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Abbreviations used in this issue
CI = confidence interval
HR = hazard ratio
RCT = randomised controlled trial
RR = relative risk
OR = odds ratio



Welcome to Issue 5 of Addiction Medicine Research Review.

In response to the impact of COVID-19, an opinion article written by an international collection of leading addiction medicine specialists reports on the possible (largely negative) consequences of the worldwide impact of this pandemic on addictive behaviours. A second opinion piece informs that people who smoke, vape, use opioids or have other addictive disorders may be more susceptible to COVID-19 and that such individuals may find it harder to access appropriate care. Other highlights covered in this issue include vitamin D supplementation during methadone maintenance treatment, e-cigarette use among US youths, cannabis and illicit opioid use in drug users with chronic pain, and the risk of overdose after pharmaceutical opioid changes in NZ.

We hope you find our selection of articles for Addiction Medicine Research Review stimulating reading and we welcome your feedback. Furthermore, if you have discovered or been involved with what you think is significant global research in this area, please let us know and we will consider it for inclusion next time.

Kind regards,
Dr Gavin Cape
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Mitigating and learning from the impact of COVID-19 infection on addictive disorders

Authors: Marsden J et al.
Summary: This editorial summarises many of the issues associated with the novel coronavirus (COVID-19) pandemic of 2020 and its effects on people with addictive disorders who are particularly at risk due to poverty, physical and mental health vulnerabilities and the disruption of service access. It is suggested that the pandemic may increase the extent and severity of some addictive disorders. In addition, research is restricted by the cessation of face-to-face data collection and other restrictions. National and international efforts are needed to mitigate these problems and to find innovative ways for public health and clinical services to address the needs of people with addictive disorders.

Comment: This is an opinion article written by an international collection of leading addiction medicine specialists. They comment on the possible (largely negative) consequences of the worldwide impact of COVID-19 on addictive behaviours. For example, with the closure of pubs, clubs and social distancing, they argue that there is likely to be an overall reduction in alcohol consumption and harms (the Ledermann Curve), however, this is mitigated by the possible rise in mortality from alcohol withdrawal and increased use due to social isolation. Similar scenarios, which seemed well-considered, are applied to opioid, methamphetamine, tobacco use disorders and gambling. They suggest that creative research and methodological innovations are already taking place and are required to monitor such changes. Overall a thoughtful summary of possibilities and concerns for individuals with addiction problems during this unprecedented worldwide event brought about by the SARS-CoV-2 virus.

Reference: *Addiction* 2020;Apr 6 [Epub ahead of print]
[Abstract](#)



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Independent commentary by Dr Gavin Cape

I am a Consultant Psychiatrist (MRCPsych and affiliate to RANZCP) and an Addiction Medicine Specialist with the Royal Australasian College of Physicians (FACHAM). I have worked as a Consultant Psychiatrist in New Zealand and Australia for over 25 years and am currently a Director of Foundation Health Tūhauora Limited, Dunedin.



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HCV = hepatitis C virus. AbbVie Limited, Wellington.
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The person shown is a model and is not a patient.



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Collision of the COVID-19 and addiction epidemics

Author: Volkow N

Summary: This piece suggests that people who smoke, vape, use opioids or have other addictive disorders may be more susceptible to COVID-19, and that the compromised lung function caused by COVID-19 may put those with an opioid or methamphetamine use disorder at risk. In addition, because of impediments to care delivery, people with substance use disorders who develop COVID-19 may find it harder to get care.

Comment: This is an opinion piece by a world leading addiction researcher, Nora Volkow. This summarises and articulates the risks of substance use on being infected by the SARS-CoV-2 virus. It informs us that people who are using substances, whether it is opioids, methamphetamine, vaping or others, are at a greater vulnerability with increased risk for infection and the likelihood of more severe consequences. She also outlines that people with addiction problems are likely to have other impediments such as poverty, homelessness as well as the stigma of being an addict, which will impact negatively on medical care and community support. She champions this group of people by stating in her final comment – “But under no circumstances can we forget or marginalise persons with SUD [substance use disorders] during this new public health crisis”. Well said!

Reference: *Ann Intern Med.* 2020;Apr 2 [Epub ahead of print]

[Abstract](#)

Exploring the effects of vitamin D supplementation on cognitive functions and mental health status in subjects under methadone maintenance treatment

Authors: Ghaderi A et al.

