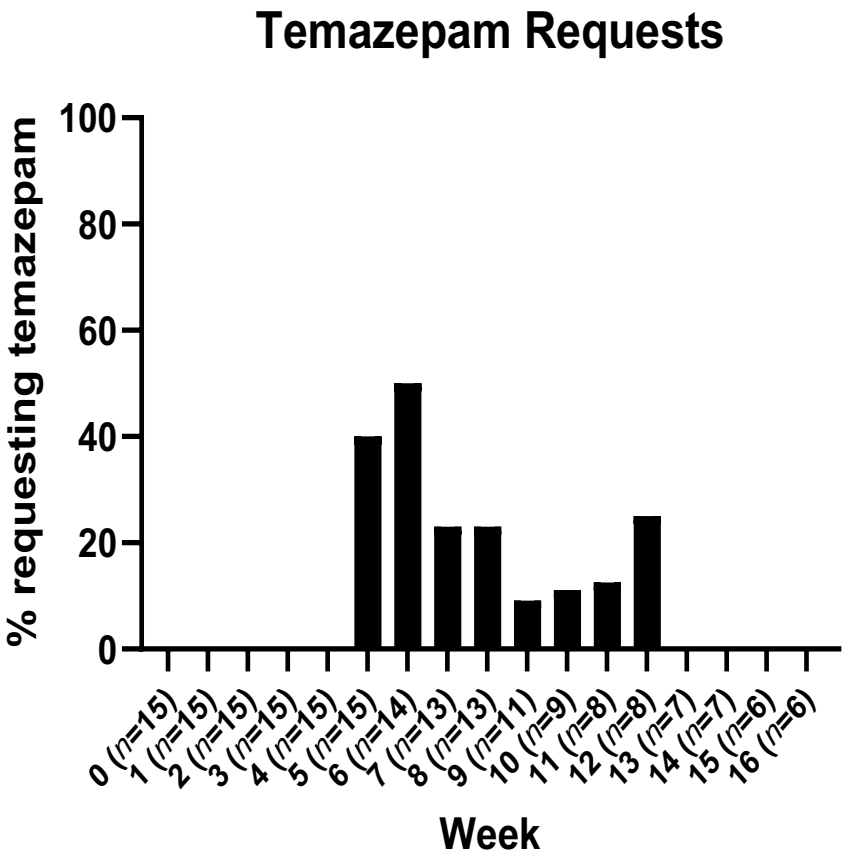
Withdrawal and cravings



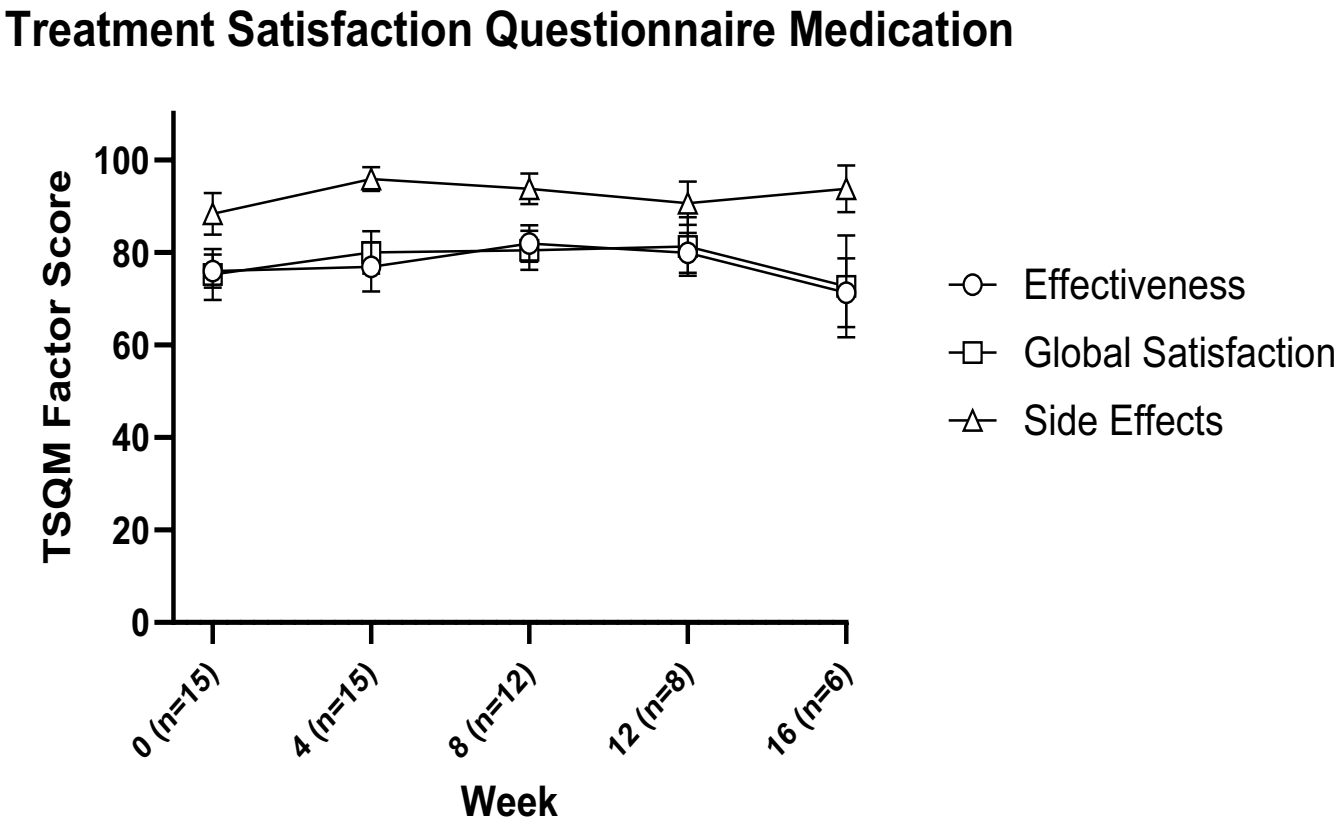
- Most participants experienced minimal or mild withdrawal symptoms, peaking during weeks 5-8
- Peak COWS
  - 67% (n=10) < mild (<5)
  - 33% (n=5) mild (5-12)
- Peak SOWS
  - 60% (n=9) mild (<16)
  - 40% (n=6) mod (16-32)

