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SPEAKERS

Steph Kershaw, Alex Guerin

S Steph Kershaw 00:00

Looks like we who we are going to be today. So I'd just like to start this webinar by acknowledging that I'm on the lands of the Kaurna people in South Australia and pay my respects to their Elders past and present, but also like to acknowledge and pay respects to the traditional custodians across Australia and recognise their continuing connection to land, water and culture, and pay my respects to the Elders of the lands that you are all on today as well. So as I mentioned today, is a special code lead webinar, which is brought to you by two Australian Government Department of Health Aged Care funded national online websites, Cracks in the Ice and Positive Choices. So for those of you who are new to our webinar series, Cracks in the Ice is a free online toolkit that aims to provide trusted, evidence based information and resources about methamphetamine for the Australian community. And we have a lot of resources dedicated for health workers, people who use methamphetamine, as well as their family and friends and community members. And I'm also pleased that we're joining today with Positive Choices, which is another online free toolkit. And its aim is to provide access to evidence based and up to date, alcohol and other drug information and educational resources for school staff, parents and students. And there's a broad range of resources across both of these portals, including factsheets, guidelines, links to online programs, as well as video content. So both Cracks in the Ice and Positive Choices run regular webinars. So for more information about those webinars, or just about what the two portals are, you can visit either of the websites, and we welcome any comments or questions that you have. So feel free to get in touch with us at anytime. And if we can help you out in your work or in your school, we'd love to be able to do that. So just going to do a little bit of housekeeping. Before I introduce today's speaker, just wanted to let you all know that as participants, you are in listen only mode. And that means that we can't see or hear you. However, you will notice that you have a Q&A button on your dashboard. And this is where you can type in any questions that you have during the webinar and send them through to us. And we'll also be having a dedicated question and answer section at the end of our webinar. Just so you know, we will also be recording today's session and we will be making the recording available on both of the portals, both Cracks in the Ice and Positive Choices and you will receive a email notification when the recording is available if you'd like to share it with your colleagues or friends. So I'm very excited to introduce today's speaker, Dr. Alex Guerin, who is a research fellow at the Center for Youth Mental Health, University of Melbourne, and a project manager at Orygen. And His research focuses on testing new

psychosocial and pharmacological treatments for young people with problematic substance use and related harms. So I'm gonna stop sharing my slides. And I'd love to thank you so much for joining us today Alex, we really appreciate your time. And we're really looking forward to hearing your presentation all around methamphetamine use in young people, and the mental health and functional outcomes. I'm sure it's going to be great. And I'll hand over to you now.

A Alex Guerin 03:30

Great, thank you very much for having me. Before I get started, I also want to acknowledge the traditional owners of the land on which this work took place, the Wurundjeri people of the Kulin nation here in Melbourne. And yeah, thank you for the introduction. I just want to introduce myself again, my name is Alex and I have a very great interest in methamphetamine use, and particularly methamphetamine use in young people. So I really hope my talk today really inspires you to look more into this vulnerable population. Going to get this is working. I'm going to show you the outline of my talk today. So there's going to be two main parts. First, I'll give you a bit of an introduction on why I think that studying young people is very important. Then I will be showing some results from a systematic review that we conducted and was published last year looking at health, cognitive and functional outcomes associated with methamphetamine use in young people. Then I will be talking to you a little bit about, a little bit more about targeting methamphetamine use in this population and show you some preliminary results from a pilot study that we are about to complete some very exciting new data. And a little bit of a conclusion and hopefully some Q&A and some discussion at the end. So I'm not sure how those webinars usually work but if there's any pressing or urgent question. Feel free to stop me anytime if you need any clarification or if you have any comments. Otherwise, we can always discuss at the end. So, I'm not sure if I need to introduce what methamphetamine is to this group, but it is a widely used psychostimulant worldwide. And importantly, the use of methamphetamine is associated with a wide range of adverse outcomes. And that's true in both adults and also, younger people. methamphetamine use typically starts in adolescents or young adulthood. And for example, in Australia, the median age of onset of methamphetamine use is 20 years old. And that's also the case in the United States where it is also 20. So that seems to be the case globally. Why do I focus on youth? Why am I interested in youth? Well, youth and adolescence is a period of very rapid and continue neurological and neurobiological development. During that time, we see a very pronounced psychological, physiological and social changes in young people as they're developing into their own individual separate from their family of origin. During this time period, as well, we can we often see a rapid transition from a recreational use of substances to problematic use, and that's a big problem. And there is some evidence that's not in methamphetamine that's more in substance use in general. But there's some evidence showing that earlier the age of onset of substance use, the greater the risk of developing a formal substance use disorder later in life, and also the greater risk of relapsing after abstinence. So adolescence, and youth is a very critical time period to look into when it comes to methamphetamine use. To date, however, most of the research in methamphetamine use has been focused in adults. And importantly, all treatments and clinical trials being done in adults, there hasn't been any clinical trials of new medication or new treatment in younger people. And it's very, very important to test new treatments in youth as well, because treatment response can actually differ between adults and younger people. To inform the development of those new treatments, it's also very important to understand outcomes that are associated with use, particularly in youth, and understand the needs of this population, because it just not the same as older people. And that leads me to the first part of this webinar, which is understanding outcomes associated with methamphetamine use, in youth. So, I'm going to go over a systematic review and meta analysis that we conducted last

