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Drugs: Licit and Illicit

Kevin Brewer

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orsettpsychologicalservices@phonecoop.coop

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Kevin Brewer BSocSc, MSc

An independent academic psychologist, based in England, who has written extensively on different areas of psychology with an emphasis on the critical stance towards traditional ideas.

A complete listing of his writings at http://psychologywritings.synthasite.com/. See also material at https://archive.org/details/orsett-psych.

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1. DRUG USE, HIV, AND COVID-19

1.1. INTRODUCTION

Commenting on the covid-19 pandemic, Gorbach et al (2022a) stated: "While supply chain issues and transmission risks reduced access to regular household items, social activities like restaurants, gyms, schools, and offices for working and middle class people in most of the world, the supply of illegal drugs and cannabis was unaffected. Drugs continued to flow while the social context in which they were used and abused changed, resulting in more overdoses, problematic use and relapse for those struggling on the margins of society" (p1).

People who use (unregulated) drugs (PWUD) and people with HIV (PWH) were especially impacted here (Gorbach et al 2022a).

1.2. NON-FATAL OVERDOSE

Soon after the covid-19 pandemic began, overdose-related fatalities among PWUD in North America were seen to increase (Moallef et al 2022) (appendix 1A). The reasons lay potentially in the response to covid-19: "For instance, border closures and other restrictions on movement may have led to disruptions and shortages in the unregulated drug supply and consequently elevated levels of highly-potent synthetic opioids, which exposes PWUD to elevated risks of overdose. In addition, physical/social distancing, and stay-at-home measures (including reductions in service hours and closing of non-essential services) may have encouraged people to use drugs alone and undermined well-established overdose prevention measures (eg: access to harm reduction services,

engagement in medication treatment for opioid use disorder)" (Moallef et al 2022 p2) (appendix 1B). Here is an example of the unintended consequences of covid-19 infection control measures.

Moallef et al (2022) investigated non-fatal overdoses using data from nine National Institute on Drug Abuse (NIDA) cohorts in the USA and Canada (table 1.1) between May 2020 and April 2021.

Non-fatal overdose was self-reported as yes or no in the past month by 4.6% of the sample of 885 users of unregulated opioids and stimulants (specifically, heroin, fentanyl, non-medical use of prescription opioids, methamphetamine, powder cocaine, and crack cocaine). A number of explanatory variables were categorised (eg: injected/non-injected; number of sexual partners; drug used; covid-19 worry).

- The NIDA established the C3PNO in 2017 to "enhance data sharing opportunities and mechanisms to facilitate collaborative research efforts among NIDA-supported cohorts that examine HIV/AIDS in the context of substance use" (Moallef et al 2022 p2).
- The cohorts are (Gorbach et al 2021):
- Vancouver (3 cohorts) - Vancouver Injection Drug Users Study (VIDUS) (sample of HIV-negative individuals injecting PWUD); AIDS Care Cohort to Evaluate exposure to Survival Services (ACCESS) (HIV-positive PWUD); At-Risk Youth Study (ARYS) (young PWUD).
- Baltimore (3) - AIDS Linked to the Intravenous Experience (ALIVE) (injecting PWUD); Johns Hopkins HIV Clinical Cohort (JHHCC) (PWH); Hopkins Heart Study (HEART) (African American PWUD/PWH).
- Los Angeles (2) - Healthy Young Men's Study (HYM) (young men who have sex with men (MSM)); mSTUDY (African American/Hispanic MSM).
- Miami - Miami Adult Studies on HIV (MASH) (PWH, cocaine use, and hepatitis C virus).
- Chicago - Multi-level Influences on HIV and Substance Use in young MSM cohort (RADAR) (young MSM).

Table 1.1 - The Collaborating Consortium of Cohorts Producing NIDA Opportunities (C3PNO) (Moallef et al 2022).

Individuals who had experienced a non-fatal overdose

were significantly more likely to be female, be unstably housed or homeless, receiving medication for opioid use disorder (MOUD), and highly daily impacted by covid-19 (eg: avoiding needle distribution sites and collecting MOUD; appendix 1C). It is known from previous research that prior overdose experience is a significant predictor of future overdoses (Moallef et al 2022).

The volunteer sample was over 70% male, and the largest number of respondents from the nine cities were based in Vancouver, and the three cohorts in this city reported the majority of overdoses. "The inclusion of three Vancouver based cohorts introduces some selection bias. In addition, survey responses could vary by study setting and by time in which data collection occurred. In particular, the burden of the pandemic differed across cohort sites and surveys completed earlier on in the pandemic may differ from those completed later in the pandemic" (Moallef et al 2022 p6). All data were self-reports.

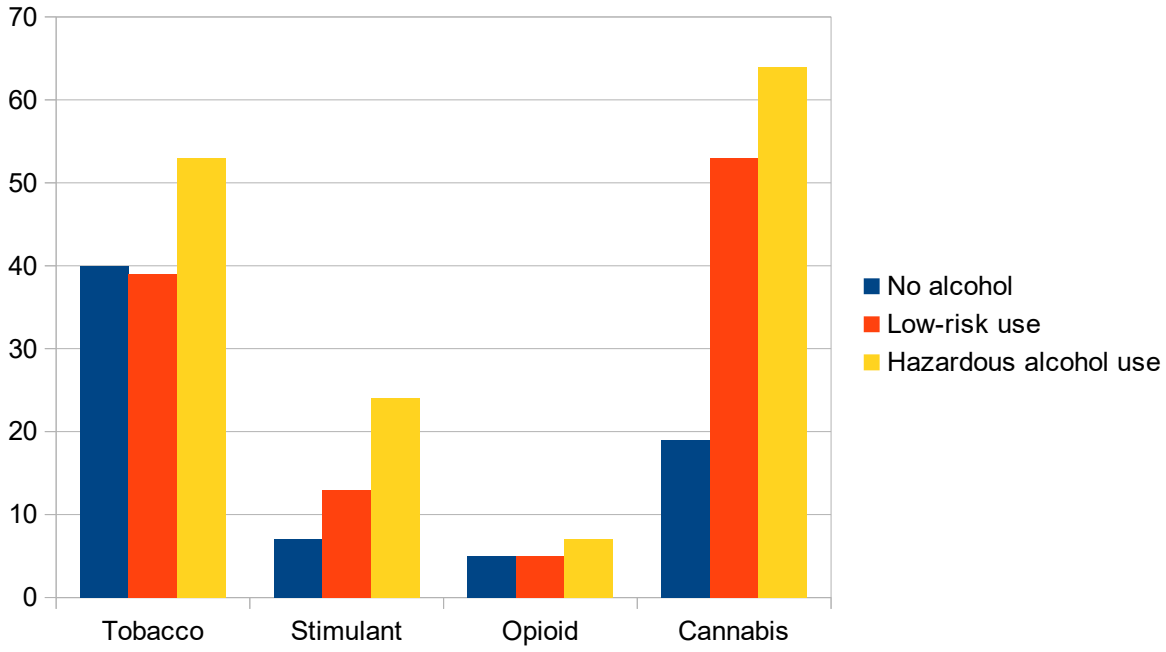
1.3. ALCOHOL USE

Pytell et al (2022) stated: "People with HIV or at risk for HIV are potentially more susceptible to the adverse effects of alcohol due to high prevalence of mental health disorders, poor physical health and chronic conditions, and risk-taking behaviours... Epidemiological evidence consistently shows the relationship between hazardous alcohol use and emergency department visits, increased sexual transmission risk behaviour, and worse HIV related outcomes in this population" (p2).

In reference to these concerns, Pytell et al (2022) reported data from nearly 2000 participants in six C3PNO cohorts. The outcome measure was alcohol use in the past month, categorised into three groups - no alcohol use, low-risk use, and hazardous alcohol use (defined as ≥7 drinks per week for females and ≥14 drinks for males).

Overall, 45% of the sample reported no alcohol use, 33% low-risk use, and 22% hazardous use. The latter group (compared to the no-alcohol group) had greater tobacco, stimulant, opioid, and cannabis use, and overdoses (figure 1.1).

This study confirmed previous research showing an association between hazardous alcohol use and other drug use. The hazardous alcohol use group was nearly three times more likely to use opioids and stimulants than the no-alcohol group, after controlling for variables, in the Pytell et al (2022) study.



(Data from table 2 Pytell et al 2022)

Figure 1.1 - Percentage of participants reporting drug use based on alcohol consumption.

"For participants who had current substance use treatment and for those who have HIV, there was a lower prevalence of hazardous alcohol use" (Pytell et al 2022 p6). The cross-sectional nature of the data meant that causation could not be established, as Pytell et al (2022) explained with three possible explanations for the above observation:

i) "For participants undergoing substance use treatment, they could be more motivated to not drink just as they are motivated to engage in substance use treatment (ie: confounding by a common factor, motivation)" (p6).

ii) "Alternatively, it may be that during the covid-19 pandemic and the resulting social distancing and isolation, engaging with people including clinicians, counsellors, and peers during substance use treatment respondents could have relatively higher social connection which may have served as a protective factor (ie: substance use treatment is protective)" (p6).

iii) "Finally, it may be that people whose drinking was well-controlled were more likely to be able to remain

engaged in substance use treatment (ie: reverse causation)" (Pytell et al 2022 p6).

The data were collected at different times during the pandemic for different cohorts. Pytell et al (2022) admitted: "Participants completing surveys early in the pandemic might be systematically different compared to participants completing surveys later. While we controlled for cohort and survey wave, our estimates may skew towards less alcohol use because early participants had yet to experience the burden of covid-19 and subsequently increased alcohol consumption. Alternatively, people who could be reached to respond to a survey during the pandemic might have had a lower prevalence of alcohol use than all people eligible to complete such a survey" (p6).

1.4. PEOPLE LIVING WITH HIV

Lesko et al's (2022) focus was PWH in six NIDA cohorts (n = 773). The outcome variable was HIV care continuation during the covid-19 pandemic as measured by visits to HIV medical services kept in the last six months, viral load measurement, and self-report of anti-retroviral therapy (ART) adherence in past seven days before questioning.

The prevalence of missed visits ranged from 8% to 26% depending on the cohort (with an average of 13% for the past month), while nearly one in five of the sample had missed at least one dose of ART in the previous week. The data were collected between May 2020 and February 2021.

The following variables were associated with missing a HIV medical services visit in the past month - unstable housing, food insecurity, anxiety, mental health problems due to the covid-19 pandemic, and substance and alcohol use. The main reasons given for missing were, in order, forgot, and appointment cancelled due to covid-19 (appendix 1D).

Non-adherence to ART in the past week was associated with the following variables - male, disruption to mental health services due to covid-19 pandemic, and substance and alcohol use. The main reason for non-adherence reported were forgot, followed by unable to get repeat/refill medication, and concern about going to pharmacy.

The data were self-reports, there was no pre-pandemic information for comparison, and the sample was

75% male. No details were collected on how health services were disrupted by the covid-19 pandemic.

Up to one quarter of PWH admit to non-medical drug use (Eaton et al 2022). "Substance use and, specifically, opioid use disorder [OUD] reduces one's ability to achieve and maintain viral load (VL) suppression. Further, HIV viremia plus substance use related behaviours - like transactional sex and sharing drug materials - contribute to HIV transmission in social and sexual networks... As a result, the combined Opioid and HIV epidemics continue to drive HIV clusters and outbreaks across the US, halting progress along the HIV care continuum..." (Eaton et al 2022 p1). The arrival of SARS-CoV-2 added "fuel to the Opioid and HIV syndemics" (Eaton et al 2022 p1).

Outpatient-based Opioid Treatment (OBOT) clinics were impacted by the covid-19 pandemic. Eaton et al (2022) analysed data from one HIV clinic OBOT service in Alabama from November 2018 to May 2021. Fifty-seven individuals had OUD and HIV. Contrary to expectations, use of service did not decline during the pandemic. "Unlike many PWH who faced access barriers, PWH receiving care at OBOT did not fall out of care but increased healthcare utilisation and maintained viral suppression despite the public health emergency" (Eaton et al 2022 p1).

Meanley et al (2022) investigated binge drinking, marijuana, and recreational drug use among PWH in the early part of the covid-19 pandemic. Data came from two US cohorts - the "Multi-centre AIDS Cohort Study" (MACS) and the "Women's Inter-agency HIV Study" (WIHS) - which was combined (the "MACS/WIHS Combined Cohort Study"; MWCCS; n = 4016; D'Souza et al 2021). Over 2100 PWH were telephone interviewed in April-September 2020, as well as prior to the pandemic (October 2018-March 2019 and April-September 2019).

The key measure was substance use, which was self-reported as at least five or six alcohol drinks in one sitting (binge drinking), frequency of marijuana use, and cocaine, methamphetamine, and heroin use since last interview.

Overall, the prevalence of binge drinking was 14-20%, daily marijuana use 10-12%, and recreational drug use 5-8%.

Analysis involved comparing two groups, binge vs no-binge drinking, daily marijuana use vs less frequently, and any vs no use of recreational drugs, and found that

all substance use declined in the early part of the pandemic compared to pre-pandemic levels. Being male, and depressed predicted any substance use, while high social support specifically predicted no recreational drug use.

The researchers could only speculate on the reasons for the decline in substance use. For example, "alcohol and recreational drug use may have decreased because of structural covid-19 mitigation practices implemented nationwide. Local mandates limited social gatherings and shuttered businesses (eg: restaurants and bars), practices that may have stymied alcohol and recreational drug use, especially among persons who consume substances primarily within social and sexual contexts" (Meanley et al 2022 p5).

The MACS and WIHS are long running studies (since 1984 and 1994 respectively), which meant that pre-pandemic data were available for comparison, but the cohorts are predominately middle-aged (four-fifths aged 40-69 years old). The sample was involved with health care services, and used to research interviews (twice yearly). About two-thirds of the sample was female.

Meanley et al (2022) accepted two other key limitations with their study. Firstly, they explained that "we did not analyse other consequences of covid-19, such as changes in livelihood, and the impact of the pandemic on loved ones. Therefore, we cannot pinpoint specific stressors or strengths that shaped our participants' substance use trajectories" (Meanley et al 2022 p6). Secondly, the confirmed, "our study is susceptible to the inherent challenges of conducting survey research, including limitations linked to self-report, subjectivity, social desirability, and the proclivity of participants to under-report behaviours on sensitive topics, like mental health and substance use" (Meanley et al 2022 p6).

1.5. SEXUAL AND GENDER MINORITY INDIVIDUALS

One group of concern is sexual and gender minority (SGD) individuals, which includes men who have sex with men, and transgender men and women. Xavier Hall et al (2022) studied this population during the covid-19 pandemic in terms of sexual risk behaviour, use of pre-exposure prophylaxis (PrEP) for prevention of HIV transmission, intimate partner violence (IPV), and methamphetamine use. Data came from volunteers in three NIDA cohorts in the USA between May 2020 and April 2021 (n = 1142 SGM individuals). An online survey asked about

social distancing behaviours (eg: self-quarantining when potentially sick), methamphetamine use in past month, anxiety (general and covid-19-related), IPV, sexual risk behaviours (eg: number of sex partners in past month), and PrEP use.

Methamphetamine use was significantly associated with no social distancing behaviours, new and more sex partners, and being a victim of IPV. These behaviours put SGM young adults at higher risk of HIV and covid-19 transmission.

The researchers concluded that "SGM young adults often live at the intersection of multiple vulnerabilities, which have been partially exacerbated by the covid-19 pandemic and related responses" (Xavier Hall et al 2022 p6).

There were no pre-pandemic measures of the variables as this was a cross-sectional study (ie: a survey at one point in time), so "conclusions about causality cannot be drawn" (Xavier Hall et al 2022 p6).

Methamphetamine use was measured by a single item, scored as "never" (0) to "daily" (4). Further details were not collected of this behaviour, and many others.

Data were collected in Los Angeles and Chicago, and the sample was quite specific: "The median age was 26. All participants were assigned male at birth and most participants were men (93.8%). The largest racial groups were Hispanic/Latinx (44.6%) and Black (29.0%)" (Xavier Hall et al 2022 p1).

