

Buprenorphine: what is it & why use it?

Dr Nicholas Lintzeris, MBBS, PhD, FACHAM

Locum Consultant, Oaks Resource Centre, SLAM

National Addiction Centre, Institute of Psychiatry

Overview of presentation

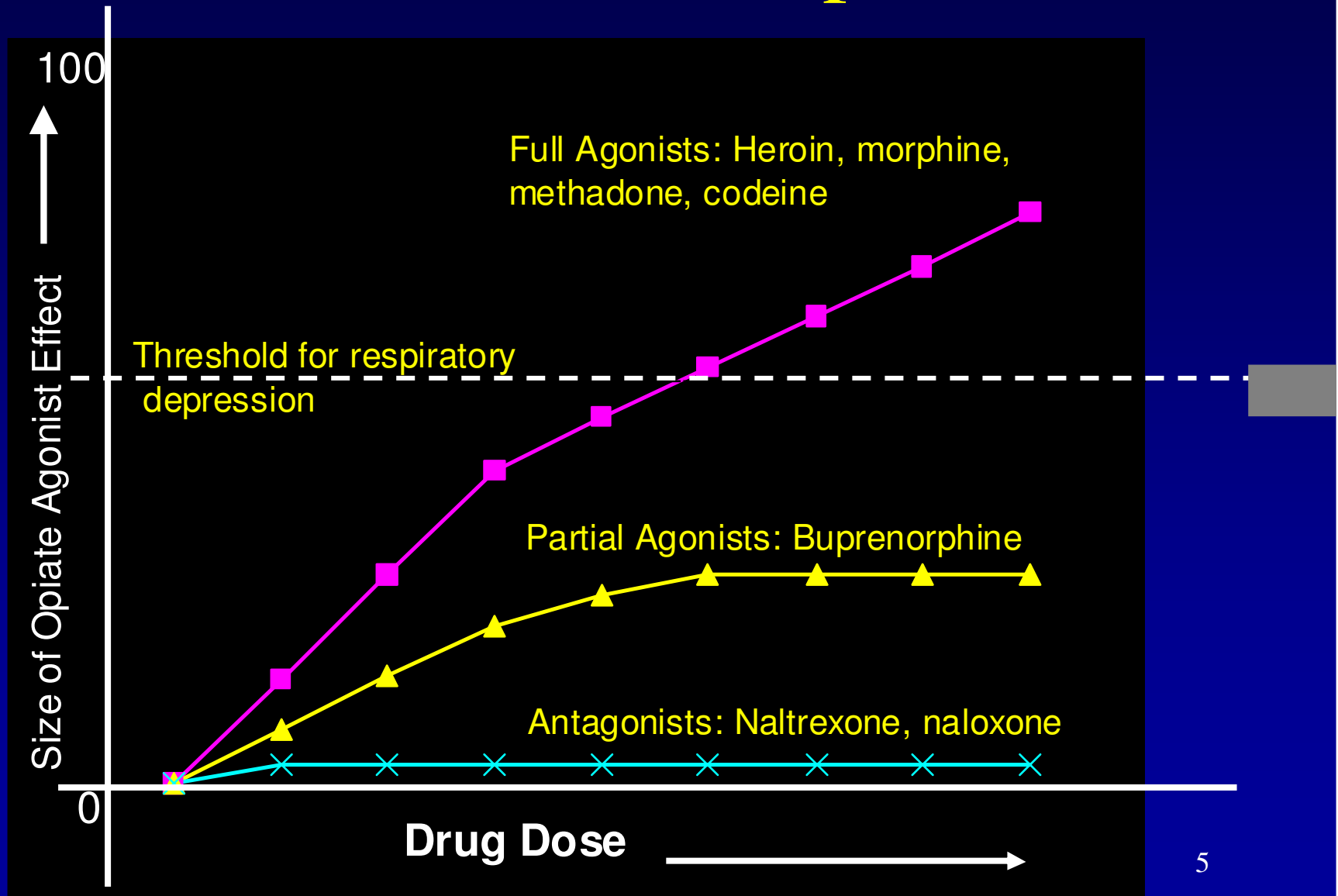
- Overview of clinical pharmacology
- Overview of evidence
 - BPN vs methadone for maintenance
 - BPN vs symptomatic / methadone for detox
 - Comparisons between maintenance & detox

Buprenorphine: clinical pharmacology

Buprenorphine

- A synthetic opioid
- Partial agonist at the μ opiate receptor
 - Low intrinsic activity only partially activates opiate receptors
- High affinity for the μ receptor
 - Binds more tightly to opiate receptors than other opiates

Classification of Opioids



Pharmacological & clinical properties

Pharmacological property	Clinical implication
Substitutes for heroin	Prevents withdrawal
Opiate-like effects	Reduces cravings Increases treatment retention
'Blocks' other opiates	Reduces heroin use
Long duration of action	Daily (or alternate day) dosing

Mode of administration

- High 1st pass metabolism
- Bioavailability: IV > SC > SL > oral
- Sublingual tablets
 - 0.4, 2 & 8 mg tablets available
 - tablets take 3 to 5 minutes to dissolve
 - only get ~ half effect if swallowed

Duration of effects

- Quick onset of action: 30–60 min
- Peak effects: 1 – 4 hours
- Duration of action is dose related
 - low dose (2 – 4 mg): 4 – 12 hrs
 - med dose (8 – 16 mg): ~ 24 hrs
 - high dose (16 – 32 mg): 2 – 3 days

Withdrawal from buprenorphine

- Opiate withdrawal syndrome on stopping long-term BPN treatment
 - Milder withdrawal than typically seen with heroin / morphine / methadone
 - Peak withdrawal experienced within first 2 to 5 days after stopping chronic BPN treatment, with mild symptoms persisting for weeks
- Minimal withdrawal if used for short courses
 - e.g. for heroin detox

Common side-effects

- Headache
- Constipation
- Nausea
- Drowsiness, sedation
- Tiredness, lethargy
- Sleep disturbances
- Sweating
- Precipitated withdrawal on commencing BPN