year and was just published at the end of last year. So if you'd like to download it, I put a QR code here, but you can also send me an email or a message after the webinar, and I'm very happy to share it with you. So the aim of this systematic review was to first review all evidence on health, functional and cognitive outcomes in young people aged between 10 to 25 years old, who use methamphetamine. And the second aim of the study was to quantitatively assess those associations using a meta analytical approach. Going to spend a bit more time on the outcomes we're interested in. So there were three different outcomes. The first one was health, and that included any mental health disorders and related symptoms, but also any physical health problems. Functional outcomes included education, employment, family problems, but also aggression and violence and involvement in the use of justice system. And cognitive outcomes were identified as performance on a number of cognitive tasks to look at the way young people think. We search a number of databases, including PubMed, Embase, PsychINFO, Medline, Psych online and EBSCO. And importantly, we get us search terms very broad to make sure we identify every single possible study out there. So we use it to methamphetamine, and a combination of youth, adolescent, juvenile and young people. Our searches returned 3614 papers, thankfully, about half of them were duplicates, and they were removed from our searches before the screening phase, which left us with about about 1800 papers to screen. We did the first round of screening just looking at the title, title and abstract of each paper to see if they were relevant. And we excluded 1500 papers from that stage. That left us with 267 papers to assess for eligibility. So myself and two colleagues went through all of these papers, the full text of the paper to see if there were eligible. We excluded exactly 201 paper and they were excluded for a range of reasons. The top three reasons being that they looked at adult population, so they didn't actually look at youth. They didn't have a comparison group, so they only looked at people who use methamphetamine without a comparison. And when I say comparison, we looked at both people who didn't use methamphetamine and people use other drugs other than methamphetamine. And the third top reason is because it didn't investigate any of the outcomes we were interested in. So following Full Text screening, we were left with 66 papers included in our review. I'm going to spend a very short amount of time on the study characteristics. And one of them I want to draw your attention to is the way methamphetamine use was defined in those paper, so in 47 of them, so just over two thirds of them. People were included if they self reported using methamphetamine. And the definition in those papers vary widely. So we identified papers where if someone had reported using methamphetamine, even just once in their lifetime, they were included, other papers they had to use daily. So quite a wide range of methamphetamine use. And in 19 of them, about a third of them, young people actually had a formal diagnosis of DSM-4 methamphetamine dependence or abuse, or DSM-5 diagnosis of methamphetamine use disorder. So what we expected to see, given the wide range of methamphetamine use definition is for instance differences between people had only used one in their lifetime and people who had a formal use disorder. In terms of settings, most studies were conducted either in schools, in the community, or in youth detention or homeless detention centers, or homeless youth shelters, with some studies also conducted in substance use and mental health treatment facilities. In terms of outcomes of interest, we identified 44 studies looking at health outcomes, with the main outcomes investigated being mood disorders and symptoms in just under half of them, and anxiety disorders and symptoms in about a quarter of them. We identified 43 studies looking at functional outcomes. And of those 43 studies, about half of them looked at education, employment, and other half looked at justice system involvement, and 4 of them looked at family functioning. Lastly, we identify just six studies looking at cognitive outcomes, with inhibitory control, the most studied in five of them. So I'm going to show you some of the results, starting with health outcomes. And I just want to flag before I keep going that we did find quite a lot of different associations in this paper. But just for the sake of time, I'm going to focus on the key findings. If you want to dig deeper, feel free to ask me for a copy of the paper or scan the QR code, which I will put up again later. So

the most striking finding was that adolescents who use methamphetamine were more than 13 times more likely to also have a diagnosis of conduct disorder. And it was verified with our meta analysis. As you can see here, the overall effect was quite strong with young people with methamphetamine disorder, it's 13.66 times more likely to also have conduct disorder. Conduct Disorder is defined as a set of behavioral problems involving aggression, law breaking tendencies and poor impulse control, and is diagnosed in children under the age of 18. Related, we found associations between methamphetamine use in youth and antisocial behaviors with young people reporting using methamphetamine, more likely to exhibit antisocial behaviors, reporting higher hostility symptoms, more likely to fight with peers, and reporting more difficulties was peer interaction. And this is very important. This was compared to people who did not use any drugs at all, but also people who use substances other than methamphetamine. So what this suggests is that does antisocial behaviors may be specific to methamphetamine use rather than just any substance use. And also should be noted that does antisocial behaviors are consistent with a conduct disorder diagnosis association, I just talked to you about and it shows that these young people probably meet criteria for conduct disorder, not just because they were involved in illicit activities related to their drug taking, but also because they had other symptoms of conduct disorder, including antisocial behaviors. As I mentioned, there were other associations or health outcomes, but due to time, I'm just going to go over them very briefly, and that's because those results didn't come out as strongly as the conduct disorder. So feel free to scan the QR code if you want to read more about it. We found marginal associations with major depressive disorder and anxiety disorder diagnosis. But interestingly, they was no association with depression or anxiety symptoms. So we only found association with diagnosis but not the individual symptoms. We also found an association with ADHD. But as I said, this did not come as strongly as the conduct disorder. And this also wasn't surprising given ADHD is often co-occurring with conduct disorder. And in terms of functional outcomes, oops, sorry, went the wrong way. In terms of functional outcomes, it was actually really hard to quantitatively assess because the way outcomes were reported were very, very heterogeneous. And what I mean by that is that they mostly relied on self report from participants or families of participants. And very few studies included standardised tools or questionnaires. So for example, when they looked at education, and no two studies had the same outcome for education, some studies look at GPA, or the studies looked at whether people had been kicked out of school, whether they had dropped out of school, whether they had completed year 11, or 12. So it was actually impossible for us to conduct a meta analysis on any of those outcomes because it was too heterogeneous. We did find, however, that methamphetamine use in youth was consistently associated with poor educational outcomes, regardless of what the educational outcome was. And what's very interesting is that it was regardless of settings, whether the participant was at school or in a treatment center or detention, regardless of frequency of use. So there were no differences between people reporting using methamphetamine daily, and people who only used a couple of times in their lifetime, and also regardless of severity of use, so there were no differences in occasional people reporting occasional use, compared to people with a diagnosis of methamphetamine abuse or dependence. We also found that methamphetamine use in its population was associated with involvement in the justice system. But there was no association in people already in detention, which is also quite interesting. And what it suggests it is possible that by the time young people reach the stage of being detained, the functional difficulties are so great that methamphetamine use might not be consequential anymore. Lastly, in terms of cognitive outcomes, we inhibitory individual control as a being consistently lower in young people who use methamphetamine and inhibitory control is the difficulty of controlling actions and behavior. So what it suggests here is that young people with methamphetamine use may be more likely to take part in more risky behaviors just because they literally cannot stop their actions. There are some key limitations to note in the studies we have reviewed, the first

