Welcome to *Cracks in the Ice* & *Positive Choices* Webinar Series

Australian Government
Department of Health and Aged Care

THE UNIVERSITY OF SYDNEY
Matilda Centre

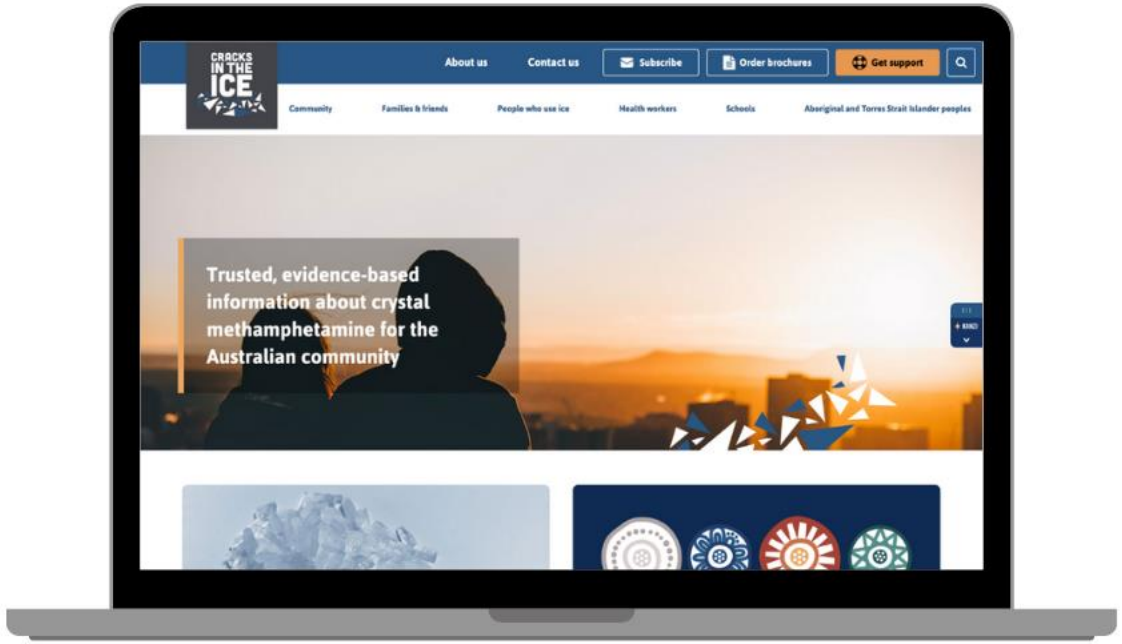
Acknowledgement of Country

We would like to acknowledge and pay respects to the Traditional Custodians of Country throughout Australia and recognise their continuing connection to land, water and culture.

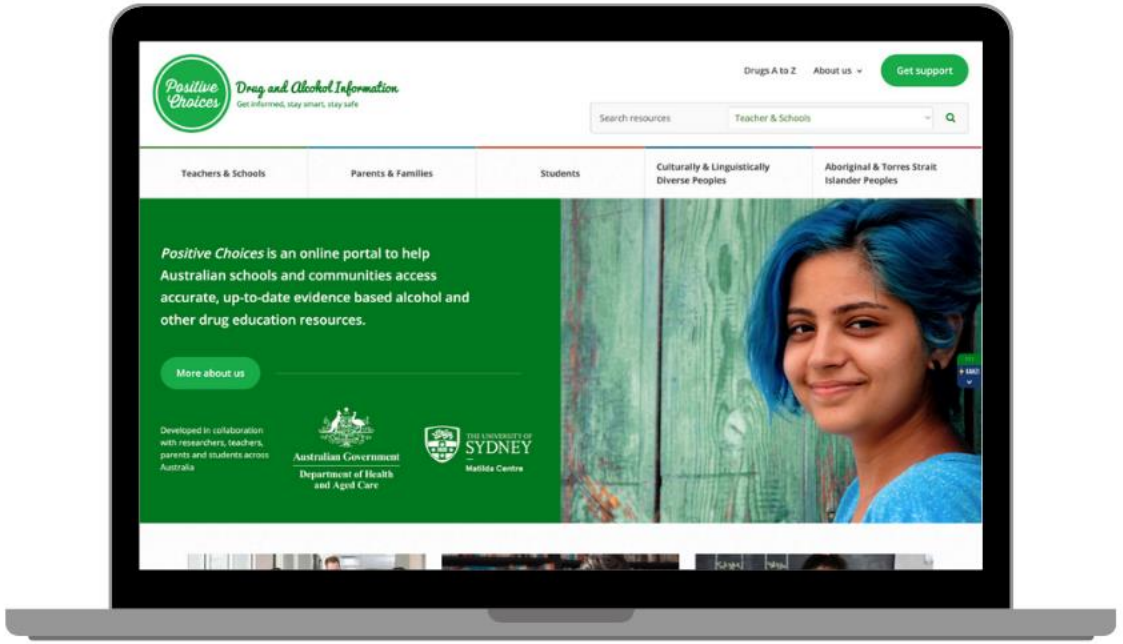
We pay our respects to those who have cared and continue to care for Country.

What is *Cracks in the Ice* & *Positive Choices*?

Cracks in the Ice (cracksintheice.org.au) is an online toolkit providing trusted, evidence-based, and up-to-date information and resources about crystal methamphetamine ('ice') for the Australian community.



Positive Choices (positivechoices.org.au) is an online portal providing access to trustworthy, up-to-date drug and alcohol information and educational resources for school staff, parents, and students.



Housekeeping

1. For more information on our webinar series for *Cracks in the Ice* and/or *Positive Choices*, visit their websites: cracksintheice.org.au and positivechoices.org.au

2. You are in listen-only mode

3. Please type your questions using the **Q&A button** on your dashboard.

4. This webinar is being recorded and will be made available via *Cracks in the Ice* and *Positive Choices*, along with a handout of the slides.

METHAMPHETAMINE USE IN YOUTH: ASSOCIATED OUTCOMES AND NOVEL TREATMENTS

Alexandre A Guérin

METHAMPHETAMINE USE IN YOUTH

1. Introduction
2. Health, cognitive, and functional outcomes – evidence review
3. Targeting methamphetamine use in youth – preliminary results from a pilot study
4. Conclusions

INTRODUCTION

METHAMPHETAMINE

- Widely used psychostimulant worldwide (WHO, 2020)
- Use associated with adverse outcomes (Marshall & Werb, 2010; Meredith et al., 2005)
- Typically starts in adolescence/young adulthood (Castro et al., 2000; Guerin & Kim 2021)

Among people who used meth/amphetamines:	
Average age of first use (years)	22 (mean) 20 (median)
Age group most likely to use (% recent use)	20–29 (2.4%)

AIHW, 2020

WHY FOCUS ON YOUTH?

