Polydrug Use: Prevalence, Predictors, Pharmacology and Psychopharmacology

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ABSTRACT. This is a brief review of polydrug use (the simultaneous or concurrent usage of more than one drug). Reviewed areas are listed below. As a result of its nature and structure, this review provides a superficial yet wide-ranging review of polydrug use as a behavioural and psychological phenomenon, covering an extensive body of research spanning decades.

- The prevalence of polydrug use: Identifying and discussing the populations that exhibit these particular behaviours, and discriminating between populations that use one drug from another.
- The predictors of polydrug use: Identifying and discussing some of the risk factors and at-risk populations for polydrug use, especially problematic use.
- The pharmacology of polydrug use: Examining research into the effects of combining multiple drugs on the body. Pharmacodynamics and pharmacokinetics are discussed but not specified.
- The psychopharmacology of polydrug use: Examining research into the effects of combining multiple drugs on behaviour, cognition and psychopathology, and the mechanisms behind these effects.

I. Introduction

Monodrug has been widely researched and its effects extensively documented. In comparison, polydrug use research is more limited. Some common drug combinations, such as alcohol with cannabis or alcohol with ecstasy, are backed by a wide range of literature. However, the vast number of possible drug combinations that can be used in addition to the wide range of possible timeframes for intake seriously limit polydrug use research. To extensively document and study each possible interaction with the multitude of variables that could affect the outcomes would be a titanic undertaking. It is, however, still an important field of research, as it is widely understood that with combinations of drugs come increased risks of adverse health effects. For example, the mixture of cocaine and alcohol causes the synthesis of cocaethylene *in vivo* (Hearn et al.,1991) which has strong euphoric effects and is thought to enable the consumption of far greater amounts of alcohol than normal for the individual under its effects, leading to a greater risk of alcohol poisoning and other adverse effects of the overconsumption of alcohol (Farré et al., 1997). This is just one example of the unique findings that are sometimes documented in polydrug research.

To that extent, this will serve as a brief review of polydrug use. Firstly some of the more common drugs are touched upon, before a review of research that examines the prevalence of polydrug use, on both macro (continental) and micro (small subsections of the population) levels. Predictors and risk factors of polydrug use are then reviewed, in order to investigate what may predispose individuals to initiate polydrug use. Concurrently, the pharmacology and psychopharmacology of polydrug use are examined. Crucially, the effects that polydrug use has on the body, the brain and behaviour of the user are also examined. Finally, thoughts about the

future of polydrug research and related issues are discussed, as well as potential gaps in research that are worthy of further investigation.

It is important to define some terms that will be used often throughout this review: the term 'polydrug use' refers to the intake of more than one substance within a certain timeframe. Many studies distinguish between simultaneous polydrug use (SPU) and concurrent polydrug use (CPU) as different behaviour, separate from each other (Ives & Ghelani, 2006): Simultaneous polydrug use covers events where two or more substances are taken in the same session of drug taking, for example smoking cannabis whilst already intoxicated on alcohol. Concurrent polydrug use refers to the taking of more than one drug throughout the lifetime drug-using history of an individual (Earleywine & Newcomb, 1997). Much of the relevant research on polydrug use focuses on SPU as opposed to CPU. One possiblecompelling reason for this trend could be that the unique effects of drugs are larger and more numerous in SPU than in CPU (Earleywine & Newcomb, 1997), presenting a greater need for immediate research on the subject.

II. Drugs of Note in Polydrug Use Research

Licit drugs of common use include alcohol and nicotine, with both drugs often appearing in polydrug research. Rates of use for these drugs are generally high, even in samples of schoolchildren (Choquet, Morin, Hassler, & Ledoux, 2004). Illicit substances most frequently include cannabis, ecstasy, amphetamine and cocaine, as documented by a longitudinal study into the drug-user habits of the UK (Ramsay, Baker, Goulden, Sharp & Sondhi, 2001). Another drug that has proved popular in polydrug research is LSD, which in some countries sees use by up to 5.4% of the population (EMCDDA, 2015b).

a. Alcohol

Alcohol is a central nervous system (CNS) depressant and is the most widely used psychoactive substance across many populations surveyed (Presley, 1993; Thomas, Farrell, & Barnes, 1996). It has been concluded that alcohol has been used intentionally since at least the Neolithic Period, based on findings of Stone Age jugs and ancient tablets depicting alcohol consumption (Patrick, 1952, pp. 12-13). Alcohol is a problematic drug for many: the prevalence of DSM-IV identified alcohol abuse and dependence in 2001–2002 were 4.65 and 3.81% in a large national survey (Grant et al., 2004). Alcohol intoxication results in deficits to behavioural inhibition (Field, Wiers, Christiansen, Fillmore, & Verster, 2010) and motor skills (Fogarty & Vogel-Sprott, 2015). Decreased inhibition is an important characteristic of alcohol use to study, as it has implications for the initiation of subsequent polydrug use. Marr (1999) observed that drug court clients often often transition into drug use following a period of sobriety from alcohol. Alcohol can also act as a ‘gateway drug’, with both licit and illicit drug use usage rates tending to increase after alcohol use begins (Kirby & Barry, 2012).

