Microdosing for Buprenorphine induction: The Bernese Method

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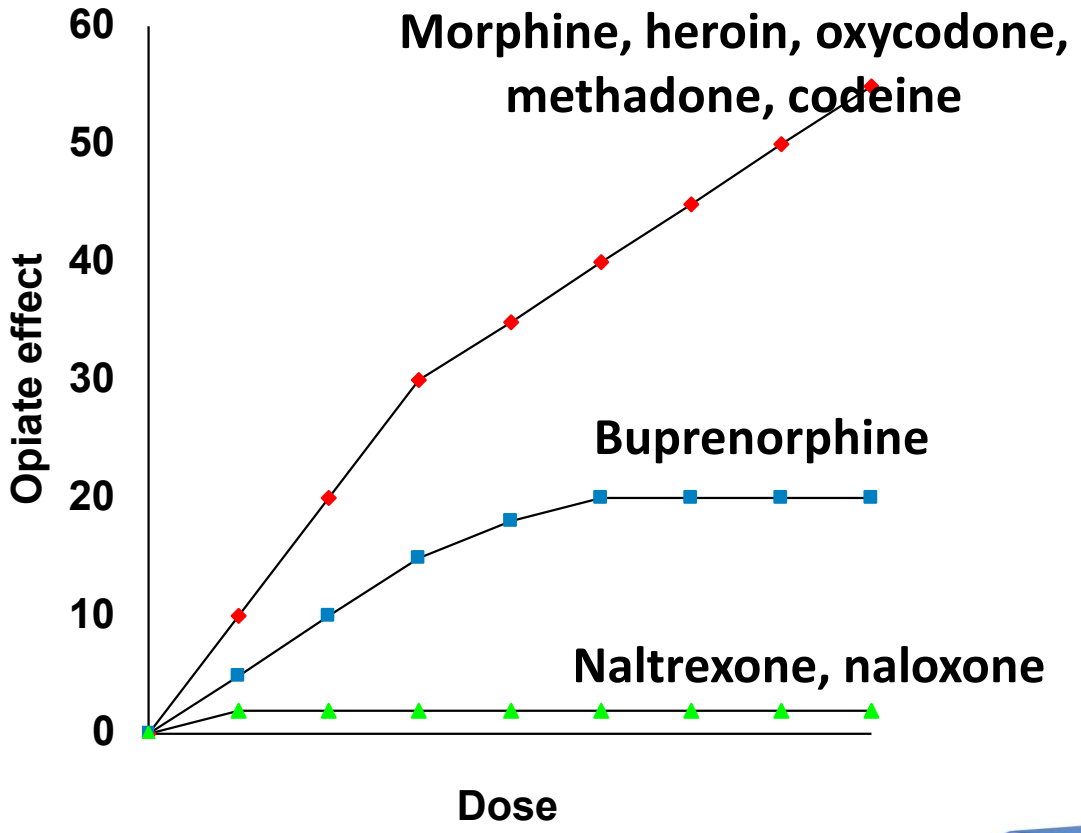
UNDER THE STEWARDSHIP OF MARY AIKENHEAD MINISTRIES

Why Buprenorphine?

- Buprenorphine is a partial μ-opiate agonist
- Lower receptor activation with a plateau effect
- Has high affinity for the opioid receptor
- Competes with other opioids for the receptors
- Binds to receptors *in preference* to full opioid agonists
- Has limited opioid effect, stopping withdrawal but not causing euphoria
- At 24 -72 hours, begins to dissipate from receptors

Reminder of activity



Why use Buprenorphine?

- Preferred OAT agent in many cases.
- Lower risk of overdose
- Ability to alter dosing frequency over methadone
- Increased number of takeaways potentially allowed
- Can allow for more travel freedom
- Long acting injectable product available (in PFP at present)

Transition difficulties

- Buprenorphine has a preferential binding to the opiate receptor
- This can result in precipitated withdrawal if commenced too soon after the last dose of another opiate
- General process is to wait until the patient is in withdrawal before commencing buprenorphine
    - This can lead some patients to avoid commencing as they may not tolerate the withdrawal state
- Transitioning from Methadone to Buprenorphine usually requires a dose reduction before being able to change products. This can often lead to destabilisation

What is microdosing?

