



NATIONAL MENTAL HEALTH RESEARCH STRATEGY

BACKGROUND PAPER: Substance use disorders (Session 4B)

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Background

Substance use disorders are serious public health concerns, with negative consequences across health, economic and social domains. Substance use contributes to the development and perpetuation of most mental disorders including mood disorders, autism spectrum disorder, psychosis and particularly suicide. Alcohol is an important cause of early onset dementia. Substance use can lead to dependence via action on reward areas of the brain and neuroadaptation.

Substance use disorders are classified within mental health disorders and often included in statistics of overall impact of mental disorders, although typically not treatment within mental health services. Alcohol (4.5%) and illicit drugs (2.7%) are collectively responsible for approximately 7% of Australia's disease burden and tobacco 8% yielding a total of 15%.¹

Despite these significant societal costs that equal all other mental disorders, the field invariably receives less investment. Substance use disorders generally lead to more harm in economically disadvantaged populations such that strategies to address these disorders present a major opportunity to reduce social disparity

Alcohol Use Disorder (AUD)

Alcohol causes the most overall harm to the Australian community, despite regular media coverage raising community concerns on methamphetamine (ice) and opioids. Australia-wide, alcohol misuse accounts for an annual economic burden estimated at \$30 billion² and is a leading cause of preventable death, being linked to over 200 disease conditions.³ Alcohol, used both acutely and chronically, is involved in over a third of deliberate self-harm episodes and suicide.⁴ Alcohol use disorders are prevalent, with approximately 1 million Australians affected. Australian hospital admissions for alcohol-related disorders have continued to rise suggesting high-risk drinkers are not responding well to public health measures.

Effective early intervention and treatment can lead to striking improvements across multiple health and social domains. Research investment in Australia for improving treatment and access to care for alcohol problems is extremely low relative to the burden of disease. There is a pressing need to improve treatment for the large number of Australians at high risk to reduce the burden of AUD.

Translational barriers

Only one in five of these individuals seek help for their drinking. It is estimated that only 3% of the AUD population receive relapse prevention medication. Thus, the majority of individuals with AUD will never receive treatment and, for those that do seek help, the nature of the treatment received may not be evidence-based.

A potential solution to this challenge would be investment in translational research regarding the dissemination of guidelines and implementation of AUD evidence-based care nationwide, especially access to evidence-based treatments in rural and regional areas.

Discovery of novel treatments

Pharmacotherapy can be a key tool for reducing the core symptoms of AUD and achieving abstinence or controlling consumption. Pharmacotherapies are guided by our increasing understanding of the neurobehavioural mechanisms underlying alcohol-seeking behaviour, reward and chronic alcohol use. At present, the only pharmacological treatments specifically indicated for AUD in Australia are disulfiram, acamprosate and naltrexone.⁵ The effectiveness of these medications are modest (although no smaller than antidepressants). They are also not suitable for many AUD patients. There have been no new treatments approved and made available in Australia for 20 years. Psychotherapies similarly have modest effect-sizes (although similar to those for mood disorders). There is a high degree of patient heterogeneity with regards to treatment efficacy and tolerability due to genetic variation and clinical comorbidities in AUD that are often not adequately examined. To allow for this heterogeneity, phase III clinical trials require more power and it is challenging to recruit at this level in Australia without adequate time and resources. Formal phase III clinical trials are costly and can take 4–5 years. We need a more efficient approach to screen novel treatments for efficacy.

Potential solutions to this challenge include:

- the development of a national clinical trials network to enhance power and capacity to answer required questions as per above (for example, in the USA they have the National Trials Network ACTIVE and in NSW the Drug and Alcohol Clinical Research and Improvement Network)
- investment for trials specifically designed to facilitate progression towards personalised medicine including examining clinical phenotypes and genotypes that are predictive of treatment response
- investment for research that utilises short clinical screening models whereby new therapeutic approaches are examined to reduce markers of dependence (e.g. alcohol consumption, impulse control, craving, neurobiological networks involved in addiction); this approach is being adopted overseas⁶ and is widely used for other disorders. Greater understanding of the neurobiological and psychological mechanisms that drive the maintenance of AUD is also required.