- Period of rapid, continued neurobiological development (Blakemore, 2012)
- Pronounced psychological, physiological, and social changes (Squeglia et al., 2009)
- Rapid transition to problematic use common (Gonzalez Castro et al., 2000)
- Early age of onset ↑ risk of developing a SUD and relapse (Perepletchikova et al., 2008; Poudel & Gautam, 2017)

METHAMPHETAMINE RESEARCH

- Research to date mostly in adults
- Treatment tested in adults
  - Treatment response may differ in youth
- Understanding outcomes associated with use in youth is important to develop targeted treatments

UNDERSTANDING OUTCOMES

Neuroscience and Biobehavioral Reviews 153 (2023) 105380

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

A systematic review and meta-analysis of health, functional, and cognitive outcomes in young people who use methamphetamine

Alexandre A. Guerin [a,b,*], Tahnee Bridson [a,b], Helena M. Plapp [b,c], Gillinder Bedi [a,b]

[a] *Centre for Youth Mental Health, University of Melbourne, Melbourne, Australia*
[b] *Orygen, Melbourne, Australia*
[c] *Royal Melbourne Hospital, Melbourne, Australia*

AIMS AND OBJECTIVES

- Aims:
  1. Review the evidence on health, functional, and cognitive outcomes in young people (10-25 years-old) who use methamphetamine

  2. Quantitively assess the associations between health, functional, and cognitive outcomes and methamphetamine use in youth using a meta-analytical approach

OUTCOMES OF INTEREST

- **Health** – mental health disorders and symptoms, physical health
- **Functional –** education, employment, family problems, aggression and violence
- **Cognitive** – performance on cognitive tasks

LITERATURE SEARCH

Databases:

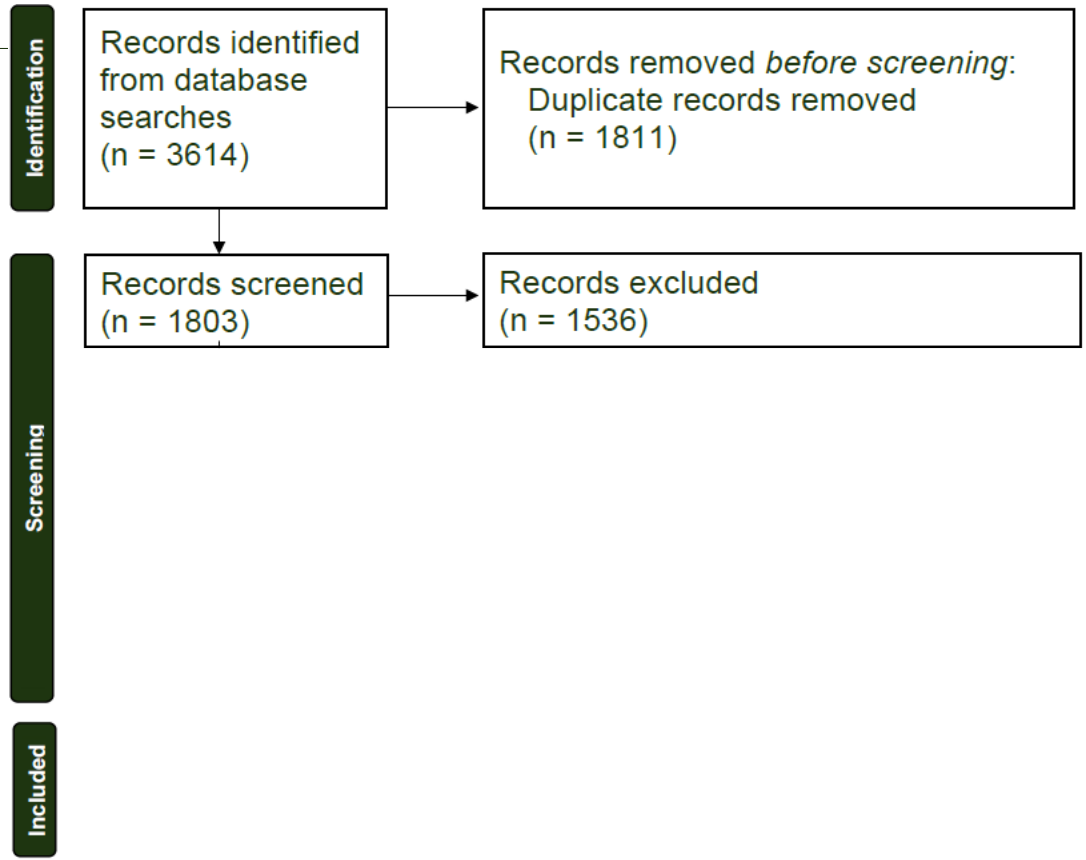
PubMed, EMBASE, PsycINFO, MEDLINE, Psychiatry Online and EBSCO

Search terms:

“methamphetamine" AND ("youth" OR "adolescent" OR "juvenile" OR "young people")

