Overview of pharmacotherapies – methadone, buprenorphine, LAIB

Victorian Opioid Management ECHO
Department of Addiction Medicine
St Vincent's Hospital Melbourne 2021

Interesting titbits

NOPSAD data 2019:

Victoria OAT – 14,085

Australia – 50,945

(Avg 20:10,000)

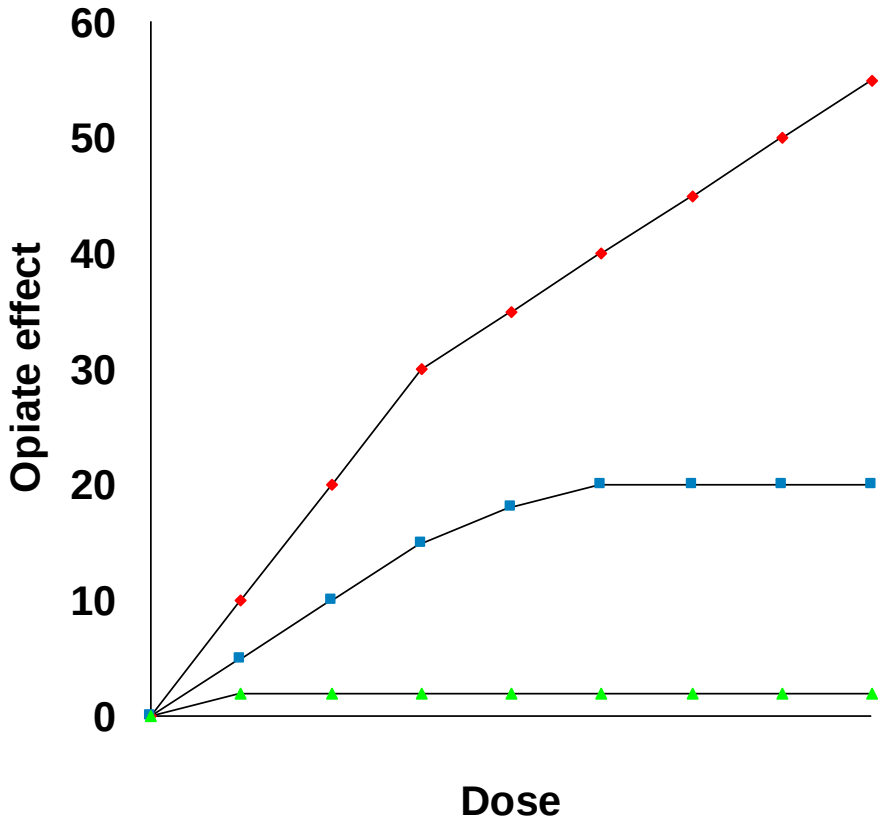
AIHW reports:

>50k prescriptions per 100k people for opioids in 2017

<1% using illicit heroin

Pharmacotherapy type	NSW	Vic	Qld	WA	SA	Tas	ACT	NT	Aust
2019									
Number									
Methadone	14,177	8,941	2,858	1,989	1,737	286	872	31	30,891
Buprenorphine	7,244	368	745	71	17	82	6	19	8,552
Buprenorphine-naloxone	n.a.	4,776	3,555	1,178	1,333	316	243	101	11,502
Total	21,421	14,085	7,158	3,238	3,087	684	1,121	151	50,945
Per cent									
Methadone	66.2	63.5	39.9	61.4	56.3	41.8	77.8	20.5	60.6
Buprenorphine	33.8	2.6	10.4	2.2	0.6	12.0	0.5	12.6	16.8
Buprenorphine-naloxone	n.a.	33.9	49.7	36.4	43.2	46.2	21.7	66.9	22.6
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

Opioids



Full agonists

- Morphine
- Heroin
- Oxycodone
- Methadone
- Codeine

Partial agonist

- Buprenorphine

Pure antagonists

- Naltrexone
- Naloxone

Methadone pharmacology

- Onset of effects - 75% oral bioavailability. Detected in plasma 15-45 mins after ingestion
- Peak plasma concentration- 2.5 - 4 hours (Eap, Buclin, Buchanan 2002)
- Duration of effects 20-36 hours: elimination t½ (Eap et al 2002, Humeniuk, Ali, White, Hall & Farrell 2000)
- Methadone is highly bound to plasma proteins, in particular to α1-glycoprotein

Most deaths in early phase of treatment occur on Day 3-4

Inter-individual variation

There is up to a **17-fold inter-individual variation** of methadone blood concentration for a given dosage, with variations in metabolism accounting for a large part of this variation

(Eap, et al., 2002).