1.6. RESILIENCE

Resilience "in general terms, is the process of coping with stress or trauma... In other words, it is a positive adaptation to adverse events, and may act as a buffer against adverse mental health outcomes" (Baum et al 2022 p2). High resilience is associated with lower mental health problems. Baum et al (2022) confirmed the importance of resilience with C3PNO data.

A sample of 1430 individuals in the six US cohorts completed the same questionnaire twice (during May-December 2020, and October 2020-March 2021). Just under half were PWH. There were three key variables measured:

i) Resilience - Measured by the "Brief Resilience Scale" (BRS) (Smith et al 2008). Six items (eg: "I tend to bounce back quickly after hard times"; "I usually come through difficult times with little trouble") each scored on a five-point scale, and then averaged between 0 and 6,

with 3.5 or above classed as high resilience.

ii) Anxiety - Symptoms measured by the "General Anxiety Disorder-7" (GAD-7) (Spitzer et al 2006). Seven symptoms (eg: "trouble relaxing"; "feeling anxious, nervous or on edge") rated for frequency over the last two weeks (0 = "not at all"' 1 = "several days" to 3 = "nearly every day"). The total score range from 0 to 21, and ten or above was classed as anxious.

iii) Substance use - Measures of hazardous drinking, and use of cigarettes, cannabis, methamphetamines, cocaine, heroin and/or fentanyl, and prescription opioids in the past month were taken.

Resilience and anxiety scores were significantly negatively correlated overall. There was no difference in resilience between PWH and HIV-unaffected participants, though the latter reported more anxiety. Higher anxiety was associated with higher substance use, and high resilience with less use of substances (except cannabis).

The key methodological weaknesses of the study were self-reported data, convenience sample, high drop-out between first and second surveys (2156 individuals completed the first survey), and risk of survivorship bias among PWH. On the positive side, the measures of resilience and anxiety were "highly validated and reliable instruments", and the sample came from six different cohorts, "consisting of marginalised and minority groups with a diverse population of PWUD, many living with or at-risk of HIV" (Baum et al 2022 p6).

1.7. PWH AND PWUD HEALTH RISK

PWH and those at risk of HIV and PWUD have an increased risk of health consequences of covid-19 because of compromised immunity, and co-morbidity of conditions. Gorbach et al (2022b) studied the use of covid-19 testing by such individuals in the first year of the pandemic. Data were available for 2331 individuals in the C3PNO studies.

Overall, 43% had ever been tested for active infection (swab test) or previous infection (anti-body test). Fewer individuals were tested than not tested in the following groups - PWH (43% vs 57%), unemployed (44% vs 56%), and drug users (46% vs 54%). These were all significant differences. "When substance use frequency was examined within variables significantly associated

with covid testing (HIV status and employment), the fewest tested were those who were HIV positive and unemployed who reported using substances intermittently" (Gorbach et al 2022b p4). Part of the explanation is that these individuals are more likely to be socially marginalised, and less likely to be in the formal economy, which is relevant when covid-19 testing was often workplace-based. Alternatively, PWH may have practised vigilance for covid-19 (eg: staying isolated) and so not needed testing (or perceived that it was not required).

The data were collected online, and "likely missed those who were the most vulnerable who did not have telephones or email addresses and possibly the most drug engaged. Therefore, the sample may be biased towards those more connected with the general population" (Gorbach et al 2022b p6). Furthermore, "because of differential access to the internet or a cell phone, not all surveys were administered in the same format. Some of the older users of opioids were those with the least ability to complete the survey as self-administered and so if they could be reached were done so for a telephone interview and that may result in systematic under reporting of substance use and other behaviours considered socially unacceptable such as not practising covid-19 protective behaviour" (Gorbach et al 2022b p6).

1.8. APPENDIX 1A - PREGNANCY-RELATED OVERDOSES

Recent increases in pregnancy-associated drug overdose mortality have been reported in the USA (eg: Margerison et al 2022).

Han et al (2024) examined US data from 2018 to 2021 using official sources. Mothers aged 10 to 44 years with a live birth were the focus. Three groups were distinguished for analysis purposes:

i) Pregnancy and post-partum overdose deaths (n = 1457).

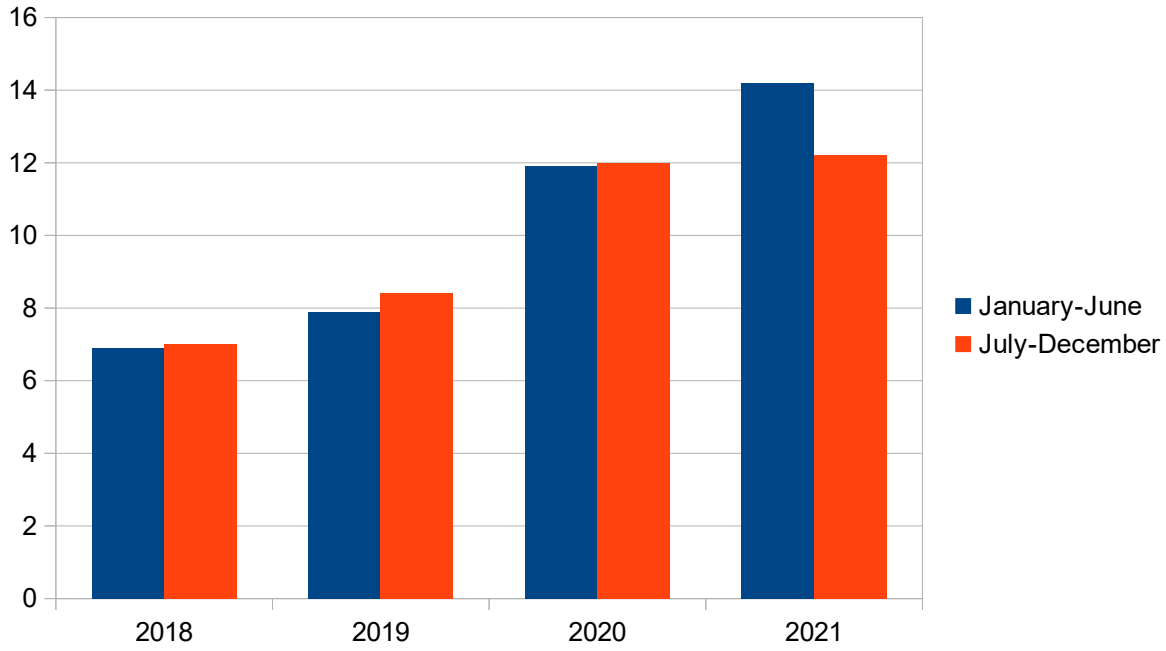
ii) Death from obstetric causes (n = 4796).

iii) Non-pregnant female overdose deaths (n = 11 205).

Control variables included race/ethnicity, age, education, marital status, place of residence/death, and poverty level, number of physicians and hospitals in

county.

Overall, pregnancy and post-partum overdose deaths increased between January-June 2018 and July-December 2021 (figure 1.2), but the rate of increase varied between different groups (eg: tripled among 35-44 year-olds). Non-pregnant female overdose deaths also increased during the study period.



(Data from table 1 p273 Han et al 2024)

Figure 1.2 - Pregnancy-associated drug overdose deaths per 100 000 mothers will a live birth.

Han et al (2024) explained: "Throughout the covid-19 pandemic, pregnancy-associated overdose mortality ratios increased among most race and ethnicity groups and each examined educational and marital status group. These increases are consistent with increases in overall overdose mortality rates among women aged 10 to 44 years, especially women aged 35 to 44 years, who had the highest overdose mortality rates. Our results suggest that increases in pregnancy-associated overdose mortality reflect the persistent US overdose crisis, especially during the covid-19 pandemic" (pp274, 276).

Comparing pregnancy and post-partum death groups, overdoses were younger than obstetric causes, had lower education level, were unmarried more often, and died in non-home, non-health care settings. Han et al (2024)

asserted: "Most pregnancy-associated overdose deaths occurred outside health care settings, indicating the need for strengthening community outreach and maternal medical support" (p270).

Table 1.2 lists they key strengths and weaknesses of the study.

STRENGTHS	WEAKNESSES
* Use of official records. * Use of standardised definitions (eg: post-partum = 1 year after birth or termination), categories (eg: ICD-10 codes for causes of death), and measures (eg: mortality ratio = per 100 000 mothers with a live birth). * Demographic information taken directly from death certificates.	* Dependent on correct coding of overdose death, pregnancy status, and other information by officials. * No information on health insurance status, family income, and employment status. * Cases missed (eg: pregnancies outside age range; unreported overdose deaths).

Table 1.2 - Key strengths and weaknesses of Han et al (2024).

1.9. APPENDIX 1B - OVERDOSES AND STOCKPILING

Overdoses increased in the USA during the covid-19 pandemic as mentioned earlier. King et al (2022) explained: "While the reason for this large spike in overdose rates is not fully known, it has been theorised that it is a result of many intersecting factors, including the inability to use drugs with peers to perform drug spotting (ie: using with a peer who can respond to an overdose), changes to drug purity and composition as a result of disruptions to drug markets, and the reduced capacity of harm reduction sites" (p2).

Stockpiling of drugs is another possible explanation. Stockpiling is known to be associated with higher-risk drug use, more frequent drug use, and poor drug quality, and these factors are all associated with overdose (King et al 2022).

King et al (2022) investigated the stockpiling of drugs with C3PNO data, and found that 11.6% of 1873 interviewees admitted to the behaviour in the previous month (between May 2020 and February 2021). Similar levels have been reported in three Australian studies during the covid-19 pandemic (King et al 2022).

Likelihood of stockpiling was significantly

associated with being greatly impacted by covid-19, and daily use of methamphetamine.

The interviews took place at different times of the pandemic in different cohorts, and this might explain the variation in stockpiling prevalence (eg: 15% in Vancouver vs 8% in Miami). No definition was offered to the interviewees of stockpiling, and so the subjective definition will vary between individuals.

1.10. APPENDIX 1C - AVOIDING HARM REDUCTION SERVICES

Higher levels of self-reported worry about covid-19 was significantly associated with avoidance of harm reduction services in Feder et al's (2022) analysis of C3PNO data. Two sub-samples of MOUD users (n = 702), and syringe service programme users (n = 304) were interviewed between May 2020 and March 2021. One quarter of MOUD respondents admitted to avoiding to pick up medication in the last month, while around one in eight avoided syringe services.

1.11. APPENDIX 1D – STIGMA AND HIV/AIDS

Stigma has been associated with HIV and AIDS since its beginnings, and still is today. Particularly in the early days (1980s and 1990s) in the USA, this led to, for example, the "strategic use of the term 'cancer' instead of 'AIDS' as an umbrella definition, and one less demarcated by aspects involving gender and sexual behaviour, evidenced the sociality of the illness. This both exposed the way in which negative representations were associated with AIDS — perceived as harmful, immoral, or deviant behaviours — and produced new meanings and demands among patients who feared stigmatising classifications in the midst of sexual panic until the commercial availability of the anti-retroviral cocktail in 1997" (Gugliotti and Miskolci 2024 p2).

Gugliotti and Miskolci (2024) outlined how a group called the "Mothers of Patients with AIDS" (MPWA), founded in 1986 in New York City, had pioneered such a strategy. This was a group founded by mothers caring for adult children with AIDS. Historical documents were analysed by researchers.

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2. THE INTERNET AND DRUGS

2.1. RESEARCHING DRUGS AND THE INTERNET

Collecting online data can help in understanding illicit drug use; for example, that "the internet has enabled people who use drugs to form online communities for support, debate, and knowledge sharing, for example in connection to harm reduction practices" (Aldridge and Bouchard 2019 p208).

Bancroft (2019) was clear: "Digital platforms allow for the often rapid production of massive data and invite the production of new methods such as virtual ethnography, crowdsourcing, web scraping, data mining or digital trace analysis... They invite new social research capacities such as the production of near real time metrics and rapid intervention analysis..., which can support research with hard to reach groups who wish to remain anonymous... They are also new sites for surveillance and policing of users and dealers, and attempts to regulate the flow of information about illicit activity" (p288).

Along similar lines, Enghoff and Aldridge (2019) commented: "Because more and more of our lives are enacted in online locations – eg: in the form of social media or online buying and selling – the 'digital traces' of these online activities become available to researchers to use as data... The distinguishing feature of these digital traces is that they have not been solicited by researchers, and so have not been created specifically to fulfil the aims of research projects. In this sense, digital trace data is akin to what social researchers have long referred to as 'naturally occurring' data (Golato 2017) or 'unsolicited' data (Robinson 2001)" (p210).

These researchers distinguished four groups who

generate drug-related online data:

i) Individuals who consume illicit drugs - eg: content created in online drug communities on harm reduction (Boothroyd and Lewis 2016).

ii) Individuals who supply illicit drugs - eg: cryptomarket data on hydrocodone (a prescription opioid medication) (Martin et al 2018).

iii) Online media outlets - eg: comments in response to stories on news websites.

iv) State-affiliated agencies and civil society groups/non-governmental organisations (eg: "Drug-Free World") - eg: their websites.

Unsolicited online data have the advantage of "real world" ecological validity, but that does not mean that individuals in forums are always telling the full truth, for example, Specifically, "unsolicited online data is also sensitive to the context of its production, albeit in different ways. Online platforms that enable user interaction may create powerful norms, beliefs and meanings shared within a specific community, and these may actively shape how new and old community members behave and contribute" (Enghoff and Aldridge 2019 p214).

Enghoff and Aldridge (2019) also commented on the ethical issues on using unsolicited online data: "In some cases, the administrators may have developed a site usage policy which sets out rules related to eg: copyright claims, authorship attribution, required acknowledgements in publications and whether automated data collection is allowed (eg: Erowid and Reddit). In other cases, the preferences of the site's administrators and users may be less clear (eg: cryptomarket forums). In both scenarios, it is worth considering a collaborative and fully disclosed approach, as many online drug-related communities (eg: Bluelight) actively support academic and other efforts to make use of their data" (p215).

2.2. DARKNET MARKETS

Illicit drugs are among many illegal goods and services sold on "darknet markets" (DNMs). "However, DNMs are much more than simple click-to-buy platforms that offer certain advantages to customers. They are also consummative zones and conceptual entities... that are

defined by knowledge, information sharing, and economics as much as by crime and criminalisation. Thus, DNMs connect all participants in a way that differs extensively from traditional methods of illicit drug trading... Even though participants are anonymous, geographically dispersed, and communicate solely through encrypted messages and forum discussions, they form a consummative community that is based on support, mutuality..., and 'constructive activism' within 'a more permissive digital reality' (Maddox et al 2016...)" (Kamphausen and Werse 2019 p281).

Kamphausen and Werse (2019) analysed discussions on five darknet forums dedicated to psychedelic drugs between June 2015 and March 2016. They stated: "Vendor threads offer insights into the structure of the drug-trade and the beliefs (ie: values, opinions, and expectations) of the participants. Social roles can be identified, and participants seem to act according to these roles. The typical roles comprise operators (ie: admins [site administrators]/mods [moderators]), vendors, and buyers, and together they form a social 'figuration' (Elias 1978) that is digitally mediated" (Kamphausen and Werse 2019 p282).

Three area of interest were the focus of the researchers:

i) Trust - How vendors/sellers gain the trust of potential customers/buyers in DNMs. A five-star rating system of vendors existed as in internet shopping generally, and this sets the reputation of the seller.

Another means is vouching for the trustworthiness of other people, but there is a risk that a friend of the vendor is doing this.

Trust was a product of the vendors, buyers, and operators of the forums.

ii) Logistics - The measures used to protect against law enforcement.

In a forum, a vendor "describes their terms of trade by giving information on updates, goods in stock, shipping, refunds, terms and conditions, and their presence on other markets. Additionally, the vendor posts their Pretty Good Privacy key to encrypt messages that potential customers may want to send" (Kamphausen and Werse 2019 p284). The key areas of risk in relation to law enforcement include the physical shipping of the drugs (domestic or international post), the database of customers kept by vendors, and marketing aspects (eg: advertising).

iii) Conflict - Failed transactions and logistics were sources of conflict between vendors and buyers on the forums. For example, "packages that do not reach their destination were never shipped because the vendor was a scammer; packages were intercepted by law enforcement or stolen by postal workers; packages arrived, but the customer lied about them in an attempt to scam the vendor; and competing vendors sent false claims about missing packages" (Kamphausen and Werse 2019 p285). Many of these issues are similar to general online shopping.