LITERATURE SEARCH

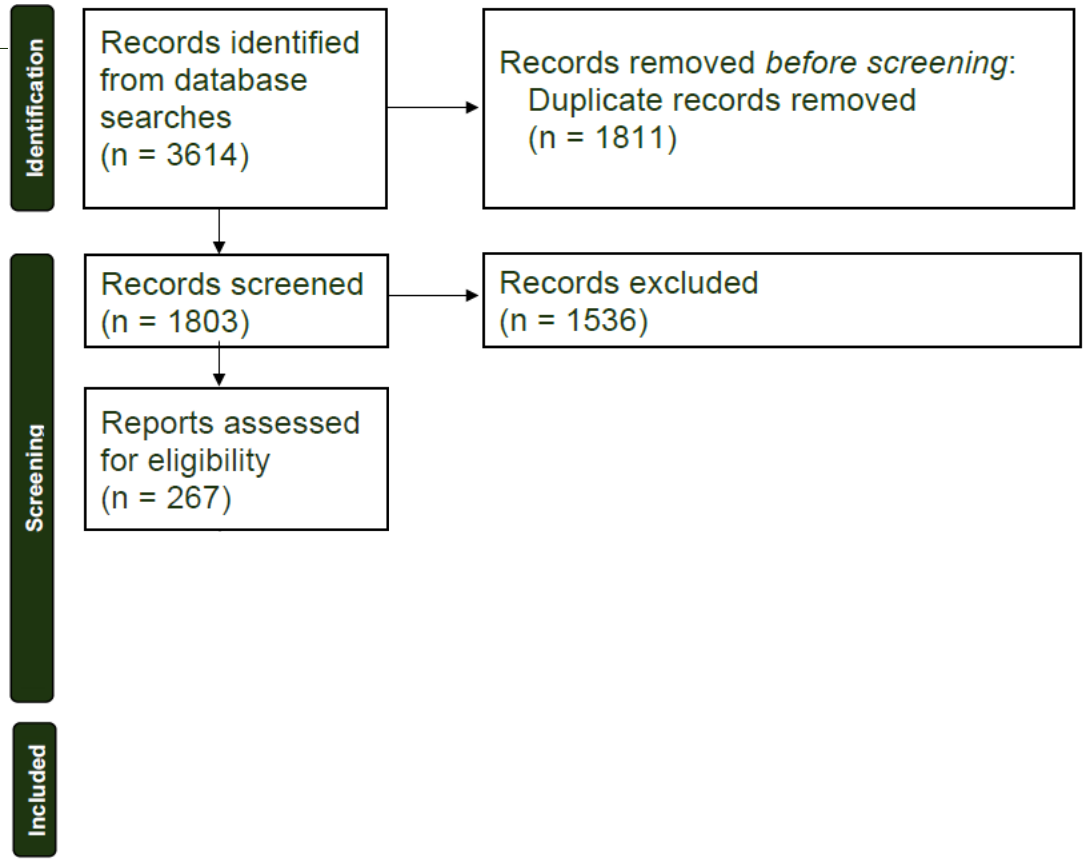
Title and abstract screen



LITERATURE SEARCH

Title and abstract screen

Full text assessment



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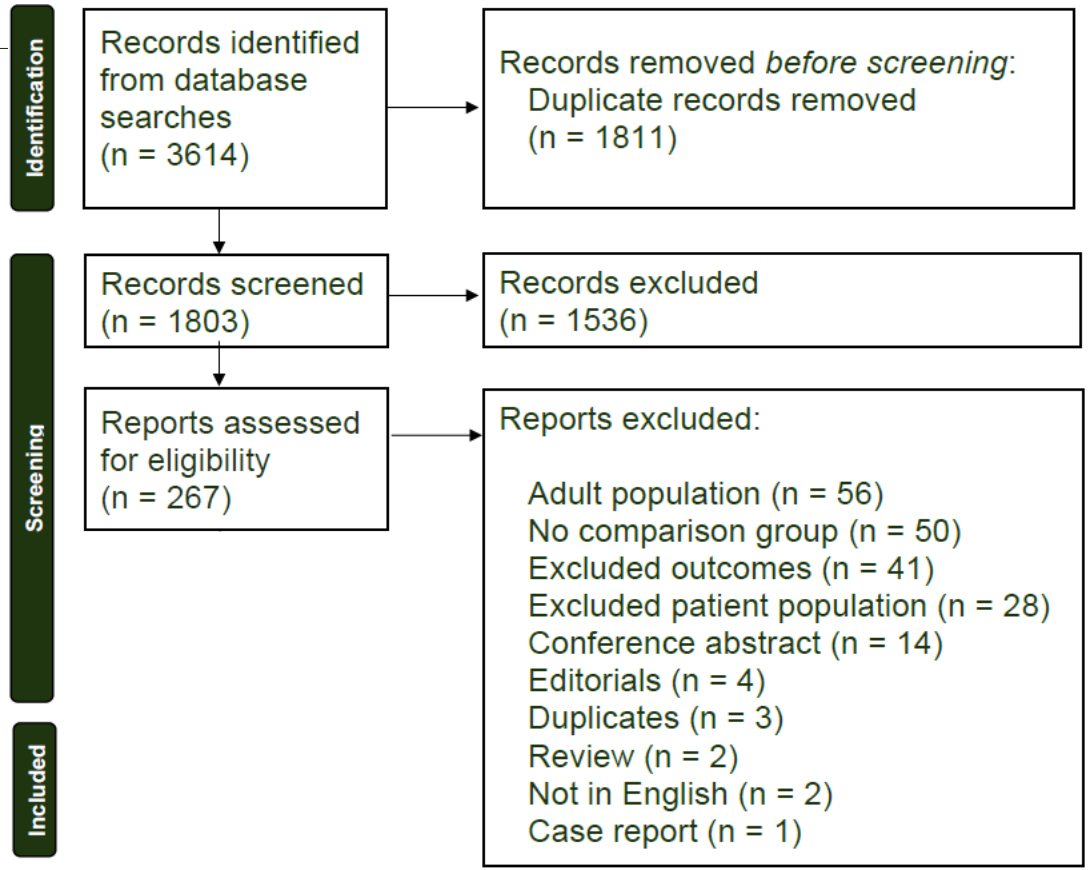
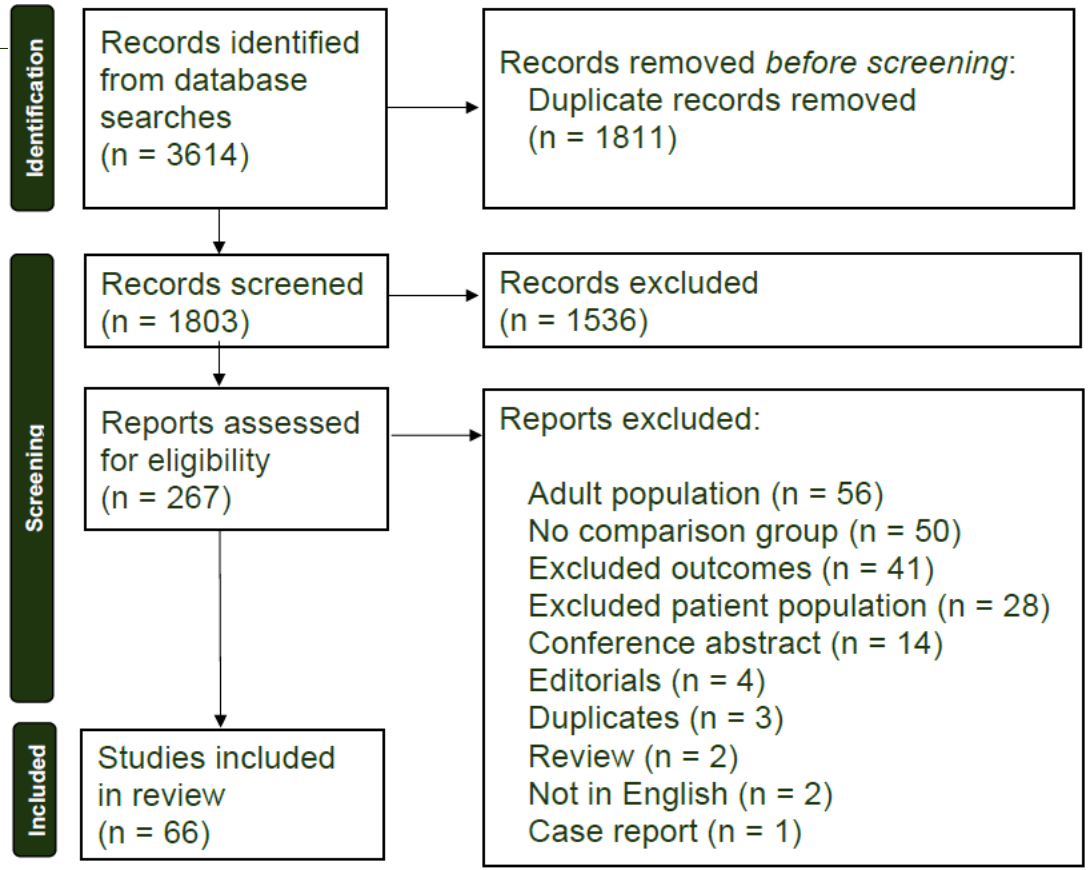