Most patients will be kept out of withdrawal between 10-40mg/day and cravings suppressed between 60-100mg/day

Brands of methadone

Both brands contain “methadone hydrochloride” 5mg/mL as the active ingredient

The two brands of methadone contain different excipients :

- Excipient in **Biodone Forte**: Water, permicol red
- Excipient in **Aspen Methadone Syrup (GSK)**: Caramel, ethanol, glycerol, sodium benzoate, sorbitol solution 70% (noncrystallising), purified water and SC345280 anise spice

Metabolism

Methadone is primarily broken down in the liver via the cytochrome P450 enzyme system with:

CYP 3A4

CYP 2D6 (to a lesser extent) (Eap, et al., 2002).

-N.B. drug interactions and CYP system.

Approximately 10% of methadone administered orally is eliminated unchanged.

The rest is metabolised and the (mainly inactive) metabolites are eliminated in the urine & faeces.

Buprenorphine

- Has high affinity for the μ, κ and δ opioid receptors
- 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 the μ receptor – partial agonism
    - At the κ and δ, works as an antagonist
- At 24 -72 hours, begins to dissipate from receptors
- Half-life of 37 hours

Precipitated withdrawal

- Precipitated withdrawal = rapid ***intense withdrawal symptoms***
  - Occurs in setting of true dependence when buprenorphine
    - Competitively occupies receptors
    - Dislodges agonists

- Starting dose 2 to 4 mg and observe for one hour

- Precipitated withdrawal 2 to 4 mg hourly until symptoms settle

Subutex + naloxone = Suboxone

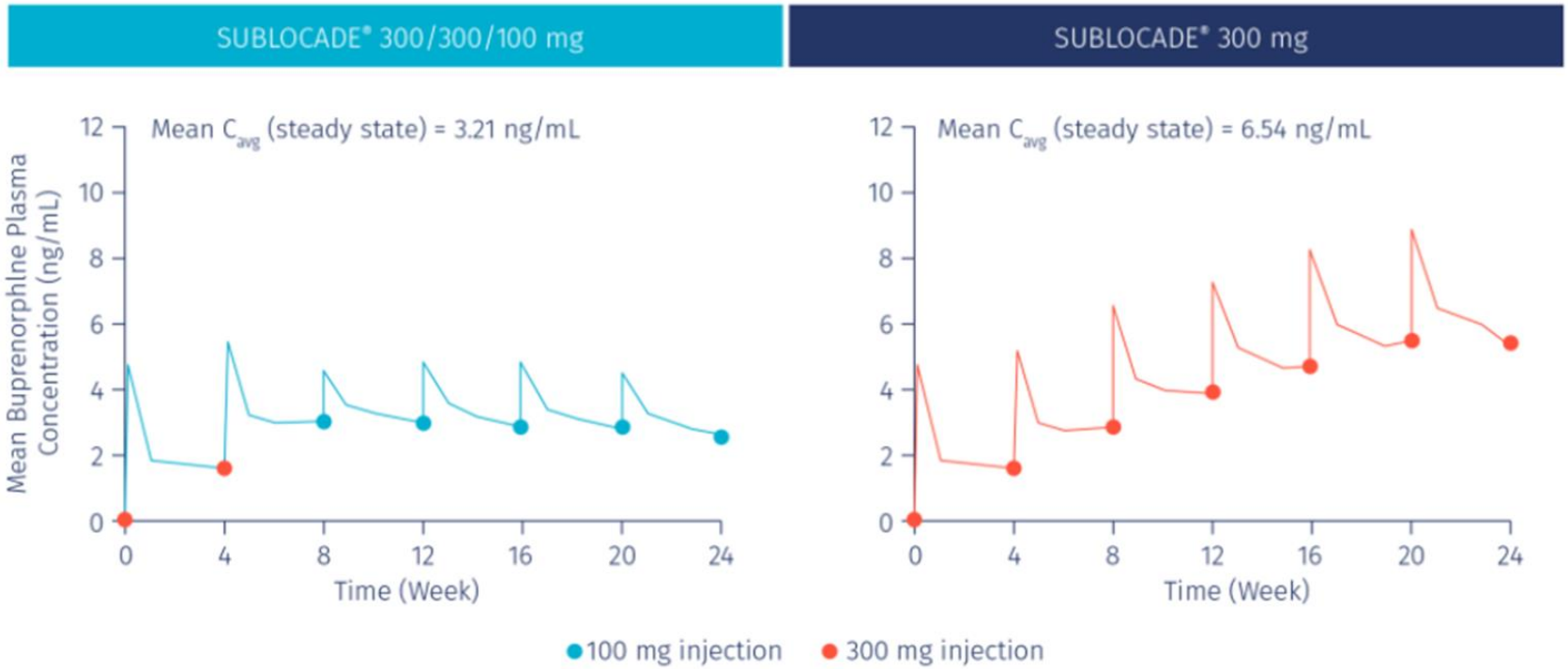
Adding naloxone is intended to reduce abuse potential