The researchers noted, however, that sometimes it was not possible to determine the cause of the conflict: "The vendor insists that they sent the orders, while the customers become angry about the allegation that they might be scammers. In turn, they blame the vendor...[;] something passes from one to another, drives their thoughts towards opposition, and manifests in verbal accusations. The vendor behaves similarly in response and a conflict arises between them" (Kamphausen and Werse 2019 p285).

2.3. PUBLIC DRUG MARKETS

The phrases "Facebook-dealing" and "Snapchat drugs" have been used in the popular media to describe drug dealing via the internet and social media (Bakken and Demant 2019).

Bakken and Demant (2019) undertook interviews with 68 sellers and thirty buyers of illicit drugs via social media in Denmark, Finland, Iceland, Norway, and Sweden, and also joined online communities.

"The use of social media in drug dealing was apparent in all five countries in the study... However, the national markets varied in many aspects, such as availability, communication form and reach, and medium used. Denmark and Iceland had very active drug markets on Facebook, while Swedes were active on both Facebook and Instagram. Finnish sellers and buyers mainly participated in a national darknet forum, similar to a cryptomarket... Norway stood out as having no public markets but an active use of Snapchat, Wickr, and other private messaging applications. Other nations also used these applications, but in combination with more public social media" (Bakken and Demant 2019 p257).

The researchers distinguished between public and semi-public/private digital drug markets. The former were characterised by high availability and openness to the

public, similar to street markets and cryptomarkets... Most commonly, sellers post about their goods on a social media platform. These posts usually include drug information, price, consistency or quality descriptions, service descriptions, and contact information. Interested buyers then contact sellers in the way that is instructed, usually a private message on Messenger or Wickr" (Bakken and Demant 2019 p247). A Swedish seller, for example, described the use of Facebook as "just a tool to reach more buyers that didn't exist before. There is always new people in the Facebook groups, while on the street you mostly meet the same people" (p258). Physical meeting was arranged for the exchange of drugs and money, usually in a public place.

Semi-public/private markets used one-to-one messaging apps, like Snapchat. "Buyers often need to know who the seller is and how to contact him or her directly, such as through a phone number, screen name, or social media nickname. Without direct access or knowledge of someone who has it, these private markets are unavailable. Many buyers mention already knowing the seller somehow, such as having attended the same school or living in the same neighbourhood" (Bakken and Demant 2019 p259). Exchange was more likely to take place in a home, as one Finnish interviewee said: "Then if you know the seller you usually make the deal at someone's apartment and then stay there to smoke together for a while" (p259). This market was perceived as safer by both buyers and sellers.

2.4. NEW PSYCHOACTIVE SUBSTANCES

"New psychoactive substances" (NPS) are a continual challenge to both public health authorities and law enforcement organisations. Defining NPS is debated as is the legality (eg: the degree of chemical modification of an illegal substance) (Rhumorbarbe et al 2019).

Researchers have tried to monitor NPS by analysing forums, blogs, information websites, and online shops.

For example, Rhumorbarbe et al (2019) studied the "Drugs-forum" website and discussions related to 42 substances classed as NPS during the period 2003 to 2018. Interest in a substance, based on "the number of views, the number of replies, the number of distinct authors involved in a discussion thread, and the number of threads related to this substance" (Rhumorbarbe et al 2019 p275), peaked quickly and then followed a downward trend. "Several hypotheses can be raised to explain this

observation. It could indicate a loss of interest for the substance, due to a decrease in availability or negative health effects reported. Alternatively, the early discussions could have covered a large number of topics, implying that potential consumers are able to find answers to their questions without having to write replies or create new threads" (Rhumorbarbe et al 2019 p276).

The researchers ended with the observation that "in the context of NPS, important differences between classes of substances were noted, in terms of market and interest from consumers. Indeed, some classes are discussed, while others are barely present. It suggests that each class – and even each substance – has its own specificities. A variety of factors may influence how a substance is going to spread or influence the market... Thus, the concept of NPS itself may not be appropriate to describe these substances, as argued by Potter and Chatwin (2018). They provide a critical view of NPS as a category. Considering each class individually, rather than under an umbrella term such as 'novel psychoactive substances' would be a more accurate way to define them and understand the specificity of each class of substances" (Rhumorbarbe et al 2019 p278).

2.5. NON-MEDICAL PRESCRIPTION DRUG USE

Non-medical prescription drug use (NMPDU) is a separate aspect of illicit drug use. "Reasons for NMPDU are highly variable and to some extent differ according to the class of drug concerned. These may include: the euphoriant, tension-reducing or relaxing effects of the drug; self-medication for a diagnosed, undiagnosed or self-diagnosed mental or physical health problem; performance enhancement (eg: in an academic context); or enhancement of the effects of drugs of abuse taken concomitantly" (Cunliffe et al 2019 p263).

One-quarter of drug-related emergency hospital presentations in Europe in 2016 were associated with misuse of prescription or over-the-counter drugs (Cunliffe et al 2019). Most common were benzodiazepines ("tranquillisers") and opioids ("painkillers"), but also stimulants (usually prescribed for conditions like narcolepsy or attention-deficit hyperactivity disorder). "There is a relative dearth of information about the non-medical use of anti-psychotic or anti-depressant medications, classes which have little by way of immediately rewarding or stimulating properties, and for

which non-medical use is therefore likely to represent self-medication" (Cunliffe et al 2019 p264).

The sources for NMPDU have traditionally been via a friend or family members (with or without consent) (ie: an individual who has a prescription). Online internet pharmacies have become a source in recent years, particularly if there is a "no prescription required" policy or the use of a "free online consultation" (Cunliffe et al 2019).

Another source is the darknet (or "cryptomarkets"; Martin 2014; ie: payment has to be made in a cryptocurrency; appendix 2A). Cunliffe et al (2019) analysed data from thirty-one such English language markets between September 2013 and July 2016, specifically psychiatric drug categories. The most popular categories of drugs were hypnotics and anxiolytics (eg: "Xanax", "Diazepam"), central nervous system (CNS) stimulants (eg: "Ritalin"), and opioid dependency products (eg: "Methadone"), while the USA and the UK had the largest market shares for these drugs. Note that non-psychiatric drugs made up nearly 90% of the sales on the cryptomarkets studied. Total sales of psychiatric drugs during the study period was around 150 000 items (compared to nearly 1.4 million for non-psychiatric drugs).

Put simply, psychiatric drugs that sedated, stimulated, or had euphoriant effects were popular. Anti-depressants, anti-epileptics, anti-psychotics, and dementia drugs, which have none of these effects in the short-term, were rarely listed for sale or purchased.

This was an example of a study using unsolicited digital trace data.

2.6. ONLINE MEDIA AND CANNABIS

Countries around the world have developed different policies in recent years towards cannabis use, and more specifically, medical cannabis. Different forms of media are involved in the debates around legalisation.

Lewis and Sznitman (2019) investigated whether the use of different media sources was associated with attitudes towards medical cannabis in an online survey in Israel. Online media tend to be more pro-cannabis use and legalisation with, for example, many medical cannabis dispensaries in the USA advertising the health benefits, "some of which remain unsubstantiated by evidence-based research" (Lewis and Sznitman 2019 p220).

Lewis and Sznitman (2019) surveyed 554 adults

recruited from an online panel (which was a response rate of 28% of those approached to participate). The outcome measures were attitudes towards medical cannabis, and towards cannabis legislation generally, both assessed by statements like, "Medical cannabis is addictive", and "The use of cannabis for any purpose (medical or recreational) should be legal". The predictive variables were media sources of information (television, radio, newspaper/magazine, internet, and social media), and information seeking (active or passive) about medical cannabis.

There was a direct positive association found between information seeking from online media sources and the attitudes towards medical cannabis. The association was stronger for male than female respondents, and for self-reported cannabis users. This relationship was in turn associated with support for legalising cannabis use generally. There were no such relationships for other media sources. "The results suggest that online sources play a more significant role in shaping attitudes toward cannabis than traditional media sources" (Lewis and Sznitman 2019 p224).

The researchers considered "whether it is in the public interest to (attempt to) regulate cannabis advertising on the internet, similar to regulations that are in place for tobacco and alcohol... On the one hand, proponents of free speech might argue that it is both undesirable and impractical to regulate content accessible on the internet and social media, including content related to cannabis. On the other hand, it could be argued that regulations should be imposed regardless of information source, and that online sources should not be exempt from regulations currently applied to mass media sources" (Lewis and Sznitman 2019 p225).

With reference to the country of the study, Lewis and Sznitman (2019) noted: "All of the 9 medical cannabis growers in Israel have a presence on social media such as Facebook" (p225).

Note that the study could not establish causality, the attitude measures used were limited, and no information was collected on the content of the media exposure.

2.7. ONLINE SURVEYS

Asking people about their drug use is a main source of data on the subject. General population surveys (GPS) question a representative sample of individuals, while

targeted surveys focus on particular relevant groups (eg: drug treatment clinic patients) [1]. The "European Web Survey on Drugs" (EWSD) is an example of the latter, completed online by individuals known to consume drugs.

The EWSD includes fourteen European countries with the first wave in 2016 and the second in 2017-18 [2]. There were four main areas of interest - use of the substance ever, frequency of use, mode of consumption, and means of obtaining the drug (including prices).

Compared to GPS, the EWSD "attracted a higher proportion of participants reporting frequent use than are found in the general population, which given that people opted in to the survey is perhaps not surprising; very occasional users are probably less likely to feel that a survey about patterns of drug users applies to them. On the other hand, the question arises as to whether people who use drugs frequently are properly covered in GPS sampling frames" (Matias et al 2019 p241) (table 2.1).

	General Population Survey	Specialist Sample
Advantage	Gives a picture of drug use across the whole population (ie: prevalence).	Gives a picture of use among high risk groups, including detailed information about aspects of use (eg: frequency; mode of consumption).
Disadvantage	Drug users are small number in the general population, so detailed analysis limited.	Problems with recruiting a "hidden" sample (ie: individuals who do not necessarily want to be known).

Table 2.1 - General population survey vs specialist sample on drug use.

Skarupova et al (2019) reported on the EWSD in the Czech Republic, with particular focus on four substances: cannabis (herbal and resin), cocaine powder, ecstasy/ MDMA, and amphetamines. Respondents were recruited via online advertisements on websites associated with nightlife culture, and cannabis legalisation, from online forums, and needle exchange projects. Six hundred and ten

[1] One dilemma is "data collection using treatment populations will provide information on those with extreme drug use patterns and will not reflect the consumption patterns of the majority of people who use only occasionally" (Matias et al 2019 p235).

[2] The most recent wave began in 2021 (https://www.emcdda.europa.eu/activities/european-web-survey-on-drugs_en; accessed 2nd April 2024).

adults completed the survey in early 2016, and 231 of them agreed to a follow-up in 2-12 weeks (158 actually completed the questionnaire twice). Those completing the follow-up were asked about their thoughts on the survey's design. The main questions revolved around ever use of a range of drugs in the previous month, year, and longer, and the frequency of those used in the past twelve months.

The most common drugs ever used in the past year were alcohol (96% of the sample), cannabis (86%), and MDMA/ecstasy (42%), while heroin use was low (1.8%). Cocaine was used by around one-third of the sample, but crack cocaine hardly at all (less than 1%).

Focusing on the sub-sample who completed the survey twice for test-retest reliability, this was "rated moderate to good" (Skarupova et al 2019 p228). For example, cocaine use in the last year was reported by 25% of the sub-sample at baseline and 29% at follow-up, while cannabis use was the same on both occasions (91%). "In contrast to last 12 months use, the reports on frequency of use in the last 30 days were less consistent between baseline and follow-up..." (Skarupova et al 2019 p231).

The researchers outlined a number of issues that could have influenced the reliability of the answers, including:

i) The question wording and type - eg: yes/no use (dichotomous) vs frequency of use (eg: number of days in the past month used).

Another issue here was the response categories offered, and how the wording was interpreted. "For instance, the lowest category ('less than once a month') implies a certain regularity or repetition and was not selected by those who used the drug only once or twice" (Skarupova et al 2019 p232).

ii) The drug used - "Drug use is a complex behaviour, often regulated by sub-cultural norms that differ for different groups of users; it involves the illegal activities of purchasing and sharing of drugs and as such it responds to market fluctuations and is prone to irregularity and instability even for more frequent users" (Skarupova et al 2019 p232). So, questions about regularity of use may not be appropriate. This was an important finding.

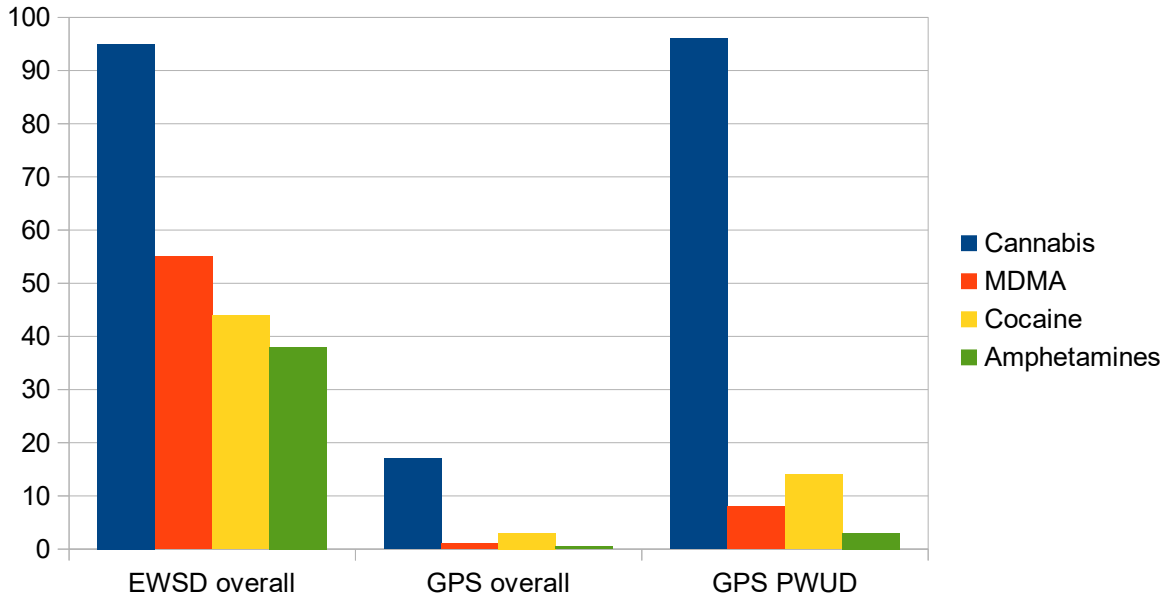
iii) Survey design - eg: layout (eg: order of drugs asked about); time period of use; estimates of amount used or number of drugs used.

iv) The use of a web survey, which "reached mainly stable, socially integrated drug users with internet access and enough time to dedicate to filling out the questionnaire. The composition of the sample also mirrors the means of recruitment..." (Skarupova et al 2019 p233).

Skarupova et al (2019) concluded: "Our data neither confirm, nor refute concerns about data quality from self-selecting samples in web surveys" (p233) [3].

The EWSD in France recruited respondents via "drug-related websites", and Facebook in mid-2016. The final sample was 2202 adults who used cannabis, MDMA, amphetamines, and/or cocaine in the past year. The findings were compared to a GPS in 2017 (Spilka et al 2022).

The EWSD sample was younger, and included more students. The prevalence rates were higher with the EWSD - eg: cannabis use in last year: 95% vs 17% in GPS (or 58% of GPS sub-sample of PWUD); 44% vs 3% for cocaine in the last year (figure 2.1).



(EWSD = European Web Survey on Drugs; GPS = General population survey; PWUD = people who use drugs)

(Data from Spilka et al 2022 table 2)

Figure 2.1 - Prevalence rate of selected drugs in France in previous twelve months (EWSD vs GPS) (%).