Drug interactions

- Sedatives
 - Mixing sedatives (e.g. EtOH, BZDs) can produce respiratory depression, heavy sedation, coma, death
- Opioid agonists / antagonists
 - BPN blocks effects of other opiate analgesics
- Hepatic enzyme inhibitors / inducers
 - appears to be less impact than with methadone

Buprenorphine: The evidence

BPN vs. methadone for maintenance

BPN vs. clonidine / methadone for detox

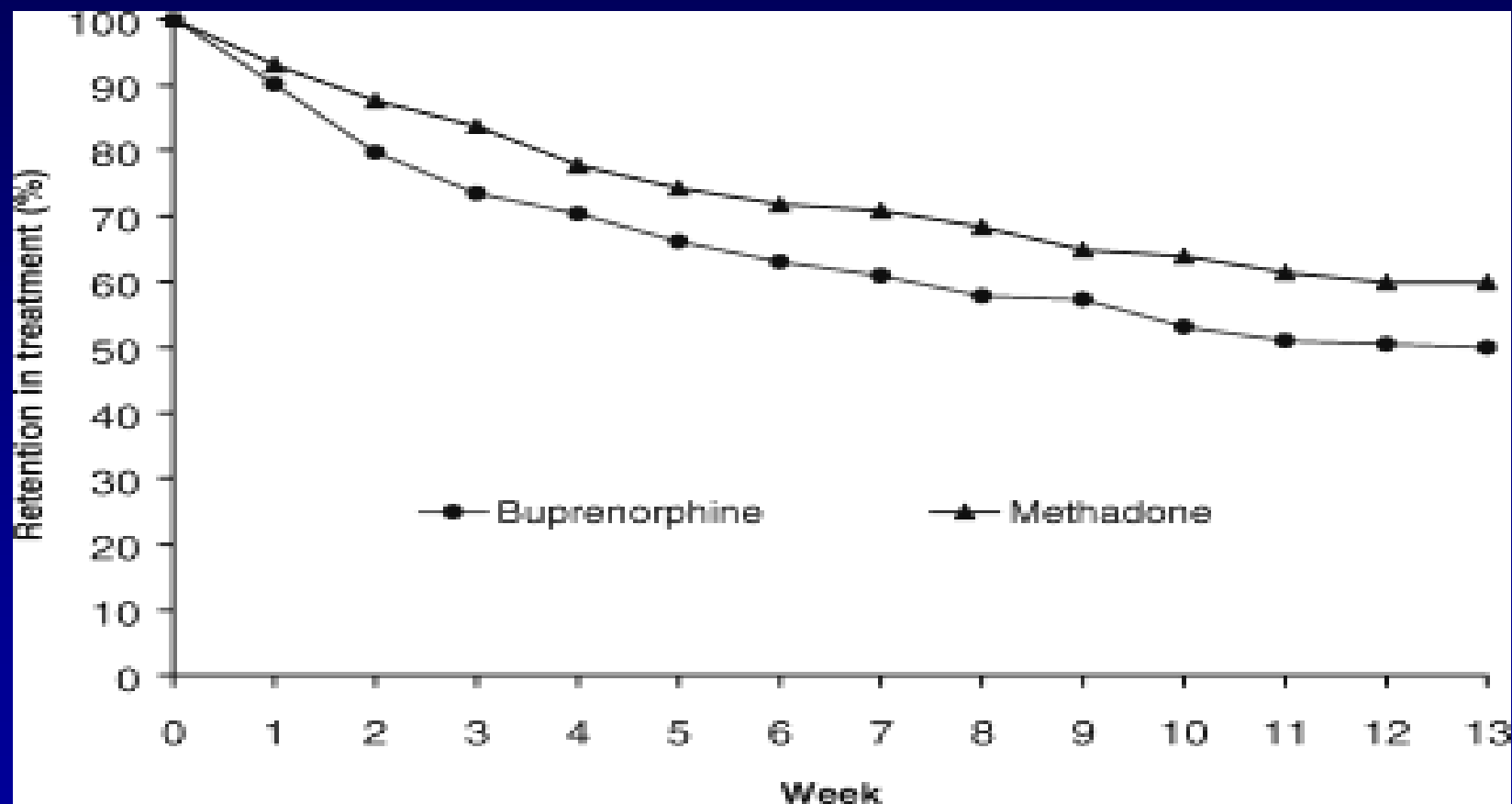
Maintenance vs detox

Maintenance Treatment

- RCTs comparing BPN to Methadone mainly done in specialist clinics
- Systematic reviews
 - West, O'Neal & Graham 2000, *Substance Abuse*
 - Barnett, Rodgers & Bloch 2001 *Addictions*
 - Mattick et al 2002: *Cochrane review* (>13 RCTs, >1000 patients)
- Main outcomes: heroin use & treatment retention

