Alcohol and drug abuse: a startling insight

Professor John Curtin explains how his research hopes to identify and tackle the neural mechanisms underpinning drug addiction, and why many patients relapse when under stress

What inspired you to work in addiction? Why do you feel research in this field is important?

I grew up with heavy drinkers among my family and friends. Throughout college, I worked regularly as a bartender. From these early experiences, I was initially intrigued by how alcohol use was woven into the fabric of our social interactions – to celebrate special occasions and to ease sometimes anxiety-provoking interactions among new acquaintances and potential 'love' interests. In these instances, the effects of alcohol are highly valued and often beneficial for drinkers.

I started a doctoral programme in clinical psychology with a research focus that emphasised these prized social psychological phenomena associated with recreational drinking. However, I had family and friends who had paid high costs for their drinking. Around the world, the societal costs of alcohol and other drugs exceed that of most other health concerns. Thus, it was not long before I shifted my focus to the causes, consequences and treatment of addiction. Rather than being a niche field, I feel that the prevention and treatment of alcoholism and other addictions should be a national priority – it makes economic sense and affects all of us.

Can you describe how alcoholics undergo so-called neuroadaptive changes that keep them dependent on the drug?

Many alcoholics consume alcohol to cope with their negative emotions (eg. anxiety) when stressed. However, we only recently realised that heavy alcohol use itself can change the alcoholic's reactivity to stressors. Animal models suggest that drinking episodes lead to short-term changes in the brain's stress systems, which in turn lead to longlasting compensatory adaptations in neural structures and chemical messenger (neurotransmitter) systems. These 'stress neuroadaptations' result in increased reactivity to stressors when sober and strong cravings for alcohol to dampen the exaggerated stress reactivity.

Does your research on alcoholism have wider implications for other addictive substances?

Yes, we believe that other addictive drugs can cause stress neuroadaptations that produce exaggerated stress reactivity. For example, our recent research demonstrates that 24 hours of nicotine deprivation leads to increased stress reactivity in smokers. New data, which we are soon to publish, show a similar trend when depriving heavy marijuana users of the drug for three days.

To date, legal and prevalent drugs like alcohol and tobacco have been our focus because their health impacts are so widespread. However, we plan to study other drugs that are emerging as important due to either legislative changes regarding their use (ie. marijuana) or notable increases in rates of use and related problems (eg. prescription opiate use).