Improving early intervention and access to care

In primary care and other health care settings, alcohol problems are often not identified until they become severe. There is a median of 18 years for a person with an AUD to access appropriate treatment. When treatment does take place, it is most often for the more severe disorders associated with severe medical and social disintegration. However, treatment before the onset of such disability is clearly preferable.

A potential solution would be investment in research to identify more effective approaches to alcohol screening, identification and referral in different clinical settings, especially in primary care.

Alcohol problems and complex comorbid mental conditions

Research regarding comorbid mental disorders has centred around anxiety and depression. However, there is a high rate of alcohol use in self-harm episodes and suicide. In addition, substance use is a major modifiable risk factor for relapse in schizophrenia. These complex patients are often excluded from clinical trials to enhance retention rate and reduce heterogeneity in treatment response, yet represent an important area

of medical need. This population receives little attention yet utilises more health services and suffers from poor prognosis.

A potential solution would be investment in research specifically designed to improve management of these complex patients. For example, suicide prevention trials of interventions that focus on alcohol and substance use, as a major modifiable risk factor of suicide, and trials of interventions aimed at improving substance use problems in severe mental illness.

Intellectual leadership

There is a lack of intellectual leadership in the field of alcohol treatment research. There is a very small research workforce relative to the burden of disease such that the current research support matrix is not working. New researchers are thin as the field does not obtain significant interest. Early–mid career scientists find it difficult to compete as the work is intensive and the field is stigmatised. The field suffers as it is more difficult to attract people and funding compared to less stigmatised areas.

Investment is required in people support, project support and infrastructure support. In the USA, there is significant investment in alcohol research with the establishment of the NIAAA whereby scientists compete for funding within the field, which protects the field. This body provides funding for PhD scholarships, research fellowships and numerous small and large projects specifically for alcohol research. One example would be to invest in a national alcohol body similar to The National Centre for Clinical Research on Emerging Drugs (NCCRED), that funds small seed research, enhances funded trials and provides small fellowships (clinician or short fellowships researchers).

Tobacco

Whilst seen as a public health problem that has been substantially managed, tobacco use is a leading cause of disability and death amongst people with mental illness.

The rate of tobacco use in individuals with psychotic disorders is greater than 60%.⁷ The focus on physical illness in people with serious mental illness emphasises metabolic syndrome but concurrent smoking is an equally serious problem, leading to morbidity and early mortality. In addition there is a high rate of comorbidity of tobacco use disorder (TUD) and other substance use problems and each problem can represent a barrier to successful treatment.

A potential solution would be to expand on addiction research with tobacco and the relationship to other substance use disorders, especially alcohol; and invest in research to further understand the mechanisms of these comorbidities and development of interventions targeted for these comorbid populations.

Psychostimulants and emerging drugs

Psychostimulants include the synthetic drugs such as MDMA ('ecstasy'), cocaine, amphetamine and methamphetamine. Of all these substances, methamphetamine use is associated with the greatest harms. Methamphetamine dependence is a significant public health concern and is associated with clinical and psychological disturbances.⁸ Given the neurobiological profile and clinical presentation of methamphetamine, pharmacotherapy is an appropriate option in addition to psychosocial support.⁹ However, currently there are no evidence-based pharmacotherapy approved for methamphetamine dependence.

Discovery of novel treatments

Many of the problems facing the AUD field can be observed with methamphetamine. Briefly, these include the cost and length of formal phase III clinical trials and the need for a more efficient approach to screen novel therapies for efficacy; the high degree of clinical comorbidity observed in the methamphetamine population including cognitive impairment and mental disorders that are often not adequately examined; and phase III clinical trials requiring more power to allow for heterogeneity and lack of treatment engagement, which is a particular challenge in methamphetamine treatment research.

One approach is to investigate novel compounds in an acute human laboratory setting, such as with neuroimaging techniques, to evaluate therapeutic potential. Similarly for AUD, the establishment of a national clinical trials network will facilitate phase III trials. NCCRED is currently addressing these issues particularly well and is an excellent model that should be extended and made an independent body. This initiative has sparked interest in research and the seed funding and clinical fellowships are excellent. NCCRED does not have committed funds to continue its work at this stage. It is vital to continue its work.