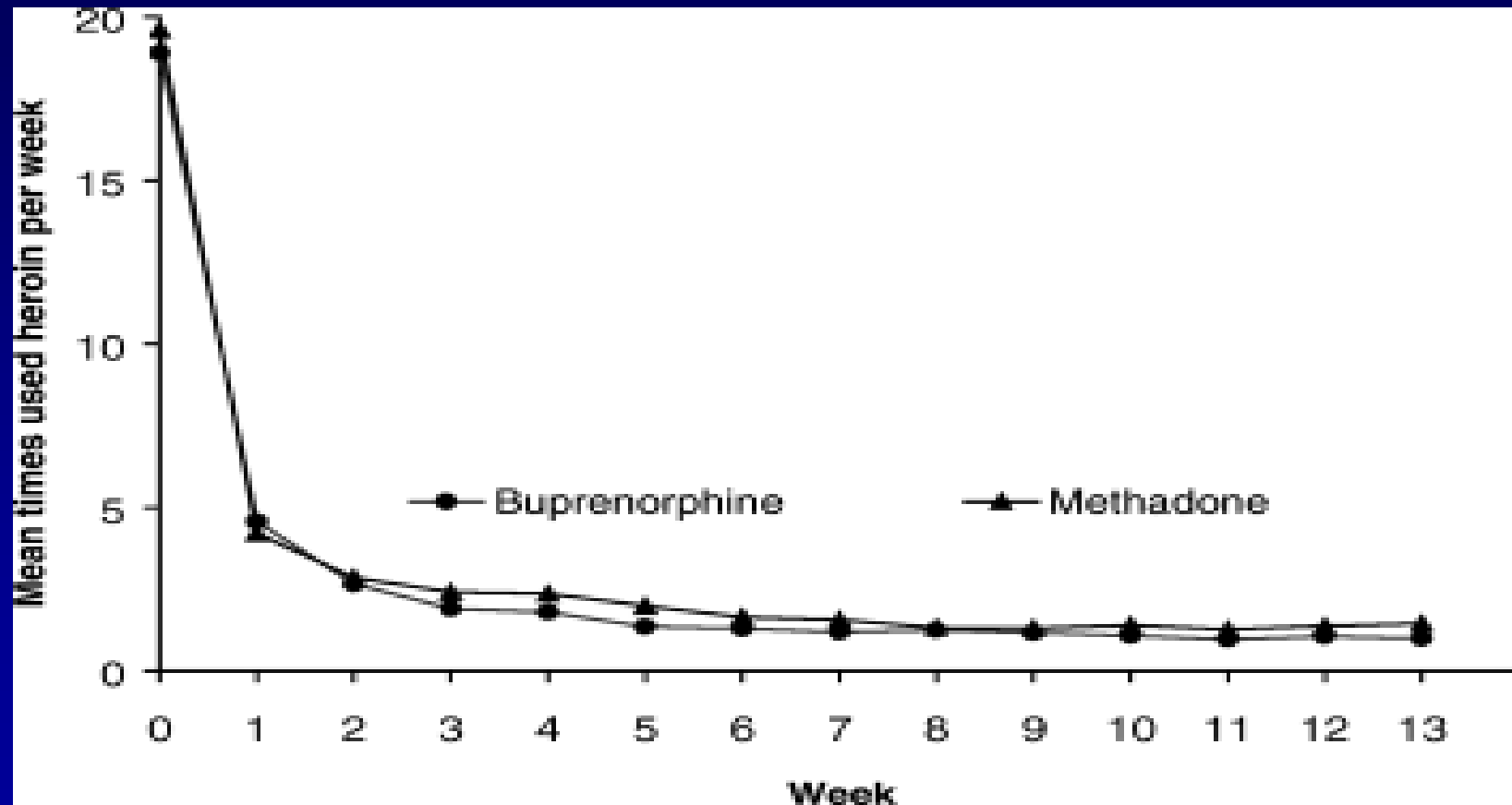
RCT BPN vs Meth: Retention

Mattick et al 2003 Addictions



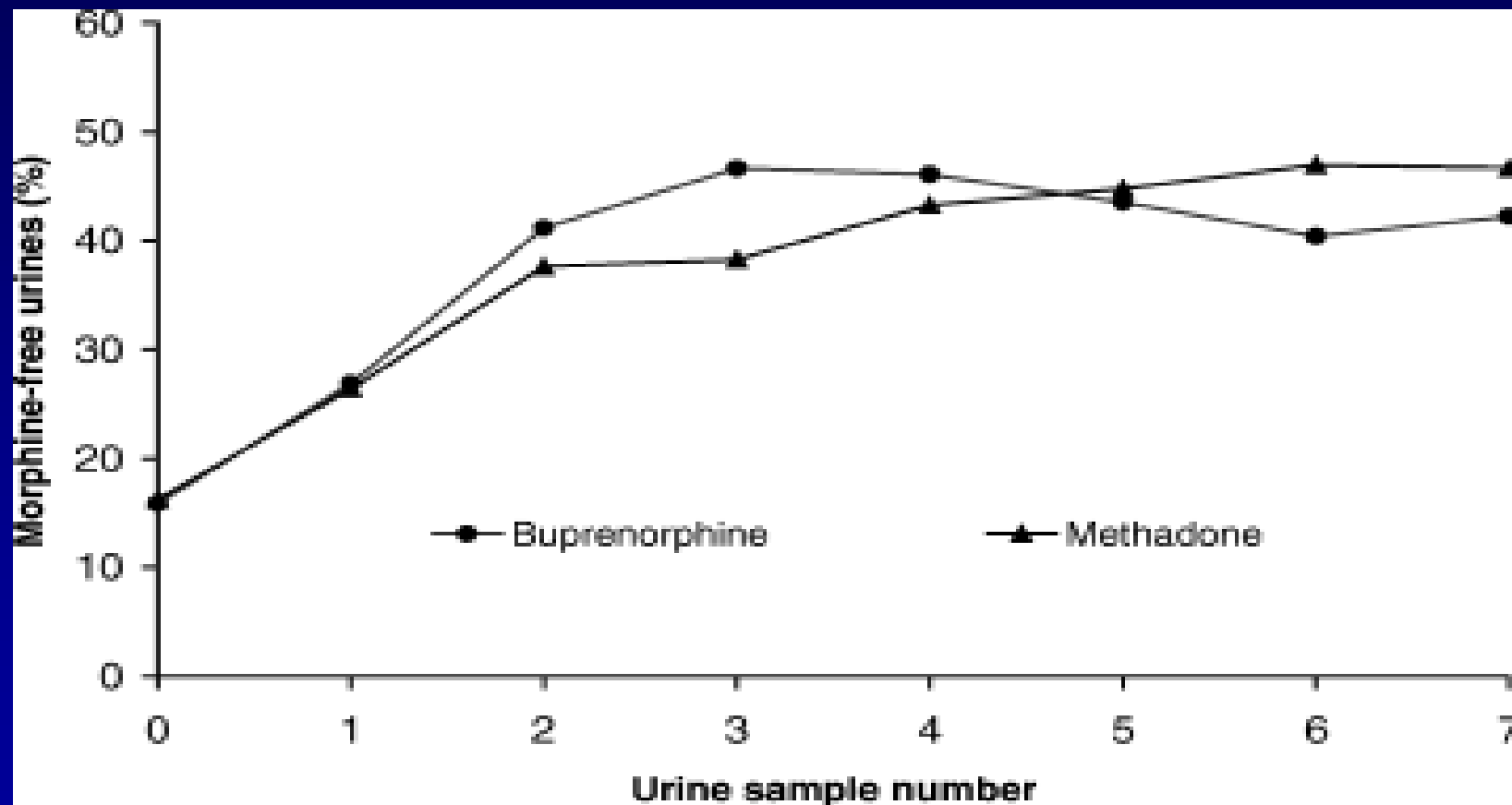
RCT BPN vs Meth: self report drug use

Mattick et al 2003 Addictions



RCT BPN vs Meth: Urine results

Mattick et al 2003 Addictions



Efficacy of BPN maintenance treatment

For heroin use & treatment retention in RCT's

High dose MMT (> 80 mg)

better than

Medium dose MMT(40-80mg) = Medium dose BMT(8-12mg)

better than

Low dose MMT (< 40 mg) = Low dose BMT (< 8 mg)

Note: No RCTs of high dose BMT (≥ 16 mg) to Meth

Choosing substitution maintenance medications

- Research has not identified whether certain types of clients respond better to buprenorphine / methadone
- Treatment choices should consider:
 - Evidence regarding safety and effectiveness
 - Individual variation in pharmacokinetics & side effects
 - Ease of withdrawal from medication
 - *Response to treatment - setting, monitoring & reviewing goals*
 - Resources
 - BPN more expensive than methadone but medication is only one factor in the cost of treatment
 - Patient preferences: expectancy & informed consent

But can GPs do it?

(Lintzeris et al submitted)

- RCT comparing BPN & Meth in primary care settings
- 139 patients - 82 heroin users, 57 methadone clients
- 20 GPs, 30 pharmacies
 - clinical guidelines & 3 hr training session
- 12 month open-label ‘naturalistic’ RCT
- Comparable outcomes between methadone & BPN for
 - treatment retention
 - heroin & other drug use
 - psychosocial functioning
 - cost effectiveness

Principles of effective maintenance treatment

- Duration of treatment
- Dose