LITERATURE SEARCH

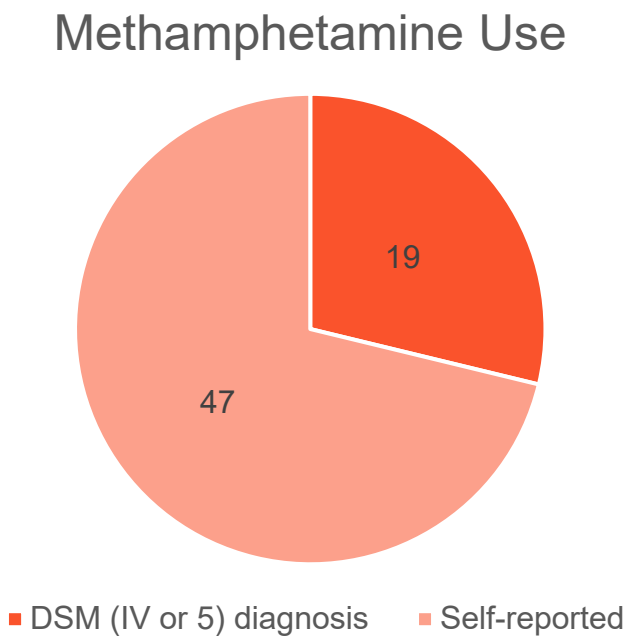
Title and abstract screen

Full text assessment

Inclusion in systematic review



STUDY CHARACTERISTICS



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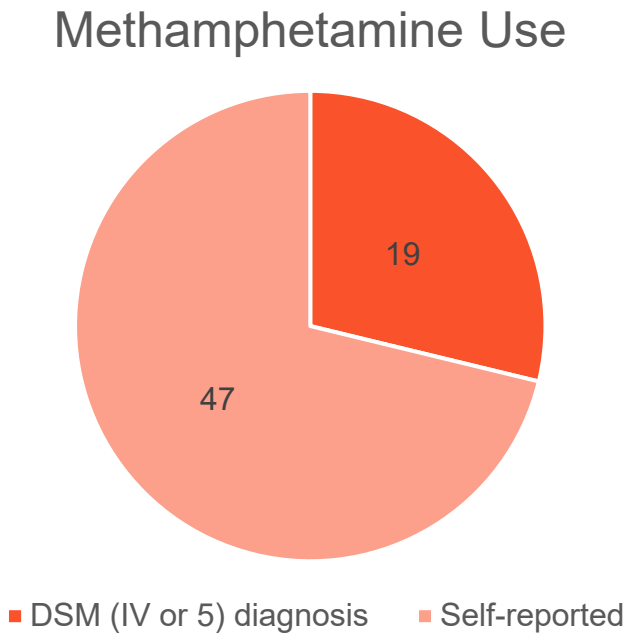
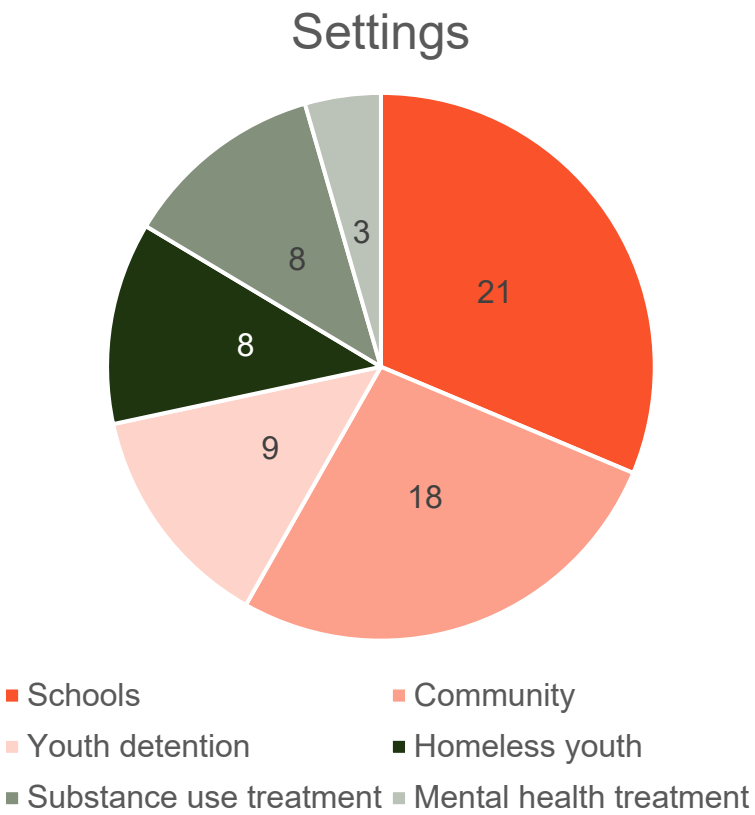




OUTCOMES OF INTEREST

- **Health - 44 studies**
  1. Mood disorders and symptoms (n = 20)
  2. Anxiety disorders and symptoms (n = 12)

- **Functional - 43 studies**
  1. Education and employment (n = 23)
  2. Justice system involvement (n = 20)
  3. Family functioning (n = 9)

- **Cognitive - 6 studies**
  1. Inhibitory control (n = 5)

HEALTH OUTCOMES

HEALTH OUTCOMES

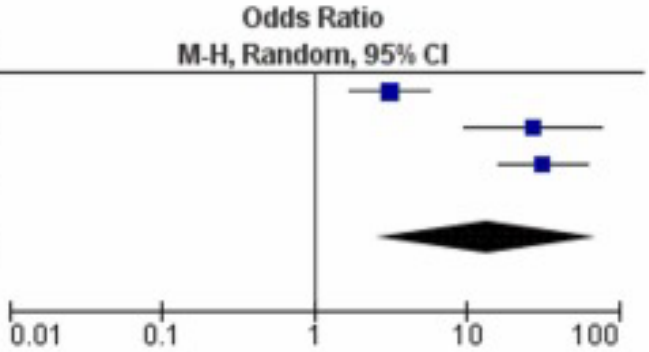
- Adolescents who use methamphetamine > 13 times more likely to have conduct disorder

B. Conduct Disorder diagnosis

Study or Subgroup	Methamphetamine Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Kaye 2020	42	64	54	143	34.4%	3.15 [1.70, 5.83]
Yen 2006a	43	200	4	400	31.6%	27.11 [9.57, 76.80]
Yen 2006b	90	200	10	400	34.0%	31.91 [16.06, 63.41]
Total (95% CI)		**464**		**943**	**100.0%**	**13.66 [2.63, 70.87]**
Total events	175		68			

Heterogeneity: $Tau^2 = 1.95$; $Chi^2 = 28.32$, df = 2 ($P < 0.00001$); $I^2 = 93\%$