[3] Self-selection is influenced by who sees the recruitment advertisements, the perceived relevance to themselves, and the motivation and/or ability to respond (Spilka et al 2022).

Matias et al (2019) noted two concerns with web surveys. Firstly, with the increasing use of this mode of survey administration, "survey fatigue and mistrust may become an issue, in the same way as they have reduced response rates to telephone surveys. There are signs of this effect in the much lower [EWSD] samples obtained in the Netherlands and the United Kingdom" (Matias et al 2019 p242). Secondly, the researchers explained, "it is difficult, while maintaining anonymity, to control for people completing the survey multiple times. One can introduce cleaning routines and build in data checks that identify for example people who are going through pressing the same key all the time, or people entering unreliable answers. We also looked at the remarks entered at the end of the questionnaire which revealed a few people who indicated that they were not being honest. However, these are not foolproof measures and in terms of questionnaire design there is a trade-off between incorporating a lot of range checks to improve data completeness against the potential irritation caused by lots of interruptions when people are completing of the questionnaire" (Matias et al 2019 p242).

2.8. SIZE OF DRUG MARKETS

How to measure the size of a drug market? The first problem in answering this question is the metric to use. For example, there is the prevalence of use in a certain time period, which is simply the number of people who ever used the drug, but this misses the "heterogeneity in intensity of use... Daily and near daily (DND) users consume much more, perhaps three times more, grams per day of use as do infrequent users... Therefore, one DND user can buy and use at a rate per month that is on the order of 75 times greater than a once a month user. That would not be a problem with monitoring markets via prevalence if the numbers of light and heavy users went up and down in the same proportions. However, that is not always the case" (Caulkins et al 2019 p293). The solution is to estimate quantity consumed and amount spent on the drug. But, and here is a second problem, such estimates are not easy in hidden drug markets.

A solution is to study legal markets, as Caulkins et al (2019) did with cannabis in Washington State, USA. The researchers used three sources of data:

i) "National Survey on Drug Use and Health" (NSDUH) - A representative general population survey of the whole

USA. Just under 1900 respondents in Washington State in 2015-16.

ii) "Cannabis Consumption Survey" (CCS) - A web survey of a convenience sample of users in Washington State in 2013 (n = 1216 completed surveys).

iii) Official data on the legal cannabis industry from the "Washington State Liquor and Cannabis Board" ("seed-to-sale database") (2016-17).

For a one-year period (1st July 2016 to 30th June 2017), the data showed sales of $1.7 billion in licensed cannabis stores, which was calculated to be the equivalent of 120-150 metric tons of the plant. This was the supply-side information.

The two surveys provided the demand-side information, which Caulkins et al (2019) calculated as $1.66 bn spent in the same period involving over 200 metric tons of the plant. These calculations came from a prevalence rate of 12-18% ever used in the past month and past year (NSDUH), and DND users consuming 1.3- 2.0 grams per day of use (CCS).

The calculations, particularly on the demand-side, made a number of assumptions, and the different sets of data were not directly comparable in many ways. Caulkins et al (2019) explained: "Demand-side estimates of consumption by Washington residents should be larger than sales recorded in state-licensed stores if Washington residents consume cannabis that is purchased from other states' legal markets, purchased on the black market, produced by a medical co-operative, or home-grown. The demand-side estimates include consumption by those under 21. Stores are not supposed to sell to those under 21 and compliance checks suggest that they rarely do. That said, it is likely that some items purchased from stores by adults are consumed by those who are under 21" (p299). The survey data were dependent on the honesty and accuracy of self-reports as with this method generally.

The study period was three years after state-licensed stores opened. Caulkins et al (2019) ended with this point: "None of the estimates are precise enough to view this story as being 'right' in its particulars, but we consider the results here as suggestive that Washingtonians may have continued to consume non-trivial amounts of own-grown and black-market purchased cannabis even after state-licensed stores were in full operation. Admittedly, given the limitations of the data and the nature of the problem, this interpretation must be

understood to be a judgment, not something that can be known with certainty" (p299).

The study was an interesting exercise in triangulation (ie: comparing different data sources on the same behaviour) that made use of web data as one of the sources.

2.9. USING TWITTER

Al-Hamid et al (2024) investigated the attitudes towards opioids using Twitter posts between October 2022 and May 2023. Six hundred and sixty-seven "tweets" were found based on the search terms "fentanyl", "opioid", and "harm". Content analysis produced five main themes:

i) Uses of opioids - A key sub-theme was doctor's over-prescription of opioids. For example, "TW99" stated: "Over prescribing upfront doesn't kill people, but it does get them chemically dependent. Then when they have to turn to heroin because pills are too much, you catch fentanyl or impure stuff" (p3).

ii) Attitudes towards the use of opioids - Opioids were used for a variety of reasons (eg: "self-medication" of mental health problems).

iii) Desired effects - Pain relief was the major reason.

iv) Adverse opioid events - More tweets about these than the positive effects.

v) Harm reduction strategies - eg: to check the purity of the substance, as "TW661" encouraged: "If your city/state has a harm reduction centre you can ask them for fentanyl testing kits, you just test a small bit of your drugs but I think safe high vs death is worth whatever you can't use after testing" (p6).

Al-Hamid et al (2024) commented on the data as "true and honest thoughts and feelings of individuals in a 'blame free environment'" (p7). Though there was no way to verify the comments posted.

2.10. SMARTPHONE APPS FOR ADDICTION TREATMENT

Smartphone-based technologies are being used with

physical and mental health cases. Wu and Torous (2019) discussed the use specifically with interventions for addiction.

Firstly, smartphones can help in data collection, and real-time assessments. This has been called "ecological momentary assessment", where individuals self-report in response to a message or reminder ping.

Secondly, smartphones can supplement clinicians and therapists by providing reminders (eg: reinforce abstinence), encouraging help-seeking, and educating users. "Since smartphone-based intervention allows individuals to access screening tools and psycho-education resources anonymously, users may perceive them as a safer method than disclosing stigmatising information and seeking help in in-person addiction treatment" (Wu and Torous 2019 pp1106-1107).

An example of an alcohol relapse prevention smartphone-based system is "Alcohol-Comprehensive Health Enhancement Support System" (A-CHESS), which provides information, adherence strategies, text reminders, monitoring alerts, and interactive social support services. GPS on a smartphone will show if an individual is near a bar or pub, and send an alert, for instance. A-CHESS has been shown "to reduce the number of risky drinking days and increase abstinence rates — although surprisingly it did not have an impact on negative consequences of drinking as compared to the control group in the 2014 study [Gustafson et al 2014]" (Wu and Torous 2019 p1107). Uptake of the A-CHESS app has been limited (Ford II et al 2015).

Mobile phone-based interventions in smoking cessation have been used and evaluated more (eg: Whittaker et al 2016). The focus of smoking cessation apps has been seen to change (Ubhi et al 2016). It was noted that "smartphone apps in 2014 focused more on coping skills for craving and smoking cessation medications, whereas the apps in 2012 focused more on identity change and rewarding abstinence" (Wu and Torous 2019 p1108).

Wu and Torous (2019) outlined three key limitations with smartphone-based interventions with addiction:

i) The practicalities of designing specific apps, and their uptake in the real world.

ii) Commercially-created apps that look good, but are low quality in terms of medical appropriateness (eg: Weaver et al 2013).

iii) Patient safety - "For instance, many smartphone apps in addiction treatment encourage substance abstinence but do not evaluate the medically adverse conditions resulting from full abstinence. The risk of seizure and delirium tremens (DT) associated with alcohol withdrawal is often not monitored by these apps. It is unclear if the app developers included trained clinicians who are aware of the medical risks and other co-morbidities of the patient population during the addiction treatment. Further, even well-designed and well-intentioned apps for substance abuse may have unintended consequences. For example, one blood alcohol level calculator app designed to reduce underage college drinking was later found to actually be increasing the rate of drinking in young men who were using the app to see who could achieve the highest blood alcohol level from drinking the most alcohol" (Wu and Torous 2019 p1109).

2.10. APPENDIX 2A - CRYPTOMARKETS

Kowalski et al (2019) examined the ease of use of cryptomarkets in an observational study of such websites, and in seven face-to-face interviews with users of crytomarkets for drugs in Australia in 2016.

The researchers summed up the key finding: "Use of cryptomarkets relies on specialised knowledge. The administrators of the cryptomarkets do not play a publicly visible role in facilitating or easing cryptomarket use while simultaneously expecting cryptomarket users to exhibit self-reliance. We argue that the current levels of complexity and obfuscation constructed in the cryptomarket environment act as a barrier to the widespread acceptance of this technology" (p254).

This quote from "Al" showed the specialist knowledge needed: "I had to do a lot of research before I could make my own purchase. I spent a lot of time reading about how the Tor network actually works. Understanding that, learning. I had a basic understanding of encryption but not enough. So, I just thought I'd top up on that. I did a lot of research on how encryption works, how PGP keys worked. That took me about two or three days to understand. I got set up. Got a clean laptop. Used TAILS, very secure, fresh, operating system, installed Tor; started looking through different marketplaces, picked one; set-up an account; made sure that the account name had nothing in common with any of my clearnet accounts,

nothing to do with, you know, Facebook or anything like that. [Used] different big passwords, as much as I could. I took every possible" (p248) [4].

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[4] "Tor" (The Onion Router") is an open source browser allowing anonymous internet browsing. "TAILS" (The Amnesic Incognito Live System") is software that provides anonymity on the internet. "PGP" ("Pretty Good Privacy") is a means of encrypting and decrypting emails.

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3. SAFER SUPPLY PRESCRIBING

3.1. SAFER SUPPLY

Opioid-related overdoses and deaths are a crisis in the USA, and to a lesser extent Canada [5]. For example, in 2018, over 67 000 overdose deaths in the USA compared to around 4600 in Canada (Ivsins et al 2020). Opioid agonist therapy (OAT) (eg: methadone) can be effective here (Young et al 2022).

"However, traditional oral OAT fails to benefit some people or may not be in line with their goals or preferences... For such individuals who continue to use non-prescribed opioids, the toxicity of the current unregulated drug supply and criminalisation of drug use places them at ongoing risk of death, overdose, infectious diseases, violence, and incarceration... In recognition of these factors, there have been increasing calls for a 'safer opioid supply' as a harm reduction measure" (Young et al 2022 p2) [6] [7].

Harm reduction strategies accept that individuals will take drugs, and focuses upon reducing the risk of death and other negative consequences through different means, including illicit drug quality checking services, naloxone distribution, and low-barrier supervised consumption services. Irvine et al (2019) estimated that such strategies implemented in British Columbia (BC) in 2016-17 prevented over 3000 potential overdose deaths.

[5] Drivers of the overdose deaths include the toxic, unpredictable, and unregulated drug supply, the shift to fentanyl and its analogies, and the presence of adulterants (eg: xylazine; etizolam) (Pauly et al 2022). Over three-quarters of opioid-related overdose deaths in 2018 in Canada involved fentanyl (Ivsins et al 2020). Fentanyl is a powerful synthetic opioid that can be up to one hundred times stronger than morphine (Ferguson et al 2022).

[6] The quality of illicit drugs vary and this is a factor in overdose death, whereas safer supply provides access to pharmaceutical grade substances.

[7] "Safer supply is defined by Health Canada as a pharmaceutical-grade alternative to the unregulated drug supply.... The Canadian Association of People Who Use Drugs, a national organisation of PWUD [people who use drugs], includes the terms 'legal' and 'regulated' in its definition, and extends the goals of safer supply from harm reduction and improved outcomes, to include furthering human rights and social justice" (Glegg et al 2022 p2). Specifically, the latter definition said: "a legal and regulated supply of drugs with mind/body altering properties that traditionally have been accessible only through the illicit drug market" (quoted in Pauly et al 2022).

"However, the overdose mortality in BC (30.6/100,000 persons in BC), as elsewhere in North America, remains appallingly high..., and these treatment and harm reduction interventions are limited in their ability to directly intervene to address the fentanyl-adulterated drug supply. In order to effectively reduce overdose events and mortality by limiting access to the toxic drug supply, immediate scale-up of pharmaceutical-grade opioid distribution is required to make safer opioids widely available to people at high fatal overdose risk" (Ivsins et al 2020 p2).

The provision of safer alternatives has been used with methadone and buprenarphine, for instance, in the context of OAT. But "emerging evidence indicates low uptake and engagement of people exposed to illicitly-manufactured fentanyl in traditional OAT programmes... It is also important to recognise a wide range of drug use patterns, including people who use illicit drugs who are not interested in drug treatment, and those for whom traditional forms of drug treatment are not suitable or desirable" (Ivsins et al 2020 p2). Thus, Ivsins et al (2020) asserted, "the non-treatment-based distribution of safer opioids is essential to fully address the overdose crisis. Providing easy access to a consistent supply of unadulterated opioids will not only prevent overdose events, but also potentially reduce drug-related harms (eg: violence related to the illicit drug market) and improve overall health and well-being, as evidenced by studies demonstrating the effectiveness (eg: high retention rates, improved social functioning) of prescribed heroin (ie: diacetylmorphine) and hydromorphone" (p2). So, safer supply prescribing of pharmaceutical grade opioids to individuals at high risk of overdose death using fentanyl-adulterated illicit opioids.

Safer supply programmes are not without critics, and so the need for research, particularly in the case of Canada where the increasing overdose deaths is a public health concern. In BC, for example, in 2020, overdose deaths were more than deaths from motor vehicle incidents, homicide, and suicide combined (Ferguson et al 2022).

3.2. SAFER SUPPLY IN CANADA

Young et al (2022) investigated "safer opioid supply" in Ontario, Canada, with a retrospective cohort study of patients with opioid use disorder (OUD) using

official health databases. Four hundred and forty-seven individuals were identified for the period 2016 to early 2020, and three-fifths were male. They were almost all urban residents, many living in the poorest neighbourhoods, and 14% had overdosed in the previous twelve months. Death while receiving safer supply (eg: immediate release hydromorphone; IRH) was rare. "Patients prescribed safer supply IRH had demographic and clinical characteristics associated with high risk of death from opioid-related overdose" (Young et al 2022 p1).

Young et al (2022) ended: "Overall, the prevalence of safer supply IRH prescribing in Ontario remains very low compared to traditional OAT, which likely reflects slow up- take in the absence of provincial guidelines and a desire for additional evidence on safety and efficacy. Although mortality in our study was reassuringly low, future research examining the effect of safer opioid supply on overdose risk, infection, and mortality are needed as calls for alternatives to the increasingly toxic unregulated drug supply continue to grow" (p8).

Glegg et al (2022) examined the impact of the covid-19 pandemic on safer supply prescribing in Canada as a whole as compared to injectable OAT (iOAT) and tablet-based iOAT (TiOAT). Data were collected for the period March and April 2020 via surveys and interviews with healthcare providers (n = 50).

The number of safer supply sites nearly trebled during the study period, while iOAT/TiOAT site number remained constant. One interviewee explained the increase in safer supply sites: "With Covid... the hesitation from leadership in the health authority went away... because of concerns about an outbreak in the shelter system... they saw that we would absolutely have to provide [safer supply] to help people stay in one spot. The risks and benefits of the prescription shifted" ("Participant 39"; pp6-7). "Participant 36" made a similar point: "I think harm reduction has been rolling along and becoming more and more accepted for a long time, and then I think Covid just kind of opened a can whoop-ass. I think it was also coincidence, but I think it definitely did push it into [being] more acceptable" (p7).

An example of a new safer supply site involved clients quarantined in a motel. While machine-dispensed services were offered elsewhere, as one of the staff described: "They don't need to wait in line, no one needs to know that they're actually picking up, when they're picking up. Someone can come in and grab their meds for the day in the morning and then go to the work for the

rest of the day. They don't have to leave work 3 times a day. So, there's the dignity in choice in giving people back their schedule and their life, and also just trusting that those who are accessing it know what's best for them" ("Participant 42"; p7).

Compared to iOAT/TiOAT services, "safer supply sites displayed a far broader range of community settings and medication options, as well as less demanding care frequency than iOAT, suggesting greater capacity for versatility in where and how services are provided provi [sic] (although this flexibility was only available after SARS-CoV2 exposure at some sites). The innovative machine dispensing model, established before the pandemic, was particularly low-barrier, cost-effective, and enabled physical distancing with minimal human resources" (Glegg et al 2022 p7).

