Promising / Novel Pharmacotherapy Approaches

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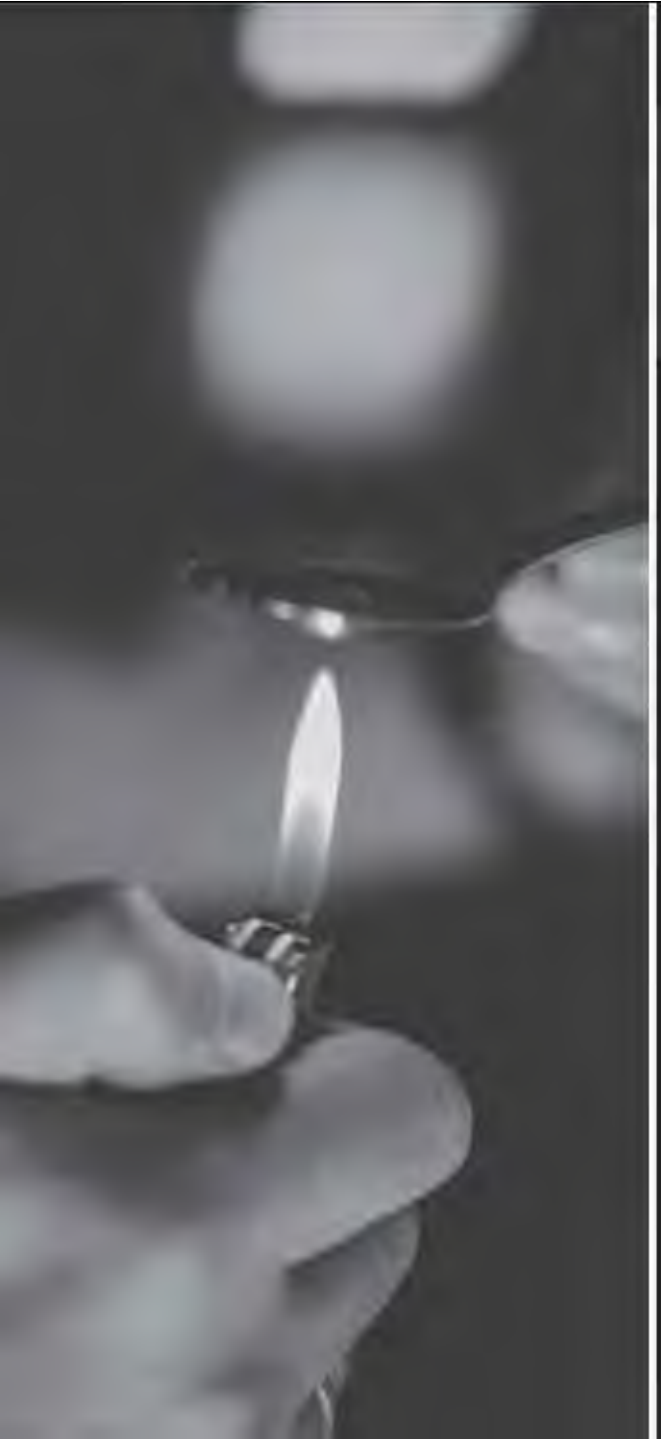


Outline

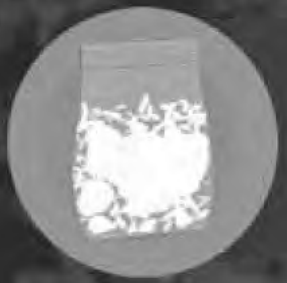
Drug Focus: Methamphetamine

1. Methamphetamine Use Disorder
2. The N-ICE Study
3. The LiMA Study

Drug Focus: Opioids

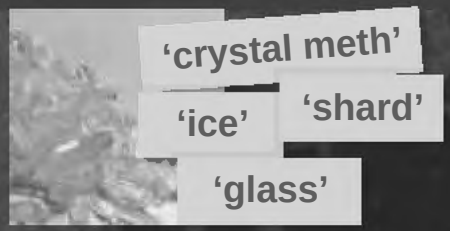
1. The DEBUT Trial

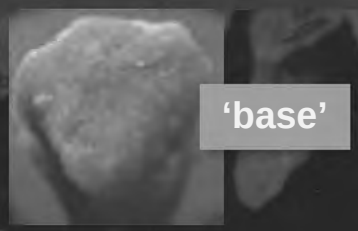
Methamphetamine

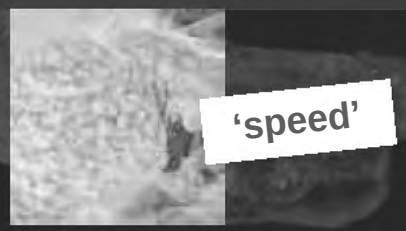


Methamphetamine is a **potent synthetic stimulant drug**. It is part of a larger family of drugs known as **amphetamine-type stimulants (ATS)**, which also includes amphetamines and ecstasy.