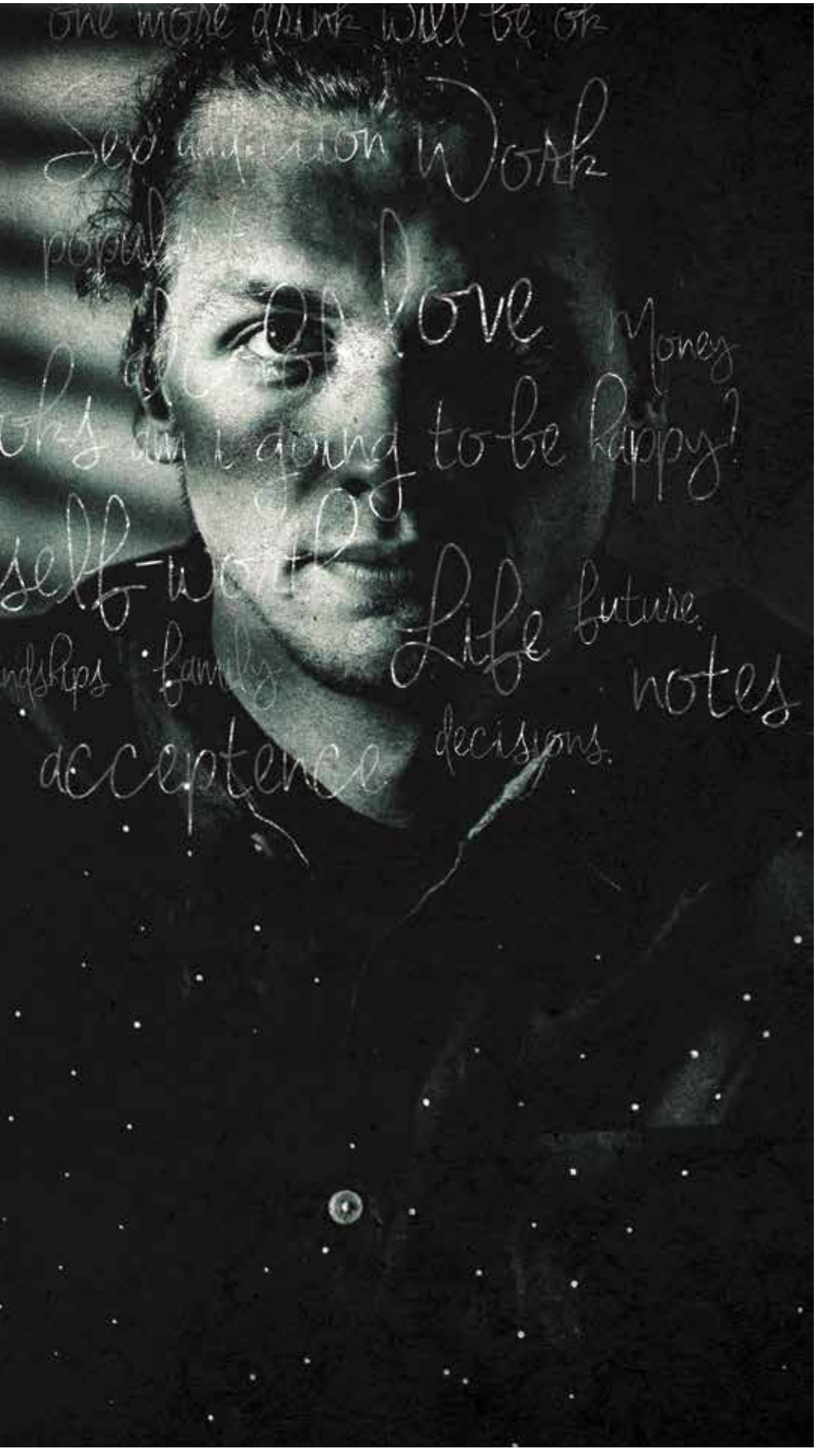
Your most recent research will be looking at stress-induced relapse via the pharmacological antagonism of norepinephrine (NE). Why are NE receptor antagonists being focused on?

The NE system appears to be one target of the stress neuroadaptations produced by chronic, heavy drug use. Stressors often cause relapse among individuals trying to break their habit and in animal models of relapse. Notably, stressors elevate NE levels in rodents and humans. Rodent experiments have also shown a precedent for reducing addictive behaviour by manipulating NE signalling.

Equally importantly, the pharmaceutical industry has made dramatic reductions in R&D for novel medications to treat neuropsychiatric conditions like addiction. It is therefore a good idea to repurpose currently available compounds that may be effective treatment alternatives. Inexpensive α1-NE antagonists are already widely available for other conditions. It is therefore prudent, both scientifically and economically, to focus our efforts on existing drugs with well-known properties.

Current addiction therapies lack efficacy in achieving long-term recovery for affected individuals. In what ways is your current research striving to tackle this treatment deficit?

Stressors and stress-induced relapse are serious impediments to long-term abstinence from drug use. Existing treatments – such as replacement therapies (eg. nicotine patches and methadone) or medications that reduce the pleasure associated with use – fail to both target reactions to stressors broadly and tackle the underlying stress-related neuropathology. Long-term maintenance using α1-NE antagonists could fill this gap. Our research into stress neuroadaptations will also better inform clinicians trying to treat patients with a mix of addiction and stress disorders. Finally, this research will help in cognitive behavioural therapy because it allows practitioners to tailor the sessions for individuals with stronger reactivity to stress, teaching them specifically to identify and cope with unpredictable stressors.