Summary: This study explored the effect of vitamin D supplementation (50,000 IU; n = 32) or placebo (n = 32) every 2 weeks for 24 weeks on cognitive function and mental health in patients receiving methadone maintenance treatment. Serum 25-hydroxy (OH) vitamin D levels were increased after 24 weeks of vitamin D supplementation versus placebo (β 14.50; 95% CI 13.17-15.83; $p < 0.001$). Vitamin D recipients had a reduction in Iowa Gambling Task (β -6.25; 95% CI -8.60 to -3.90; $p < 0.001$), and increases in Verbal Fluency Test (β 2.82; 95% CI 0.78-4.86; $p = 0.007$), Reverse Digit Span (β 2.06; 95% CI 1.18-2.94; $p < 0.001$), visual working memory (β 0.75; 95% CI 0.33-1.16; $p = 0.001$), Beck Depression Inventory (β -2.76; 95% CI -3.97 to -1.55; $p < 0.001$), and Immediate Logic Memory (β 1.32; 95% CI 0.27-2.37; $p = 0.01$), although the latter was nonsignificant after Bonferroni correction.

Comment: An interesting longitudinal study on a small sample (n = 64) of methadone treated opioid-dependent people with alteration in one nutritional factor, vitamin D. Half the participants were given a placebo and half given vitamin D supplements for 6 months. Those who received vitamin D supplementation had beneficial effects on cognitive functions and some mental health parameters, such as depression. Of course, higher numbers and repetition are required to establish a more robust association between low serum 25(OH) vitamin D levels and improvement with supplementation. Perhaps there are other factors involved in the perceived improvement of the participants by the researchers as has often been the case when studies on nutrition and cognitive effects are undertaken. However, this finding remains of interest.

Reference: *J Addict Med.* 2020;14(1):18-25

[Abstract](#)

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Research Review publications are intended for New Zealand health professionals.

Shared genetic risk between eating disorder- and substance-use-related phenotypes: Evidence from genome-wide association studies

Authors: Munn-Chernoff MA et al.

Summary: This study used data from eight genome-wide association studies (GWAS) to estimate the genetic correlation between eating disorders (anorexia nervosa with and without binge eating, bulimia nervosa) and substance use and disorder phenotypes (drinks per week, alcohol use disorder, smoking initiation, current smoking, cigarettes per day, nicotine dependence, cannabis initiation, cannabis use disorder) using study sample sizes of ~2400 to ~537,000 per phenotype. Positive genetic correlations were identified between alcohol use disorder and anorexia nervosa ($r = 0.18$; false discovery rate $q = 0.0006$), cannabis initiation and anorexia nervosa ($r = 0.23$; $q < 0.0001$), and cannabis initiation and anorexia nervosa with binge eating ($r = 0.27$; $q = 0.0016$). However, the correlation with alcohol use disorder and anorexia nervosa was not significant after covariant analysis for major depressive disorder. Negative genetic associations occurred between smoking initiation, current smoking, and cigarettes per day and anorexia nervosa without binge eating ($r = -0.19$ to -0.23 ; $q < 0.04$).

Comment: This research explores the possibility of unifying aspects of a fundamental human drive, appetite. Specifically, questioning if there is a genetic link between the observed characteristics of those with a diagnosed eating disorder and those with substance use disorders. A large number of researchers were responsible for this article that spans an enormous research effort with study sample sizes per phenotype ranging from ~2400 to ~537,000 individuals! Their conclusion is that there are "complex and substance-specific relationships among these behaviours". This seems to confirm that genetic factors are important in the genesis of these appetite-driven disorders, but environmental factors have strong determination of the resultant phenotype. There is still much mystery to tease out when the expression of heritable traits are modified by environmental influences.

Reference: *Addict Biol.* 2020;Feb 16 [Epub ahead of print]

[Abstract](#)



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Submissions close: Friday 5 June

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Become a presenter: <https://www.frontlinementalhealth.com.au/present/>

Submissions close: Wednesday 15 July 2020

2020 STOP Domestic Violence Conference

Become a presenter: <https://stopdomesticviolence.com.au/present/>

Submissions close: Friday 31 July 2020

The overall effect of parental supply of alcohol across adolescence on alcohol-related harms in early adulthood

Authors: Clare PJ et al.

Summary: This Australian prospective longitudinal cohort study assessed the effect of parental alcohol supply on alcohol-related outcomes in adolescence based on data from 1906 first year secondary school students (average age 12.9 years) interviewed annually for 7 years. Self-reported parental supply of alcohol (including sips/whole drinks) during 5 years of adolescence had a greater risk of binge drinking (RR 1.53; 95% CI 1.27-1.84) and alcohol-related harms (RR 1.44; 95% CI 1.22-1.69) in the year following exposure versus no supply. Each year of earlier initiation of parental supply also increased the binge drinking (RR 1.10; 95% CI 1.05-1.14) and any alcohol-related harm risks (RR = 1.09; 95% CI = 1.05-1.13) versus later or no initiation.