limitation I have alluded to it just before but some of the measurements were very heterogeneous. And that was true to both exposure and outcomes by exposure and meant the measurement of methamphetamine use was, differed widely between studies becuase some studies only reporting a single lifetime use versus studies tha reported diagnosis of methamphetamine use disorder. So we had a very wide range of people included in a systematic review, and also heterogenous measurement of outcome. And I mentioned that, for example, the education was measured widely differently across studies. There was also a lack of adequate controls in most of the studies, and one of them we identified was lack of control for acute methamphetamine use. We know that acute use has a direct effect on health outcomes, for example, with people currently intoxicated on methamphetamine, more likely to report anxiety symptoms, and people going into withdrawal, more likely to report depressive symptoms. And we also know the acute methamphetamine use has a direct effect on cognitive performance. Because Methamphetamine is actually can be a cognitive enhancer. So if people had used methamphetamine earlier in the day before doing their cognitive tasks, it's possible that they would have done better than people who were going through withdrawal instead. So future studies, studies should aim to control for acute use. Lastly, there was very limited causal evidence in any of the studies we reviewed because of lack of longitudinal studies. What that means is we actually don't really know what the direction of the effects in the studies reviewed. For example, let's get back to the conduct disorder diagnosis. It is very unclear at this stage, whether young people with conduct disorder are more likely to start using methamphetamine earlier in life, or is it that young people who start using methamphetamine early in life are more likely to engage in illicit behaviors and then meet criteria for conduct disorder. So there is a bit of work left to be done to establish the directionality. So in summary, in this first part of the talk, I showed you that there's a strong association between conduct disorder and methamphetamine using youth. Young people who use methamphetamine are more likely to be involved in the youth justice system compared to their peers. They also have more educational problems, and poorer performance on inhibitory control tasks. As a bit of a continuation of this first part, just want to highlight that the purpose of this paper was not to further stigmatise this population, it is really to show that they are very vulnerable groups. Young people who use methamphetamine are very vulnerable group that have a lot of things that going on in their lives. And they are at risk of experiencing more ongoing complex issues during the lifetime. So it's very very important to focus on this population and develop new targeted intervention and pretty much provide the support they need. And I just want to flash the paper again, as I said, it's already submitted, this is your last chance to scan the QR code if you are interested. For the second part of this webinar, I want to talk to you a bit about the work we've been doing in the last few years developing this new targeted treatment for people for young people use methamphetamine. Without repeating myself, I just want to reiterate that substance use experimentation does start in adolescence. And much of it is normative so a lot of people if not everyone will experiment with substances at some point. However, what we also see is that substance use disorders do onset early so you can see in the graph here, the 25% of people in this category have a substance use disorder. So I showed you in the first half that methamphetamine use in youth is associated with a range of negative outcomes. And there is some evidence in drugs other than methamphetamine that those outcomes can be improved by early treatment. So ideally, what we want to do is intervene as early as possible, when the methamphetamine use is still recreational before people develop a formal substance use disorder. In other substances, like opioid, alcohol and nicotine use disorder, medication form a very key part of treatment. And importantly, the best practice in treatment of substance use disorders is to combined both medication and psychosocial interventions. And that's to help bolster the effects of this psychosocial treatment that are already existing. Unfortunately, for us, there's currently no efficacious medication for methamphetamine use disorder. And I just want to very quickly draw your attention to a systematic review and meta analyses that were