- The use of small, incremental doses of buprenorphine to minimise the risk of precipitated withdrawal and allow for a smoother (not complete) transition from another opiate to buprenorphine.
- The main principle is based on the long half-life of buprenorphine (roughly 37 hours).
- Repeated daily dosing with incremental increases leads to a slow build-up of buprenorphine on the opiate receptors with a lower level of withdrawal symptoms due to receptor preferential binding

Does it work?

- A number of case series and case reports have been published.
- Original research published in 2016 from Hämmig et al from Bern, Switzerland (hence Bernese method)
- Several case reports and case series exist (Klaire et al 2018, Sandhu et al 2019 are good examples)

- The principle makes intuitive sense
- No RCT exist to determine whether the methodology is stronger than standard practice

Principles of transition

- Patients continue on their current opiate regimen (prescription or otherwise)
- Buprenorphine is introduced in a very low dose fashion
- This is then slowly up-titrated until the expected effective dose is achieved

- Once the daily buprenorphine dose is approaching the therapeutic range, the doses of other opiates can be down-titrated accordingly.
    - For illicit users, this will often be self regulated
    - For prescribed opiates, this can be managed in discussion with the patient

- Once the therapeutic dose is achieved, all other opiates can be ceased entirely.

Is it totally withdrawal free?

- No.
- Patients should expect to have some elements of withdrawal during the transition.
- The expectation is that the withdrawal symptoms that patients experience will be much less than either precipitated withdrawal, abstinent withdrawal or of OAT reduction

- The case reports describe mild symptoms in most cases if any withdrawal has been experienced.

How is the transition done?

- Patient continues usual dose of opiate
- Commence buprenorphine at an extremely low dose. This could either be 200microg or 0.25mg depending on whether you choose to use Temgesic or Subutex (Subutex requires splitting the tablet)
- This dose is then up-titrated over several days. The length of the titration will be patient specific and depend on a number of factors
  - Which opiate the patient is transitioning from
  - Total OMEDD
  - Methadone

Examples:

Table 1. Buprenorphine/naloxone micro-dosing titration schedule.[a]

Day	Buprenorphine dose	Buprenorphine/naloxone strength to use
1	0.25 mg sublingual daily	Buprenorphine 2 mg/naloxone 0.5 mg
2	0.25 mg sublingual twice daily	Buprenorphine 2 mg/naloxone 0.5 mg
3	0.5 mg sublanguage twice daily	Buprenorphine 2 mg/naloxone 0.5 mg
4	1 mg sublingual twice daily	Buprenorphine 2 mg/naloxone 0.5 mg
5	2 mg sublingual twice daily	Buprenorphine 2 mg/naloxone 0.5 mg
6	4 mg sublingual twice daily	Buprenorphine 2 mg/naloxone 0.5 mg
7	12 mg sublingual daily	Buprenorphine 2 mg/naloxone 0.5 mg

[a]Starting on day 8, continue buprenorphine/naloxone 12 mg/3 mg (one tab) sublingual once daily.

Table 1 Buprenorphine dosing and use of street heroin in case 1

Day	Buprenorphine (sl)	Street heroin (sniffed)
1	0.2 mg	2.5 g
2	0.2 mg	2 g
3	0.8+2 mg	0.5 g
4	2+2.5 mg	1.5 g
5	2.5+2.5 mg	0.5 g
6	2.5+4 mg	0
7	4+4 mg	0
8	4+4 mg	0
9	8+4 mg	0

Abbreviation: sl, sublingual.

Another example

	Buprenorphine/Naloxone*		Hydromorphone	
	Dosing	Total Daily Dose	Dosing	Total Daily Dose
Day 0	N/A		1-4 mg IV q4h PRN	3 mg
Day 1	0.25g SL q4h	1 mg	1-4 mg IV q4h PRN	11 mg
Day 2	0.5 mg SL q4h	2.5 mg	1-4 mg IV q4h PRN	15 mg
Day 3	1 mg SL q4h	5 mg	1-4 mg IV q4h PRN	15 mg
Day 4	2 mg SL q4h	8 mg	1-4 mg IV q4h PRN	4 mg
Day 5	16 mg SL daily	16 mg	Discontinued	

*Expressed as milligrams of buprenorphine in buprenorphine/naloxone sublingual tablet.