The effects of stress on addiction

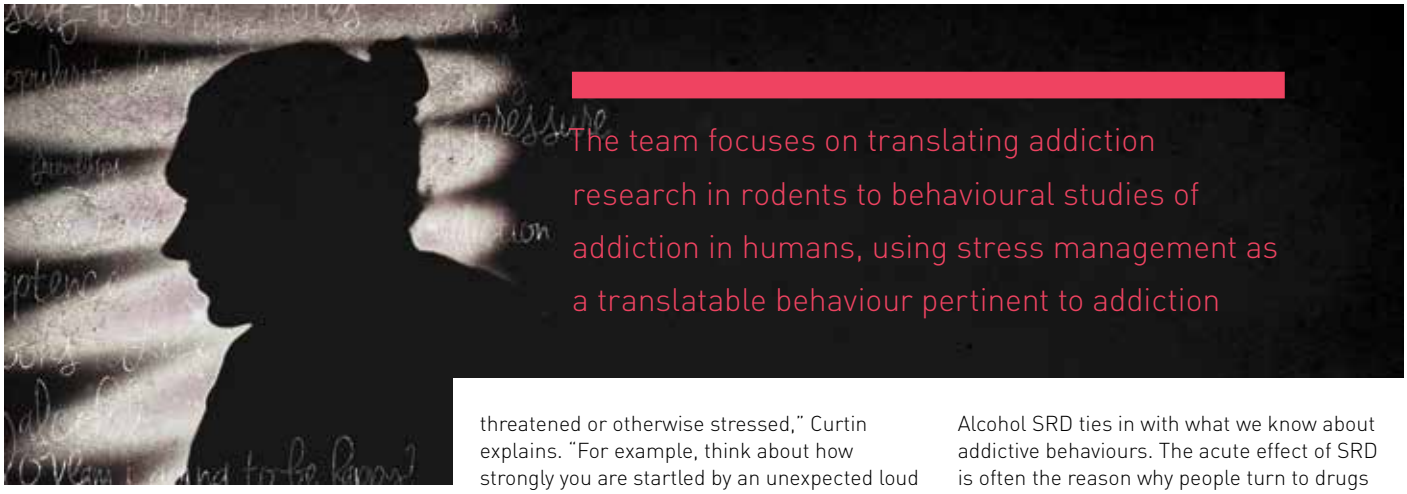
Our response to the stress of modern life can often be helped by a glass of red wine. However, alcohol abuse can make us even more vulnerable to stress. A laboratory in the **University of Wisconsin-Madison**, USA, is exploring why this is and how to reverse this process

AFTER A STRESSFUL day at work, many people like to relax and socialise with an alcoholic drink in hand. Others may find relief in smoking tobacco or marijuana. Humans consume psychoactive substances such as these because they increase feelings of wellbeing. However, these substances also have a darker side. According to the World Health Organization (WHO), nearly 6 per cent of all global illnesses in 2012 were linked to alcohol consumption. Similarly, tobacco smoking was responsible for 11 per cent and 6 per cent of deaths in males and females respectively in 2014. Even though the harmful effects of alcohol, tobacco and other drugs create issues for healthcare systems worldwide, the risk of addiction makes these problems particularly difficult to solve.

A research group at the University of Wisconsin hopes to tackle addiction in alcohol- and drug-dependent patients by uncovering the neuroadaptations responsible for the disease. The team is focusing on translating addiction research in rodents to behavioural studies of addiction in humans, using stress management as a translatable behaviour pertinent to addiction. Head of the research group Professor John Curtin elaborates: "It has historically been very difficult to study stress mechanisms in humans; however, researchers have recently built an assay of stress responses in humans based on a close translation of methods and measures from animal models – an assay that we now use heavily in our research".

STRESSING CIRCUMSTANCES

The assay itself measures how a state of anxiety increases startle responses to unexpected stimuli. In other words, how much more do you jump when startled in a tense situation compared with normal? "Not surprisingly, people startle more vigorously when they are



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STRESS NEUROADAPTATIONS IN ADDICTION

OBJECTIVES

- To research the stress neuroadaptations that lead to alcohol and drug addiction through translating addiction research in rodents to clinical studies of addiction in humans
- To test the mechanisms of drug addiction in humans and identify novel treatments

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PROFESSOR JOHN J CURTIN is a clinical psychologist and the Director of Clinical Training at the University of Wisconsin, Madison. He has substantial expertise in the use of pharmacological manipulations and psychophysiological, behavioural and self-report measures of affective processes in preclinical and clinical research in addiction. His programme of research focuses on the role of stress mechanisms in the aetiology and treatment of alcohol and other drug (AOD) use disorders. More recently, he has begun to exploit emerging mHealth capabilities on mobile devices to dynamically monitor and predict AOD relapse in patients following treatment.

threatened or otherwise stressed," Curtin explains. "For example, think about how strongly you are startled by an unexpected loud noise during a scary scene in a horror film."