- Quality of therapeutic relationship
- Regular review, supervision & monitoring
- Participating in psychosocial services

Bio-psycho-social model for chronic condition

BPN in Detox

Objectives of detoxification

Detox is not a 'cure' for heroin dependence

- Most heroin users relapse after withdrawal
- Need long-term treatment to achieve long-term changes

Short-term intervention that aims to:

- Interrupt a pattern of heavy & regular drug use
- Alleviate withdrawal discomfort
- Prevent complications of withdrawal
- Facilitate post-withdrawal treatment linkages

Components of detoxification program

- Assessment & client-treatment matching
- Supportive care
 - ‘safe’ environment
 - provision of information
 - supportive counselling
 - regular monitoring
- Medication
- Post-withdrawal linkages

Detox medications

- Substitution medications
 - *methadone*
 - codeine, dihydrocodeine, propoxyphene
 - *buprenorphine*
- Symptomatic medications
 - *alpha adrenergic agonists: clonidine; lofexidine*
 - benzodiazepines
 - antiemetics, NSAIDs, antidiarrhoeal agents
- Opioid antagonists
 - *naltrexone*

Summary of BPN efficacy in detox

- *BPN better than clonidine ± BZDs in relieving withdrawal symptoms, better completion rates, cost effectiveness & post-detox treatment retention*
 - Nigam et al 1993; Cheskin et al 1994; Schneider et al 2000; O'Connor et al 1997; Lintzeris et al 2002
- *BPN less withdrawal severity than methadone*
 - Petitjean et al 2002, Seifert et al 2002, Bearn et al 2003
- *BPN less severe withdrawal & comparable NTX induction rates than rapid antagonist detox*
 - O'Connor et al 1997, Bochud Tornay 2003