3.2.1. British Columbia

Nearly one-third of "apparent opioid toxicity deaths" in Canada between 2016 and mid-2021 occurred in BC, a province containing around one-eighth of the country's population (Selfridge et al 2022). Thus the response of this province's government to look for harm reduction strategies like safer supply prescribing.

Selfridge et al (2022) studied a specific example of safer supply prescribing in one community health centre in Victoria, providing services to a local inner-city population, including OAT for around 900 clients annually. Medical records for the period 25th March 2020 to 31st August 2020 (the period of the covid-19 pandemic) were analysed, with particular reference to prescribing of hydromorphone ("Dilaudid"), oxycodone, and sustained-release oral morphine ("M-Eslon").

During the study period, 286 clients were prescribed one or more of these novel opioid alternatives. Over 80% of the sample were homeless at the beginning of the study. The main outcome measure was 60-day adherence to the novel opioid alternatives, and around three-quarters of the sample met this standard at follow-up in October 2020. This group were more likely to be older, reporting chronic pain, and complex mental disorders, for example, as well as already receiving OAT prior to these novel opioid alternatives. In the final analysis (adjusted for demographic variables), "higher dosages of the opioid alternatives and co-prescription of mental health medications and OAT emerged as independent predictors of adherence" (Selfridge et al 2022 p6).

This study showed the importance of the appropriate dosage of all drugs/medications. This is "not surprising; sub-optimal OAT dosing has previously been linked with treatment drop out... A holistic approach to providing care to PWUD that works to identify barriers and provide suitable and appropriate medication therapies may help to ensure that clients are experiencing the full benefits" (Selfridge et al 2022 p6).

The study was "relatively short", lacked a control/comparison group, and relied on medical records (with the risk of "misclassification and selection biases"). The researchers admitted: "Given the lack of an equivalent control group, we cannot rule out unmeasured confounders of the associations with 60-day adherence" (Selfridge et al 2022 p6).

3.3. VIEWS OF DRUG USERS

What about the views of drug users towards safer supply prescribing? Pauly et al (2022) investigated this question in relation to the development in Victoria, British Columbia, Canada, of "Victoria SAFER (Safer Alternative For Emergency Response) Initiative". Sixty-three adults participated in focus groups in late 2020, recruited via organisations working with PWUD. The focus groups used open ended statements to elicit response like, "Safe supply would work well if...". Sixty-eight unique responses were recorded, and they were divided into six clusters during analysis (table 3.1):

1. "Right dose and right drug for me" - Seventeen statements related to access in safer supply to the right combination of drugs to replace illicit substances. "Some cited that, hydromorphone, one of the RMG [8] medications, did not provide the sense of euphoria that some participants sought and was an inadequate replacement for more potent fentanyl" (Pauly et al 2022 p3).

2. "Safe, positive and welcoming spaces" - Twelve statements reflected "the importance that participants placed on non-stigmatising spaces where they are treated with care and compassion. Participants wanted to access safer supply without fear of stigma, judgements, blame, or having to be labelled with a disorder in order to get help. They highlighted the need for a programme that provided wrap-around care, not just drugs, where they felt welcomed and valued by people that they felt

[8] "Risk Mitigation Guide" (name of strategy in British Columbia).

comfortable talking to" (Pauly et al 2022 p3).

3. "Safer supply and other services are accessible to me" - Nine statements around ease of access.

4. "I am treated with respect" - Seven statements that "made it clear that to be effective, participants expect to be treated with respect by people who understood their life circumstances and experiences. Important considerations included being cared for by people who communicated well, followed through, treated participants as individuals, and understood what they were going through. Importantly, they wanted to be trusted, and be seen as deserving of care" (Pauly et al 2022 p5).

CLUSTER	STATEMENT
Right dose and right drugs for me	* If drugs are strong enough and doses high enough so I don't have to add street drugs to give it legs * Access to a combination of drugs (eg: you need both up and down)
Safe, positive and welcoming spaces	* Programme isn't short term * There was a team with peers on it
Safe supply and other services are accessible to me	* No shortage of drugs * Access to housing, survival supplies and services (eg: showers, food, essentials)
I am treated with respect	* There was respect and trust * Treated like I deserve care and fee safe
I can easily get my safer supply	* Prescribers who understand dope * Peers who have experience with drugs and are like me
Helps me function and improves my quality of life (as defined by me)	* No daily witnessing and daily pick ups are onsite where you live * Alternatives to get that monkey off your back and improve your life

(Source: Pauly et al 2022 tables 1-6)

Table 3.1 - Example of responses to the statement, "Safe supply would work well if...", based on six clusters.

5. "I can easily get my safer supply" - Fifteen

statements emphasised continuous access to safer supply.

6. "Helps me function and improves my quality of life (as defined by me)" - Eight statements here.

Pauly et al (2022) noted the importance of non-stigmatising and respectful services: "This is unsurprising given the degree and severity of stigma that drug users confront on a daily basis within society more broadly and when accessing health- care in particular... To avoid the harmful effects of stigma and stigmatising processes, people who use drugs may avoid or delay seeking care. Structural stigma is often deeply embedded in health care systems in the form of 'societal-level conditions, cultural norms, and institutional policies that constrain the opportunities, resources, and well-being' [Hatzenbeuhler and Link 2004] of those who are stigmatised..." (p6).

Opioid preference of PWUD is important because safer supply prescribing should offer what is wanted. US research, for instance, showed a general preference for heroin over fentanyl or fentanyl-adulterated heroin, and those PWUD who preferred fentanyl were younger, heavier drug users, and homeless (appendix 3A), for example (Ferguson et al 2022). "Fentanyl and its analogues are notable for its rapid onset but short duration of fentanyl-associated high, and some PWUD describe its ability to break through their heroin tolerance or buprenorphine blockade as highly desirable" (Ferguson et al 2022 p2).

Ferguson et al (2022) found similar results in data collected in the "BC Harm Reduction Client Survey" (HRCS) in late 2019 (n = 621). "The eligibility criteria for participation in the HRCS included being 19 years or older, self-reported substance use of any substances other than or in addition to cannabis in the past six months, and ability to provide verbal informed consent" (Ferguson et al 2022 p3).

Just over 400 respondents used opioids and reported a preference, with heroin most popular (58%), followed by fentanyl (23%), and the remainder a prescription opioid. Those who preferred fentanyl over heroin varied significantly on three demographic variables - age (younger), geographical area (lived in Fraser Health Authority area of the five regional public health authority areas), and Indigenous identity (less likely).

3.4. APPENDIX 3A - HOMELESS POPULATION

"Homelessness and substance use are often described as intricately related... There is a widely accepted view that substance use has been regarded as both a cause and consequence of homelessness. In numerous studies, more than two-thirds of homeless individuals have reported that substance use had been a major cause of their homelessness... Other studies have also stated that substance use had been a consequence of homelessness rather than a cause" (Coombs et al 2024 p1). Research, however, is difficult with individuals who experience homelessness.

Coombs et al (2024) performed a review of quantitative studies on substance use prevalence and patterns of misuse among the homeless population. Thirteen databases of academic articles were searched for publications in English between 2007 and 2021. Homeless was defined (using the United Nations' definition) as "being without suitable or permanent accommodation... This 'umbrella term' includes street dwelling homeless, also known as rough sleepers, those in sheltered in accommodation and staying with friends or family" (Coombs et al 2024 p2). Twenty-five relevant articles were found, all covering homeless in the USA, Canada, or Western Europe, and most used a cross-sectional research design. Table 3.2 lists some key methodological differences between the studies.

Substance use was more prevalent among males than females, and alcohol was most common overall (mean prevalence of 50%), though "new psychoactive substances" (NPS) have recently increased in popularity.

- Measurement of substance use - eg: self-report; psychometric questionnaire.
- Definition and measurement of substance abuse/misuse.
- Sample characteristics and recruitment - eg: both males and females; recruitment after hospitalisation; Vietnam veterans.
- Demographic variables and risk factors (eg: mental health problems; adverse experiences) measured.
- Substances studied.

Table 3.2 - Key methodological differences between the studies in the review.

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4. GENETICS OF ADDICTION

4.1. INTRODUCTION

The resemblance between identical twins in a behaviour would suggest an important role for genetic factors. Furthermore, if the similarity between identical (mono-zygotic; MZ) twins is greater than between non-identical (dizygotic; DZ) twins. This idea has been applied to substance use (initiation and quantity use, for example).

4.2. CIGARETTES

Kendler et al (2019) examined the initiation of cigarette use and snus use (a moist powdered tobacco held in the mouth [9]), and the quantity of them used in a Norwegian sample of adult twins.

Data came from the "Norwegian Institute of Public Health Twin Panel" in 2017, and included responses from 1103 pairs of twins (546 MZ and 557 DZ). Questions were asked about age of initiation of cigarette use and snus use, and average daily use.

Cigarette use and quantity of use were positively correlated higher between the two MZ twins than DZ twins, which would suggest the importance of genetic factors in these behaviours, but "correlations for both initiation and quantity of snus use in DZ twins were substantially more than half that observed in MZ twins suggesting the importance of shared family environment" (Kendler et al 2019 p110) (table 4.1).

The researchers offered the "plausible explanation" for the findings that "the universal availability and widespread use of cigarettes reduces familial-

[9] "Snus has been a subject of increasing interest because of evidence that it may have less adverse health effects than cigarettes... and may be an effective substitute for cigarettes comparable in efficacy to nicotine patches..., and it may be more strongly associated with smoking cessation than smoking initiation... Furthermore, despite declines in cigarette use, snus use is increasingly popular in Norway" (Kendler et al 2019 pp108-109).

SUBSTANCE	BEHAVIOUR	MZ TWINS	DZ TWINS	COMMENT
Cigarettes	Initiation	.79	.37	MZ greater than DZ by large amount suggests genetics important
	Quantity used	.74	.32	
Snus	Initiation	.81	.54	Smaller difference between MZ and DZ suggests shared environment important
	Quantity used	.78	.50	

(Data from table 2 p110 Kendler et al 2019)

Table 4.1 - Correlation of behaviours between twins.

environmental influences on its use, while for the rarer forms of tobacco, within-family social learning effects... play a stronger role in decisions to initiate use" (Kendler et al 2019 p111).

Previous research on twins has provided "strong support for an important role of genetic factors in twin resemblance, with shared environmental effects tending to be stronger for initiation than quantity consumed and stronger in younger versus older samples" (Kendler et al 2019 p108).

Maes et al (2018) gave the overview of more than fifteen published adult twin studies from around the world of smoking initiation as having a median heritability of 57%. Direct cross-cultural comparisons, however, are rare (Maes et al 2018).

Maes et al (2018) compared the USA and Australia using data from the "Virginia 30 000" and the "Australian 25 000" samples, which included twins and extended kin. In total, there were 50 318 adults with eighty-eight distinct biological and social relationships.

Heritability for smoking initiation was 55% overall. Shared environment (ie: sibling, twin, and cultural transmission) was estimated to account for around one-third of the variance in age of initiation. The remainder was unshared environment. The findings from the different correlations were very similar for both countries.

Such studies as this one involve highly complex statistical analysis of large amounts of data as in the 88 correlations, but some correlations only had a few cases even with the large data set. The samples were volunteers, and there would have been non-participating relatives, though information about them was given by participating relatives.

4.3. GENOTYPE-BY-TIME INTERACTION

Disordered gambling behaviour has increased in prevalence in the USA, for example, in the last fifty years. Establishing the genetic contribution to such behaviour is faced with great social change in this period (eg: the expansion of legal forms of gambling). Slutske (2018) noted that such such change can "shape the relative importance of genetic and environmental contributions to individual differences in the behaviour" (p119).

She used the example of cigarette smoking in the 20th century in the USA. The first half of the century saw prevalence rise from nearly zero to over 40% of adults, but later decline to 15% by the 21st century. This up and down pattern mirrored product marketing, then evidence of health risks (in the 1960s) and subsequent restrictions on advertising and sales. Data from US twin studies showed a heritability of around 60% for smoking prior to health concerns, while this figure dropped drastically post-health risk evidence. "These changes in heritability observed in different birth cohorts are examples of a phenomenon that might be termed genotype-by-time interaction — a genotype-by-environment interaction (Shanahan & Hofer 2005) where the relevant environment is change occurring across historical periods" (Slutske 2018 p120).

Theories for the genotype-by-time interaction include (Slutske 2018):

i) Social control model – Genetic differences are dampened by social forces over time (eg: heritability of smoking post-health concerns in later 20th century).

ii) Social trigger model – Genetic differences are amplified by social forces over time (eg: heritability of smoking in the first half of the 20th century).

iii) Social push model – Genetic differences are hidden or highlighted by the changing social forces over time (eg: in the cigarette restriction period of the 21st century, smokers are more likely to be those with greater vulnerability to nicotine addiction).

4.4. DRUG ABUSE

Drug abuse (DA) is "strongly transmitted within families... as a result of both genetic- and familial-

environmental effects" (Kendler et al 2020 p1). Using extensive data available in Sweden, Kendler et al (2020) considered whether it is possible to intervene to stop the family transmission of DA. The question is, "for parents with a family history of DA, what distinguishes those who transmit the familial vulnerability to their children so that they likely go on to develop DA versus those who break the transmission pattern and raise unaffected children?" (Kendler et al 2020 p1).

The study centred on children born between 1970 and 1990 who had at least one grandparent registered with DA (n = 45 837). After removal of dead and emigrated cases, there were 44 250 children of high-risk parents. Follow-up covered from age 15 and into their 30s.

In the Swedish general population, the prevalence of DA was 0.8% for the grandparental generation, 2.2% in the parental generation, and 4.7% in the children's generation. In the study sample, the prevalence was 8.1% for parents and 8.9% for the children.

Risk factors were compared for the children who developed DA and those who did not. Two groups of factors were found – parental, and environmental. The first group included a high-risk parent marrying another high-risk parent, mental illness, low education, and receipt of welfare/benefits, while the general environmental factors included neighbourhood deprivation, and number of drug dealers in the locality.

The strongest risk factors for DA by the children was parental DA, and criminal behaviour (CB), and a "broken family". Applying the findings to advice to a high-risk parent, the researchers stated: "(1) avoid marrying a spouse who develops CB, (2) raise a child in a community where few if any of his/her peers go on to develop DA, (3) maintain an intact family while raising the child, (4) and (5) avoid yourself developing DA or CB and (6) do not move frequently while raising your child" (Kendler et al 2020 p5). These are modifiable risk factors.

Kendler et al (2020) observed: "Of particular interest, our results suggest that, even if only theoretical, if high-risk parents were able to achieve most of these goals, the chances that their child would develop DA would be reduced by approximately 50%, which would be close to baseline rate expectations in the population. That is, by taking these steps, the parent could effectively wipe out the impact of their familial risk for DA on their children's probability to develop DA" (p5).

4.5. COCAINE USE

Personality Disorder (PD) is a risk factor for substance use disorders (eg: Hasin et al 2011). Gillespie et al (2018) investigated the specific link between PD traits and cocaine use using the "Norwegian National Institute of Public Health Twin Panel" data. The twins were born between 1967 and 1979, and the relevant data were collected between 1999 and 2004 (ie: during young adulthood). Ten PDs and traits were assessed by a clinical interview, and cocaine use was self reported. Complete data were available for 1419 twins.

All PDs, except schizoid, and obsessive-compulsive, predicted cocaine use. The relationship was strongest for anti-social, borderline, and histrionic PD traits. Twin analysis showed anti-social PD traits explained the majority of genetic risks in cocaine use, followed by borderline PD traits. In other words, the strong correlation between anti-social PD traits and cocaine use "is driven largely by common genetic risks" (Gillespie et al 2018 p24). Previous research has shown that PDs have high heritability as does cocaine use (Gillespie et al 2018).

4.6. NORMAL DRINKING

Approximately 10-15% of men and 5% of women are officially diagnosed with alcohol dependence, so the vast majority of people have "normal drinking" (Verhulst et al 2018). Research has looked at the genetic component of alcohol problems, but what about of normal drinking?