Amphetamine was common in Australia until the late 1990s when it was supplanted by methamphetamine. In Australia methamphetamine is sold on the street under various names:

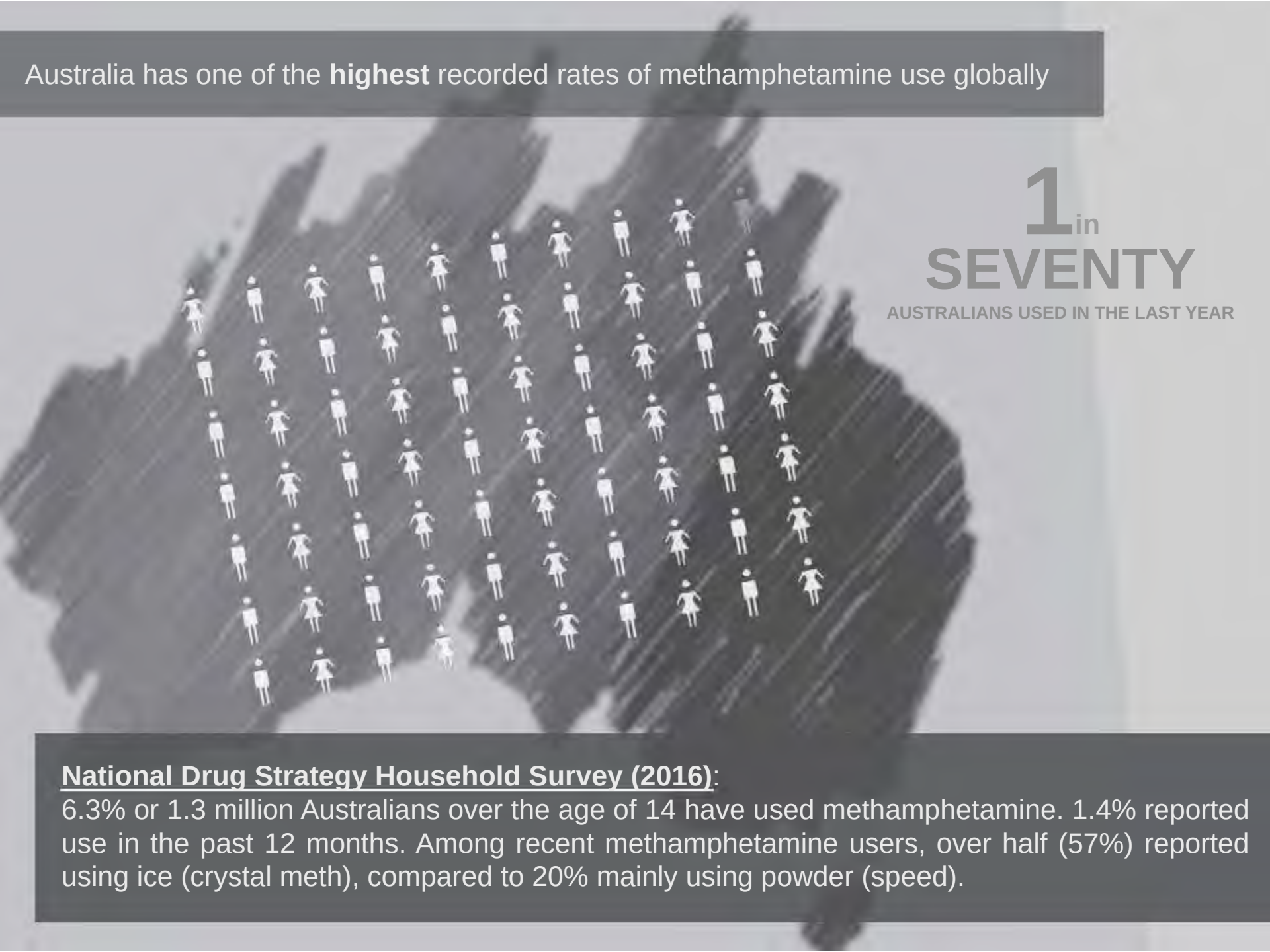






Methamphetamine is made in Australia and imported from other countries. It is manufactured in **clandestine laboratories** from chemicals, including those used in cold and flu medications (e.g. pseudoephedrine).

Australia has one of the **highest** recorded rates of methamphetamine use globally



1 in SEVENTY

AUSTRALIANS USED IN THE LAST YEAR

National Drug Strategy Household Survey (2016):

