

# The complex web of addiction, disease and mental health



Investigations into the relationships between substance abuse and infection, until recently, have focused primarily on socio-economic factors. **Dr Jennifer Loftis** of VA Portland Health Care System (VAPORHCS) and Oregon Health & Science University (OHSU), has gone a step further, uncovering the tangled web of co-morbidity associated with chronic infection, inflammation and substance use. This opens new avenues of treatment for those suffering from disease and/or recovering from addiction.

**S**ubstance use disorders (SUD), including excessive alcohol consumption and dependency, pose a major problem to health services around the world. Methamphetamine (known colloquially as meth), a potent psychoactive stimulant used as a recreational drug, is known to have long-lasting effects on the immune system of the brain. It is common in SUD for these substances to be used concurrently. Similarly, substance abuse is known to be associated with increased prevalence of infections such as hepatitis C (HCV) and human immunodeficiency virus (HIV), as well as cognitive and psychological problems such as depression and anxiety. Dr Loftis has shown that the links between these different aspects of the physical and mental health of individuals with a substance use disorder are not as simple as first thought.

## ALCOHOL FUELS THE FIRE

Looking first at the impact of alcohol consumption on HCV infection, Dr Loftis saw that HCV is associated not just with liver damage, but also central nervous system (CNS) damage and neuropsychiatric impairments. Alcohol abuse is known to exacerbate these effects, so Dr Loftis and her colleagues set out to investigate the role of alcohol in regulating viral persistence and CNS immunopathology (damage to the immune system of the brain and spinal cord). Using a mouse model and HCV-like virus, the team showed that mice given ad libitum access to alcohol entered into a vicious cycle. Infection with the virus prompted increased

alcohol consumption, and increased alcohol consumption raised viral titres (the measure of viral particles in circulation) and increased viral persistence in the brain. Like others in her field, Dr Loftis came to the conclusion that, 'Alcohol use may exacerbate the adverse effects of chronic viral infections, such as HCV, on brain and behaviour'.

## METH ADDS TO THE DAMAGE

Evidence suggests that it is immune factors such as cytokines and chemokines (immune system signalling molecules), as well as dysregulation of the cell adhesion molecules which support the blood-brain barrier, which contribute to the cognitive and psychiatric impairments associated with meth use. Using a cross-species translational approach, Dr Loftis demonstrated that both mice and humans experienced changes to the mix of immune factors on exposure to meth, with humans in remission shown to have an associated reduction in cognitive abilities. The fact that at least some cognitive difficulties only appear in remission, suggests that the neuronal damage caused by these inflammatory processes may contribute to the long-lasting neuropsychiatric symptoms that are experienced by some individuals in recovery. Recent research by the team has found that adults in early recovery can experience attention, memory and executive function problems.

## THE DISEASE STRAND

Patterns of behaviour in substance abuse, such as injection drug use, are known to increase the prevalence of blood-borne

**Individuals with a substance use disorder may be more likely to suffer from infection and psychiatric symptoms, and those infections may be prolonged and more severe**