Rodent assays use a burst of noise to startle the animal and then repeat this after stressing the rodent with electric shocks to its feet, using accelerometers on the cage floor to measure how much it jumps. The human assay is similar but measures a startle response instead by attaching recording electrodes to muscles surrounding the eye and measuring how much the muscles twitch when the human is startled by a loud noise. The increased startle seen during stress – known as startle potentiation – is the behaviour of interest to Curtin and his team.

KNOWING IS HALF OF THE BATTLE

An interesting observation has emerged from studies into startle potentiation. In essence, subjecting the rodent or human to an aversive stimulus that they do not expect (eg. randomly given electric shocks) will elicit a stronger startle potentiation than a stimulus that they do expect (eg. systematically given electric shocks). This means that the uncertainty of receiving the aversive stimulus causes more stress to the subject than knowing when the stimulus is imminent, bringing to mind the common English proverb: "Better the devil you know than the devil you do not". This distinction is important because the two stimulus presentations indicate two different states of mind in mammals. First, the certain threat results in a targeted phasic fear response. Second, the uncertain threat causes a non-specific, sustained anxiety response. These differences follow different neural circuits and are differentially influenced by alcohol intake.

FEARLESS DRINKERS

Alcohol intake suppresses startle potentiation – a phenomenon known as alcohol stress response dampening (SRD). A correlation between blood alcohol level and startle potentiation was demonstrated in the research group's 2013 study. A particularly fascinating aspect of this finding was that startle potentiation was suppressed by alcohol doses much more when exposed to uncertain threats than to certain ones, showing that alcohol must act through different pathways to suppress the startle potentiation to each type of threat.

Alcohol SRD ties in with what we know about addictive behaviours. The acute effect of SRD is often the reason why people turn to drugs and alcohol during unpredictable times of hardship. However, evidence from the group also indicates that sober alcoholics show more startle potentiation in response to uncertain threats than controls. This indicates to us that repeated alcohol SRD triggers neuroadaptations in the alcoholic that, in compensation for the alcohol dose, crank up the baseline stress response, leading to stress-induced cravings upon withdrawal of the drug. Drug-induced neuroadaptations are not one-off events, as Curtin elucidates: "Unfortunately, these stress neuroadaptations may also persist for long periods of time following abstinence and elevate risk for relapse during future stressful periods".

KILLING TWO BIRDS WITH ONE STONE

Rodent studies have implicated areas of the amygdala brain region in expressing fear and anxiety. Furthermore, two prominent chemical messenger systems within this circuitry – the norepinephrine (NE) and the corticotropin-releasing factor (CRF) systems – have also been linked to stress responses in rodents. The research group's upcoming studies now aim to translate the rodent findings into human patients using two main approaches.

First, the team proposes to measure the effect of α1-NE receptor antagonists on startle potentiation in healthy humans. If the drugs reduce potentiation during uncertain threat, then this is good evidence that NE mediates the alcohol SRD effects. Furthermore, doing the same test in alcoholics will tell us if NE antagonists are efficacious therapies for stress-induced relapse in alcoholics. These two approaches provide a way to simultaneously test the mechanisms of drug addiction in humans and identify novel treatments. "The use of viable medications as pharmacological manipulations represents a powerful synergy to test basic aetiologic mechanisms while translating to treatment rapidly and efficiently," Curtin asserts. Given that patients with other substance addictions may also show similar trends in startle potentiation, the group's latest strategy shows great promise for improving the lives of not only alcoholics but also countless patients with other addictions.

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