BPN Vs Clonidine: Withdrawal symptoms

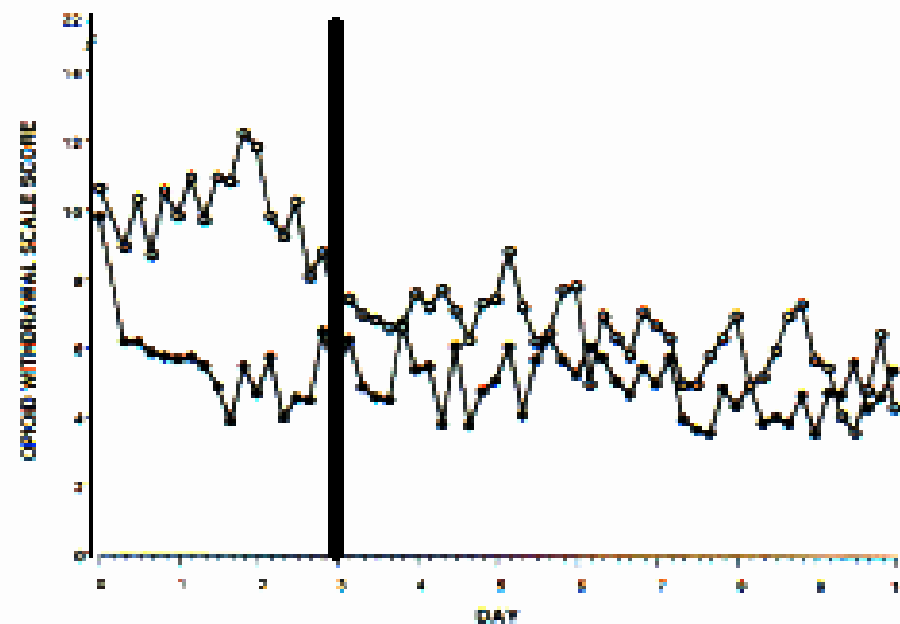
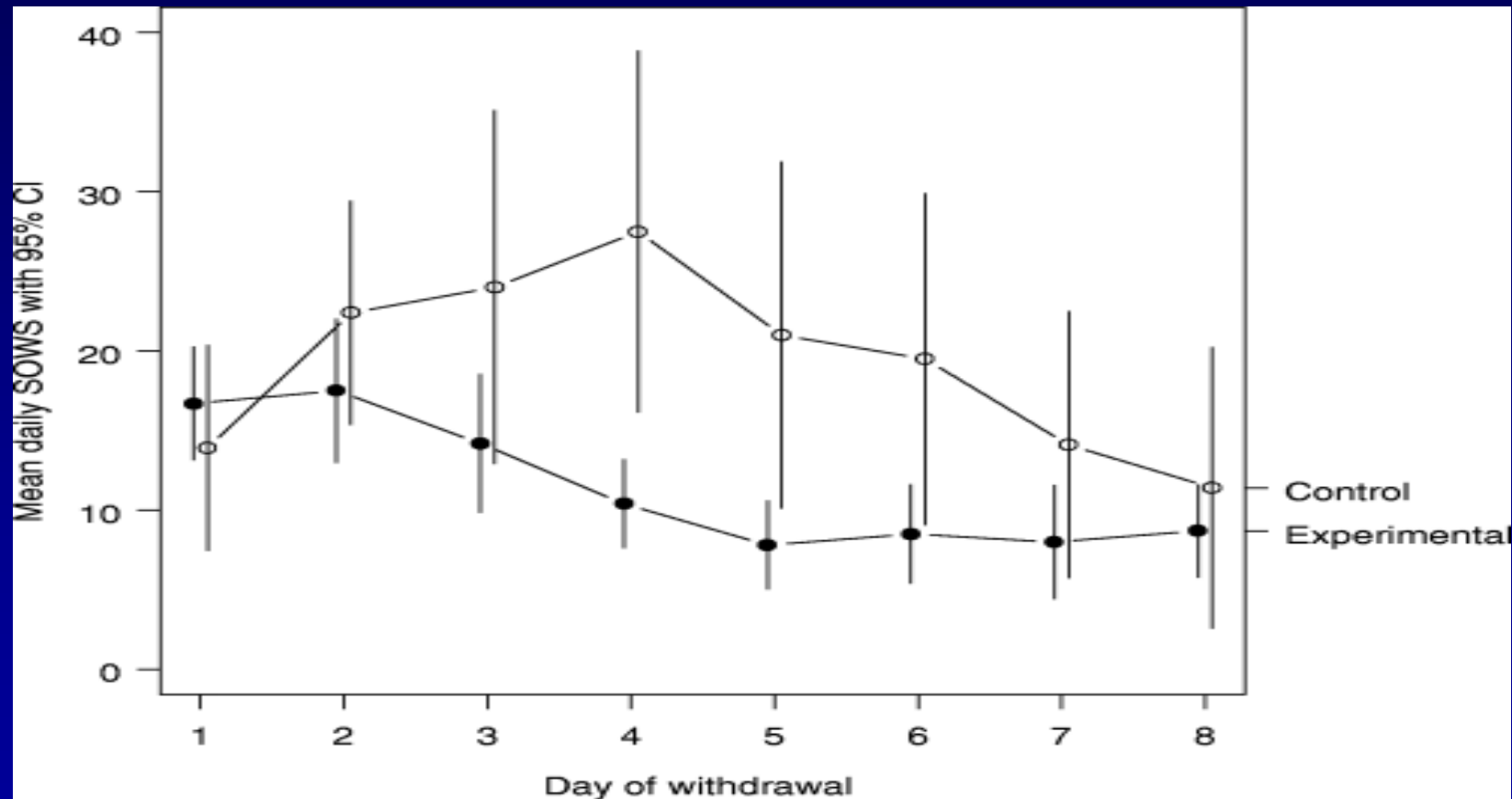


Fig. 3. Mean (area under curve) patient self-reported opioid withdrawal symptoms (maximum score = 22.) (●) Buprenorphine, (○) clonidine.

Cheskin et al (1994) Drug & Alc Dependence 36, 115-121

Outpatient RCT: BPN vs clonidine + BZDs

Lintzeris et al 2002 Addictions 11, 1395-1404



RCT Meth vs BPN for detox

Petitjean et al 2002

- N = 37 (19 BPN, 18 Meth)
- Inpatient unit, Basel
- Completed detox:
 - 88% BPN, 89% Meth
- Conclusion:
 - more rapid reductions with BPN
 - more withdrawal in BPN group early but less withdrawal when medication ceased