TABLE 2. Titration schedule for Case 2

	Buprenorphine/Naloxone*		Hydromorphone	
	Dosing	Total Daily Dose	Dosing	Total Daily Dose
Day 0	N/A		3 mg PO q4h regular 2-4 mg PO q4h PRN	24 mg
Day 1	0.5 mg SL q3h	2.5 mg	3 mg PO q4h regular 2-4 mg PO q4h PRN	26 mg
Day 2	1 mg SL q3h	8 mg	3 mg PO q4h regular 2-4 mg PO q4h PRN	24 mg
Day 3	12 mg SL daily	12 mg	Discontinued	

*Expressed as milligrams of buprenorphine in buprenorphine/naloxone sublingual tablet.

Another example

Table 2 Opioid doses, withdrawal symptoms, cravings, and mental state in case 2

Day	BUP (mg)	DAM (mg)	MET (mg)	Full agonist MEQDD (mg)[a]	SOWS score	Withdrawal symptoms (SOWS)	Craving[b]	Stress[c]	Overall[c]	Relaxed[c]	Tense[c]	Remarks
1	0.2	800	600	160	0		0					
2	0.4+0.4	800	40	140	1	Mild feelings of coldness	0					
3	0.8+0.4	800	40	140	0		0	5	84	74	15	
4	1.2+0.4	800	40	140	0		0					
5	2	800	40	140	0		0					
6	2.4	400	80	130	0		0	15	64	57	44	
7	2.8	800	40	140	0		0					
8	3	800	40	140	3	Mild feelings of coldness, mild runny eyes, mild yawning	0					
9	3.4	800	40	140	1	Mild runny eyes	0	18	85	76	6	
10	4	800	40	140	2	Mild feelings of coldness, mild yawning	0					
11	4.8	800	80	180	3	Mild feelings of coldness, moderate yawning	0					
12	6	800	60	160	0		0	5	78	76	4	
13	6	800	40	140	1	Mild runny eyes	0					
14	6	400	90	140	3	Mild feelings of coldness, mild yawning, mild runny eyes	0					Morning: last medication dispensing before vacation
15	6	0	180	180	7	Moderate feelings of coldness, mild runny eyes, mild aches and pain, moderate sleeping problems, mild yawning	2	35	80	81	24	Vacation
16	6	0	180	180	5	Mild feelings of coldness, mild runny eyes, mild aches and pain, moderate sleeping problems	2					Vacation
17	6	0	180	180	Missing		Missing					Vacation
18	6	0	180	180	Missing		Missing	20	73	79	26	Vacation
19	6	0	80	80	Missing		Missing					Afternoon: first medication dispensing after vacation
20	6	0	120	120	0		0					
21	6	400	80	130	0		0	15	80	73	26	
22	7.2	400	40	90	0		0					
23	8.8	400	80	130	0		0					
24	10.8	800	40	140	0		0	5	94	94	6	
25	13.2	400	40	90	0		0					
26	16	800	40	140	0		0					
27	20	400	60	110	0		0	7	95	92	3	
28	24	800	40	140	0		0					
29	24	0	0	0	1	Mild yawning	0					Cessation of full agonists, diarrhea in the morning
30	24	0	0	0	0		0	8	93	84	16	
31	24	0	0	0	0		0					
32	24	0	0	0	0		0					
33	24	0	0	0	0		0	9	85	85	15	

Case discussions

- 35 year old female
- 1.7g injected heroin per day
- Trialled conventional withdrawal and buprenorphine induction with significant withdrawal symptoms and was unable to tolerate symptoms.
- Returned to heroin use
- Offered microdosing induction.

- Commenced on:
- 200microg daily
- Increased each day by 200microg until 1mg reached
- Then double each day 2mg -> 4mg -> 8mg -> 16mg
- Once 8mg had been reached, pt self ceased heroin use.
- Stabilised on 16mg.
- Pt experienced some withdrawal symptoms on 4mg day and 8mg day, but these were much more tolerable than standard dosing regimen.

Case discussions

- 42 year old man.
- On methadone 80mg
- Desires to change to buprenorphine to allow him to travel interstate for work (requests 6 takeaway doses once stabilised sufficiently). Has been stable on methadone for several years.
- Has trialled conventional reduction, but destabilised and returned to stable dose.
- Patient told to continue usual methadone dose
- Commenced on 200microg buprenorphine
- Additional 200microg increases daily until 1mg reached.
- Increased to 2mg – experienced some mild/moderate withdrawal, but manageable
- Increased to 3mg – tolerated increase.
- Titrated further to 16mg buprenorphine over a 2 week period to allow patient to down-titrate methadone as well. At the end of the titration, patient stabilised on 16mg daily and no methadone

References

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any
questions?