Verhulst et al (2018) analysed data from two samples (in the USA and Australia). The Australian sample included around 20 000 respondents from over 8000 families, and the US sample approximately 23 000 respondents in 6000 families.

Four separate measures of alcohol consumption were used:

i) Drinking quantity – Number of drinks in a typical week based on numerical categories (eg: 4-6; 42 or more).

ii) Drinking frequency – How often alcohol was consumed in the past year (eg: "more than once each day"; "once or twice a month").

iii) Drinks in the last week – Number of drinks of different types (beer, wine, liquor).

iv) Age of first drink or started drinking regularly.

Comparing all the different correlations between family members (genetically related and unrelated), it was found that "drinking quantity, frequency, and number of drinks in the past week have large broad genetic variance components, and smaller but significant environmental variance components, while age of onset is driven exclusively by environmental factors" (Verhulst et al 2018 p163). There was a high degree of similarity between the two samples. "Interestingly, discrepancies were primarily found at environmental rather than at the genetic levels. This is exactly where these behaviours would be expected to differ, given that drinking norms are different in the two countries" (Verhulst et al 2018 p175).

Assortative mating was also important (ie: choice of a spouse/partner with similar drinking behaviours).

Some relationships were less represented in the samples. "The twins, who formed the core of the sample, were reasonably complete, but the children of the twins, as well as the spouses and siblings, were less well represented. Because there were 18 possible relatives, it is nearly impossible for any family to have all possible members. Specifically, the current analyses span three generations and allow the twins to have two brothers, two sisters, two sons (each), and two daughters (each). These would be very large families by modern standards" (Verhulst et al 2018 p176).

The study used two types of statistical analysis known as "twin-only design" and the "extended twin design". The former design divides the difference between twins into genetic, and shared and unshared environment components. The extended twin design, because it includes correlations between many different family members, additionally divides the shared environment into special twin environment, non-parental environment, and intergenerational cultural transmission, and the inclusion of spouses allows for estimates of assortative mating. This latter approach provides "a more nuanced perspective" (Verhulst et al 2018 p163).

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5. POLYSUBSTANCE USE

5.1. SOUTH ASIA

"Polysubstance use" describes the use of more than one drug for therapeutic or recreational purposes either sequentially (on separate occasions) or concurrently.

COUNTRY	STUDY	DETAILS
India	Venkatesan & Suresh (2008)	Retrospective out-patient-based study of one hospital (n = 839) (polysubstance = 3 or more substances): 12.8% (1985-86), 10.6% (1995-96), 20.4% (2005-06)
Pakistan	UNODC * (2013 quoted in Mandal et al 2023)	National survey of drug users: 20% more than one illicit substance in past year
Afghanistan	Afghanistan National Drug Use Survey (2009 quoted in Mandal et al 2023)	40% of drug users had used two or more substances simultaneously in past year
Nepal	Chapagain et al (2020)	National survey of 1125 adolescents: 70% of drug users are polydrug users
Bangladesh	Maruf et al (2016)	110 patients admitted to a private de-addiction clinic: 90% polysubstance users
Sri Lanka	Herath et al (2018 quoted in Mandal et al 2023)	Survey of over 400 drug users: large majority used alcohol and tobacco as well
Bhutan	UNODC (2009 quoted in Mandal et al 2023)	12-18 year-olds in one area: all those using drugs reported polydrug use in last month
Maldives	No data found by Mandal et al (2023)	

(* United Nations Office on Drugs and Crime)

Table 5.1 - Example of studies on prevalence of polysubstance use in eight South Asian countries.

"Multiple substances are used together at the same time

or in close time either to enhance and experience the desired effects of combinations or to manage the adverse effects of craving or withdrawal or it may reflect different contexts and motivations for substance use" (Mandal et al 2023 p269).

Polysubstance use has a number of negative associations, including increased risk of addiction and overdose, lower educational and occupational achievements, physical health problems, and mortality, as compared to mono-substance use (Mandal et al 2023).

Mandal et al (2023) reviewed the evidence on polysubstance use in eight countries in South Asia (table 5.1). Overall, there was limited research, and the studies that existed varied in their definition of polysubstance use.

5.2. CANNABIS AND HEROIN/OPIOID USE

Longitudinal studies provide data that allow inference of causal relationships. This is the case with cannabis and heroin/opioid use. For example, among individuals with opioid use disorder (OUD) at baseline, those using cannabis reported substantially reduced opioid use (eg: Lake et al 2019). But other longitudinal studies have found cannabis use increases illicit opioid use (eg: Olfson et al 2018). There are other longitudinal studies that find no relationship between cannabis and opioid use (eg: Epstein et al 2015) (Wilson et al 2024).

Wilson et al (2024) noted the relative short-term nature of the above studies, which gave their study at advantage, having data covering 18-20 years. This is the "Australian Treatment Outcome Study" (ATOS), with a cohort of over 600 adults entering treatment for heroin dependence in Sydney recruited in 2001 and 2002. Follow-up was made 3, 12, 24 and 36 months, and 10-11 and 18-20 years later. Two hundred and sixty-two participants were still involved in the study (ie: had completed all follow-ups).

The prevalence of heroin use more than once a day decreased from 55% of the sample at baseline to 6% at last follow-up, while daily use of cannabis had increased from 41% to 45% at three months, but declined to 20% at 18-20 years. There was no overall relationship between cannabis and heroin use. However, there were some significant relationships at different time periods. For example, "an increase in cannabis use 24 months after baseline was significantly associated with an increase in heroin use at 36 months... Additionally, an increase in

heroin use at 3 months and 24 months was significantly associated with a decrease in cannabis use at 12 months... and 36 months" (Wilson et al 2024 p135).

This study differed from previous research in that the sample had enrolled for treatment (table 5.2). So, "it may be argued that participants would be less likely to engage in the use of other substances, and that subsequent treatment episodes could moderate a potential cannabis-heroin relationship. However, studies of people in treatment and not in treatment have both reported contrasting results; hence it is unclear whether the presence and direction of a cannabis-opioid relationship differs according to treatment status" (Wilson et al 2024 p141).

Another difference is that previous studies have used binary self-reports (yes or no) of drug use or urine tests. Wilson et al (2024) used the "Opiate Treatment Index" (OTI), which calculates a score based on self-reports. The researchers explained: "As a composite of quantity and frequency of use, the measure provides greater specificity, more adequately reflecting changes in cannabis and heroin use at each follow-up and increasing the precision of the estimates in this study" (Wilson et al 2024 p141).

No measures were taken of different cannabis products used and the variations in cannabinoid concentrations.

Concluding about cannabis and heroin use, Wilson et al (2024) stated: "Overall, there was insufficient evidence to suggest a unidirectional or bidirectional relationship between the use of these substances" (p135).

STUDY	METHODOLOGICAL DETAILS
Lake et al (2019)	1152 drug users, and/or people living with HIV who reported major or persistent pain in Vancouver, Canada between 2014 and 2017. Daily cannabis and opioid use in last six months.
Olfson et al (2018)	Data from National Epidemiological Survey on Alcohol and Related Conditions (NESARC) in USA 2001-2 and 2004-5 waves (n = 34 619). Cannabis and prescription/non-prescription opioid use.
Epstein et al (2015)	116 outpatient heroin and cocaine users on methadone-reduction treatment over ten weeks.

Table 5.2 - Three longitudinal studies of cannabis and heroin/opioid use.

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6. SLEEP AND HEALTH AND ALCOHOL

6.1. OVERVIEW

There is growing evidence that excessive alcohol consumption disrupts sleep and circadian rhythms, and that disrupted sleep and circadian rhythms stimulate alcohol consumption (Rosenwasser 2015a). Rosenwasser (2015b) commented: "Of course, it is very difficult to infer causal relationships from clinical and epidemiological data, and even more difficult to isolate and identify controlling variables. Thus, as is the case for other psychiatric disorders, animal models have proven to be extremely useful in this regard" (p311).

The animal studies have established the causal relationships for alcohol consumption altering circadian rhythms, and disrupted circadian rhythms increasing alcohol consumption. However, the most common type of studies, rodent studies, including a number of variables, like forced- or free-choice ethanol (alcohol) consumption, the concentration of ethanol in the drinking water, the lighting conditions (eg: continuous darkness; light and dark 12 hours each), and choice and sex of species (Rosenwasser 2015b).

Two aspects of sleep are important – the architecture, and homoeostasis. The former describes the phrases and cycles within a night's sleep, including non-rapid eye movement (NREM) (Stages I-III) and rapid eye movement (REM) sleep, with different electrical activity in the brain as measured by electroencephalography (EEG). Sleep homoeostasis is the "pressure to sleep" which builds up over the period of wakefulness. In a situation of stable circadian rhythms, sleep pressure will build up leading to consistent sleep times with short onset latency (ie: time in bed before sleep) and low insomnia (difficulty falling and staying asleep).

Alcoholics show alterations in sleep which includes less sleep time overall, and differences in the length and cycles of REM sleep, while mice given ethanol-

containing drinks and kept under constant lighting conditions show shortened circadian rhythms, for example (Nascimento et al 2015). Alcoholics can also have profound insomnia, and consequently excessive daytime sleepiness (Thakkar et al 2015).

"Acute alcohol intake, in non-alcoholic social drinkers, reduces the time to fall asleep (sleep onset latency); consolidates and enhances the quality... and the quantity of NREM sleep. It is this sleep-promoting characteristic of alcohol that makes it one of the most commonly used 'over the counter' sleep aids... However, alcohol-induced sleep promotion is short-lived and sleep is severely disrupted during the second half of the night" (Thakkar et al 2015 p299).

The impact of ethanol on the brain, specifically the areas linked to circadian rhythms, like the suprachiasmatic nucleus (SCN), has been studied in live animals (in vivo) and in cells (in vitro). Prosser and Glass (2015) combined both methods in a series of experiments.

This work showed ethanol's effect on the SCN and circadian rhythms, but also "circadian influences on ethanol consumption" (Prosser and Glass 2015 p321). In the former case, for example, in rodents, ethanol inhibits the resetting of the circadian clock by light.

6.2. GENES

The circadian rhythms are known to be controlled by particular genes (eg: "Circadian Locomotor Output Cycles Kaput"; Clock), and there is evidence of alcohol impacting the expression of such genes (eg: lower expression of Clock in alcohol dependent individuals) (Parekh et al 2015).

Research has also show that Clock, for example, plays a role in drug abuse via reward-related brain activity (eg: mice with a Clock mutation consume more cocaine than controls) (Parekh et al 2015).

Disruption of the neurochemical dopamine seems to be key. "Circadian rhythm disruptions and addiction vulnerability go hand in hand. Moreover, chronic exposure to alcohol and other substances leads to lasting changes in rhythms that contribute to the cycle of addiction and relapse. Recent studies have determined that genes that control circadian rhythms are keenly involved in regulating the dopaminergic reward circuitry and this regulation may be the cause of this increase in

vulnerability and the plasticity that contributes to addiction" (Parekh et al 2015 p347).

One of the bodily processes influenced by circadian rhythms is related to the gut and digestion. Gastro-intestinal disruption may even promote excessive alcohol consumption (Forsyth et al 2015).

Alcoholism can lead to problems like alcoholic liver disease (ALD), but only in a sub-set of such individuals. So, additional factors to alcohol must be involved in the development of conditions like ALD. Forsyth et al (2015) proposed that circadian-disrupted gastro-intestinal problems is one factor. "Gut leakiness" (the increased permeability of the intestine) may be a product of circadian disruption, and this would allow more alcohol to pass out of the gut. Genetically engineered mice with clock gene mutations have been found to show gut leakiness (Forsyth et al 2015).

Perreau-Lenz and Spanagel (2015) added environmental stressors interacting with circadian genes to account for AUD. Stress can impact circadian rhythms through disrupted sleep, say, and this links to alcohol consumption as well as negative life events leading to alcohol intake as stress relief. But studies with mice, for example, show that genetic vulnerability is important. Genetically engineered mice with particular variants of circadian genes consumed more alcohol than controls after stressors like the forced swim test (eg: Dong et al 2011).

The study of circadian genes in humans usually involves comparing cases (eg: AUD) and controls for gene variants, or searching for variants carried by genetic relatives of individuals with AUD but not in families of controls. Other studies have looked at average weekly alcohol intake and gene variants, or frequency of excessive drinking (Partonen 2015).

Some circadian gene variants have been found to associate with AUD only if AUD co-morbid with another mental disorder like depression (Partonen 2015).

6.3. INSOMNIA

Insomnia is a negative experience generally, but for individuals with alcohol use disorders (AUD), it is associated with relapse, for example. "Why poor sleep is associated with relapse is unknown. Possible mediators

include impaired executive functioning (eg: impulse control, judgment, decision making), negative affect, enhanced sensitivity to stress, and self-medication" (Brower 2015 p419).

One review (Zhabenko et al 2012) calculated that just over half of AUD patients had insomnia (though individual studies went as high as 90%). "The wide variability in range across studies is likely due to differences in sample characteristics (eg: demographics, drinking severity, duration of abstinence, and co-morbidity), as well as definitions of, and methods used to measure, insomnia" (Brower 2015 p418).

Insomnia can be alcohol-related (ie: when the individual is drinking) and withdrawal-related (ie: when they are not drinking) (Brower 2015). The reasons for persistent insomnia despite abstinence include (Brower 2015):

a) Pre-morbid insomnia – A continuation of insomnia from before the development of AUD.

b) Co-morbidity – Many physical and mental disorders cause insomnia.

c) Use of other substances than alcohol, and medications, which cause insomnia.

d) Stress.

e) Environmental factors – eg: noise; temperature; poor sleep hygiene (eg: irregular sleep schedules)).

In terms of treatment of insomnia for individuals with AUD (and anybody), the main options are (Brower 2015):

i) Education – eg: sleep hygiene programme (table 6.1).

ii) Cognitive-Behaviour Therapy for Insomnia (CBT-I) – eg: addressing the negative thoughts around insomnia and sleep. Brower (2015) reported two randomised controlled trials of CBT-I with AUD patients that found reductions in insomnia symptoms, but the number of participants were small (eg: 17 patients).

iii) Medications, including melatonin agonists (which increase melatonin), and anti-depressants, anti-psychotics, and anti-convulsants (for their sedating

effects). The anti-convulsant Gabapentin is best studied for insomnia (eg: five randomised controlled trials with AUD patients, of which three found significant reductions in insomnia) (Brower 2015).

- Quiet, comfortable sleeping room.
- Regular sleep and waking times (within 1 hour, including at weekends)
- No daytime napping
- Avoid stimulation, alcohol, and caffeine prior to bedtime (eg: 3 hours before)

(Source: Brower 2015 table 1 p421)

Table 6.1 – Main features of a sleep hygiene programme.

6.4. ADOLESCENCE

Hasler et al (2015) argued that changes in adolescence lead to an increased risk of AUD. They explained: "Adolescence is a time of marked changes across sleep, circadian rhythms, brain function, and alcohol use. Starting at puberty, adolescents' endogenous circadian rhythms and preferred sleep times shift later. This can lead to a mismatch with the schedules imposed by secondary education. Consequently, adolescents often suffer from circadian misalignment, sleep disturbance, and sleep loss. In parallel, adolescent brains are undergoing structural and functional changes in the circuits subserving the pursuit and processing of rewards. Alcohol use initiation typically occurs during adolescence,
resulting in risk for alcohol use disorder" (Hasler et al 2015 p377).

The researchers reviewed the evidence to support their position, including:

i) Cross-sectional studies – eg: insomnia symptoms in the past year associated with increased use of alcohol (and other substances) in a sample of nearly 4500 12-18 year-olds in the USA (Roane and Taylor 2008).

While comparisons of adolescents with and without AUD find that the former group had more self-reported sleep problems (eg: Clark et al 2001).

ii) Longitudinal studies – eg: parent-rated childhood (3-8 years old) sleep problems predicted alcohol problems in adolescence (eg: Wong et al 2010).