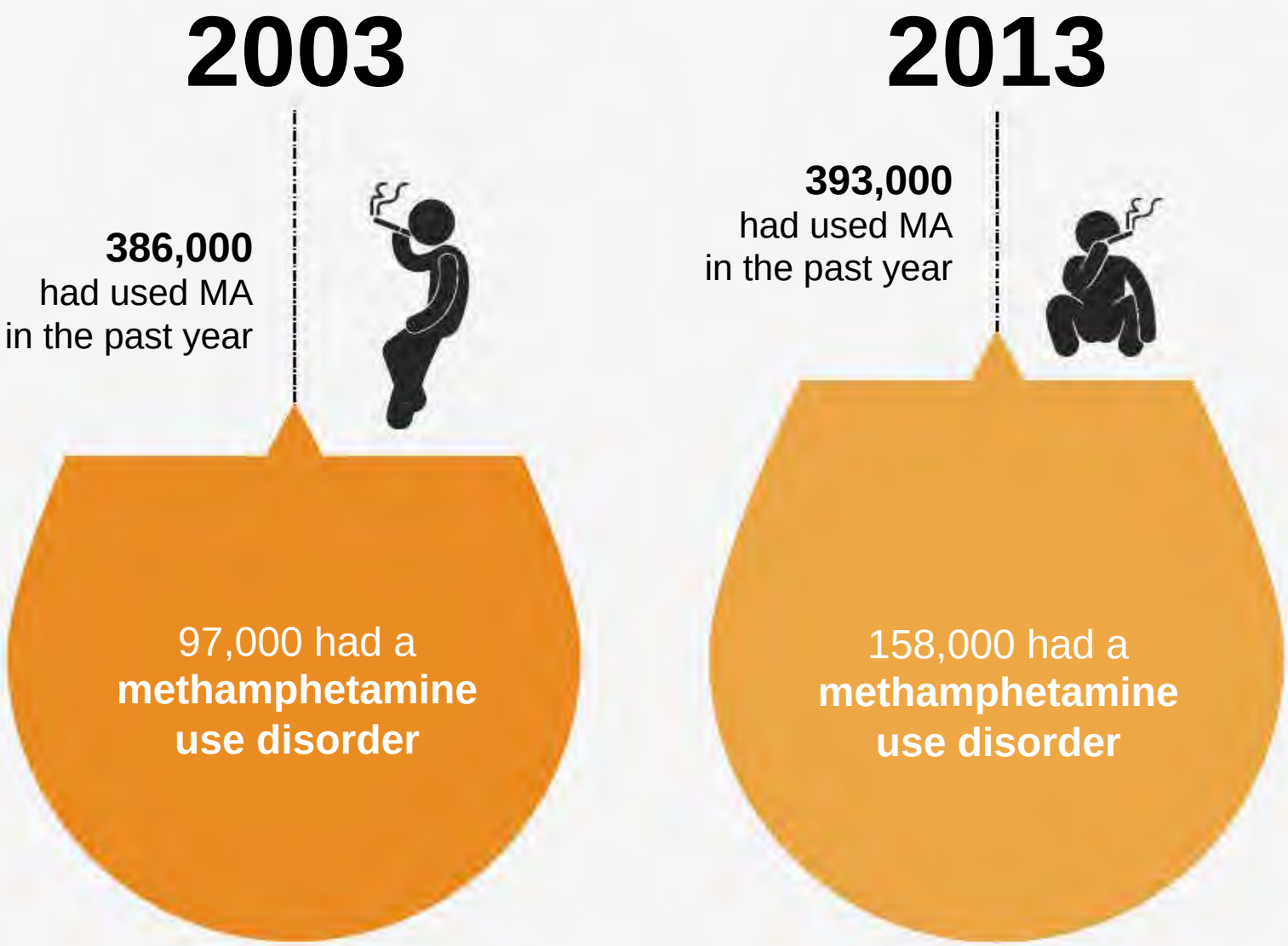
6.3% or 1.3 million Australians over the age of 14 have used methamphetamine. 1.4% reported use in the past 12 months. Among recent methamphetamine users, over half (57%) reported using ice (crystal meth), compared to 20% mainly using powder (speed).

Methamphetamine Use Disorder

(DSM-5)

Problematic use of methamphetamine (MA) leading to **clinically significant impairment or distress** characterised by <u>at least two</u> of the following within a **12 month period**:

IMPAIRED CONTROL CRITERIA	Significant time is spent obtaining, using and recovering from MA	**SOCIAL IMPAIRMENT CRITERIA**	Recurrent use results in failure to fulfill role obligations at work, school or home	**PHARMALOGICAL CRITERIA**	Tolerance to MA, manifested by needing more MA to achieve intoxication or the desired effect AND/OR a reduced effect with use of the same amount	**RISKY USE CRITERIA**	Recurrent MA use in situations where physically hazardous
	MA taken in larger amounts or longer periods than intended		Continued use despite persistent or recurrent social or interpersonal problems related to MA use		Withdrawal from MA, manifested by the characteristic withdrawal syndrome AND/OR use of MA or a closely related substance to avoid withdrawal symptoms		MA use continues despite knowingly having a recurrent or persistent physical or psychological problem that is caused by or exacerbated by MA use
	Persistent desire or unsuccessful attempts to cut down/control use		Important social, recreational or occupational activities are given up due to MA use				
	Craving to use						



McKetin 2017; ABS 2017; AIHW 2013 NDSHS; Sara et a. 2011

Most people seeking treatment for their methamphetamine use will receive help from community drug treatment services. The main types of services can be categorised as **detoxification** (withdrawal management), **residential rehabilitation** and **out-patient counselling**

There are currently no approved medications or 'pharmacotherapies' for methamphetamine use disorder

There have been various medication trials with mixed results.

- Most are focussed on agonist therapies (eg. dexamphetamine) which replace the effects of methamphetamine with a similar acting drug
- *Cochrane 2013*: No significant differences to placebo

New generation of medications

Restore homeostasis (equilibrium) to brain regions disrupted in addiction (Kalivas 2009)

Treatment Options

N-ICE

The N-ICE Trial is a world first clinical trial for methamphetamine dependence.

The N-ICE Trial will establish if **N-Acetyl-Cysteine** (NAC) can **reduce craving** for ice and help people **stop** using ice.