- Naloxone - very low bioavailability: <2% absorbed
- Meant to block the effect of buprenorphine if it is injected
- Only precipitates withdrawal if injected in presences of opioid

Long Acting Injectable

- Single Point of contact
    - Prescriber is the administration point
    - No need to attend pharmacy by patient
- Weekly and Monthly preparations
- Minimises frequency of contact with health system
    - Two edged sword
- Increases a patient's autonomy and freedom
- Travel becomes less of a concern
- Significantly reduced stigma
- Reduced costs **

Sublocade

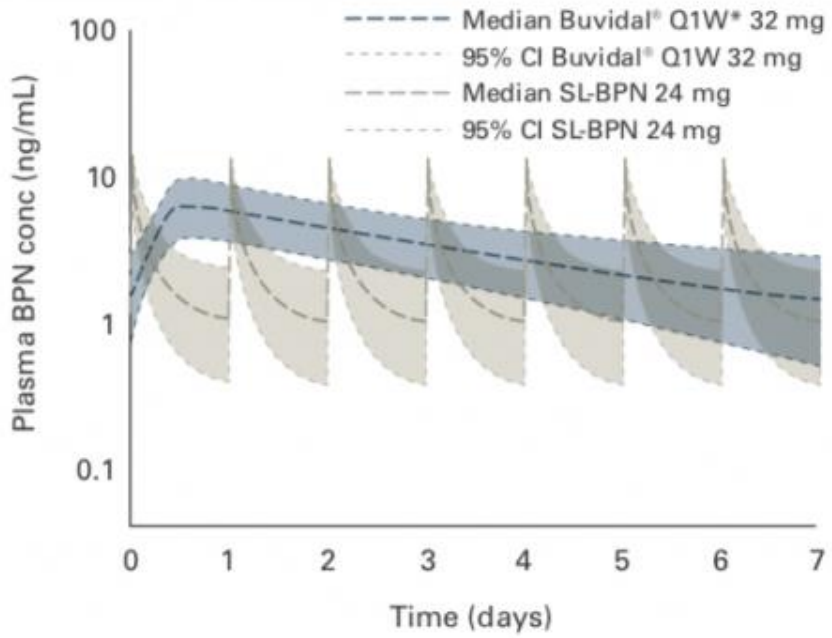


BPN plasma concentrations were assessed before each injection, at 4 h and 24 h after injection, and at each weekly visit over the dose schedule

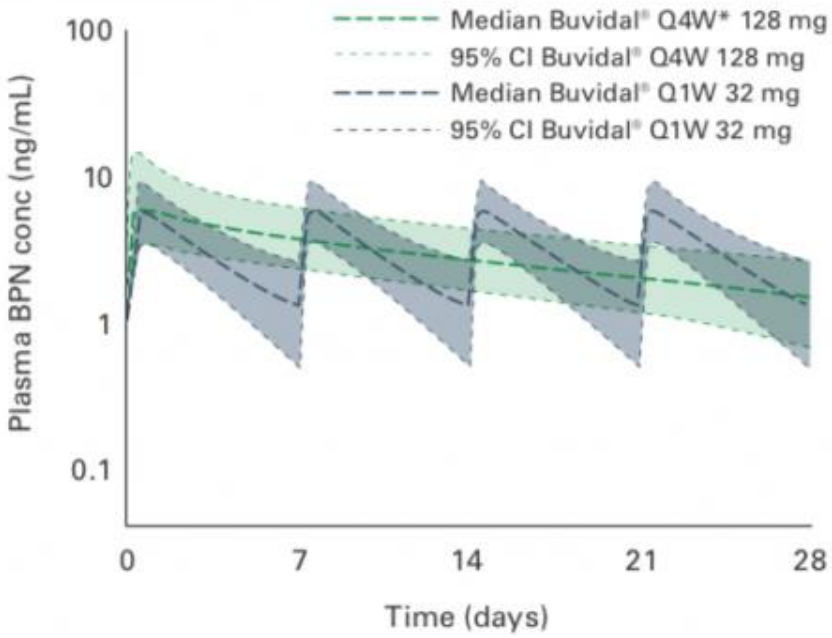
Buvidal

Illustration of population pharmacokinetic (PK) profiles for Buvidal® and SL-BPN

Buvidal® Weekly and daily SL-BPN



Buvidal® Monthly and Buvidal® Weekly



Downsides?

- Both products reduce patient/prescriber/pharmacy contact
- Injections are painful Sublocade > Buvidal
  - Sublocade pain reduced with ice pack pre-dose
- Buvidal has smaller window for dosing than Sublocade
  - Buvidal - 5-7 days for weekly and 3-5 weeks for monthly
  - Sublocade – Minimum 26 days post last dose, long half life allows for wider maximum time
- Increased risk to administrator of BBV in event of needle-stick injury
  - Mediated by appropriate testing and treatment of patients