Comment: What is a parent to do? How can parents introduce drinking alcohol to their children as a safe and enjoyable activity? This longitudinal, large sample cohort of adolescents seems to imply that the initiation of young adolescents to alcohol by parents is beset with problems and harms. This research was carried out by leading addiction researchers in Australia over a 7-year period of follow-up from age 12 years. Those children who were supplied alcohol by their parents had a greater risk of binge drinking and alcohol-related harms compared to those children who were not supplied with booze by their parents. This, of course could be specific to Australian adolescents but their findings and methodology appears to be robust and needs to be taken seriously. The question remains – What is a parent to do?

Reference: *Addiction* 2020;Feb 7 [Epub ahead of print]

[Abstract](#)

e-cigarette use among youth in the United States, 2019

Authors: Cullen KA et al.

Summary: This cross-sectional analysis of data from 19,018 US students (Grades 6 to 12) in the 2019 National Youth Tobacco Survey examines the prevalence of e-cigarette use including frequency, brands and flavoured product use. Current e-cigarette use was reported by 27.5% (95% CI 25.3-29.7) of high school and 10.5% (95% CI 9.4-11.8) of middle school students; of these 34.2% (95% CI 31.2-37.3) of high school and 18.0% (95% CI 15.2-21.2) of middle school students reported frequent use. Exclusive use of e-cigarettes was reported by 63.6% (95% CI 59.3-67.8) of high school and 65.4% (95% CI 60.6-69.9) of middle school e-cigarette users. Among current exclusive e-cigarette users, 72.2% (95% CI 69.1-75.1) of high schoolers and 59.2% (95% CI 54.8-63.4) of middle schoolers used flavoured e-cigarettes.

Comment: This research is a snapshot of school-age youth in the US and their use of e-cigarettes or vapes. This is likely to be an accurate point prevalence of this behaviour as this involved large numbers of those researched (over 19,000 participants between 10 and 19 years old). Over a quarter of high school students and over a tenth of middle school students had smoked an e-cigarette in the previous 30 days. These results seem to indicate high levels of use and some observers have labelled this a 'youth epidemic'. An interesting finding is that the preferred type of e-cigarettes was a flavoured variety, which to me would be similar to flavoured alcohol drinks or alcopops, designed to appeal to the young. These results are alarming, and I wonder whether there needs to be more regulation on the sale of this commodity. A longitudinal cohort study would be useful to determine whether there is likely to be a cross over to other smokable products.

Reference: *JAMA.* 2019;322(21):2095-2103

[Abstract](#)

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Prescription of benzodiazepines, Z-drugs, and gabapentinoids and mortality risk in people receiving opioid agonist treatment

Authors: Macleod J et al.

Summary: This analysis of data from the UK Clinical Practice Research Datalink (1998-2014; n = 12,118) examined whether prescription of benzodiazepines, Z-drugs, and gabapentinoids in patients receiving opioid agonist treatment, irrespective of treatment duration, would increase the risk of overall mortality. Over 36,126 person-years of follow-up, 657 deaths and 29,540 opioid agonist treatment episodes occurred; 42% being benzodiazepine co-prescription and 29% concurrent prescription. Concurrent benzodiazepine prescription was linked to increased methadone treatment duration (adjusted mean duration 466 days [95% CI 450-483] vs 286 days [95% CI 275-297]). Benzodiazepine co-prescription increased the risk of drug-related poisoning (adjusted HR 2.96; 95% CI 1.97-4.43; $p < 0.001$), with a dose-response effect, but not non-drug-related poisoning (adjusted HR 0.91; 95% CI 0.66-1.25). Co-prescription of Z-drugs was also associated with increased risk of drug-related poisoning (adjusted HR 2.75; 95% CI 1.57-4.83; $p < 0.001$), but not non-drug-related poisoning (adjusted HR 0.79; 95% CI 0.49-1.28), while gabapentinoid co-prescription was not associated with drug-related poisoning (HR 1.54; 95% CI 0.60-3.98) but was associated with increased non-drug-related poisoning (HR 1.83; 95% CI 1.28-2.62; $p = 0.001$). Concurrent benzodiazepine prescription increased mortality risk depending on duration of opioid agonist treatment (adjusted HR 3.34; 95% CI 2.14-5.20; $p < 0.001$).