Recruitment is occurring in Melbourne, Geelong and Wollongong

National Drug Research Institute, Curtin University
Perth, WA


Rebecca McKetin (Coordinating Investigator)


Nina te Pas (Trial Coordinator)


Wenbin Liang (Statistician)


Nicole Edwards (Trial Coordinator)

Barwon Health, Deakin University
Geelong, VIC


Olivia Dean (Site Lead Investigator)


Alyna Turner (Site Coordinator)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Turning Point/Eastern Health, Monash University; Burnet Institute
Melbourne, VIC


Dan Lubman (TP) (Site Lead Investigator)


Brendan Quinn (BI) (Site Coordinator)


Victoria Manning (TP)


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University of Wollongong
NSW


Peter Kelly (Site Lead Investigator and Site Coordinator)


Haylie Raftery (PhD Candidate)

Illawarra Drug and Alcohol Service, Illawarra Shoalhaven Local Health District (ISLHD), Wollongong, NSW


Barbara Sinclair (Medical Director D&A Service ISLHD)


David Reid (director D&A service ISLHD)

University of Newcastle
NSW


Amanda Baker


Gregory Carter

La Trobe University, Melbourne, VIC


Peter Higgs

What is NAC?

- **Listed by WHO as an essential medicine**
  - Paracetamol overdose
  - Mucolytic therapy for cystic fibrosis / COPD
  - Kidney disease
- **A range of other potential uses**
  - Influenza
  - Fertility treatment
  - Psychiatric disorders
    - Alzheimer's, bipolar, MDD, OCD, schizophrenia
    - Addictions
- **Sold as supplement online / OTC** (not approved in Australia)
  - Safely used as a supplement (not a natural substance!)
  - Few side-effects (nausea, GI irritation)

How does NAC work?

NAC is an amino acid precursor for cysteine

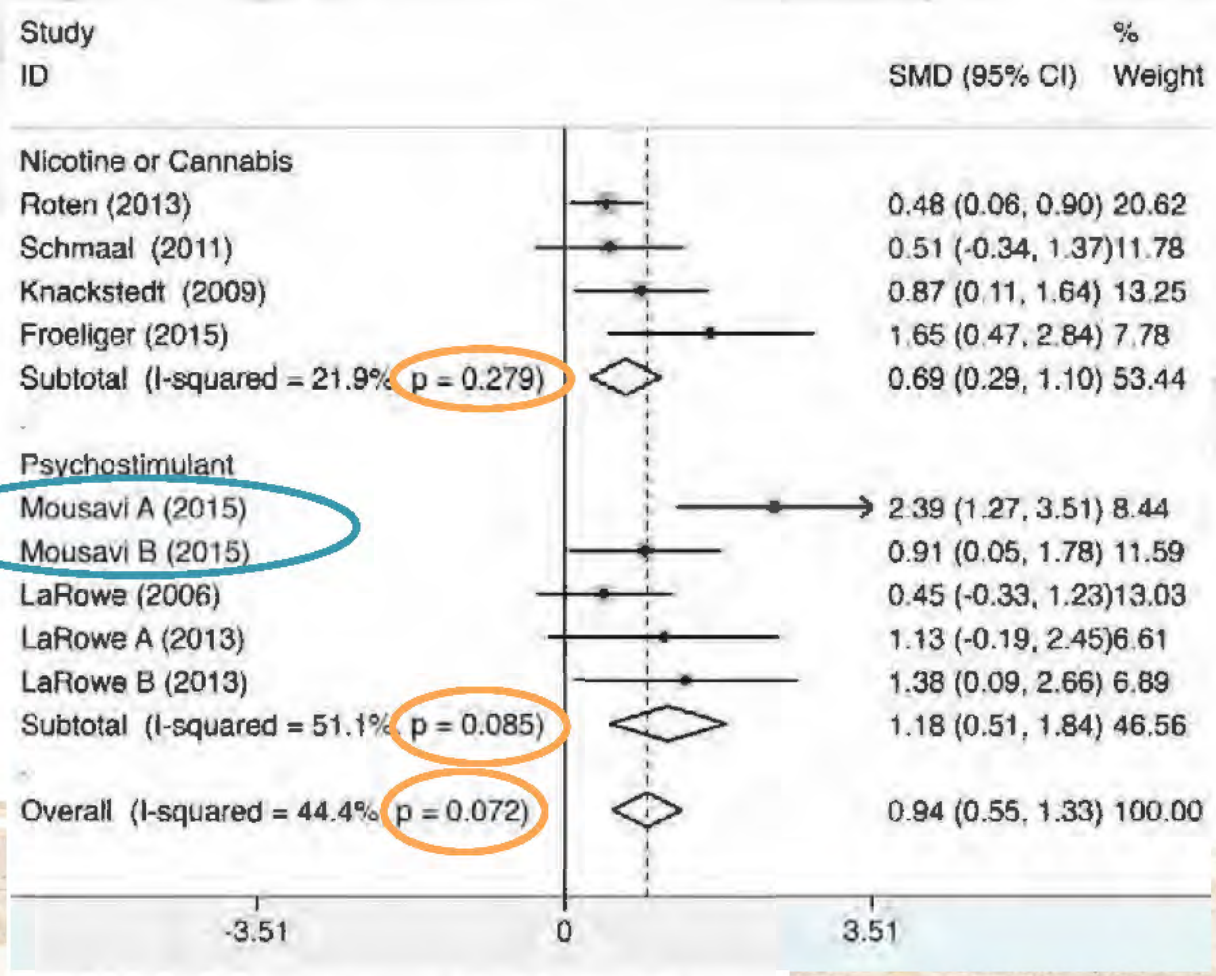
Cysteine has 2 key metabolic roles:

1. **Antioxidant activities** *(glutathione - precursor)*
2. **Modulation of the glutamate system** *(reward / reinforcement pathway)*

Addresses 2 types of psychiatric disorders

1. **Oxidative stress** *(schizophrenia, bipolar disorder, depression, anxiety)*
2. **Impulsivity / compulsivity** *(SUDs, gambling)*

NAC: The Literature



MA

FIGURE 2. Forest plot of effect sizes (Hedges' *g*).