Figure 1: Buprenorphine and methadone doses

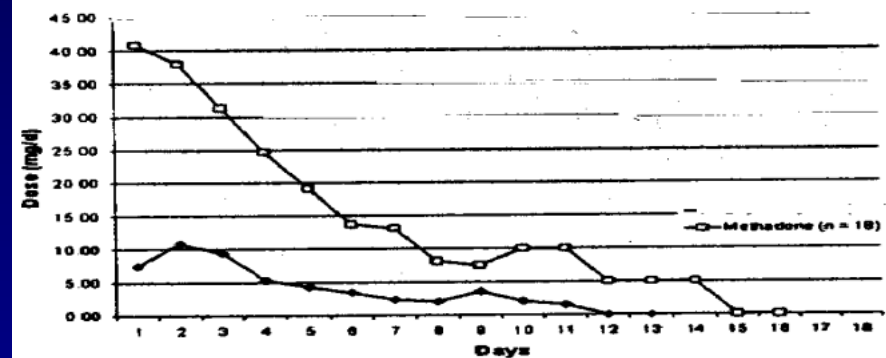


Figure 2: SOWS scores

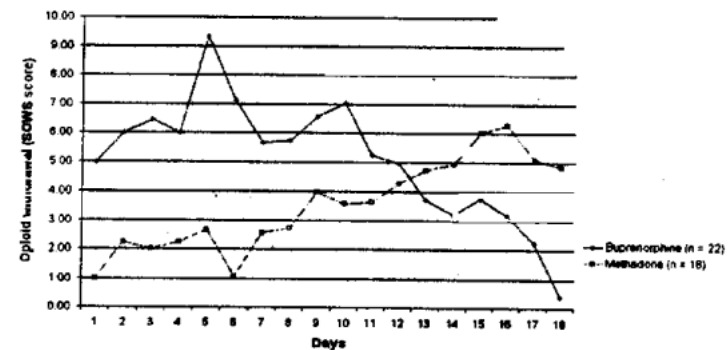


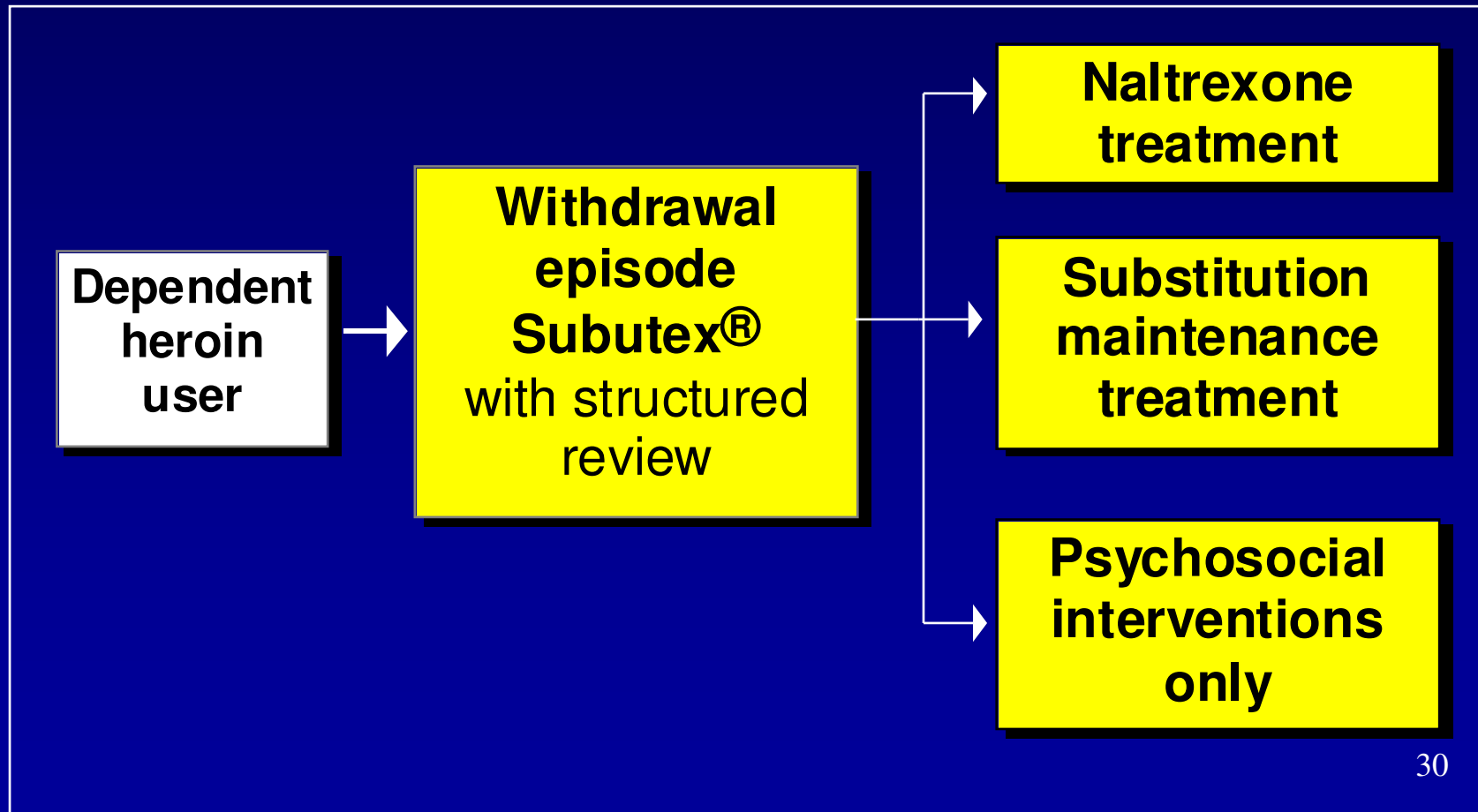
Fig. 2. Time course functions and drug effects for buprenorphine and oral methadone on opiate withdrawal severity. Data points show the mean of all subjects in the buprenorphine and the methadone group (ITT-analysis). Significantly higher SOWS-Scores were found in the buprenorphine group on day 8 ($p < 0.05$). Patients in the methadone group had higher scores on days 13, and 16 after the detoxification phase ($P < 0.05$).

But can GPs do it?

(Gibson et al submitted MJA)

- RCT comparing detox services delivered in specialist clinic vs. GP/pharmacy settings
- N=115, Sydney, 8 day detox (using 5/7 BPN)
- Outcomes:
 - Retention in detox: 71% primary care vs 78% clinic
 - Heroin use during detox (UDS negative)
 - Day 5: 31% in primary care c/w 32% clinic
 - Day 8: 27% primary care c/w 32% clinic
 - Similar post-detox treatment retention