published in the last few years. While the details some evidence for some medication, to reduce methamphetamine use, and also manage withdrawal symptoms, the strength of evidence remains still quite low. And importantly, all studies to date, as I've said before, have been conducted in adults there. So there hasn't been any clinical trials done in adolescents and younger people for this condition. So this brings me to the work we have been doing at Orygen and that's to test new candidate medications to help young people manage their substance use. And my, part of my work in the group is to look at methamphetamine. And one of the studies I'm going to talk to you about today is testing ketamine, subcutaneous ketamine as a potential new candidate medication to help young people manage the methamphetamine use. Ketamine is a non competitive antagonist at the NMDA receptor. It is already well characterised and already approved for use in Australia and anesthesia and also in sub anesthetic doses in depression. We're not quite sure how it works, but we believe it is possible that it normalises glutamatergic dysregulation in substance use disorder, which in turn can facilitate new learning. Importantly, there's some evidence in the US showing that a single dose of ketamine can improve cocaine and alcohol use outcomes. So it seems promising in substance use disorders. But there's currently no research in methamphetamine use. Yet, although there are some studies about to start. Just want to go back very quickly to those cocaine use disorder study that I just mentioned. And that's because cocaine and methamphetamine are quite similar in regards to use patterns, but also in regards to pharmacology. They are both psychostimulants acting on similar pathways in the brain. There has been a lot of studies in the past looking at medication, potential new medications for cocaine use disorder, but there's never been anything quite like ketamine, so it seems quite promising. In two laboratory studies in non treatment seeking participants they found that a single IV intravenous infusions of ketamine improved motivation to quit cocaine and also reduce cocaine self administration and in a randomized control trial that was conducted in adults who use cocaine, five years ago, they found that a single IV infusion of ketamine in combination with a mindfulness based relapse prevention approach, improve the abstinence outcomes, reduced relapse and reduced craving. Importantly, the ketamine was well tolerated in this population, and they were no adverse event related withdrawal in this trial. Just a reminder that it was done in adults. So there's still a bit of work to be done in adolescence before we can move on to a formal RCT. And that brings me to the study I've been leading for the last few years. It's called methamphetamine use in young people sub anesthetic ketamine open label trial or Maskot study for short. As the name suggests, it is an open label design, which means everyone enrolled in the study received the medication, so we didn't have a placebo control group at this stage. We originally planned on recruiting 20 young people aged 15 to 25 years old with moderate to severe methamphetamine use disorder. But it should be noted that at the start of this year, we actually increased the recruitment age range to 15 to 35 years old, to improve recruitment rates. Participants were recruited online via our website and social media ads, and also by our alcohol and other drugs services, where we left flyers and also asked clinicians to refer their clients if they thought this study was appropriate for them. And I'd also like to thank NCCRED for funding this pilot study and supporting our work. So because it's a small open label study, the primary aim was to first test the safety and tolerability of two ketamine doses, administered subcutaneously seven days apart in young people with methamphetamine use disorder. We assessed safety by looking at the change in ketamine use frequency and craving between baseline and after treatment. And that's really important because what we didn't want to do is have young people stop using methamphetamine but then started using ketamine recreationally after taking part in the study. Because as a lot of you will know, the ketamine we administer the medical grade ketamine we administer is very different than the ketamine you would get when you use it recreationally. We also looked at whether ketamine had an effect on liver chemistry by looking at liver function tests after treatment, and tolerability was assessed as a number of participants withdrawing from the study due to adverse medication effects. We

had a long list of secondary aims but today I just want to focus on the preliminary efficacy of those two ketamine doses. And that was assessed by looking at the change from baseline in methamphetamine use frequency withdrawal and craving at follow up. This is a quick overview of what the study entailed. All participants had to undergo a screening session first, and that was to make sure the study was right for them and actually fit their needs. If they were eligible, they were invited to take part in the baseline assessment during this baseline visit. We administered a number of questionnaires and measures and then they started that first ketamine treatment day on day zero. So all the ketamine sessions were conducted at the Royal Melbourne Hospital clinical trial center. So a typical session, in a typical session, participants will arrive in the morning and have a chat with a doctor make sure that we're feeling well enough to undergo the session. Then at about 11am they would receive their subcutaneous injection of ketamine starting with a small dose of 0.75 milligram per kilogram. And then we monitored the participant for four hours, so the study doctor was there with them in the room for four hours to monitor for any side effects that would emerge after receiving the ketamine, also to look at Vital Signs and we also administered a number of questionnaires to look at drug effects, psychotic and dissociative symptoms, and mysticism. After the four hours, the participants were discharged. The next day, I would give them a brief phone call to check up on them to see if they were doing okay after the treatment session. And then seven days later, a week later, they came back to the RMH to do the second session, which was identical to the first except if they had tolerated the initial dose on the first day they would go up at those 2.9 milligram per kilogram of ketamine. And if they didn't tolerate the first dose and we put down a dose 2.6 milligram per kilogram of ketamine. The procedure was the same in both sessions, another phone call the following day, and then seven days after the final treatment, they would come back to Orygen for the no treatment assessment, where we administer the same questionnaires we did at baseline to compare our pre and post treatments. We also have three follow ups at day 21, 28 and 42. So in total it took about, it took between sorry, six to nine weeks to complete the full study. So, as I mentioned, we recruited people online and via flyers that we dropped off in alcohol and other drug clinics, specifically targeting youth. And I can't see the top of my screen. So I'm gonna have to try to remember what it says there. We received, I believe it's 144 expression of interest all up. And that's either via our website or direct referral frin clinicians. I know there's 144 people, 58 of them could never be contacted. So I was never able to get on to them to speak to them about the study and invite them for a screening session. 54 of them did not pass the phone pre screening where we asked them some very basic question just to see if the study will be the right fit for them. The most common reasons for failing the pre screening phone cal was that they were no longer interested in taking part in the study, they will not currently using methamphetamine, they were not in the age bracket that we were interested in, although as I said, we did increase the age range later. And a big chunk of them were known prior to screening that they've met an exclusion criteria. So we didn't want to waste their time by inviting them for screening. And that's usually because they were currently taking a medication that would be contraindicated for ketamine. So we ended up inviting 20 people for a screening session, eight people did not want to proceed and one of them explicitly told us they were no longer interested and seven people just did not come to the screening session without providing a reason. So that left us with 12 people who underwent the full screening session. Seven of them did not pass the screening for several reasons. The first one and three of them met criteria for severe depression. One of them had a severe sedative use disorder, they use too much GHB, which is also contraindicated for ketamine use. Two of them did not complete screening. So they completed the first part, but they never came back for the second half. And one of them started on ADHD medication during the screening session. So between two individual appointment, they started taking dexamphetamine. So that left us with five people enrolled in the study, one of them never commenced treatment because they had to withdraw. And that's