Duailibi et al. *The American Journal on Addictions*, 26: 660–666, 2017

Trialling NAC in MA Use Disorder

1. **Relieves craving for MA**
   (small cross over trial in Iran)
   - Reduced use?
   - Reduced severity of dependence?

2. **Protects against neurotoxic effects of MA**
   (antioxidant effects)
   - Ameliorates MA-related neuropsychiatric sequelae?
     - Depression
     - Psychosis
     - Hostility/agitation
   - Trialled for depression, bipolar disorder, schizophrenia/psychosis

N-ICE STUDY OBJECTIVES

To test whether 2400mg daily oral NAC will:

1. Reduce methamphetamine use relative to placebo (**primary objective**)
2. Reduce methamphetamine dependence, craving and withdrawal
3. Reduce psychiatric symptoms

NAC group 12-week supply 2,400mg oral NAC/day

COMPARED TO

Placebo group 12-week supply of oral placebo/day

N-ICE STUDY DESIGN

STUDY TYPE:	Phase II double-blind placebo controlled
SETTING:	Community (Melbourne, Wollongong, Geelong)
DURATION:	~18-month recruitment (3 month follow/up)
PARTICIPANTS:	n=180 (60 participants per site)
DATA COLLECTION:	Initial screen, baseline survey + 12 x weekly follow-ups

ADJUNCTIVE CARE:

- All participants receive a copy of the "*On Ice*" self-help brochure
- All get referral information
- Participants are free to get other help/treatment during the trial

ELIGIBILITY CRITERIA

Individuals eligible to participate must meet all inclusion and none of the exclusion criteria:

INCLUSION	EXCLUSION
• Dependent on MA	• Enrolled in drug treatment
• 18 – 60 years old	• In need of acute psychiatric / health care
• Want to reduce MA use	• Contraindications for NAC

• Willing to comply with trial protocol	• NAC hypersensitivity
	• Pregnant
	• Unwilling to use contraception
	• Taking contraindicated medications (e.g. nitroglycerin)
	• Known / suspected systemic disorder
	  • Cancer
	  • Epilepsy / Seizures
	  • GI ulcers / stones
	  • Asthma

N-ICE

STUDY ENDPOINTS

PRIMARY ENDPOINT

Methamphetamine use

- Days of use – TLFB calendar system
- Number of positive weekly saliva tests

TIMELINE FOLLOWBACK CALENDAR

2018	SUN	MON	TUES	WED	THURS	FRI	SAT
		1	2	3	4	5	6
J	7	8	9	10	11	12	13
A	14	15	16	17	18	19	20
N	21	22	23	24	25	26	27
	28	29	30	31	1	2	3
F	4	5	6	7	8	9	10
E	11	12	13	14	15	16	17
B	18	19	20	21	22	23	24
	25	26	27	28	1	2	3
M	4	5	6	7	8	9	10
A	11	12	13	14	15	16	17
R	18	19	20	21	22	23	24
	25	26	27	28	29	30	31
A	1	2	3	4	5	6	7
P	8	9	10	11	12	13	14
R	15	16	17	18	19	20	21
	22	23	24	25	26	27	28
	29	30	1	2	3	4	5
M	6	7	8	9	10	11	12
A	13	14	15	16	17	18	19
Y	20	21	22	23	24	25	26
	27	28	29	30	31		

N-ICE

STUDY ENDPOINTS

SECONDARY ENDPOINTS

- **Methamphetamine craving** *(Craving Experience Questionnaire)*
- **Methamphetamine dependence** *(Severity of Dependence Scale)*
- **Methamphetamine withdrawal** *(Amphetamine Withdrawal Questionnaire)*
- **Depression** *(Montgomery Asberg Depression Rating Scale - MADRS)*
- **Positive psychotic symptoms and hostility** *(Brief Psychiatric Rating Scale BPRS)*

OTHER

- Tolerability *(Treatment Satisfaction Questionnaire for Medication)*
- Safety *(AEs, SAEs using REDCap)*
- Adherence *(eCAP)*
- Data for costing

N-ICE

www.facebook.com/nicetrial

http://www.nicetrial.info

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THE LIMA STUDY

limastudy.info

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Recovering ice addicts treated with ADHD medication in Australian trials

By [redacted] political reporter Richard Willingham

Updated 25 Sep 2018, 10:03pm

PHOTO: Researchers hope the ADHD medication will decrease cravings in recovering ice addicts. (NSW Police: AAP)

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ADHD treatment trialled in bid to help ice addicts kick deadly habit

By Mark Doman

Updated 24 Oct 2014, 4:01pm

A drug used to treat inattentive and impulsive children could be the key to weaning addicts off the deadly drug ice, researchers say.

Lisdexamfetamine was recently listed on Australia's Pharmaceutical Benefits Scheme for the treatment of attention deficit hyperactivity disorder (ADHD) in children between the age of six and 18 years old.

But researchers at Sydney's St Vincent's Hospital are hoping higher doses of the drug could help serious ice users control cravings.

Associate Professor Nadine Ezard will explain the trial at the Australian Drugs Conference in Melbourne today.

PHOTO: Researchers hope a new treatment could help reduce the withdrawal symptoms from ice addicts. (NSW Police: AAP)

"People can take this drug once a day. It has a slow onset across the whole day," she said.