General health, rescue medications





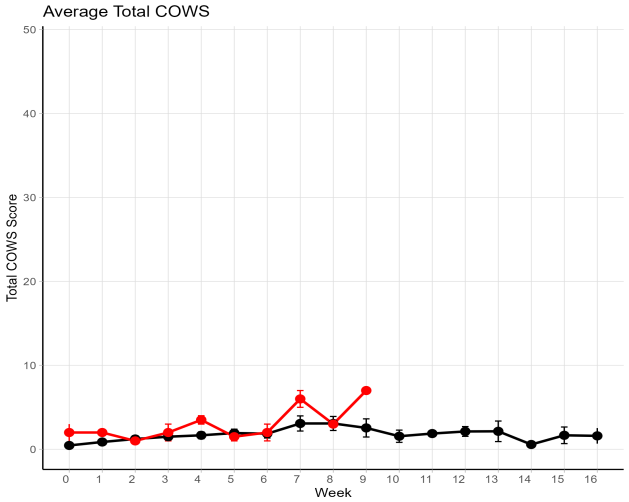
Consumer perspectives

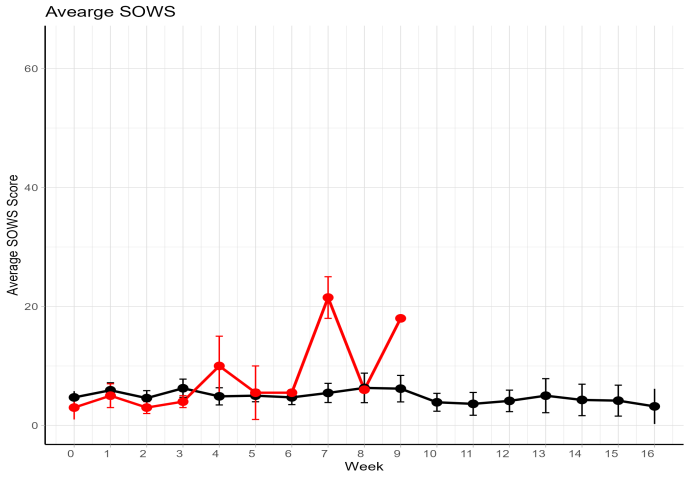


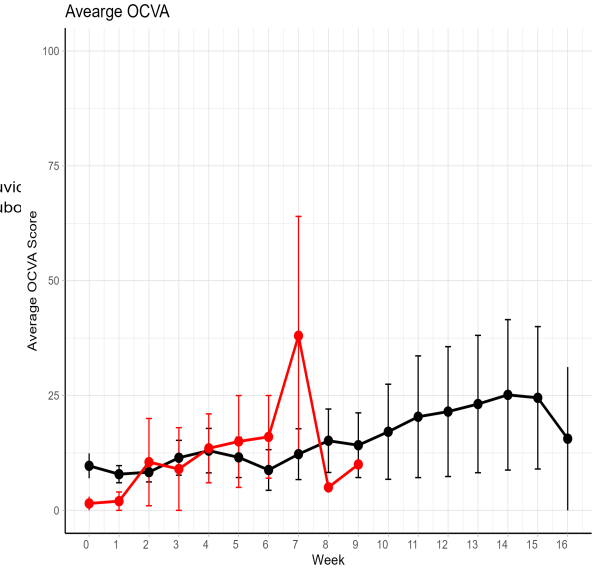
Overall experience of withdrawal compared to prior attempts (n=10)

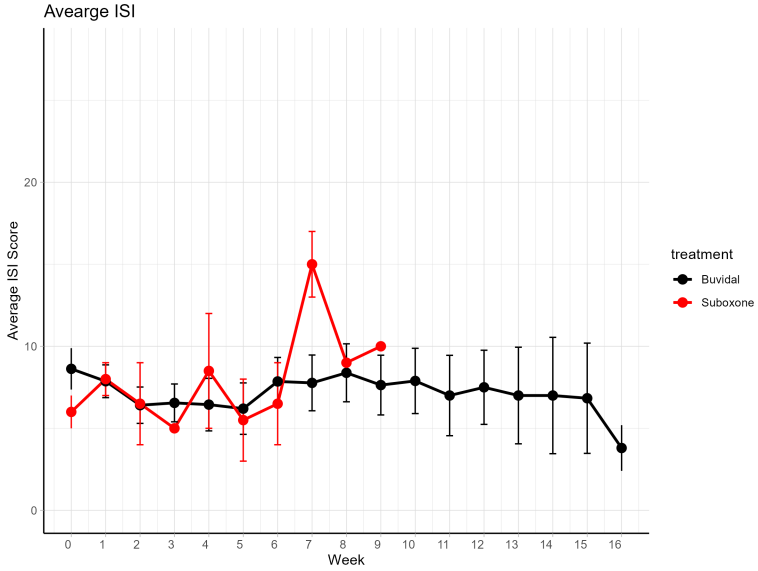
- 6/10: Very much better
- 3/10: Much better
- 1/10: A little better
- 0/10: No different
- 0/10: Worse

Comparing LAIB (n=15) v SL BPN (n=2)









Study strengths and limitations

- Small numbers (n=15) may not capture 'outliers'
- Residential unit setting
  - allowed for assessment of withdrawal and cravings without confounders of other substance use / environmental 'triggers'
  - but not a 'real-world' examination of outcomes following cessation OAT (relapse to opioid use, other substance use)
- Limited 'comparison group': inability to recruit SL BPN patients …
  - Further research is needed to compare cessation LAIB v SL BPN outcomes (cessation rates, substance use, health, withdrawal severity, cravings)
  - *Nevertheless, experience of withdrawal from LAIB appears to be different to stopping SL BPN*

Questions re:
Withdrawal from LAIB:

- ✓ When will withdrawal commence?
- ✓ How severe will it be?
- ✓ When will symptoms peak and how long will they last?
- ? Are withdrawal outcomes better than stopping methadone / SL BPN?

Conclusions

- Our findings suggest that withdrawal from LAIB is milder than stopping SL BPN or methadone treatment
- We examined cessation from 64mg Buvidal Monthly.
  - Would findings be different if stopping higher Buvidal doses?
  - Should patients lower their dose prior to stopping (e.g. from 160, 128 or 96mg)
- Should we consider transferring patients on methadone or SL BPN to LAIB when planning cessation of OAT treatment?
  - A milder withdrawal syndrome does not necessarily mean better treatment outcomes
  - Definitive clinical trials are needed!
- **We need to develop better clinical approaches to support patients to successfully exit OAT – particularly important as we have an ageing cohort of patients on OAT, and can harness new technologies such as telehealth**