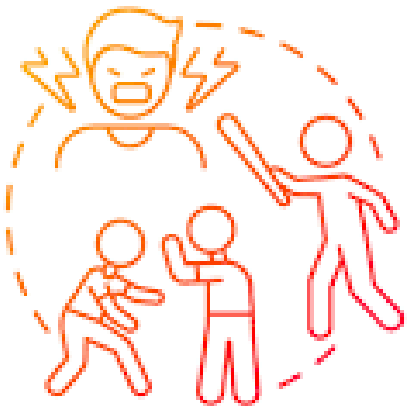
Test for overall effect: $Z = 3.11$ ($P = 0.002$)



HEALTH OUTCOMES

- Adolescents who use methamphetamine > 13 times more likely to have conduct disorder

- Behavioural problem involving aggression, law-breaking tendencies, and poor impulse control (APA, 2013)



ANTISOCIAL BEHAVIOURS

- More likely to exhibit antisocial behaviors (Embry et al., 2009; Kaye et al., 2020; Yen et al., 2006)
- High hostility symptoms (King et al., 2010)
- More likely to fight with peers (Oetting et al., 2000)
- More difficulties with peer interactions (Kaye et al., 2020; Yen et al., 2006)

OTHER HEALTH OUTCOMES

- Marginal associations with major depressive disorder and anxiety disorder diagnoses
- No association with depressive or anxiety symptoms
- Association with ADHD
  - Often co-occurring with conduct disorder

FUNCTIONAL OUTCOMES

FUNCTIONAL OUTCOMES

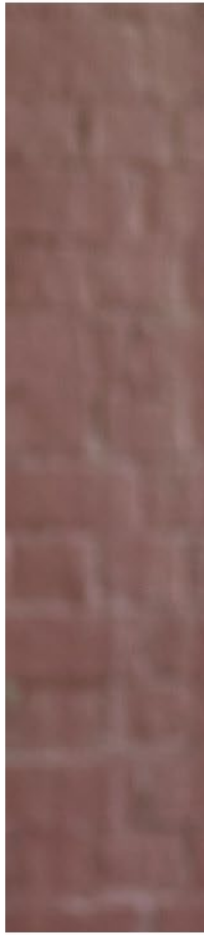
- Too heterogenous to quantitatively assess
- Methamphetamine use in youth consistently associated with poor educational outcomes
- Methamphetamine use in youth associated with involvement in justice system
  - No association in people already in detention

COGNITIVE OUTCOMES

INHIBITORY CONTROL

- Youth who use methamphetamine ↓ inhibitory control performance
- Difficulty controlling their actions and behaviours

LIMITATIONS



KEY LIMITATIONS

1. Heterogenous measurement of exposure and outcomes

2. Lack of adequate controls

3. Limited causal evidence due to lack of longitudinal studies.

SUMMARY

- Strong association between conduct disorder and methamphetamine use in youth
- YPMs more likely to be involved in youth justice system
- Educational problems associated with methamphetamine use in youth
- Poorer performance on inhibitory control task

CONCLUSIONS

- Very vulnerable group
- Risk of experiencing ongoing complex issues
- Targeted interventions and support needed

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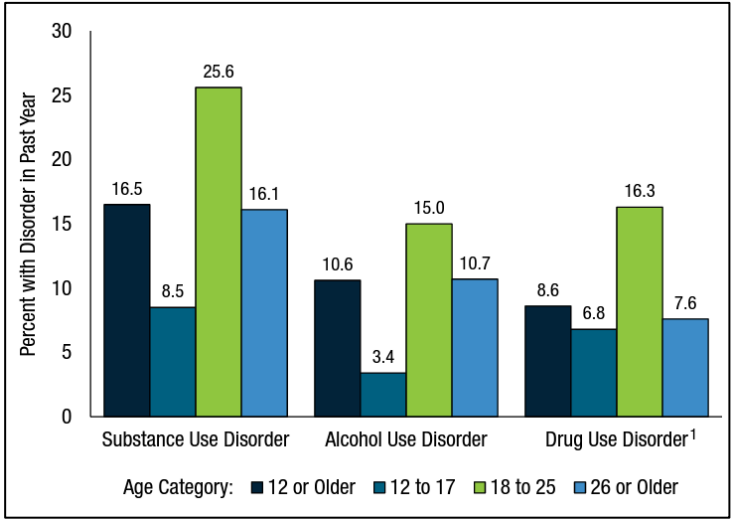
TARGETING YOUTH METHAMPHETAMINE USE

SUBSTANCE USE IN YOUTH

- Substance use experimentation starts in adolescence, much of it normative AIHW, 2017
- Substance use disorder (SUD) onsets early NSDUH 2021; NSMHWB 2020-21
- Methamphetamine use in youth associated with negative outcomes Guerin et al, 2023
- Outcomes improved by early treatment Dennis et al, 2005
- Ideally, intervention at the earliest possible stage



PHARMACOTHERAPY FOR SUBSTANCE USE DISORDERS

- Medications for opioid, alcohol, and nicotine use disorders – key part of treatment Ray et al, 2020
- Best practice in treatment for substance use disorders – combined pharmacotherapy and psychosocial interventions Ray et al, 2020
- Medications needed to bolster effects of psychosocial treatments
- No efficacious medications for methamphetamine use disorder

PHARMACOTHERAPY FOR METHAMPHETAMINE USE DISORDER

Table 3 Brief summary of findings.

	Abstinence	Use	Retention	Harms
All Antidepressants	★★	∅	★★	★
Aminoketone: Bupropion	★	★	★★	∅
Atypical Antidepressant: Mirtazapine	NA	∅	∅	∅
SSRI: Sertraline	∅	NA	∅	NA
Atypical Antipsychotics: Aripiprazole	∅	★	∅	∅
Psychostimulants and Other Medications for ADHD				
All Psychostimulants: Modafinil, Dexamphetamine, Methylphenidate	★	∅	★	NA
Methylphenidate	NA	★	★	NA
Atomoxetine	NA	∅	∅	∅
All Anticonvulsant and Muscle Relaxants: Baclofen, Gabapentin, Topiramate	∅	∅	∅	∅
Topiramate	NA	★	★	★
Medications used for other substance use disorders				
Naltrexone	∅	★	★	★★
Varenicline	NA	∅	∅	∅

Shading represents the direction of effect:

(No color)	Unclear
Grey	No difference
Green	Evidence of benefit
Red	Favors placebo

Symbols represent the strength of the evidence:

NA	No evidence or not applicable
∅	Insufficient
★	Low
★★	Moderate
★★★	High

Chan et al., 2019

TABLE 2 Summary of meta-analysis and GRADE assessment results

Outcome	Intervention	*N* studies	*N* participants	I^2	Differential statistic (95% CI)	GRADE rating
Withdrawal symptoms					Standardised mean difference	
	Amineptine	1	43	[a]	−0.26 (−0.86, 0.34)	[a]
	Mirtazapine	1	31	[a]	0.17 (−0.54, 0.89)	[a]
	Modafinil	1	19	[a]	0.86 (−0.09, 1.82)	[a]
	Total	3	93	49	0.17 (−0.43, 0.77)	⨁⨁◯◯ Low
Craving					Standardised mean difference	
	Amineptine	1	29	[a]	−0.19 (−0.92, 0.54)	[a]
	Modafinil	1	19	[a]	0.95 (−0.01, 1.92)	[a]
	Total	2	48	71	0.34 (−0.77, 1.45)	⨁◯◯◯ Very low