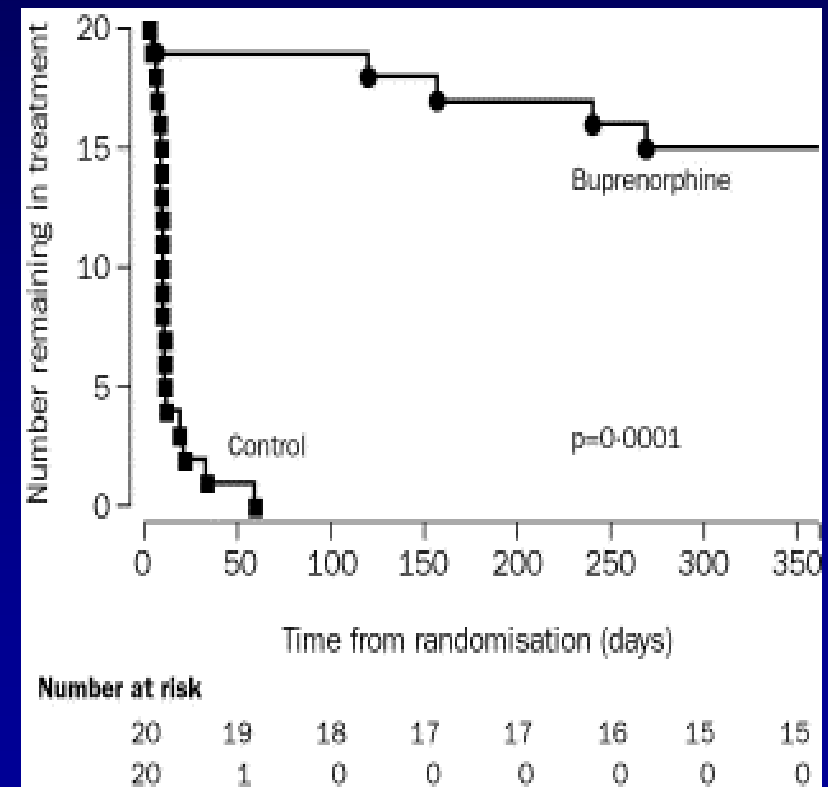
Subutex[®] as a gateway to treatment



RCT BPN Maintenance vs Detox

Kakko et al Lancet 2003

- 40 subjects randomised to
 - 1 week detox / 1 year maintenance
 - counselling for 1 year
- Heroin use
 - BPN Detox = all relapsed
 - BPN Maintenance = 75% (SD 60%) Opiate Negative UDS
- Mortality (p=0.015)
 - BPN Detox 4/20 (20%)
 - BPN Maintenance 0/20



RCT Meth maintenance vs gradual detox

Sees et al JAMA 2000

- N=154 randomised to
 - 1 year methadone maintenance or
 - 6 months gradual reduction + intensive psychosocial
- Results: Maintenance group had
 - better treatment retention
 - less heroin use
 - fewer HIV risk practices
 - fewer legal problems

Key points about detox

- Do not expect 'cures' from detox programs
- Short term treatment usually = short term changes
- Medication only one aspect to good detox
- BPN increases post-detox options

Summary of evidence

- BPN safe & effective detox medication
 - ?Becoming gold standard detox medication, BUT
 - Detox less effective than maintenance treatment
- BPN safe & effective maintenance medication
 - about as good as methadone in flexible dose studies
 - research cannot identify who does better on BPN / Meth

Practical aspects of using buprenorphine

Commencing BPN treatment

When to stop treatment

Induction into BPN treatment

Induction from either :