because they couldn't complete the protocol due to logistical reasons, it was too complicated for them to attend the treatment sessions at the RMH. So that does seem to be a bit of the barrier and future studies, we should really look into them. One person has just started treatment, we don't have any data yet, and three people have completed the full study. So I'm gonna spend the last ten minutes of this talk going through the preliminary data we obtained from those first three people that completed the full protocol. So they were all females, and the age range between 22 to 32 years old, and they reported using on average methamphetamine 6.5 days a week at baseline so that's before they started treatment. In the primary outcome, we found no change in the ketamine use frequency or craving after the ketamine treatment. And none of the participants started using ketamine after being treated. So that's really great news. There was also no abnormal liver chemistry after treatment, the ketamine, the small ketamine doses didn't seem to have any effect on liver chemistry. So while it is a small sample size, so far, we have a pretty good safety signal. In terms of durability of the ketamine injections, they will no withdrawals during treatment. So as I said, we had someone withdraw before they even started, and all adverse events that emerged during the ketamine sessions resolved before they were discharged from the hospital. And no serious adverse events were reported at any point in time during the study. I just want to briefly talk to you about what happens in those ketamine sessions. So one of the questionnaire we administered during the ketamine treatment session is what we call the drug effect questionnaire. And it's a number of questions pretty much asking the participant about their experience with the medication they just received. So they asked a number of questions. For example, do you feel a drug effect right now and they asked to slide a little slider on an iPad between zero to 100, zero being not at all and 100 being extremely. So what we find when we ask, do you feel the effects of the drug so that's the light yellow, we found that 15 minutes post ketamine infusion, they pretty much all reported feeling the effect of the ketamine extremely so nearly close to 100 for the first session, but what's really good to see is that it goes back down to zero before discharge, so by the time they were discharged and longer feel the effects of the ketamine. And the same thing happened in the second session except slightly higher, which would make sense given that the dose was higher as well. But similarly to the first session, the drug effect does go back to zero before discharge. We also asked them if they liked the effect of the drug they received. And it does go up the screen, but it does go up at about a 60 and remains fairly stable throughout the session. And likewise, in the second session, it was around the 50 mark. So while we can conclude from there is that they it's not that they liked the drug, they didn't like it or not like the drug, they were very much like, Yep, this is, this is nice, this is fine. The important question we were asking ourselves is, will they want to get more of the drug, and that's the orange dots. So when we asked "Would you like more of the drug?" we found that they went for about 25 At the start, and it does go back to zero as well, in the first session, which is very good to hear. In the second session, it did remain somewhat high throughout the entire session and never really went back to zero. So even at discharge reported wanting some more of the drug, but none of them went in, in the wild and sourced ketamine. So that's all good. In terms of vital signs, I'm not gonna spend too much time on this, but there was a slight increase in systolic blood pressure in the first 15 minutes, which was to be expected. But it went back down to baseline very quickly. And the same increase can be seen in the second session, except it lasted about half an hour before going back to baseline. There were no changes in diastolic pulse, diastolic pressure sorry, pulse and oxygen saturation. However, we did see a slight increase in respiration rate in the first half hour post infusions in the second session, but it also went back to normal. So it seems to be safe and all effects seem to be very short lived. Now let's have a look at the secondary outcome. And I want to draw your attention to methamphetamine use, I really want to stress now at this stage, we cannot comment on the efficacy of ketamine at all based on our pilot data. And that's for two key reasons. The first is that it is an open label study where everyone got the ketamine, so we didn't have any appropriate controls to compare it to.