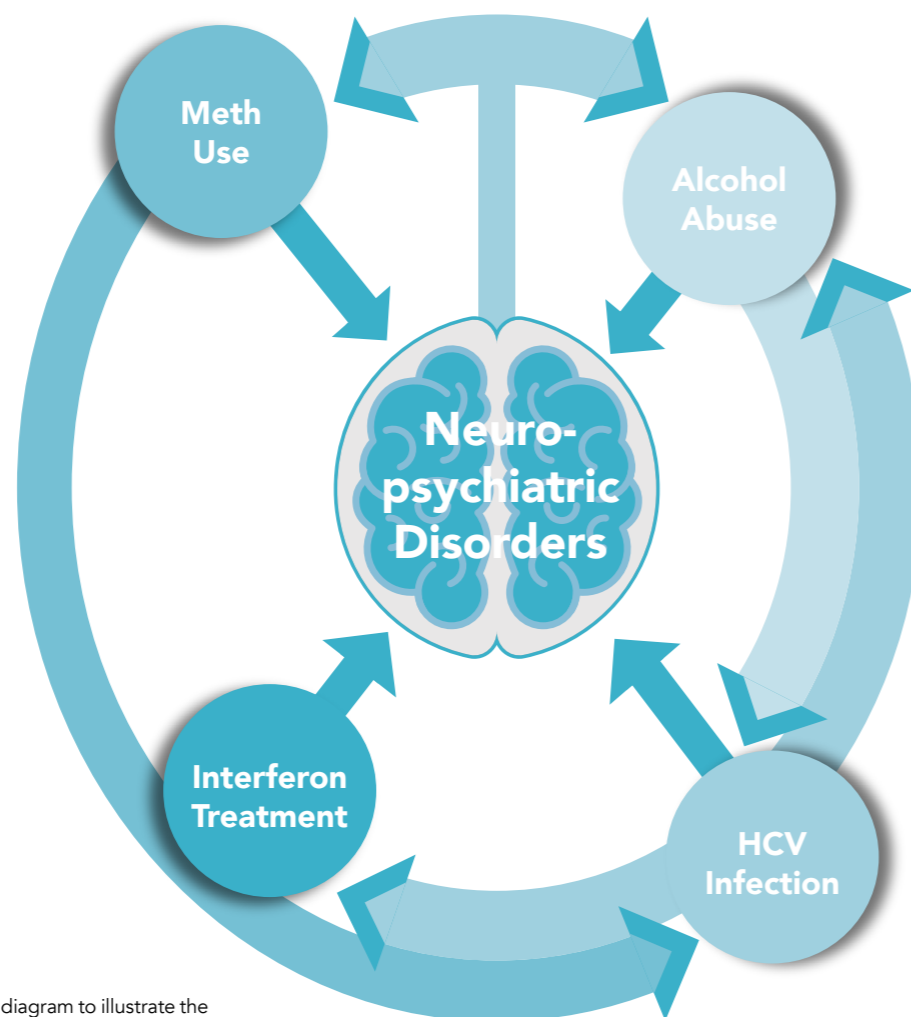
infections such as HCV and HIV among persons with SUD. These can contribute to poor disease management and abstinence relapse either directly, through neural injury, or indirectly through the effects of neuropsychiatric symptoms of cognitive dysfunction, depression and anxiety. Dr Loftis and her colleagues have shown that this means that individuals with a SUD may be more likely to suffer from infection and psychiatric symptoms, and those infections may be prolonged and more severe. Highlighting research which shows that even mild cognitive impairments can have significant effects on real-world outcomes such as employment, treatment adherence and quality of life, Dr Loftis has suggested there is a need for neuropsychological screening for those with both severe infections and SUD.

#### INTERFERING INTERFERONS

This is particularly important considering her research on HCV treatment using interferons. Interferon-alpha therapy aims to assist the body in eliminating the virus by provoking a sustained virological response (patients continuing to be clear of the virus after treatment has stopped), preventing the virus from replicating so the natural immune system can cope. However, Dr Loftis has shown that during the therapy patients experience significantly increased psychiatric symptoms such as depression. Although these are usually short term and improve on completion of the therapy, particularly if it is successful, it gives another example of how immune system changes impact on neuropsychiatric indicators.

Thankfully, new HCV treatment options such as direct acting antiviral therapies (DAA) are set to overturn the problems associated with interferon therapy such as long treatment time, poor viral clearance rates and the side effects mentioned above. Current DAA regimens of just eight to 12 weeks have shown a 90–95% sustained viral response rate. However, research is needed to assess the impact of HCV on CNS function and

**Recent research by the team has shown that adults in early recovery from some substances of abuse can experience more attention, memory and executive problems than adults actively using**



A diagram to illustrate the complex web of possible interactions between SUD, viral disease, treatment strategies and neuropsychiatric symptoms. Dr Loftis has uncovered many of the mechanisms underlying these interactions, as detailed in the article.

mental health outcomes following the newer antiviral agents.

#### A NEW THERAPEUTIC TARGET FOR SUBSTANCE USE DISORDERS

This complex interplay between the immune system and the CNS, mediated by substance abuse and resulting in cognitive and emotional dysfunction, is where Dr Loftis and her colleagues have targeted their investigations. They believe that, in untangling these relationships, new therapies

may be uncovered which treat the root causes of the CNS pathology. This would in turn result in psychiatric recoveries and drive improved health outcomes for both the prevalent infections and the SUD.

Current pharmacological therapies for SUD such as meth addiction focus on the neurotransmitters (brain signalling molecules) involved in the drug's effects, blocking or changing their action to combat the effects of the drug. The research team at VAPORHCS and OHSU believe that this approach fails to combat the full range of drug actions in the CNS. "One key limitation of neurotransmitter-based therapies is that, alone, they do not offer a mechanism for repairing stimulant-induced neuronal injury," says Dr Loftis, "which might be vital for successful recovery". By failing to include an element of brain repair in the therapy, cognitive dysfunction continues in abstinence and results in increased likelihood of relapse.