"The idea is that, if it works, it might help those symptoms of withdrawal that trigger a desire to use methamphetamine."

St Vincent's Hospital currently offers dexamphetamine as a treatment for a small number ice users as a last resort measure.

Users must attend the hospital for daily doses and must be monitored because improper use can give people ice-like highs.

But lisdexamfetamine has researchers excited because of the way it converts to dexamphetamine in red blood cells.

> So even if you crush it up and inject it, it's not going to work quicker, you're not going to get higher quicker.
>
> [redacted] Evard, St Vincent's Hospital

THE LIMA STUDY

BACKGROUND

Ezard et al,
2016 BMC Psychiatry

Initial **pilot study**
NHMRC grant for **multisite** study

ANZCTR
Australian New Zealand Clinical Trials Registry

Sydney (*St Vincent's, Western Sydney LHD*), **Newcastle** (*HNELHD*) and **Adelaide** (*DASSA*) have been running LIMA since 2017

Turning Point is a latecomer to the party, and Is the only trial site in **Victoria**

AIM

The aim of The LiMA Study is to test if **lisdexamfetamine** is effective in reducing **methamphetamine use, cravings and withdrawal symptoms**.

STUDY DESIGN

This will be a **randomised double-blind placebo-controlled study.**

One group will receive **lisdexamfetamine** and another will receive a **placebo**, in addition to **counselling**. The participants, clinicians and researchers involved in the study will not know to which group they have been allocated. The two groups will be compared and the findings will contribute to evidence for the **future use of lisdexamfetamine in the treatment of methamphetamine dependence**.

180 PEOPLE will be recruited

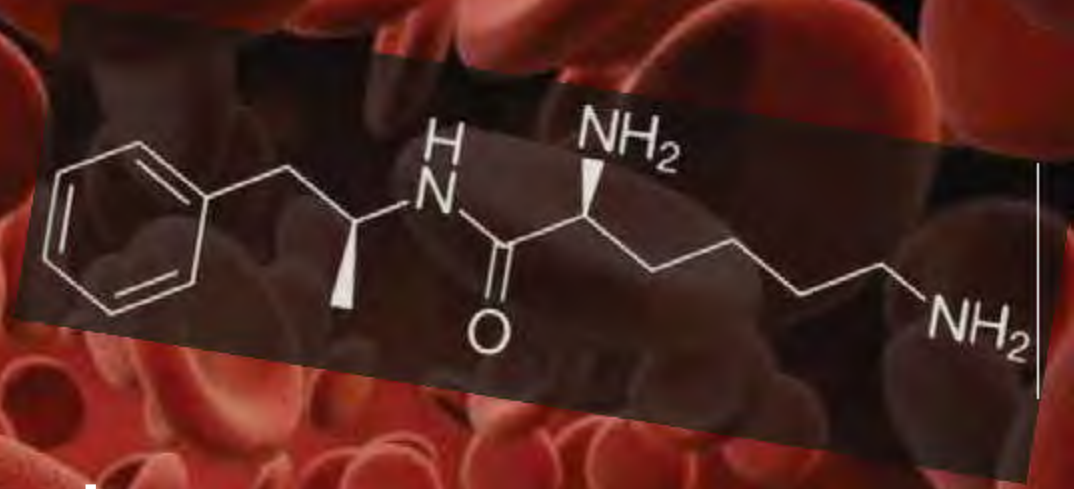
To the **LiMA Study** being conducted in specialist treatment centres in **Sydney, Newcastle, Adelaide and Melbourne.**

WHY LISDEXAMFETAMINE?

Stimulant agonist treatments have not been shown to be effective in trials for methamphetamine dependence (e.g. dexamphetamine)

A range of features of **lisdexamfetamine** suggest it could provide a more effective alternative as a long-acting stimulant

- **Slower** onset of action and **longer** duration of action (compared to dexamphetamine)
- Less diversion / abuse liability
  - Crushing / extraction does not release dexamphetamine
  - Snorting, smoking or injecting does not affect time / concentration of dexamphetamine



lisdexamfetamine

- Dexamphetamine **pro-drug**
- Converted ‘in vivo’ (in the body)
  - Within red blood cells
  - To dexamphetamine
- Peak concentration
  - 3.5 hrs after dose
- Duration of action
  - Approx 10-12h
  - Therefore can be **once daily** medication