- dependent heroin use
- methadone treatment

- from < 40 mg:	OK
- from 40-60mg:	difficult
- from > 60 mg:	do not attempt

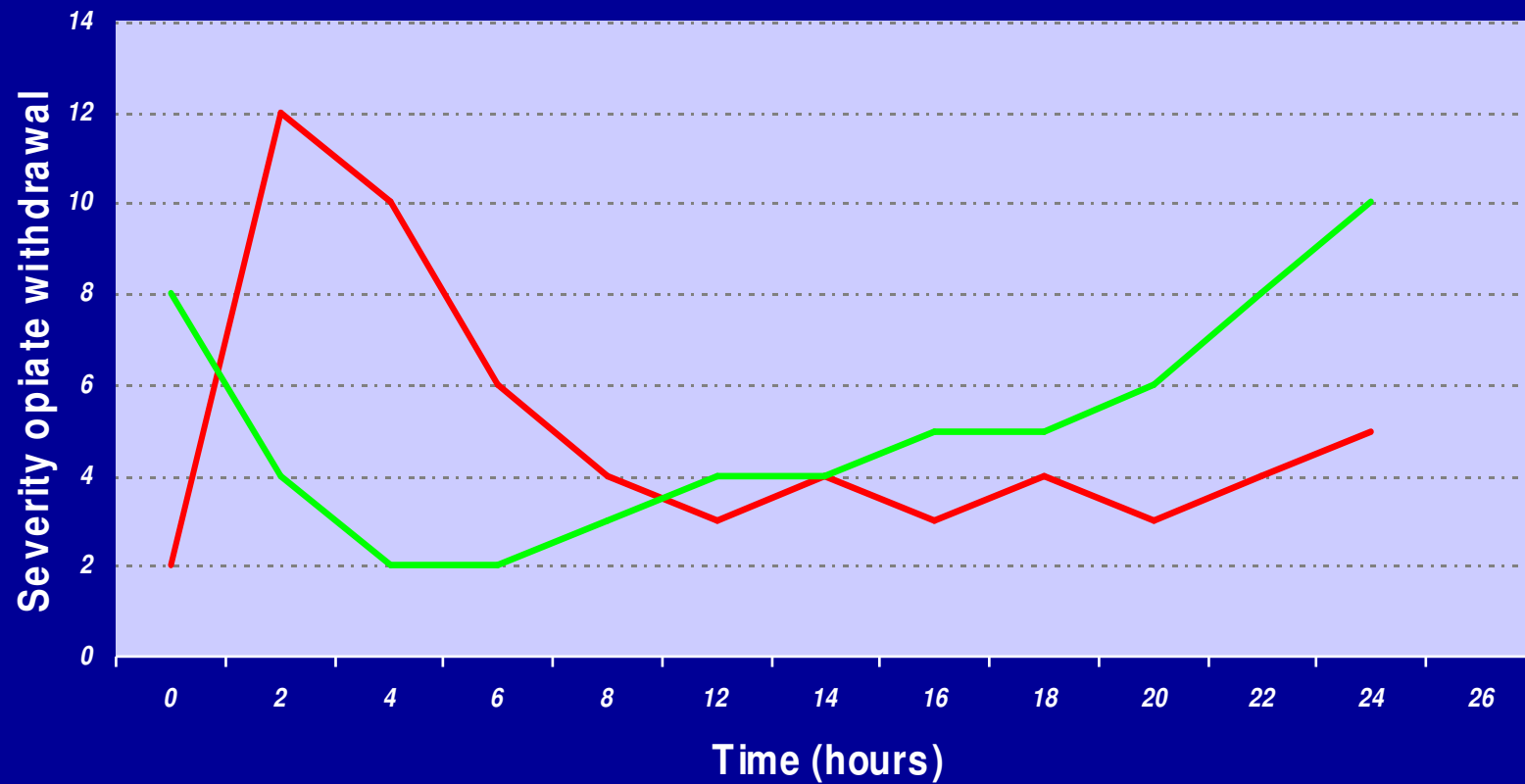
Precipitated withdrawal

- Buprenorphine (high affinity) competes with & displaces full agonists (heroin, methadone) from receptors
- Buprenorphine has lower opioid activity than full agonists
- Reduction in opioid activity experienced as withdrawal
- Only likely to occur if first dose of buprenorphine is given whilst client experiencing effects of other opiates
 - Within 6 to 12 hours of recent heroin use
 - Within 24 - 48 hours of client on methadone

Features of precipitated withdrawal

- More common features include:
 - sweating, anxiety, abdominal cramps, diarrhoea, nausea
- Commences ~ 30 to 90 minutes after 1st BPN dose
- Peaks within 1.5 - 3 hrs after 1st dose & then subsides
- Minor symptoms may continue after 2nd or 3rd dose
 - Symptoms may persist for days if continued heroin use prior to each BPN dose

“I’ve been in withdrawal”



— Precipitated withdrawal — Not enough buprenorphine

Preventing precipitated withdrawal

- Time of first buprenorphine dose – delay dose until patient in opiate withdrawal
 - > 6 - 8 hrs after last use of heroin
 - > 24 hrs after low methadone dose (<40 mg)
 - > 48 hrs after 'medium' methadone dose (40 - 60 mg)
- Size of first buprenorphine dose
 - less risk with low dose (e.g. ≤ 4 mg)
- Role of dispensing pharmacist
 - assess patient prior to dose
 - communication with patient & doctor
- Provide information to patient & carers

Initial doses for heroin users

	Dose
<i>Maximum initial dose</i>	8 mg
High physical dependence & patient in withdrawal at 1 st dose	6 to 8 mg
High physical dependence & <ul style="list-style-type: none">• no withdrawal features at 1st dose• high-risk sedative drug use• significant medical condition (e.g. liver failure, drug interactions, respiratory)	4 mg or less
Low level physical dependence	4 mg or less

Reviewing patients during induction

- ‘Good’ induction = regular & frequent review
 - Patients often need reassurance, particularly if precipitated withdrawal or early side-effects
 - Review every 1 - 2 days if possible
 - Should review patient before 3rd dose
- Dose increases only after review with clinician
 - Do not authorise ‘automatic’ dose increases
 - Increases in bup dose can occur daily
- Dose increases usually by 2 to 4 mg at a time

Examples of induction doses (heroin users)

	Day 1	Day 2	Day 3	Day 4	Day 5	Day6	Day7
A	4	6	8	8	8	10	10
B	8	12	12	16	16	16	20
C	2	6	6	6	8	8	8

Doses

Induction

- Commence 4 to 8 mg daily
- Frequent & rapid dose increases possible (by 2 to 4 mg)

Maintenance

- Daily doses: 12 – 24 mg (max 32mg)
- (Alternate day dosing possible for most clients)

Withdrawal

- More rapid dose reductions possible (e.g 2 – 4 mg / week usually well tolerated)

Difficulties encountered in transferring from methadone to BPN

- Precipitated withdrawal on commencing buprenorphine
- Prolonged 'dysphoria'
- Destabilisation of 'stable' patients
- Treatment drop-out
- Inconvenience (and resources) of transfer procedures

Factors implicated in ppt'ed withdrawal in M to B transfers

- Methadone dose
- Time interval between last methadone and first buprenorphine dose
- Buprenorphine dose
- Patient expectancy and supports
- Concomitant use of heroin / medications

Low dose methadone transfers (<40 mg)

Stabilise methadone dose & prepare patient

Cease methadone

Commence bup 20 - 28 hrs after last methadone dose

Last methadone dose	Initial bup dose	Day 2 - 3 bup doses
20 - 40 mg	4 mg	4 to 8 mg
10 - 20 mg	4 mg	4 to 6 mg
1 - 10 mg	2 mg	2 to 4 mg

When should we stop treatment?

- Chronic condition needs long term treatment
- Premature cessation of treatment usually results in relapse to dependent heroin use
- Consider ending treatment when
 - no illicit drug use for months / years
 - stable social environment
 - stable medical / psychiatric conditions
 - patient has a life that does not revolve around drugs

BPN & livers

- BPN metabolised mainly in liver. At normal doses BPN appears to have no adverse effects in 'healthy' livers
- Concerns with:
 - some patients with liver disease (e.g. HCV, EtOH) have had elevation in LFTs after commencing BPN
 - high dose BPN can be toxic (e.g. 100mg at a time, injecting BPN)
- Recommend LFTs at start of treatment & reviewed 1 - 3 months later

BPN & Pregnancy

- So far so good
 - 300+ babies born on BPN with no short term adverse effects with ? milder Neonatal Abstinence Syndrome
 - But, inadequate numbers & no long-term follow-up to be certain of safety & hence methadone still considered the ‘devil we know’
- Clinical recommendations
 - get informed consent if going to use in pregnancy
 - do not transfer pregnant meth patient to BPN (ppt wd)