Comment: This is a prospective observational study utilising a huge number of 'opioid assisted treatment' patients obtained from UK government administrative data and linking deaths with the prescription of benzodiazepine, Z-drugs and gabapentinoids. Each of these families of medicines act predominantly on the GABA receptor, the main central nervous depressant receptor. This study informs us that benzodiazepine co-prescription in opioid-dependent individuals is of itself a cause of increased risk of death from drug-related poisoning rather than a marker of other patient characteristics that influence risk of death. It is less strong for the Z-drugs or gabapentinoids. This study is perhaps the most conclusive statement of something that is already known in addiction circles, there is a need for the clinician to be cautious when prescribing benzodiazepines to those patients on opioid-assisted treatment.

Reference: *PLoS Med.* 2019;16(11):e1002965
[Abstract](#)

Frequency of cannabis and illicit opioid use among people who use drugs and report chronic pain: A longitudinal analysis

Authors: Lake S et al.

Summary: This Canadian study used data from two prospective cohorts (2014-17; n = 1152; 36.8% female; median age 49.3 years) of people who use drugs (PWUD) who reported major or persistent pain to investigate the longitudinal association between cannabis frequency and illicit opioid use. Overall, 40% reported daily illicit opioid use, and 36% daily cannabis use during follow-up periods. The most common reasons for cannabis use were pain (36%), sleep (35%), stress (31%) and nausea (30%). After adjustment (demographic characteristics, substance use, health-related factors) daily cannabis use was associated with lower odds of daily illicit opioid use (adjusted OR 0.50; 95% CI 0.34-0.74; $p < 0.001$).

Comment: In any Western population there are PWUD to ameliorate the effects of chronic pain and this includes the use of illicit opioids and cannabinoids. This study found that people who used cannabis every day had about 50% lower odds of using illicit opioids every day compared to cannabis non-users or occasional users. Data were obtained through using two large prospective studies of PWUD in Canada between 2014-17. The conclusion supports the hypothesis that cannabis may be a potential substitute for illicit opioids among PWUD and be a safer alternative for those persons with chronic pain. It suggests that RCTs of cannabis coupled with low-dose opioids to treat chronic pain among PWUD are required to test this further. This is of special interest with the New Zealand referendum on cannabis this year.

Reference: *PLoS Med.* 2019;16(11):e1002967

[Abstract](#)

Intermittent theta burst transcranial magnetic stimulation for methamphetamine addiction: A randomized clinical trial

Authors: Su H et al.

Summary: This Chinese multicentre trial tested whether 4 weeks (20 sessions; 900 pulses/day) of intermittent theta burst stimulation (iTBS) using transcranial magnetic stimulation (rTMS) over the dorsolateral prefrontal cortex reduced craving in 126 methamphetamine users. The trial suggested that iTBS reduced craving and improved cognition and sleep quality.

Comment: I have always wanted to find a use for rTMS in the addiction field! A non-invasive, safe treatment with the potential to stimulate parts of the brain to function better. This was a multicentre RCT of 126 participants (reasonable size) with severe methamphetamine use disorder given either iTBS (a novel form of rTMS) or sham treatment over the dorsolateral prefrontal cortex for 4 weeks. There was reduced craving, improved cognitive functioning and better sleep in those receiving the real treatment following discharge from the treatment centres. Of course, many questions remain and include whether the beneficial effect is long lasting, does it only apply to methamphetamine and whether this effect can be repeated in further trials. We await the future.

Reference: *Eur Neuropsychopharmacol.* 2020;31:158-161

[Abstract](#)

Pharmaceutical opioid changes risk overdose increase in New Zealand

Authors: Ponton R & George J

Summary/Comment: This letter in the New Zealand Medical Journal by a pharmacist and a needle exchange worker highlights the 'law of unintended consequences'. Sometimes this adage may be paraphrased as the 'road to purgatory is paved with good intention'. What may initially be seen as beneficial (good intention) to one population may actually turn out to be harmful (a state of suffering) for another. In this case, the authors warn that a change to the available preparation of long-acting morphine from tablets (Arrow Morphine LA) to capsule (m-Eslon) form may provoke a rash of opioid overdoses. This may also "have the unintended consequence of opening the illicit opioid market for widespread fentanyl use to develop in New Zealand". They point out the uniqueness of illicit opioid use in New Zealand and express concerns about the higher overdose rate (and deaths) from Australia who already have powdered fentanyl in the illicit supply chain.

Reference: *N Z Med J.* 2020 Mar 13;133(1511):95-96

[Abstract](#)

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