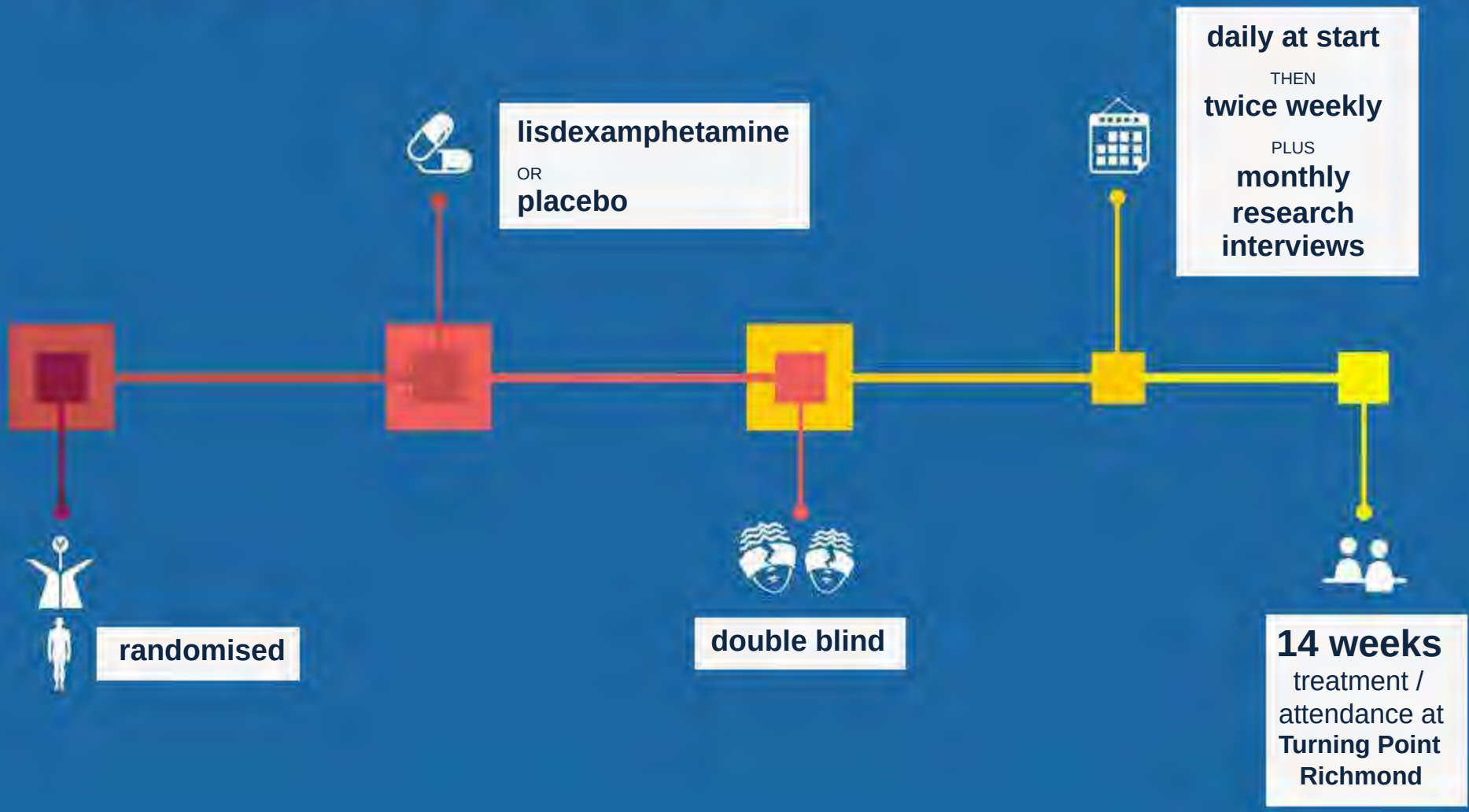
lisdexamfetamine

POTENTIAL SIDE EFFECTS & ADVERSE EFFECTS

Most common side effects are also seen with methamphetamine and other stimulant use:

- Loss of appetite
- Dry mouth
- Headache
- Insomnia
- Diarrhoea
- Agitation
- Irritability
- Nausea
- Weight loss
- Increase in heart rate
- Increase in blood pressure

THE LIMA STUDY



EXCLUSION CRITERIA

- Unstable other substance use
- No significant (unstable) psychiatric illness
  (as judged by trial psychiatrist)
- A range of cardiovascular illnesses

INCLUSION CRITERIA

- Adults with methamphetamine dependence
- Other treatments haven't worked

Interested?

We will be starting up at Turning Point Richmond in February 2019
Contact shalini.arunogiri@monash.edu for further details

and now for something completely different...

Opioid Use Disorder

Opioid agonist pharmacotherapy (methadone, buprenorphine) is gold standard, evidence based treatment

- **Mortality** (incl. overdose deaths)
- **Morbidity** (incl. blood borne viruses)

But several limitations exist

- Need for daily supervised dosing (*especially at start of treatment*)
- Inconvenience (*work, travel, life*)
- Rural and regional settings - limited dispensing points
- Stigma

Long acting injectables are the first innovation in this field for over 15 years, and considered a game changer

LONG ACTING INJECTABLE (LAI) TREATMENTS FOR OPIOID USE DISORDER

LAI BUPRENORPHINE

Buvidal (*CAMURUS/ Braeburn*)	**Sublocade** (*Indivior*)
Slow release formulations	
Delivers dose over a week (**Buvidal**) or a month (**Buvidal + Sublocate**)	

Weekly/Monthly
Buvidal®
PROLONGED-RELEASE
SOLUTION FOR INJECTION
BUPRENORPHINE

Sublocade™
(buprenorphine extended-release)
injection for subcutaneous use Ⓒ
100mg·300mg

LAI BUPRENORPHINE

INTERNATIONAL TRIALS OF SAFETY AND EFFICACY

Buvidal (*CAMURUS/ Braeburn*)	**Sublocade** (*Indivior*)
7 international multisite trials, including Phase 3 trial of 428 patients	2 clinical studies, up to 840 patients

Buvidal received TGA Approval in Aus 28 Nov 2018

Sublocade awaiting TGA Approval, approved by FDA in USA 30 Nov 2017

Pros and Cons

1. **Convenience and freedom**
- No need to attend pharmacy daily/regularly
- Can travel without needing to take medication/ set up dispensing and permits

2. May be helpful for stable patients who are working; people in rural/regional settings where there are limited dispensing points

3. May also work for people with chaotic lifestyles who are **struggling to dose** at pharmacy regularly

4. Reduction in **stigma** (dispensing points/pharmacy etc)

5. **Change in role of medication within an individual's treatment plan and life**
- Centrality of daily dosing - now can inject and forget?
- Could this impact on people whose dosing added structure, routine etc. to day to day life, needing to leave home, social outlet?