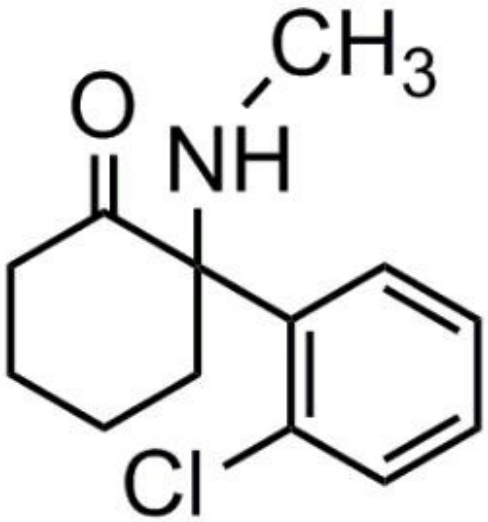
Acheson et al., 2023

NEW CANDIDATE MEDICATION

- Ketamine

KETAMINE

- Non-competitive antagonist at NMDA receptor
- Well characterized, used in anesthesia, and sub-anesthetic doses in depression Sanacora et al, 2017
- ? normalize glutamatergic dysregulation in substance use disorders, facilitating new learning Dakwar et al, 2020
- Improves cocaine and alcohol use outcomes Dakwar et al, 2019; 20
- No research in methamphetamine use



KETAMINE AND COCAINE USE DISORDER

- Cocaine and methamphetamine – similar use pattern and pharmacology
- Very promising results

- Single i.v. infusion (0.41 mg/kg) - ↑ motivation to quit cocaine Dakwar et al, 2017
- Single i.v. infusion (0.60 mg/kg) - ↓ cocaine self-administration Dakwar et al, 2014

KETAMINE AND COCAINE USE DISORDER

- Single i.v. infusion (0.50 mg/kg) - ↑ abstinence, ↓ relapse, ↓ craving Dakwar et al, 2019
- In combination with mindfulness-based relapse prevention
- Well tolerated; no AE-related withdrawals

MASKOT: MethAmphetamine use in young people: Sub-anaesthetic Ketamine Open-label Trial

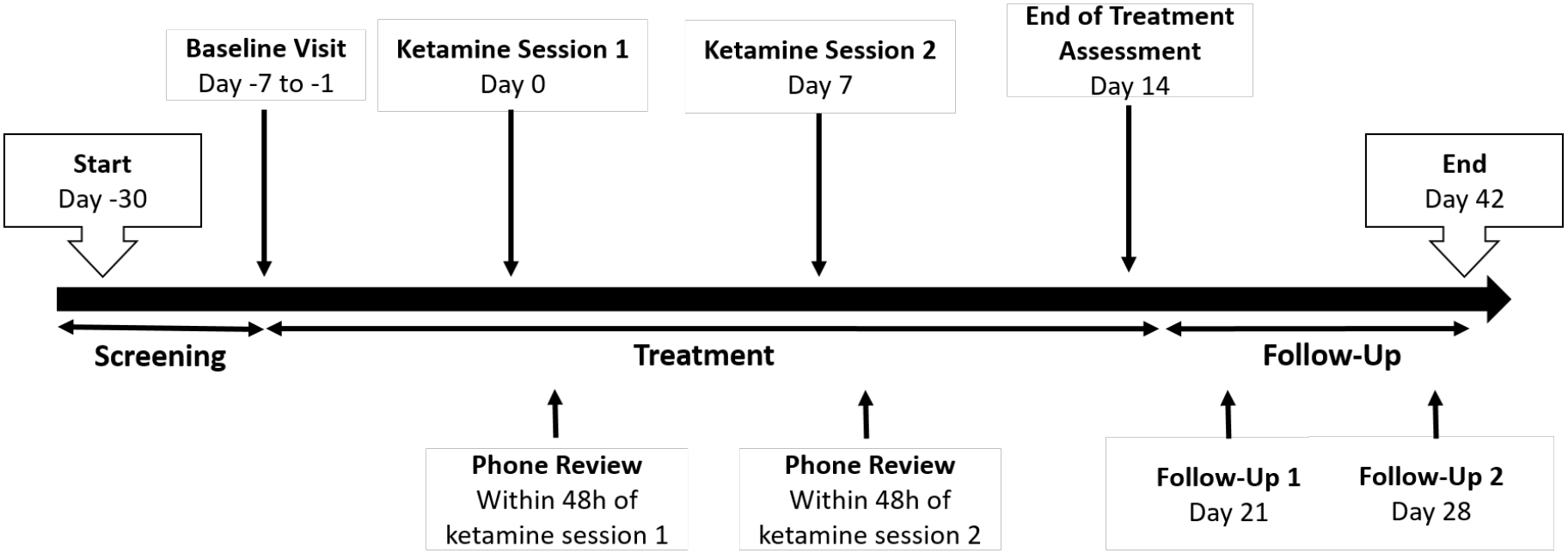
- Open-label design
- N = 20, young people (15-25 years old – **NOTE: increased to 15-35 years old in 2024**) with moderate to severe Methamphetamine Use Disorder (MAUD)
- **Recruited online and via AOD services**

NCCRED National Centre for Clinical Research on Emerging Drugs

MASKOT

- Primary Aim: Safety and tolerability of 2 ketamine doses 7 days apart in youth with MAUD.
  - Change in ketamine use frequency and craving;
  - Liver Function Tests after treatment;
  - Number of participants withdrawing due to adverse medication effects.
- Secondary Aim: Preliminary efficacy of 2 ketamine doses for MAUD in youth.
  - Change from baseline in methamphetamine use frequency, withdrawal, and craving at follow-up

MASKOT


Start
Day -30
Baseline Visit
Day -7 to -1
Ketamine Session 1
Day 0
Ketamine Session 2
Day 7
End of Treatment Assessment
Day 14
End
Day 42
Screening
Treatment
Follow-Up
Phone Review
Within 48h of ketamine session 1
Phone Review
Within 48h of ketamine session 2
Follow-Up 1
Day 21
Follow-Up 2
Day 28

RECRUITMENT

Considered for eligibility (n = 144)

Could not be contacted (n = 58)
Failed Pre-Screening (n = 54):
- Not interested in participating (n = 11)
- Not currently using methamphetamine (n = 12)
- Not aged between 16-25 years old (n = 2)
- Know prior to screening to meet one or more exclusion criteria (n = 29)

Pre-screened, not approached for consent (n = 12)

Consent requested (n = 20)

Consent Refused (n = 8):
- No longer interested (n = 1)
- No reason provided (n = 7)

Consented – Screen Fail (n = 7):
- Severe depression (n = 3)
- Severe sedative use disorder (n = 1)
- Did not complete screening (n = 2)
- ADHD medication use (n = 1)

Enrolled in MASKOT (n = 5)

Withdrawn before commencing intervention:
- Unable to complete protocol (n = 1)

Currently in treatment (n = 1)

Completed MASKOT (n = 3)

PRELIMINARY DATA

- n = 3 completed full protocol
- n = 3 female; age range = 22-32 years-old
- Methamphetamine use at baseline = 6.5 days/week

PRIMARY OUTCOME

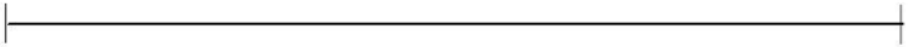
- **Safety:**
  - No change in ketamine use frequency/craving after treatment
  - No abnormal liver chemistry after treatment

- **Tolerability:**
  - No withdrawals
  - All adverse events resolved at discharge
  - No serious adverse events

KETAMINE SESSIONS – DRUG EFFECT

Do you FEEL a drug effect right now?

