

thinkaHEAD



Harmful substance use and the brain

Information sheet for health professionals

This information sheet aims to increase awareness about the impact of harmful substance use on the brain. It provides a technical level of detail for health professionals and people requiring in-depth information on brain changes.

In this resource, the term 'harmful substances' refers to non-prescription substances such as alcohol, tobacco, inhalants and illicit drugs, that are taken to alter mood, cognition and behaviour.

All substances of abuse change the chemical structure of the brain. There are differing mechanisms by which these drugs exert their influence, however all drugs interfere with and disrupt normal neurotransmission and can directly damage the structural and functional integrity of the neurons.

Cumulative effects can result in persistent or permanent changes in the brain and it is these changes that can influence the risk of developing a dementia.



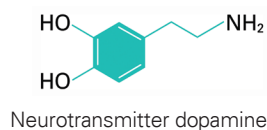
Normal brain activity



Reduced brain activity of drug addiction

The mode of action of many drugs is to target the mesolimbic dopamine reward system. For example, some drugs promote dopamine release in the nucleus acumbens. Whilst there can be variable results across individuals, the strength of the dopamine signal usually correlates to the risk for addiction. Some drugs are more highly addictive than others because of their aggressive targeting of dopamine availability within this reward system.

The compensated response to regular highly increased drug induced levels of dopamine is the down regulation of dopamine receptors on receiving neurons. This mechanism helps feed the need for more of the drug and works



alongside complex influences such as the amygdala's role in conditioned learning, recognition of environmental cues and the hippocampus's role in declarative memory, both of which contribute to addiction reinforcement. Ultimately, there is a cyclic response associated with drug taking, altered chemical messaging, memory, cueing and cravings that create a repetitive downwards spiral until the person either experiences the acute effects of withdrawal or seeks out higher and more frequent doses to respond to and reduce the occurrence of cravings.

Different drugs use different mechanisms and target a range of neurotransmitters. For example, heroin (diacetylmorphine) has a chemical structure that is similar to the brain's natural opioids, enkephalin and endorphin. It works through mimicking, and so is able to engage with the opioid receptors, stimulating a significant response as heroin is approximately 2-3 times more potent than natural opioids. Nicotine mimics acetylcholine and stimulates the cholinergic system. Marijuana mimics cannabinoid neurotransmitters such as anandamide which has an important role regulating appetite, pleasure and reward. There are more than 400 known components of marijuana with tetrahydrocannabinol (THC) being the main psychoactive cannabinoid. Synthetic marijuana, commonly known as spice, Kronic or K2 is a mixture of dried plants and herbs, artificially sprayed with synthetic cannabinoids. It is manufactured to specifically mimic THC, by binding powerfully with CB1 receptors acting as a full agonist. It produces excessively more neurotoxic potency than marijuana.

Other drugs directly interfere with the processing of neurotransmitters. Cocaine for example, has a far greater affinity for the dopamine carriers preventing free dopamine from being transported away from the synapse. Dopamine builds up in high concentrations in the synaptic cleft. This result of increased synaptic dopamine levels leads to cocaine's ability to excessively stimulate the receptors of the receiving neurons. The dopamine bombardment accounts for the powerful and addictive potential of cocaine, either in its powder form or crystal 'crack cocaine' form. Both direct and indirect assaults on the brain occur as communication circuitry is changed and through the known adverse cardiovascular effects. This includes constricted blood vessels, increased heart rate,



Normal brain

Brain with Alzheimer's

heart attacks, strokes and seizures. Resulting hypoxic effects on the brain can permanently compromise brain cell function and this too can increase the risk for developing dementia.

Other well-known stimulant drugs include the amphetamine group including the crystalline form of methamphetamine, known as 'ice', which is of particular concern due to its rapid action. Methamphetamine is a potent form of amphetamine requiring much smaller doses to have a significant effect. All forms of stimulants increase breathing and blood pressure and in some cases, high body temperatures. Amphetamine and methamphetamine neurotoxicity in the brain causes direct damage to dopamine and serotonin terminals. Long term methamphetamine use leads to memory loss, psychosis, paranoia and aggression. Its other effects on body also impact on brain health and include hepatocellular injury and cardiovascular damage.

A comparative study by Chang and Ernst (2000) at Harbor-UCLA Medical Centre in Torrance, USA used magnetic resonance spectroscopy to examine specific brain structures of both methamphetamine users and non-users. It found abnormal brain chemistry in the brains of the methamphetamine users which correlated to the history of drug use. The metabolite n-acetyl-aspartate (NAA), which is found only in neurons, is an important measure of nerve cell density and viability. The study found that NAA levels were reduced in methamphetamine users across the frontal white matter and the basal ganglia than was found in non-users. It was noted that these reduced levels of NAA are comparable to levels seen in the brains of people who have Alzheimer's disease. Other findings in the study support direct damage to neurons of methamphetamine users that suggest the drug is significantly neurotoxic and can result in long-term or permanent changes in cognition. Other studies point out that structural brain damage can occur due to multiple micro-strokes resulting from methamphetamine use which has similarities to changes seen in vascular dementia.

A 2015 study undertaken by The University of Utah (Lyo et al) looked at the effects of methamphetamine on the developing, adolescent brain. The study found greater, more widespread grey and white matter alterations in adolescent methamphetamine users than in adult users. It was concluded that smaller amounts of methamphetamine inflicted greater damage to the frontal cortex of vulnerable, developing brains compared to adult users raising concerns for cognitive development, judgment and decision making in this group.

3,4-Methylenedioxymethamphetamine (MDMA), commonly known as ecstasy is structurally related to the stimulant amphetamine and to the hallucinogen mescaline. It strongly stimulates the serotonergic system and to a lesser degree, promotes dopamine and noradrenaline availability. MDMA is known for its hyperthermia side effects, potentially leading to

rhabdomyolysis related kidney failure. This increased body temperature can unbalance the brain's normal homeostatic temperature parameters which are unable to dissipate heat, increasing drug toxicity and magnifying neuronal damage.

Some drugs, such as alcohol, modulate neurotransmitters and act on ion channels. Alcohol and its metabolite acetaldehyde are directly toxic to neurons and can cause cortical atrophy. A major concern of alcohol addiction is its association with thiamine deficiency. This primes the conditions for the development of Wernicke's encephalopathy and Korsakoff syndrome, both of which impact brain function. For example, the main symptom of Korsakoff syndrome is short term memory loss and inability to learn new information. Other indirect brain assaults occur from hepatic encephalopathy, an outcome that can occur from cirrhosis and impaired neurotoxin filtration through the liver which causes psychotic like symptoms and regression into an earlier part of life. Alcohol related dementia is a well-known consequence resulting from the progressive neurological changes found with prolonged and excessive drinking.

References

Ernst T, Chang L, Leonido-Lee, M and Speck O (2000) Evidence for long-term neurotoxicity associated with methamphetamine abuse: a 1H MRS study. *Neurology* 54(6):1344-1349

Lyo IK, Yoon S, Kim TS, Lim SM, Choi Y, Kim JE, Hwang J, Jeong HS, Cho HB, Chung YA and Renshaw, PF (2015) Predisposition to and effects of methamphetamine use on the adolescent brain. *Molecular Psychiatry*, 20(12):1516-24

Acknowledgements

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FURTHER INFORMATION

Dementia Australia offers support, information, education and counselling. Contact the National Dementia Helpline on 1800 100 500, or visit our website at dementia.org.au



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