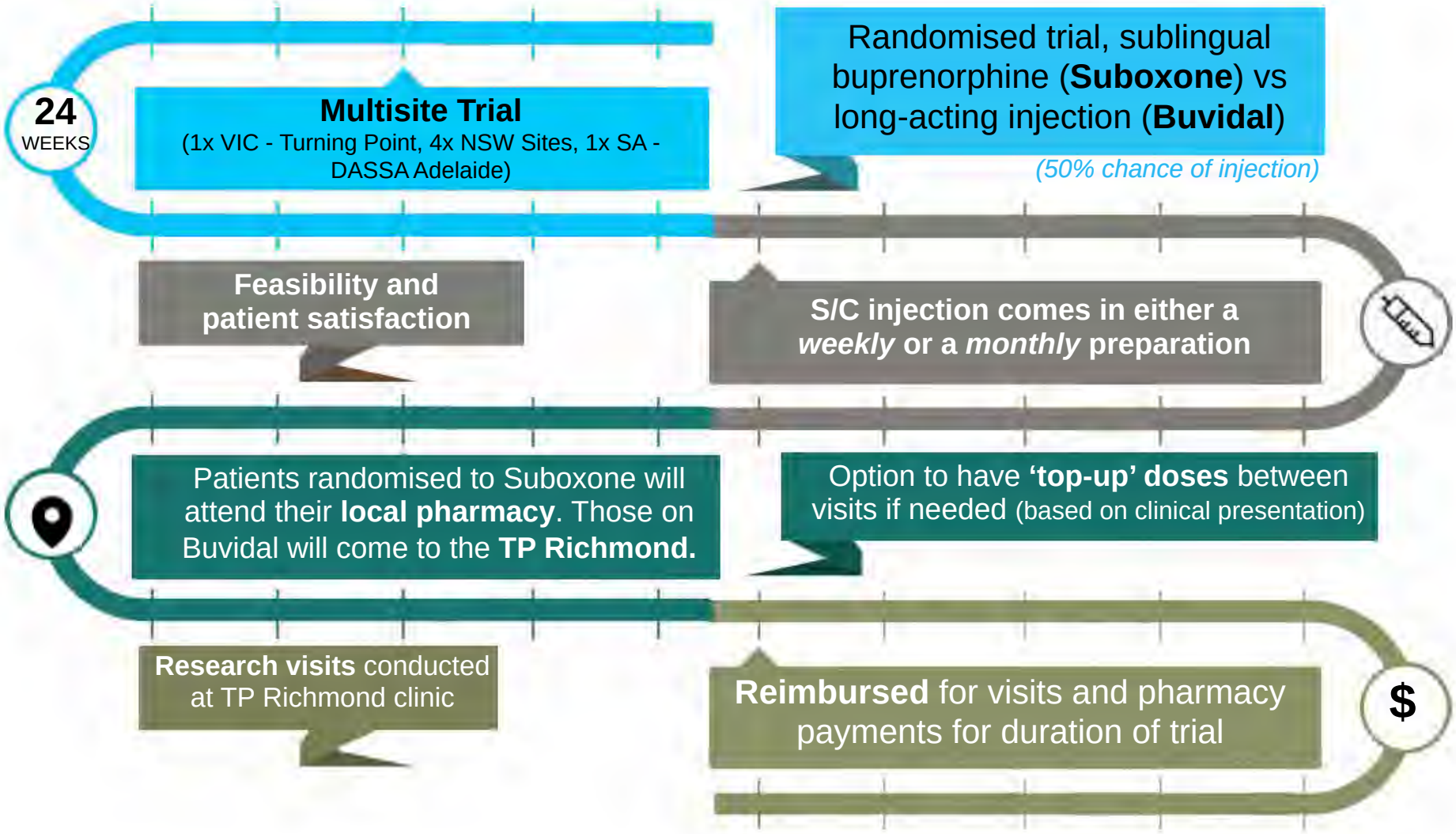
camurus.

A Randomised, Open-Label, Active-Comparator, Multi-Center Trial Comparing a Once-Weekly and Once-Monthly Long-Acting Subcutaneous Injectable Depot of Buprenorphine (CAM2038) to Buprenorphine Standard of Care in Adult Outpatients with Opioid Dependence

‘**DEBUT**’ Trial at Turning Point

ACTRN12618001759280

DEBUT Trial at Turning Point



DEBUT Trial at Turning Point

broad inclusion and exclusion criteria

Inclusion Criteria:

- Unstable psychiatric or physical health disorders
- Pregnancy exclusion; women need to use contraception during trial

Inclusion Criteria:

- Willing to transfer care to Turning Point for duration of trial
- Willing to have blood and urine tests for screening
- Willing to participate in research visits (between 1-3 hours long)

If you are interested, please contact

Site Name and address: Turning Point, 110 Church St, Richmond VIC 3121
Study Coordinator name: Prof. Dan Lubman (Contact Ms. Michelle Sharkey)
Phone number: (03) 8413 8413