And the second reason is that we still have a very small sample size of three. So while this is informative to to inform future studies, we can't comment on preliminary efficacy. Nonetheless, as I mentioned earlier, on average, they reported using methamphetamine 6.5 days a week before treatment. And what we found is a week after treatment, they all had reduced their methamphetamine use to about 2.3 days a week, it's very promising. And two weeks after the end of treatment, we found that two of the participants went back to using a little bit more, whereas one participant actually went down even further to about one day a week of use. Once again, just want to stress that we cannot comment on efficacy at this stage. I do want to spend the last five minutes of this talk talking about recruitment challenges and that's because we have faced quite a few challenges trying to engage people in this study for various reasons, including reasons completely out of our control. We opened recruitment in June 2021. And that was literally weeks before we went back into six months lock down here in Melbourne and all research studies at the Royal Melbourne Hospital sites were put on hold. So we couldn't recruit for about nine months, I think. And we open recruitment again in mid 2022. We also started by recruiting people on social media by using Facebook and Instagram ads. And at the start, we had very limited success with very, very few expressions of interest coming through via those ads. So what we did is we refocused the ads, we workshop them, and we also use different social media platforms, not just Facebook and Instagram. We did get some expression of interests at the start of the study. But interestingly not a lot of them lead to actual interest. So I showed you the flow chart earlier, we did receive a total of 144 expression of interest, but about a third of them I could never contact so even though they say they were interested, and another big chunk of them when I would speak to them on the phone about the study they were no longer interested in taking part. So yeah, we did have some difficulties engaging young people in this particular research study. We did explore a number of recruitment solutions which did help with a number of expressions of interest we received. The first one was to directly go to youth alcohol and other drug treatment services. And we formed a partnership was Western Health drug health services, we had an existing partnership with YSAS. And I also gave flyers and spoke to people at Uniting Care Re Gen in Coburg and also Each in Ringwood. And that really did help with getting referrals directly from clinicians. And what we believe happened is that if a young person was already engaged with a clinician, that were much more likely to be wanting to engage with treatment study that may help them manage their methamphetamine use. As I briefly mentioned, we also targeted other social media, because what we found early on is that young people don't tend to use Facebook and Instagram anymore. So we went for social media that may actually reach our target. So we have ads on Snapchat, Tiktok, and also some video ads on Spotify. And that did lead to a few more expression of interests. Last year, we updated all our advertising material as well, we removed any negative language in the flyer. And importantly, we also removed all mentions of reducing methamphetamine use. So instead of saying, "Do you want to reduce methamphetamine use?", we just went "Do you use methamphetamine?". And that's because we believe that maybe young people were just not ready to reduce, maybe they just wanted to like manage their use rather than stop using. Lastly, at the start of this year, we updated our inclusion exclusion criteria, the first thing we did was to remove the severe depression criteria. I don't know if you remember in that flowchart, the three people were excluded because they made criteria for severe depression. And the reason why we remove these criteria is because there is evidence in young people that ketamine may actually help manage depressive symptoms as well. And the second criteria we change was a inclusion age. So we looked at people aged up to 35 years old. So we were first restricted from 15 to 25. And then we went up to 35 years old, which is still considered young adulthood. While this flyer does recommend solutions and seeing a lot more expression of interests and referral, enrollment rates are still quite low. So as you saw, we only enrolled five people. So I would love to hear if anyone in the audience has any suggestions, any comments, any feedback on how we can try to engage this population a little

bit more in research. So in conclusion, I hope what I convey today is a methamphetamine use in youth is associated with a range of negative outcomes. It is a vulnerable population with very complex needs, that needs specialised support, and new treatments targeting youth are clearly needed. And what we showed is that ketamine may be a promising treatment in this population. However, we have faced some challenges, particularly in terms of recruitment and engagement in research studies. And before I wrap up, I'd like to acknowledge a number of people and funding sources. I want to acknowledge all the participants who took part in this study, not just people who took part in the study but people I spoke to on the phone as well before enrolling, and just really want to thank them for their time and commitment to the study. And also want to thank a number of our funding partners. NCCRED specifically because they have funded a pilot study. And I'm very grateful that they fund this important work. So the Gandel Philanthropy and Medical Research Future Funding, which funding my salary, and also the National Institute on Drug Abuse in the US, which are supporting our group. And here's a picture of our group. So this is me here. And this is Gill Bedi, who's the leader of the substances research group. And lastly, if you have any questions, any any feedback, or just want to have a chat that says, feel free to email me here, or you can also link with me on Twitter, or X, or whatever it's called nowadays. Thank you very much for your time.

S Steph Kershaw 44:07

Amazing, thank you so much, Alex, we really appreciate your time. And it's so interesting to hear about what are some of the outcomes associated with methamphetamine use in young people, and some of the, you know, recent research happening in the space, although obviously there is a need to do more research. Now we've got some time for questions, which is perfect. Some questions have already come through during the session. But just a reminder to all our participants. If you do have a question, please submit it using the Q&A box at the bottom of your screen. And we will do our absolute best to get through as many questions as we possibly can. Alex, are you ready for the many questions?

A Alex Guerin 44:46

Sure. Just want to flag I may not be able to answer every question but I'm very happy to have like separate conversations as well with different people, different groups. I love talking about this and yeah

S Steph Kershaw 44:59

That's perfect. That's what we want to hear and totally no pressure. But, you know, something may be outside your expertise. And that's totally fine. One question that has come up is around those functional impacts of methamphetamine use. So for someone who has stopped using, is there much knowledge about what happens in over the long term? You know, do the cognitive emotional outcomes change for people? What happens in that long term?

A Alex Guerin 45:27

That is a very, very great question. I don't know of studies in youth, particularly looking at that I know there's a couple of longitudinal studies in adults showing that cognition can actually

know there's a couple of longitudinal studies in adults showing that cognition can actually resolve and go back to pre methamphetamine use, when methamphetamine use is discontinued for a period of time. So when people abstinent. In youth, I'm not quite sure, you would expect to see the same thing. But as I mentioned, this is a very big limitation of the current literature, where there's very, very few longitudinal studies, because it's just not a population that is studied very much. I mean, we only identify 66 papers, which may sound like a lot, but compared to other drugs, it's barely anything really.

S Steph Kershaw 46:12

Yeah, it does seem that you know, young people and methamphetamine use really is a overlooked population. Do you think that part of that might come back to you know, for young people under the age of 16? You need parental consent? Is that? Do you think a particular barrier? Or do you really think even over the age of 16, engaging those 16 to 25 year old is quite difficult.