6.5. ALCOHOL AND LITHIUM

Over the years alcoholism has been treated with various drugs including lithium, naltrexone, valproate, and carbamazepine. The latter two are anti-convulsants, and lithium is no longer used as a treatment for alcoholism (Nascimento et al 2015). But there are individuals with co-morbid alcoholism and bipolar disorder (who receive lithium). As mentioned above, ethanol shortens the circadian rhythms, but lithium is known to lengthen them. Nascimento et al (2015) showed this in a study with mice.

Thirty-three male mice were given drinking solutions containing lithium, alcohol, or both, or water only as a control. The circadian rhythms were measured by free-running ten-minute activity periods in constant darkness (24 hours) or 12 hours light/12 hours darkness. The opposing effects of lithium and alcohol on circadian rhythm length was confirmed. The drinking solution containing both substances produced little change in length which suggested that the effect of each substance was negated. Both substances have physiological impacts which impact sleep in different ways.

6.6. HEALTH ISSUES

Cardiovascular disease is a risk with alcoholism. The cardiovascular system is regulated by the autonomic nervous system (ANS), and by the medulla oblongata in the lower brainstem. Chronic alcoholism produces a pathology in this system (de Zambotti et al 2015).

But does abstinence (or detoxification) lead to recovery of this system? de Zambotti et al (2015) found evidence that it did in a study comparing fifteen recently detoxified alcoholics and thirteen healthy controls. Measurement of heart rate variability was made during sleep, as this "offers the advantage of stable periods to evaluate ANS functioning free from wake-related external influences" (de Zambotti et al 2015 p410). These measurements were taken within one month after the last alcoholic drink (baseline), and then two and four months later.

At baseline, the heart rate of the alcoholic group

was significantly higher than the controls (mean 77 vs 57 beats per minute). At four months the alcoholic group showed a marked reduction in heart rate compared to the baseline.

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7. NEW DRUGS IN THE 21ST CENTURY

7.1. INTRODUCTION

"New (or novel) Psychoactive Substances" is "a catch all term for chemical compounds that have been modified and developed to mimic the effects of drugs that are already prohibited" (Chatwin et al 2018 p297) (appendix 7A). They grew in popularity in the 2010s. Other "new drugs" in the 21st century receiving less attention are "Human Enhancement Drugs" (HED) (Chatwin et al 2018) (appendix 7B). "Initially called 'legal highs' (in United Kingdom prior to May 2016), most of these substances fell outside of existing drug legislation, which could account for their notable rise in popularity" (Addison et al 2018 p313).

These new categories of drugs intersect with "traditional" drugs, and Chatwin et al (2018) argued for the study of all categories together.

7.2. DRUG SERVICE PROVISION

Ralphs and Gray (2018) reported that the "European Early Warning System" had identified over 500 NPS by 2016. They commented: "Of the plethora of new or novel substances that have been identified, only a smaller number have cemented themselves amongst the traditional menu of illicit drugs in the UK. These include nitrous oxide, mephedrone, ketamine, GBL (gamma butyrolactone), GHB (gamma hydroxybutyrate) and synthetic cannabinoid receptor agonists (SCRAs), often referred to as 'Spice' in the UK. The consumption of these drugs is often associated with particular sub-populations such as students, clubbers, LGBT [lesbian, gay, bisexual, trans], prison and homeless communities" (Ralphs and Gray 2018 p301).

Ralphs and Gray (2018) concentrated on two of these groups in their six-month study in north-west England

(Manchester) - homeless individuals and SCRA, and "men who have sex with men" (MSM) and "chemsex" (the mixture of sex and substances like GHB, GHL, and methamphetamines). A key issue is whether separate drug services are required for NPS.

Ralphs and Gray (2018) interviewed thirty-eight SCRA users (including five women), and fifteen "chemsex" participants, as well as thirty-one staff from local drug-related services. The research found "a notable shift in the drug using landscape. It highlights how the homeless community – traditionally associated with alcohol dependency and problematic intravenous heroin and/or crack cocaine use – are now switching to smoking synthetic cannabinoid receptor agonists, while men who have sex with men (MSM) and engage in chemsex – who have traditionally been strongly associated with the recreational use of ecstasy and other stimulants – are now developing problematic intravenous drug using habits" (Ralphs and Gray 2018 p301).

The first trend is summed up by this quote from a young man living in supported housing: "It [Spice] has replaced a lot of other drugs... A lot of my friends have given up heroin and crack addictions, and they now smoke the Spice. I'm the same. I've given up an alcohol, crack and heroin habit and I just smoke Spice. I gave up cannabis as well" (p303). While a worker from a LGBT service organisation reported that "[A]bout 29% of our [chemsex] population are injecting" (p303).

The perception of traditional drug services can be seen in two quotes from "homeless" men: "Why would I want to go to a place with druggies?", and "Do you know what they're for, them drugs services? To give new needles and I don't use needles, so why do I need to go there?" (p305). A worker in a LGBT service organisation made a similar point about their client group: "We need to work differently... because a lot of people [engaged in chemsex] probably wouldn't access a needle exchange because they associate it with opiate drug users. There's so much stigma attached to using a needle exchange" (p306).

Ralphs and Gray (2018) proposed three changes to drug services - improved integration of services (ie: mental health, and substance abuse programmes), clearer referral pathways for "new drugs" user groups, and innovative strategies to engage these groups with appropriate services.

7.3. POLICE CUSTODY SUITE STUDY

Ralphs and Gray's (2018) study can be interpreted as suggesting that "NPS should not be viewed as a distinct problem in their own right, but rather as part of a pattern of complex polydrug use and other non-drug-related issues" (Chatwin et al 2018 p298). Likewise with Addison et al's (2018) study of a police custody suite setting in north-east England.

Fifteen police staff and 25 self-identified NPS users in custody were interviewed. The following themes emerged from the analysis:

i) NPS users - One senior female police staff member described the variety of users: "One is your drunk and disorderly [...] those type of individuals could be absolutely anybody. It could be your professionals; it could be people that partake in crime in other types of criminal activity. [...] Then, you've probably got that separate group of some other people who are struggling with, possibly, mental health issues, don't have the support network around them, the likes of your homeless people. People who are on the fringes of criminality" (p314).

While the users "described the appeal of NPS being linked to the brightly coloured foil packaging. NPS were often specifically given names that were related to youth culture around computer gaming, adventure sports, superhero characters and iconic films" (Addison et al 2018 p315). Twenty-three varieties of NPS were named by interviewees.

ii) "Psychoactive Substances Act (PSA) 2016" - Under this legislation, NPS became illegal to produce or supply (but not consume) in the UK (Addison et al 2018) [10].

"While the PSA deterred a minority of participants, those who self-identified as still using (n = 21) reported that they were accessing NPS illicitly through street dealers and at social events via friends and associates. Few reported using the Internet to access NPS. A number of these participants were already involved in criminal activity to fund their lifestyles prior to the PSA. Further, participants often found themselves in custody because of acquisitive, violent or Public Order offences, whilst also using NPS" (Addison et al

[10] Evans-Brown and Sedefov (2017) commented critically on such legislation: "In reality, most new substances are disposable, as manufacturers have replacement substances ready for sale even before a substance is controlled; the recipes for many thousands more are in the scientific and patent literature ripe for the picking" (quoted in Addison et al 2018).

2018 p315).

iii) NPS and other substances - A male ex-NPS user compared "Spice" to heroin thus: "At least with heroin, if you take that you couch out and you fall asleep, or with cocaine you're high, you can still move, you know what's going on. With that you were high, you couldn't move, but you knew what was going on and it was just not a buzz that I liked" (p315).

Experienced users of traditional substances struggled with the right dose of NPS as shown by these two quotes: "I thought for two years that you had to smoke it like weed to get a buzz, but no one actually realises you only need a couple of flakes to get that buzz"; "I got something called Red Dragon. It's a pre-rolled spliff type thing of legal high. It is so strong and so lethal that I took one drag from it and ended up in the back of an ambulance" (p315).

iv) The intersection of NPS and other substances in custody - From the staff perspective, "detention officers faced a number of issues identifying whether a person had taken NPS, taken another drug and/or consumed alcohol. This impacted upon their ability to manage risk, safety and provide care to NPS users. Often these officers were reliant on the user declaring the substance they had taken, or the officer finding the substance when booking the detainee into custody" (Addison et al 2018 pp315-316).

One male detection officer said: "Sometimes you just don't know what they've taken. They can be fine one minute, then they're kicking off the next, then they're crying, and then they're trying to fight the world, and then they start self-harming, and then they go back crying, and then they're fine again. You just don't know what they're going to do next" (p316).

Another detection officer described the uncertainty of how to care for users: "It's a lot more stress, because we aren't medically trained. We've got a Level 3 First Aid... We've got one custody nurse and she's great and she'll go round [but we are a 50 cell complex with other health issues] you've got such a massive strain and stress that [NPS] then on top - it's like the cherry on the cake [...] because they are so unknown: with heroin and cocaine and stuff you know what it is, you know how to treat it, you know what to look out for, you know the symptoms and you know the dangers of it. With this, you don't know, so we try to edge on the side of caution and send them to hospital or the nurse" (p317).

Addison et al (2018) ended: "The intersections and associated harms of NPS with other substances are not clearly understood by users in this study nor staff responsible for keeping them safe" (p318). NPS were rarely used in isolation, so polydrug use was often the issue, and this was "adding pressure to already overstretched police staff" (Addison et al 2018 p317).

7.4. PSYCHONAUTS

"Psychonauts" is a term coined by Newcombe (1999 quoted in Ruane 2018) to describe "a scientific explorer of inner space", or, in everyday language, individuals who enjoy trying different drugs in a relatively controlled way (eg: starting with small doses of new substances), and documenting their experiences. "Psychonauts seek out and experiment with new substances, though not usually to exclusion; most also enjoy (and indeed many prefer) more established recreational drugs and alcohol" (Ruane 2018 p337).

Online communities [11] and peer sharing represent the psychonauts' "experience reports". "These collections of anecdata, though necessarily non-rigorous, can be very extensive – and often represent the great majority of available information, or the only information, about newer substances" (Ruane 2018 p337). A science-like vocabulary is used in "trip reports".

Psychonauts want their knowledge to benefit others, including in relation to harm reduction. Ruane (2018) explored this idea with participant observation in volunteer drug crisis care services at music festivals in the UK, USA, and Portugal in 2014 and 2015, with interviews with 23 fellow volunteers ("sitters"), and a Facebook survey. Thirty-two individuals, classed as "festival psychonauts", were the main data source for the following themes:

a) Perceptions of the "landscape of old and new drugs" - The influx of NPS was not seen as "inherently threatening", and the lumping of many new substances under this label was criticised. "For this and other reasons, blanket statements about the effects and risks of 'NPS' rang false to the psychonauts, and were associated with propaganda and misinformation. If they saw newer substances as dangerous, they related this to lack of information about using them safely" (Ruane 2018 p339).

[11] O'Brien et al (2015) updated the term to "cyberpsychonauts".

b) "Sitters" - A number of psychonauts who volunteered as sitters felt that they knew more than medics about very new substances. Ruane (2018) noted: "Sitter Gus told me about one medical team who had given the care space a briefing about ketamine which was wrong in almost every detail... Psychonaut sitters were in a stronger position, equipped with collective understandings from forums and newsletters, extensive knowledge of drug chemistry and research, and often personal experience" (p340). But even experienced sitters were not aware of all new substances as they proliferated.

The personal experience and knowledge was used to "power a distinctive form of emotional support in which the sitter empathised with the visitor, conveyed understanding of what was happening to them, provided reassurance and normalisation through sharing similar experiences of their own, and offered narratives to help make sense of it afterwards" (Ruane 2018 p340).

c) "Responsible dealers" - Some psychonauts took the role of acquiring drugs for friends. Ruane (2018) explained: "Most of the psychonaut dealers I spoke to said they strove to deal drugs 'responsibly', and described this explicitly as a form of harm reduction... By providing carefully measured doses of good-quality substances, telling customers what to expect and sometimes supervising first-time users of a substance, the dealers hoped to reduce their customers' risks of being dosed incorrectly, sold dangerous adulterants or left to cope with a difficult experience alone. Invoking legal terminology, one described this practice to me as a 'duty of care'" (p341).

d) "Invocations of science in a data vacuum" - A lack of real scientific data, mainly because of the "near-complete moratorium" on research on psychoactive substances for many years, meant that the "science-infused" language of psychonauts was taken as fact (though it was based on anecdotes).

The psychonauts "invocations of science could be viewed as ritualised forms of magical resistance... rather than practical strategies. Scientific language and science-infused practices form a discursive wrapper for their activities, reassuring them that they are enacting drug use cautiously and responsibly, helping to legitimise their activities to themselves and each other, and providing a sense of insulation from the unpredictable chaos of new drug experiences – but not

actually giving them much control of the situation, especially in the turbulent surroundings of a festival" (Ruane 2018 p342).

Ruane (2018) summed up: "Understanding of drug experiences gave psychonaut sitters and mentors advantages over other festival support workers, but tough policing practices fostered mistrust of sitters and increased the risks of 'responsible dealing'. Ultimately, psychonauts' 'scientific' approach may be more effective as a reassuring discursive strategy than a practical way of reducing harm" (p337). A way to cope "in the face of largely uncharted chaos" (Ruane 2018 p343).

7.5. MAINSTREAM MEDIA

"The modern history of drugs is often described as one of cyclical bouts of public anxiety. Intoxication is as recurrent an object of 'panic' episodes as child abuse, immigration or street crime" (Alexandrescu 2018 p356). NPS are the latest focus as Alexandrescu (2018) described in a study of media reporting from 2009 and 2017 in Romania and the UK. "In Romania, a drug news cycle focussing on NPS began with a notion of problematic use among 'good youths' harming themselves with synthetic cannabinoids and moved on, rather shyly, towards underclass injecting users transitioning from opiates to synthetic cathinones and other amphetamine-type stimulants (ATS). The former were depicted as valuable in themselves, the latter as a threatening, contagious presence. Similar patterns were also observable in the British media, but with classes of 'legal highs' changing roles. Mephedrone and other ATS were first seen as a threat to experimenting, young users, only for the synthetic cannabinoids grouped under the 'Spice' umbrella-term to later intersect with, and appear to alter the condition of, lower class groups such as rough sleepers or prison inmates" (Alexandrescu 2018 pp356-357).

For Romania, 575 digital news items from the websites of four national daily newspapers between 2009 and 2013 were found using the search term "ethnobotanicals". From the UK, two data sets were constructed. The first of 110 news items from four British tabloids 2009-2011 around mephedrone ("meow meow"). The second set of 99 items published by the "Manchester Evening News" in 2016-2017 on "Spice", and particularly its use by rough sleepers in the city.

Overall, three themes were produced from the analysis - "time" (the threat of NPS to young users and their future), "space" (NPS and anti-social behaviour), and "institutional assemblages" (NPS markets, regulation and policing).

An example of the "time" theme from Romania describes the medics in hospitals as fighting a "guerilla war in the hospitals": "Tens of children ended up in the hospital intoxicated with ethnobotanical plants. At the 'Grigore Alexandrescu' [paediatric] Hospital in the Capital alone, in the past two months 16 teenagers aged between 12 and 17 were checked in experiencing symptoms such as dizziness, drowsiness, cephalalgia [head pains], vertigo, visual hallucinations, nausea and vomiting. Medical tests revealed that they had been intoxicated after using cigarettes that contained ethnobotanical substances" ("Romania Libera 2010; p359). While this extract from the "Manchester Evening News" in 2017 is an example of the "space" theme: "One friend who works nearby tells me of finding human faeces in a phone box on her lunch hour. Even a public official mentions in passing that she has seen someone defecating in the middle of the day in the gardens, as children play on the slides. [...] As I walk to meet him [the newspaper's photographer], between the now-closed food market stalls I see a small old man swaying about like a zombie accompanied by a woman wrapped in a duvet. Suddenly everywhere I look, there are pale, wasted people. It's dystopian, like a horror movie" (p362).