## Q&A

#### Why does chronic infection cause cognitive impairment?

Clinical studies indicate that neuropsychiatric impairments may be present in up to 50% of patients with chronic HCV infection, and these symptoms may be independent of the HCV viral load. Chronic infection likely contributes to cognitive problems and other neuropsychiatric symptoms through multiple mechanisms, including altered immune signalling, neuronal impairment, reduced cortical thickness, and disintegrity within white matter tracts of the brain.

#### How does substance abuse impact on neuropsychiatric disorders?

Like HCV infection, chronic exposure to alcohol and other drugs of abuse induces inflammatory responses that contribute to the drug's adverse CNS and neuropsychiatric effects. This growing body of research shows, for example, that neuroinflammation is evident in the brains of adults with a history of alcohol abuse, with increased activation of microglia and elevated expression of central and peripheral inflammatory factors. Animal studies also show that alcohol induces gliosis, and specifically, activation of immune receptors that stimulate microglia and the induction of pro-inflammatory factors that putatively contribute to alcohol-induced BBB permeability and neuropsychiatric symptoms.

#### How will your work address the underlying issues in substance use disorders?

I have had the privilege of conducting research on substance abuse for more than 15 years. My translational research programme investigates the neurochemical mechanisms contributing to psychiatric symptoms and cognitive impairments in the context of substance abuse and chronic viral infection, with a particular focus on pharmacotherapeutic treatment development for substance use disorders. These pre-clinical and clinical studies have identified molecular targets (e.g., glutamatergic receptors and inflammatory signalling pathways) and specific brain regions involved in drug-induced neurotoxicity and the adverse behavioural effects that contribute to addiction. Through collaborations with clinicians and other scientists, this work has led to the testing of hypotheses regarding how genetic risk factors and circulating inflammatory cytokines affect central nervous system and psychiatric functioning and how immunotherapeutic strategies may help to treat these conditions – with the ultimate goal of moving collective research findings closer to clinical application and improving treatment outcomes.

The team are currently testing and evaluating a range of potential immunotherapy agents with the aim of repairing the damage caused by chronic inflammation of the CNS and promoting functional recovery. Unique ligands which bind to receptors on immune cells, originally shown to reduce inflammation in models of multiple sclerosis and stroke, have the potential to effectively address the neuropsychiatric effects of meth use. Dr Loftis identifies this as part of a combination

therapy which may include behavioural therapies (for example, cognitive therapy or psychotherapy) and potentially vaccines developed to suppress the action of drugs of abuse. This approach has the potential to finally break the complex web of interplay between drug and alcohol abuse, infectious diseases and psychiatric disorders which impacts so heavily on sufferers.

#### CONFLICT OF INTEREST STATEMENT:

OHSU and Dr Loftis have a significant financial interest in Artielle Immunotherapeutics, a company that may have a commercial interest in the results of this research and technology. This potential individual and institutional conflict of interest has been reviewed and managed by OHSU.

## Detail

#### RESEARCH OBJECTIVES

Dr Loftis' work explores the complex relationship between substance abuse and viral infection and the effect of these on the cognitive health of sufferers. She has a particular interest in chronic hepatitis C viral infection, alcohol abuse and methamphetamine abuse.

#### FUNDING

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#### COLLABORATORS

Marilyn Huckans, PhD; Arthur Vandenberg, PhD; Methamphetamine Abuse Research Center (NIDA-funded; PI: Aaron Janowsky, PhD)

#### BIO

Dr Loftis completed a BA in Psychology and in Business Economics at University of California at Santa Barbara and an MA in Clinical Psychology from Fairleigh Dickinson University in New Jersey before completing her PhD in Behavioral Neuroscience at OHSU. She is currently a Research Scientist at VAPORHCS and Professor in the Department of Psychiatry at OHSU. In addition to her research work, she makes time to mentor students and provide community outreach.

#### CONTACT

Jennifer Loftis, PhD  
VA Portland Health Care System  
3710 SW US Veterans Hospital Rd.  
Mail code R&D 16, Portland, OR 97239  
USA

**E:** [loftisj@ohsu.edu](mailto:loftisj@ohsu.edu)

**T:** +1 503 220 8262 (ext. 57155)

**W:** <http://www.ohsu.edu/xd/education/schools/school-of-medicine/departments/clinical-departments/psychiatry/faculty/loftis.cfm>

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