A Alex Guerin 46:37

That is a very, very great point. And I didn't mention in my talk, this was actually something we came across, we've had young people under the age of 18, even, contacting us wanting to take part in the study. But unfortunately, we needed guardian consent for them to take part and as soon as they knew that, they pretty much say sorry not interested. So it's probably when the guardian or the parents or the parental figure doesn't know about the use, they don't really want to take part. So that's actually a very good point. This might be one of the reasons why there's not a lot of research in this population. Quite a few of the studies I reviewed were done in school, so they were just like anonymous surveys, which can be a good way of, of doing this kind of research, but also has limitations. Like for example, just a self reported use methamphetamine. Yes, no. It's just not as sensitive as having someone come in and do for clinical interview or diagnostic interview.

S Steph Kershaw 47:32

Yeah, for sure. And just around, you know, how do can encourage more young people into research? I know that there's been a lot of consideration in the field around peer involvement and getting young people into research teams and having them look over recruitment adverts. Was that something that you considered or would consider for further research?

A Alex Guerin 47:57

Absolutely. Well, that's something we are doing for pretty much all the upcoming projects or projects are about to start running. So we really value especially at Orygen with very value, youth participation and having young people with lived experience actually contributing to the research, because in the end, I have mentioned several times that you know, we need to come up with new treatments targeting their needs. But if we don't ask them directly what the needs are, then how can we do that. For this particular study, a small pilot study, a big barrier was funding. So we did, we did get funded to do the research, but it was a small pilot study, a small grant, unfortunately, we just did not have the resources to engage someone. But I completely

agree with you, all subsequent studies, have youth advisors and lived experience advisors. And it's built into all of our projects now. And yeah, we did have people review all that advertising material that for this study, and some people did have feedback about, you know, toning down the language or not making it as negative.

49:02

Yeah,

S Steph Kershaw 49:02

Yeah, I mean, amazing to hear that you've got young people involved in the research, I think, yeah, that's definitely leading the way in innovation. And it is a real barrier for other researchers in the field, you know, those small amounts of seed funding, you know, we often don't have enough to do as much consultation or inclusion as we'd like. Just going down a slightly different track, we've had a couple of questions about trying to better understand their relationships with methamphetamine, and outcomes looked for. So for example, did the conduct disorder start before the menthamphetamine use or whether methamphetamine use sort of lowered your impulse control because of it? Yeah, I know, it's a very tricky question.

A Alex Guerin 49:47

It is a fantastic question. And I'm really glad I don't know who asked the question, but that's I'm really glad they did because this is pretty much where my research program is going at the moment try to understand this relationship. Where does it start? As I mentioned, earlier, Is it young people? Is it children with conduct problems using methamphetamine earlier in life because of the poor impulse and the law breaking tendencies? Or is it if you start using methamphetamine early in life, then you are more likely to engage in criminal activities then meet criteria. So that is a fascinating question. I don't have an answer. But I am definitely working on this and really want to explore this further.

S Steph Kershaw 50:27

So maybe in five years time you can come back and give us the answer! One thing that is discussed quite a lot is the link between ADHD and youth, because obviously, a lot of the ADHD medications like Ritalin are a type of stimulant. So is there any link or what's the research between ADHD in youth and methamphetamine use?

A Alex Guerin 50:52

So I'm not going to comment on the research itself, just because I'm not fully across it. So I don't want to say something wrong. But I'm going to answer this question by just providing some personal experience with the participants we've had, we have found that a number of them, not necessarily large number, but a number of them have reported that they started using methamphetamine as a self medication because they suspected they had attentional

deficit symptoms, not necessarily ADHD, but they found that the use of methamphetamine did help them with those Attention Deficit symptoms. So that wouldn't surprise me there was a stronger link between ADHD and methamphetamine use. I mean, if youhave looked at the full paper, you'll find that we did find an association. I didn't really comment on it, just because the quality of the papers we reviewed was fairly low. So the quality of evidence, the strength of evidence was fairly low. And there's actually not that many people are looking at ADHD and methamphetamine use directly. There's, yeah, there's certainly something there. I'm not gonna comment on the literature just because I'm not quite across ADHD.

S Steph Kershaw 52:01

But yeah, I mean, totally fair. I'm also not very across that field, but we'd love to know more about it as well. From a sort of prevention perspective, are you aware of any work exploring with young people about which potential outcomes of methamphetamine are the most important to them?

A Alex Guerin 52:22

Wow, those questions are really great. I'm going to look into, we really want to do a priority setting exercise, and literally ask young people, so what do you actually, what do you want to do? Because well, my understanding, what I understand is not a lot of people, and it's not just in youth, but not a lot of people who use drugs just want to completely quit and be abstinent. A lot of people just want to be able to manage their use, they can go to school, they can complete their degree, they can go to work, you know, three days a week. So very, I think it is fascinating that someone asked, because that's exactly what I want to do. And I want to work with both young people and also clinicians, peer workers, social workers, just trying to understand what they actually want.

S Steph Kershaw 53:09

Yeah, yeah.

A Alex Guerin 53:10

My Yeah, my sense is a lot of clinical trials have been done in the past, even ours, which is looking at can the drug reduce drug use, can the medication reduce drug use, but not it's not the end goal for a lot of people.

S Steph Kershaw 53:24

Yeah, exactly. You know, we've seen a lot of discussion at the moment about, you know, what is actually recovery? Is it abstinence? Or, you know, yeah, it's quite an interesting field.

A Alex Guerin 53:36

Alex Guerin 53:56

And I think it's particularly relevant to young people as well, because a lot of them and that's, that's based on findings from a different study I've been running, a lot of them just don't see their substance use as a problem yet. They use it recreationally, and yes, it does affect their sleep and their work and things like that. But they don't really see as a problem. So when they come to us, we try to focus on those different aspects. But yeah, so very, very fascinating question. Really want to get into this more.