Alexandrescu (2018) commented generally: "Research has suggested that media coverage of issues related to alcohol and other drug (AOD) use can set the public agenda and funnel interest towards traditional and emerging substances often in selective, biased ways, influencing individual and collective attitudes to risk, further on shaping political debates and policy-making decisions... Oversimplifying media narratives of danger conveying complexity-flattening definitions of impending harm, fatality, decadence and addiction can stimulate interest and increase prevalence of substance use – more so when coupled with unbalanced and inaccurate information disseminated by media organisations subject to no quality control mechanisms... This appears to have also been the case with the reporting of NPS in the publications under study in anticipating strings of bans and new cycles of legislative controls without advancing deeper structural explorations of the issue" (p362).

Media representations can thus make it difficult for

service providers to deliver "sensible drug information" to users and for users to heed it. Blackman et al (2018) explored this issue in interviews with thirteen professionals who work with young people (in the "Young Person's Drug and Alcohol Service"; YPDAS) in South-East England in 2016-2017.

"Sensible drug information" is an approach to drugs that emerged in the USA in the late 20th century with the group "Students for Sensible Drug Policy". The aim is to move policy away from "war on drugs" and abstinence to harm reduction strategies (eg: drug safety testing at nightclubs). Critics of this approach see it as the normalisation of drug use, as "Barry" described: "You can't get away from misrepresentation that the universal message of harm reduction can be misunderstood as normalisation; some agencies and media will assert that it is normalisation, which is the problem. What can you do about it?" (p322).

The interviewees described the challenge of dealing with NPS in relation to traditional illicit drug - for example, "Amanda" said: "NPS certainly brought change. Staff wanted to keep up, quite fearful that we might be left behind, keeping up with the cultural changes and then discussions about changes in legislation" (p322). While "Justin" was more specific: "At first we saw Mephedrone being used when MDMA was less effective around 2009, then it become popular as M-cat and meow meow. The media coverage was extensive. Different services were placed in a situation of a need to know. Our response first could be seen as a 'loss of face', but turned into a positive force to collect a knowledge base of research" (p322). This is what "Steve" said on the subject: "It became clear that legislation and prohibition would not necessarily impact on choices made by potential users, especially vulnerable, disenfranchised groups, We realised the pragmatic common sense, harm reduction messages should be shared with families, other professionals and the media. We were learning about the chemical make up of substances, the effects on the brain. We became more scientific; there was no 'blagging' it" (p323).

It did not help if users doubted the service providers: eg: "It can be hard to do sensible drug information with cannabis; because they will argue that 'you're lying'. Weed is so accepted through friends. For some it's understood as one of their 5 a day! They've seen Professor Green's documentaries and the BBC's Drug Map of Britain" (p323).

Three main themes were proposed by the researchers -

"barrier" (obstacles to a harm reduction approach, including funding, and opposition), "transition" (co-operation which aided change), and "integral" (where an open discussion on the subject was possible).

7.6. APPENDIX 7A - "NPS"

Potter and Chatwin (2018) made a number of criticisms of the category "NPS", including:

i) The lumping together of many different substances obscures the differences between them.

Newcombe (2015 quoted in Potter and Chatwin 2018) noted attempts at sub-categories based on the source of the substance, the legality, the action in the brain, and the chemical groupings. The UNODC (2013) identified nine broad categories based on action in the brain and the chemical groupings - synthetic cannabinoid receptor agonists, aminoindanes, synthetic cathinones, tryptamines, ketamine and phencyclidine type substances, piperazines, phenethylamines, plant-based substances, and other substances (Potter and Chatwin 2018).

An alternative approach is to categorise NPS under general categories of substances, as in Adley's (2015 quoted in Potter and Chatwin 2018) groupings - stimulants, empathogens, psychedelics, dissociatives, cannabinoids, depressives, and opioids (Potter and Chatwin 2018).

ii) The separation of NPS from "traditional" substances.

This suggests that NPS are entirely different to "traditional" substances. Potter and Chatwin (2018) highlighted this critique with a focus on the term, "novel (or new) psychoactive substances":

a) "Novel" (or new) - Potter and Chatwin (2018) asked: "how long does something remain new for and when, if ever, do drugs stop being novel and become decategorised?... Does 'new' refer to newly discovered (or re-discovered), newly marketed, newly formulated or newly used in more widespread (sub)cultural contexts...? This is more than a semantic criticism: the label 'new' implies that we have limited knowledge of a substance (eg: of patterns of use or associated harms) that may suggest a different policy – or academic – response compared to where we have an established evidential base to inform us" (p331).

b) "Psychoactive" - "Stevens et al (2015) remind us that not all such substances are harmful (eg: lavender oil and morning glory seeds), that many have legitimate uses (eg: nitrous oxide) and that the psychoactive effects of substances about which very little is known can be hard to determine" (Potter and Chatwin 2018 p331).

c) "Substances" - "Why, for example, are ketamine (first synthesised in 1962) and nitrous oxide (1772) sometimes referred to as NPS, whereas mephedrone (1929) is always included, but MDMA (1912) almost never is? Even more striking, however, is the fact that over the same period as the emergence of NPS as a category, another huge grouping of new substances has also emerged: HED. These can be divided into six categories (Evans-Brown et al 2012): muscle drugs (eg: anabolic-androgenic steroids), weight loss drugs (eg: Xenical); image-enhancing drugs (eg: melatonin), sexual enhancers (eg: Viagra), cognitive enhancers (eg: Ritalin) and mood and behaviour enhancers (eg: Diazepam). Despite many of these categories containing the potential for psychoactive effect, and despite clear overlap in terms of their marketing and distribution, these substances receive a fraction of the attention of those ascribed the label NPS and are rarely discussed in the same fora" (Potter and Chatwin 2018 p331).

The category of NPS can also suggest that the substances are different in their use, and in the policy response required.

In conclusion, Potter and Chatwin (2018) commented that "a failure to see the rise in NPS as just one of a number of emerging trends in contemporary drug scenes, alongside the development of online markets or the rise in domestic drug production operations, for example, impairs our ability to understand the wider societal, cultural and theoretical underpinnings of drug use. NPS are not particularly special: treating them as such can have dangerous and far-reaching consequences" (p329).

7.7. APPENDIX 7B - LIFESTYLE DRUGS

HED (or "lifestyle drugs" or "performance and image enhancing drugs") are those "consumed in order to improve one's lifestyle, health or beauty, which places their use on the borderline between a health need and lifestyle wish... Medicines like Viagra to treat erectile dysfunction are included, as is Orlistat to lose weight

or cognitive enhancers such as Ritalin to boost concentration. While most lifestyle drugs are medicines available through official sources for particular purposes and requiring a prescription, they are also taken for non-authorised reasons to improve someone's life, physical function or appearance, as opposed to a medicine which is taken specifically to cure or manage an illness" (Koenraadt and van de Ven 2018 pp345-346).

Koenraadt and van de Ven (2018) investigated the purchasing online of illicit lifestyle drugs in the Netherlands in the context of buying medicines generally through the Internet. In the latter case, over 50 000 adults were surveyed in August 2015, of which 10% had purchased any type of medication online.

A sub-sample of 447 respondents, who had purchased illicit medicines via "surface websites" (ie: not the "darkweb"), were interviewed in more detail. Men tended to buy "sexual enhancers", "muscle-enhancing drugs", and anti-depressants and ADHD medication (without a prescription), while women bought weight-loss drugs.

Within this sub-sample, 153 individuals had purchased weight-loss drugs, and/or sexual enhancers. "A key attribute for respondents to purchase these lifestyle drugs online – besides financial motivations – is ease or convenience" (p352), Koenraadt and van de Ven (2018) explained, and they continued: "However, our study also illustrates that it is important to identify specific motives for online purchasers of different types of drugs. For example, an important motive for purchasing sexual enhancers online is that buyers do not want to discuss their use with their doctor... while for purchasing weight-loss drugs, the fact that some of these illicit lifestyle drugs are not available in the Netherlands plays a role..." (Koenraadt and van de Ven 2018 pp352-353).

An interesting finding was that the main source of drugs was not online pharmacies, as assumed, but second-hand vending sites, and specialist websites for lifestyle drugs.

A key concern with purchasing drugs online is their quality, which is linked to the risk of being scammed. The researchers noted that "most people in this study who purchase lifestyle drugs online report that they trust the website they employ. Trust in this context refers to the confidence customers have in these websites and does not necessarily reflect the quality of the purchased illicit drugs. In online markets, this 'quality check' is usually based on having a reliable friend who has ordered via the same website, 'trial and error' practices, a

review by others, and discussing these online sources on forums and social media platforms... However, most of these self-implemented harm-reduction strategies currently used by users are not evidence based and may not be effective or even cause greater harm such as testing the product oneself (the 'trial and error' approach)" (Koenraadt and van de Ven 2018 p353).

Koenraadt and van de Ven (2018) went on that "our data show that the majority of online purchasers mention that they are very satisfied with the quality of their illicitly purchased lifestyle drugs and, if they seek more, would return to the same online supplier. Chaudry and Zimmerman (2009) also note that there is a common belief that fakes can offer the same quality of the trademarked product and highlight a lack of consumer concern for intellectual property rights (IPR). 'Consumer complicity' (Hall & Antonopoulos 2016) seems to be an important driver for the illicit online market for lifestyle drugs" (p353).

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8. MISCELLANEOUS

8.1. EARLY INITIATION

Adolescence is a common time for initiation of illicit drug use. Risk factors for initiation include childhood adversity, peers, and high impulsivity, while protective factors include supportive social networks, and their attitudes against drug use (Nashed et al 2024).

Nashed et al (2024) used data from the "National Surveys on Drug Use and Health" (NSDUH) in the USA 2015 to 2019 to identify factors involved in adolescent drug use initiation. From the five years of the survey data, 28% of the over 212 000 respondents (12 years old and above) had drug use before eighteen years old.

Early initiation was associated with being male, White, and living in a large metropolitan area [12]. Based on generations, the age of initiation "appears to be occurring at younger ages" (Nashed et al 2024 p5).

The NSDUH is a nationally representative household survey, but it does not include homeless, or institutionalised individuals, or active-duty military personnel. There is the possibility that the "results may be biased given that older generations who may have initiated earlier could have died from other causes earlier on in life" (Nashed et al 2024 p5). Also "not every type of drug use was assessed, although this national survey captures the most commonly used substances" (Nashed et al 2024 p5).

Reference

Nashed, D et al (2024) Characterising early initiation of illicit drug use by generation: A retrospective study Emerging Trends in Drugs, Addictions, and Health 4, 100144

[12] Early initiators were also more likely to report poor general health, and mental illness in the past year.

8.2. OBESITY DRUGS

The drug brand name "Wegovy" (drug type: semaglutide) has been hailed as a "wonder drug" for weight loss, such that supplies in some pharmacies ran out in the USA in 2021 soon after its launch. There were also shortages of "Ozempic" (brand name), a version of the same drug used with type 2 diabetes, which was applied "off-label" for weight loss (Wilson 2023a).

Semaglutide mimics the hormone GLP-1, which is normally released after eating. "Saxenda" (brand name) (drug type: liraglutide) is an alternative, but it is less potent for weight loss (Wilson 2023a). There is also "Zepbound" (drug type: tirzepatide) which mimics GLP-1 and another gut hormone GIP (Wilson 2023b).

Other drug candidates focus on another gut hormone PYY, and glucagon and amylin produced by the pancreas. In the pipeline are an injection combining semaglutide and analogue of amylin, a drug mimicking GLP-1 and glucagon, and the "triple G" that mimics GLP-1, GIP and glucagon (Wilson 2023b).

The shortage of GLP-1-mimics has led to the use of illegal sources online. In October 2023 there were cases, reported by the "Medicines and Healthcare Products Regulatory Agency" (MHRA) in the UK, of individuals who ended up in a coma after using counterfeit versions of "Ozempic" (Wilson 2023a).

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Wilson, C (2023a) Obesity revolution New Scientist 16th/23rd December, p21

Wilson, C (2023b) A new era of obesity treatments New Scientist 30th December, p8

8.3. HYPE

Jonathan Iliff, who is involved in studies on psychedelics to alleviate depression, warned against self-medication: "One such chap on my ward had taken to try and treat himself and, in the process, had made things worse" (quoted in Wilson 2023).

Reference

Wilson, C (2023) Psychedelics hype may lead people to self-

medicate New Scientist 14th October, p13

8.4. OTOTOXICITY

Sensori-neural hearing loss (SNHL) is the most common cause of hearing loss, and its causes include genetically inherited, or through ageing, noise exposure, or ototoxicity (ie: the side effect of drugs and medications). There may be between 150 to 600 drugs (licit and illicit) with ototoxic potential (Reynard and Thai-Van 2024).

Reynard and Thai-Van (2024) undertook a literature review of the topic, finding 77 relevant articles published between 2013 and 2023. Reported ototixicity cases were generally rare, but they have been found with immunosuppressants, anti-malarials, non-steroidal anti-inflammatory drugs and analgesics, and anti-biotics, for example. While a French surveillance study of mRNA covid-19 vaccines (Thai-Van et al 2023) found less than two cases per one million doses for sudden SNHL. Sudden SNHL was defined as a loss of 30 dB or more within 72 hours, and the follow-up period was 21 days after vaccination. The study covered a one-year period (Reynard and Thai-Van 2024).

Reynard and Thai-Van (2024) found one review of the ototoxic effect of illicit drugs (Hughes et al 2022), covering amphetamines, cocaine, and heroin.

The mechanisms of SNHL from drugs is varied, but often relates to prior vulnerability (eg: candidate genes) or via other side effects (eg: amphetamine-induced SNHL from temporal lobe stroke). Multiple drugs together (ie: polypharmacy) is a risk factor (Reynard and Thai-Van 2024).

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8.5. KETAMINE

Ketamine has grown in interest in recent years as a rapid-acting and effective anti-depressant. It is primarily an antagonist of the glutamate receptor N-methyl-D-aspartate receptor (NMDAR) (ie: it blocks NMDARs) (Jiang et al 2024).

An early study with humans, Zarate et al (2006), showed the benefits of a single dose of ketamine for treatment-resistant depression within 1-2 hours, and lasting for some individuals 1-2 weeks. "These rapid and sustained anti-depressant effects of ketamine were widely replicated by a subsequent series of reports" (Jiang et al 2024 p2).

There are two main points of debate around ketamine use as an anti-depressant. First, how does it have its anti-depressant effect? Jiang et al (2024) presented two camps in answer to this question – "NMDAR-dependent" (ie: the impact is via blocking NMDARs) and "NMDAR-independent" (ie: ketamine works on other molecules, like dopamine or serotonin). It could be both, however. Jiang et al (2024), though favouring the NMDAR-dependent camp, admitted: "Currently, we cannot exclude the possibility that some of these alternative molecular targets may also be engaged, synergistically with NMDARs, to contribute to ketamine's anti-depressant effects" (p10).

The second debate is around the efficacy of ketamine in clinical trials. As there are trials showing positive results, there are those that fail to find anti-depressant effects of ketamine. The difference in findings, as in any clinical trials, may be related to methodological issues and differences between studies, including the dosage, the sample of participants, and the outcome measures.

NMDAR inhibitors, other than ketamine, have been tried as anti-depressants. Jiang et al (2024) summarised the evidence thus: "(i) many NMDAR inhibitors do show rapid and sustained anti-depressant efficacy in animal studies; (ii) in clinical studies, the non-unanimous clinical efficacy of NMDAR inhibitors may be accounted for by their different inhibitory mechanisms, pharmacological properties, therapeutic windows, dosing regimens or routes of administration; and (iii) although not as efficacious or as consistent as ketamine, some of these inhibitors (eg: ... memantine; lanicemine...) also caused anti-depressant responses in some clinical tests" (p8).

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8.6. DRUG INDUCED LIVER INJURY

"Drug induced liver injury" (DILI) varies from jaundice to death, and results from drugs successfully tested on non-human animals that are toxic to humans (eg: "Troglitazone" (anti-diabetic and anti-inflammatory drug) linked to 63 liver-failure deaths) (Staff Writer 2024a).

Over 90% of drugs that pass preclinical tests in animals fail in human clinical trials, while half of those that pass are likely to be later withdrawn or re-labelled due to adverse reactions in humans not detected in animals (Staff Writer 2024a). Drug discovery and development can take a decade and cost $2 billion per drug (Staff Writer 2024b).

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