Not at all (0) **Extremely (100)**



KETAMINE SESSIONS – DRUG EFFECT

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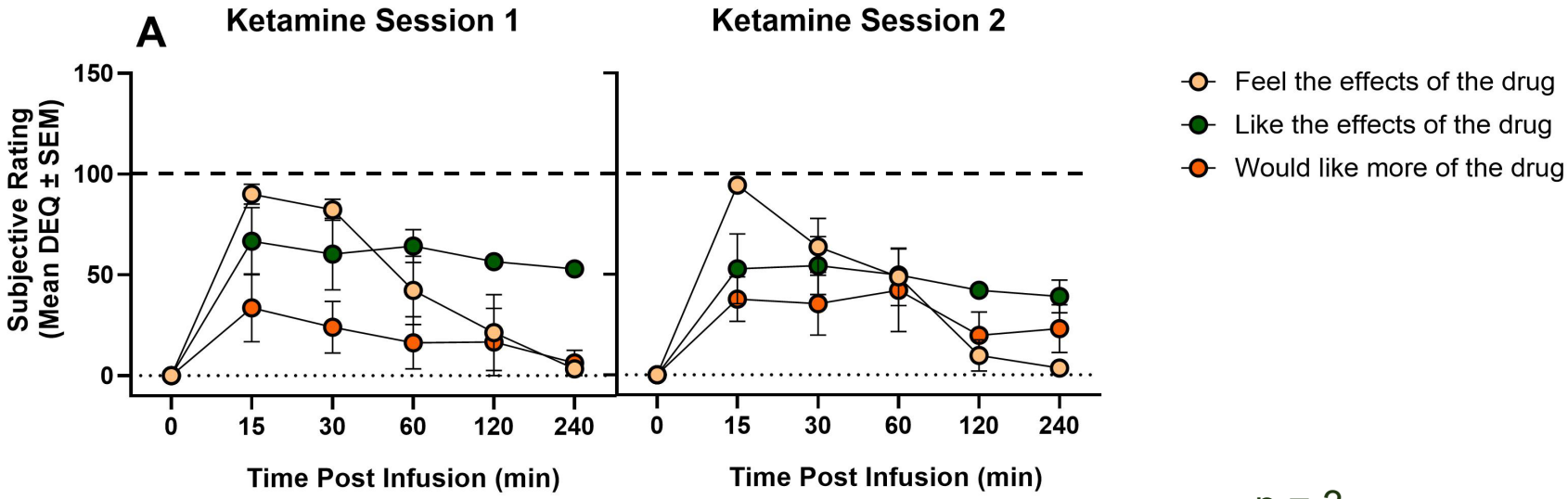
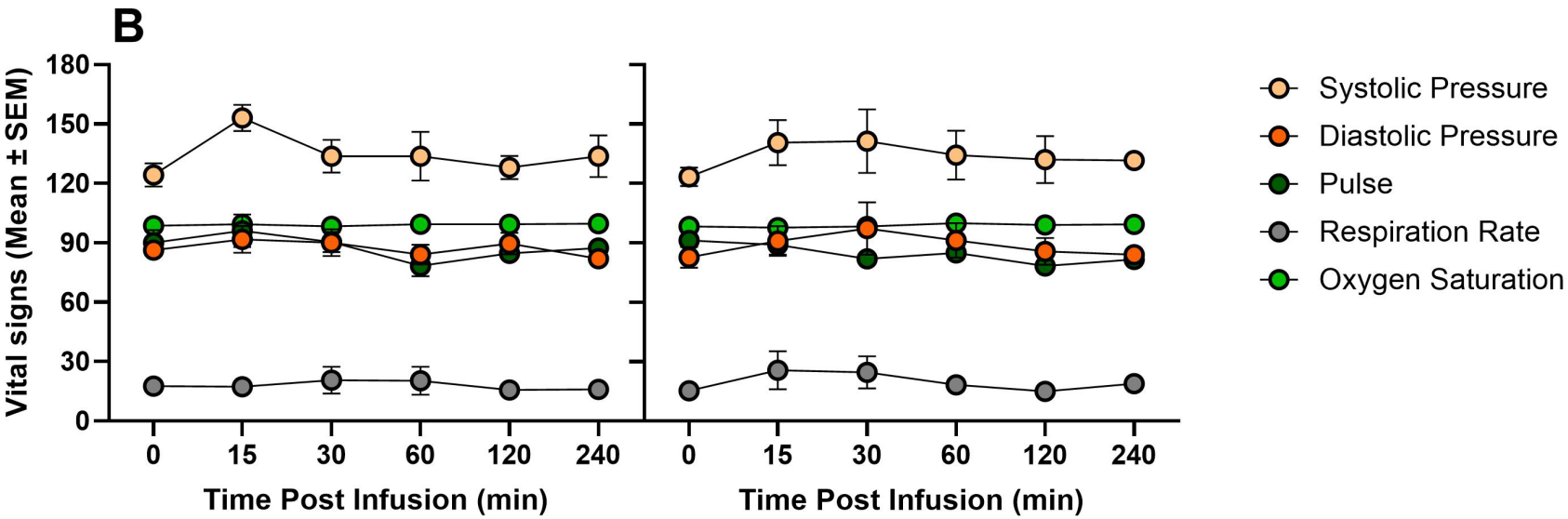


n = 3

KETAMINE SESSIONS – VITAL SIGNS



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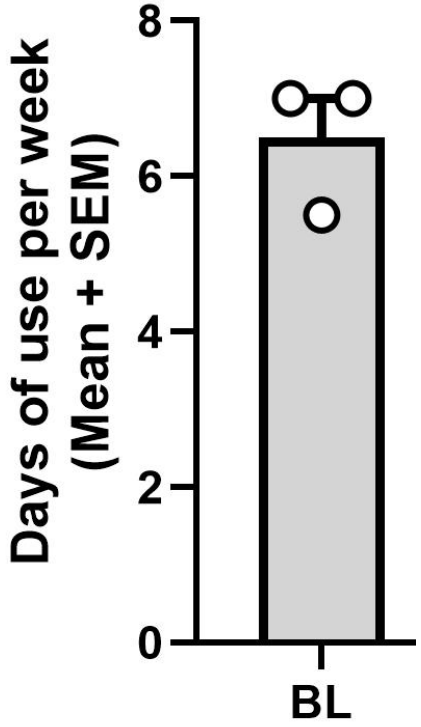
SECONDARY OUTCOME – METHAMPHETAMINE USE