S Steph Kershaw 54:02

Yeah. So actually, a lot of questions have come in about your maskot study. So I hope you don't mind. I'm going to ask them in quick succession. Is it still available? Or has it been trialed in Sydney?

A Alex Guerin 54:18

It has not been tried in Sydney. And I know they might. Yeah, there will be, well no. It hasn't been tried in Sydney. Sorry.

S Steph Kershaw 54:27

No, no, that's ok.

A Alex Guerin 54:29

In terms of is a study is still ongoing, we are actually wrapping up now. But there will be more studies. So I'm still very happy to take on board any advice and any comments.

S Steph Kershaw 54:41

Yeah, well, there's a lot of interest in it. One person pointed out that it seems like all enrolled in the study were female, and usually they're underrepresented. So do you have any thoughts around that?

A Alex Guerin 54:55

Fascinating once again, great question. =I did my PhD in the same field, but I worked with adults, and I pretty much exclusively had males engaging in the study. So it was a bit of a surprise to me as well. Yeah. Most people enrolled identify as female. I don't have anything else to say about this. It's just interesting. Is it that males, in this age range, don't see, as I said, don't see the substances uss a problem and don't feel like they have to do anything about it. And that females may be more, I hate using this word, women may be more at the stage, where they're like, Oh, this is probably a problem. I should probably try to reduce or manage it.

Maybe that's the case. I can't answer this question. But I also found it very interesting. And it's the same in the number of people we screened they were all pretty much all identifying as female, except for a couple of participants, who were male.

S Steph Kershaw 55:53

Was there any, have you had any thoughts about involving regional areas in future trials to increase accessibility?

A Alex Guerin 56:03

Yeah, sorry, I didn't mean to interrupt you. Absolutely. So we really want to make this as accessible as possible. The main limitation, the main barrier for this particular trial is the fact that they had to come in to the hospital to receive the infusions, and that it did take all day. The other studies we've run, some of them were completely online. So that was very accessible for anyone in Victoria. And we also currently running another study, different indication, different drug, but it's also run across Victoria. So we have a site in Geelong as well. So yes, we really want to engage more regional populations. But yes, we did have some people expressing interest on Mildura and Ballarat, but even Ballarat was slightly too far to get into Melbourne just to get the ketamine, because the problem is they can't drive the day of receiveing the ketamine we require that they be driven home by someone else, or we provide a taxi voucher. So yes, it is it is a big barrier. And we really want to do better in the future with bigger studies with more budget, and ideally, well we can't do the ketamine sessions in people's homes, but we could find some solution.

S Steph Kershaw 57:24

Yeah, yeah. And so we've got probably only time for one or two more questions. Are there any studies sort of going back to that long term? Looking at you starting in youth and going through to adulthood? So are there any sort of cohort studies that you're aware of, or follow up studies that really look at those long term?

A Alex Guerin 57:49

Yeah, I mean, there are there are very big studies being run in the United States. I know that the ABCD cohort. I don't know if people have heard about these, like they've been following children for years and years and years and do record like substance use and things like that. So I'm not sure at what point at what stage it is at the moment. But I think this is going to be super informative in the future to see what happens. And really, I'm sure there are many more, but the ABCD is a good one. It's also publicly available, like anyone can request data and analyze. So yeah, there are some studies. Exciting.

S Steph Kershaw 58:25

Yeah. And it sounds like we also need to create an Australian version over here.

A Alex Guerin 58:29

I would love to have I mean, I know, researchers at the Monash have their own like population they've been following for a while, but they're not youth, they're adults. But yeah, we need more like registries here. We should all work together.

S Steph Kershaw 58:46

Well, thank you so much, Alex. Sadly, that's all we've got time for today. But I just wanted to let you know that lots of people have been reaching out to connect you about recruitment and to find out more about your research and how they can support it. So we'll make sure to share some of those links with you.

A Alex Guerin 59:01

Absolutely, I was gonna ask, is it any chance to get like the questions I haven't had the chance to answer?

S Steph Kershaw 59:08

Of course, I will send you everything.

A Alex Guerin 59:11

And also please do email me or reach out on Twitter. I'm always, as I said, very happy to discuss anything really, whether it's criticism, feedback, comments, or just a discussing.

S Steph Kershaw 59:24

That's amazing, Alex. Yeah, we really appreciate that offer. And I'm sure you'll receive many emails and requests from people, today's definitely sparked a lot of discussion and interest in this field, which is great. I'd like to thank you again for your time and for sharing all these valuable insights with us. Just a reminder to all of our participants, you know, sometimes we're talking about functional outcomes and depression and anxiety it can raise some concerns or distress so you know, if you do feel like you need to talk to someone, there are support services available on both Cracks in the Ice and Positive Choices, including Lifeline, which you can call on 13 11 14. Again, apologies to anyone who didn't get their question answered. But Alex is always, as he said, very keen to have a chat. So feel free to reach out and we can connect you if you need. And just lastly, we will be holding more webinars and putting new resources on both Cracks in the Ice and Positive Choices throughout this year. So please, I encourage you to subscribe to our mailing list if you're interested in receiving future updates. So thank you again, everyone, for joining us today to Alex for an amazing presentation. And just for all the really

interesting conversation that's happening in this space, it's an area I think that we're all very passionate about. And so thank you again for joining us. I do hope that you will have a wonderful day. So thank you. Thank you so much.