Cannabis use

Cannabis is the most commonly used illicit drug. Evidence-based treatments, especially, psychotherapies have been studied to treat cannabis use disorder (CUD) with various approaches being shown to have clinical utility.¹⁰ Increasing research regarding medical cannabis over recent years has seen the regulatory arena move away from recommendation of enforcement of cannabis use as illegal towards consideration of its potential use in medical conditions. Consumer demand and widespread community support led to recent legislative changes in Australia with cannabis products now legally available.

Improving and discovering novel treatments

Many of the challenges faced conducting research in other areas of substance use are also relevant to CUD treatment research. Briefly, these include the need for a more efficient approach to screen novel therapies for efficacy, heterogeneity in the treatment population and lack of treatment engagement.¹⁰

A potential solution would be to investigate novel therapies in an acute clinical laboratory setting, to evaluate therapeutic potential more efficiently (phase II). In parallel, for phase III studies, the establishment of a national clinical trials network will facilitate phase III trials to address problems with power and treatment engagement.

Expanding use and legalisation

These are facilitated by potential health benefits and an absence of mental health concerns that are beyond the evidence base. Experience from the USA suggests that this may lead to increased use with corresponding increases in harm. It is possible that the number of individuals with CUD will increase in the coming years as cannabis becomes even more widely accepted and the perceived risk continues to decline.

Research is required with regard to the legal framework and regulatory environment. Overseas policy research has identified approaches to legalisation without increased harms. Continued research that monitors harms associated with medical cannabis is also needed.

Opioids

Opioid dependence is the second most prevalent drug use disorder and is an increasing and serious global health problem with substantial morbidity and mortality. An epidemic of prescription drug poisoning (overdose) is recognised in other OECD countries. The United States has been particularly affected, with more deaths from overdose every year than were sustained in the Vietnam War. Life expectancy in the United

States has declined for the past two years primarily because of the impact of drug overdose, making this the major public health challenge of today. Australia is on a similar trajectory.¹¹ Opioid overdose is a greater problem in regional settings and in economically depressed areas. Opioid substitution treatment (OST) is an effective and safe intervention that reduces illicit opioid use and harms such as overdose. Highly effective strategies for the management of opioid use disorder have evolved over recent years, including methadone, buprenorphine/naloxone and long-acting injectable buprenorphine.

Translational barriers

Access to these evidence-based options is limited in many regional areas lacking accredited prescribers. There is a need to invest in research examining barriers to and facilitators of implementing treatment in regional and rural areas. Examples of feasible inexpensive interventions include telehealth, dissemination of training into regional areas and dissemination of long-acting injectable forms of treatment. Prescription monitoring programs have been introduced in only two states and have been discussed for over a decade.

Improving the model of care

The model of care still requires some improvement insofar as there is a lack of an evidence base to guide clinicians through certain treatment challenges. These include physical and mental comorbidities and transitioning from opioid substitution treatment when appropriate.

A potential solution would be research programs that aim to improve the model care for opioid substitution treatment, including management of specific comorbidities and exiting from the methadone program and the role of secondary medications that are effective for that.

Conclusion

Harms from substance use present a great challenge to the nation. There are effective approaches that can address these problems. The recommended aim is to strengthen treatment of substance abuse, particularly harmful and chronic use of alcohol and opioid overdose. Alcohol has been particularly neglected as a health problem. This aim could be achieved in the following ways:

- enhance national coverage of treatment interventions (e.g. pharmacological and psychosocial and aftercare services) via investment in implementation and health services research
- invest in phase II trials to facilitate discovery of novel treatments and innovative approaches
- enhance national clinical research capacity for phase III trials to address genetic and clinical heterogeneity in treatment response via a national clinical trials network
- optimise national clinical research capacity by building clinical outcomes in routine clinical work that enables more pragmatic trials
- improve our understanding of major barriers to effective treatment including complex but common comorbidities such as schizophrenia, cognitive impairment and suicidality
- enhance intellectual leadership through the funding of specific bodies (similar to the NCCRED model) which stimulate research interest to improve treatment outcomes in priority areas.

There is opportunity to improve the health, welfare and prosperity of Australia if these strategies are adopted.

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