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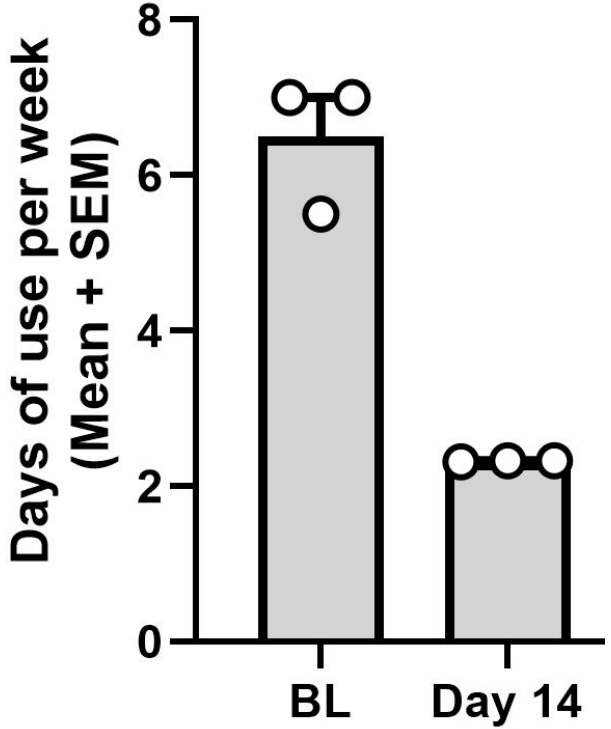
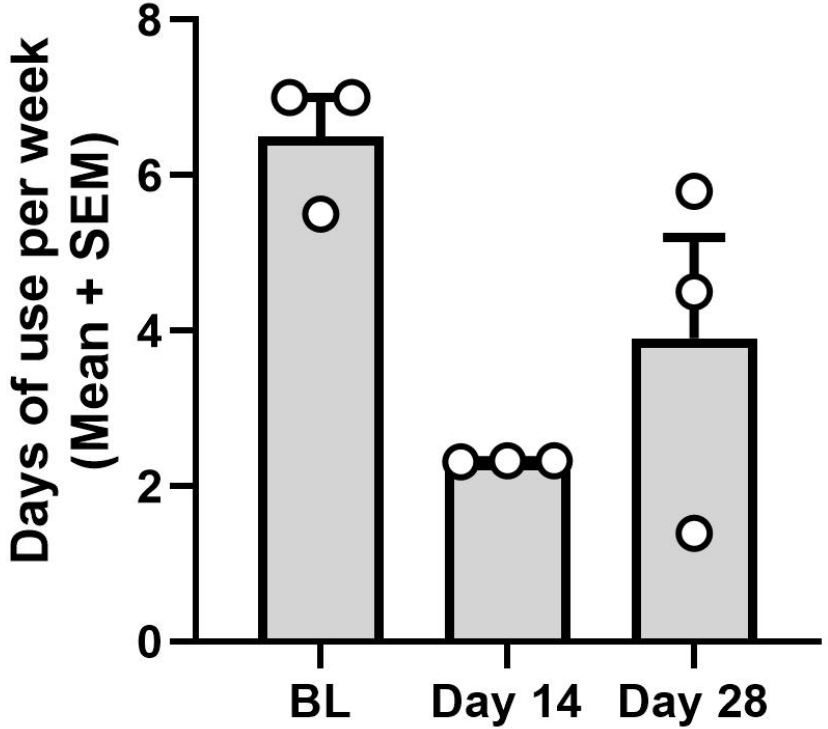
SECONDARY OUTCOME – METHAMPHETAMINE USE



n = 3

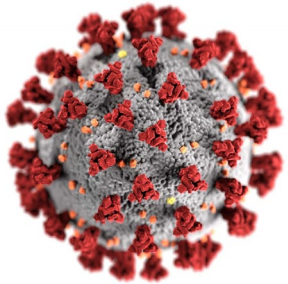
SECONDARY OUTCOME – METHAMPHETAMINE USE

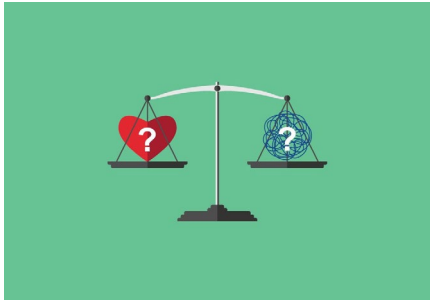


n = 3

RECRUITMENT CHALLENGES

- COVID-19
- Social media – limited success initially
- Few EOIs leading to interest - ambivalence?
  - Difficulties engaging youth





RECRUITMENT SOLUTIONS

- Youth alcohol and other drug treatment services

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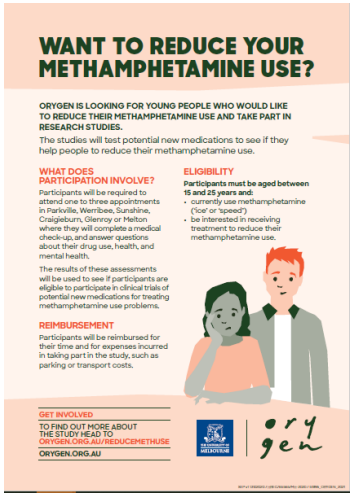
- Youth alcohol and other drug treatment services
- Targeting other social media

RECRUITMENT SOLUTIONS

- Youth alcohol and other drug treatment services
- Targeting other social media
- Updated advertising material



RECRUITMENT SOLUTIONS

- Youth alcohol and other drug treatment services
- Targeting other social media
- Updated advertising material
- Updated inclusion and exclusion criteria
  - **Removed severe depression**
  - **Increase recruitment age to 35 years old**

Improved number of EOIs – enrolment rates still low

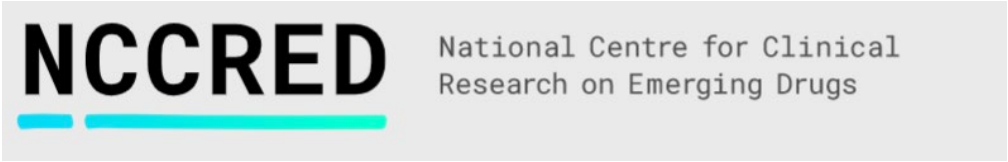
CONCLUSIONS

CONCLUSIONS

- Methamphetamine use in youth associated with negative outcomes
- Vulnerable population with complex needs
- New treatment targeting youth are needed
- Ketamine is a promising treatment
- Challenges

AKNOWLEDGEMENTS

- Participants
- Funded by , NCCRED, Gandel Philanthropy, Medical Research Future Fund, National Institute on Drug Abuse



REVOLUTION IN MIND

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THANK YOU

alex_guerin13

Q&A

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