b. Nicotine

Nicotine is a stimulant drug that acts as a nicotinic acetylcholine receptor agonist (Malenka, Nestler, & Hyman, 2008, p.234) and is a powerful addictive substance with an estimated 1.3 billion smokers worldwide (Smith, 2015). The most popular delivery method for nicotine is smoking. Smoking is a trend that is on the decline in recent times (Syamlal et al., 2015), a trend that is thought to be due to numerous acts of legislation and public information schemes. For example, in Australia, legislation has recently been put into action that made cigarette packets plain in appearance. The aim of this regulation is to reduce sales, increase cessation of use and make health warnings more salient (Chapman, 2015). A large (n = 15,745) survey found that the

introduction of plain packaging had significant and consistent effects on cognitive, emotional and avoidant responses to the on-pack health warnings in line with the scheme's intentions (Dunlop, Dobbins, Young, Perez, & Currow, 2014). Despite many public interventions and information about nicotine's association with cardiovascular disease, respiratory system cancers and potential birth defects (Jerry, Collins, & Streem, 2015) there is still a large portion of the general public still using the drug (AIHW, 2011).

c. Cannabis

Cannabis is the most prolific of the illicit drugs used worldwide (Ramsay, Baker, Goulden, Sharp, & Sondhi, 2001; EMCDDA, 2015) and is often used recreationally for relaxation, to induce euphoria and to increase sexual libido (Osborne & Fogel, 2008). It is also used medicinally, with positive effects such as increasing appetite in the sufferers of HIV/AIDS, treating chronic pain in those with multiple sclerosis or acting as an anti-emetic for those undergoing chemotherapy (Consroe, Musty, Rein, Tillery, & Pertwee, 1997; Parrott, Morinan, & Moss, 2004, p255; Borgelt, Franson, Nussbaum, & Wang, 2013). Trends indicate that cannabis use is a growing phenomenon in most of the world, with large and consistent increases in the incidence of cannabis use amongst college students (Gledhill-Hoyt, Lee, Strote, & Wechsler, 2000) and increases in the overall number of cannabis use disorders in recent years (Compton, Stinson, Grant, Colliver, & Glantz, 2004). In the UK however, trends indicate that cannabis use is decreasing (EMCDDA, 2015). These trends, alongside with popular conceptions of cannabis as "the ultimate gateway drug" (Gledhill-Hoyt et al., 2000), make cannabis an important substance to study in the context of polydrug use.

d. MDMA/Ecstasy

MDMA (also known by its street name, ecstasy) is a stimulant drug that enjoyed a positive reputation in the 1980s as a party drug and was used by many college students in America. Before long, the risks of MDMA abuse began to be identified, including its association with premature death, impairments in responding to water intake and highly dangerous neurotoxicity, prompting debates about its safety and legality (Dowling, Bost, & McDonough, 1987; Baggott et al., 2015; García-Cabrerizo & García-Fuster, 2015). MDMA has neurochemical similarities to amphetamines and some hallucinogens; hence it causes a mixture of stimulant and hallucinogenic effects. It enhances serotonergic signalling in the brain by activating serotonin receptors, inhibiting serotonin reuptake and stimulating the release of intracellular serotonin from the presynaptic vesicles. (de Bruin et al., 2001). A large acute dose of MDMA can release 80% of the brain's intracellular serotonin stores into the synaptic cleft (de Bruin et al., 2001). MDMA also has neurotoxic effects, depleting the amount of serotonin available in the body over time and reducing the density of serotonin reuptake sites (McCann, Shaham, Ricaurte, & Ridenour, 1994; García-Cabrerizo & García-Fuster, 2015).

e. Amphetamine and Cocaine

Amphetamine and cocaine are two similar drugs that act as stimulants. Historically, amphetamine has been available as a general tonic and depression cure, with its problematic properties not fully recognised until around the 1950s. Amphetamine acts as a dopamine agonist and a noradrenaline agonist, increasing their release and inhibiting their reuptake. Its physiological effects include increased heart rate, increased perception of pleasure, reduced appetite and more rapid psychomotor responding (Ricaurte, Sabol, & Seiden, 2003). Cocaine was used in folk medicine in South America for thousands of years as it was the first effective

anaesthetic, though in modern times its only accepted medical use is as a topical anaesthetic in minor surgeries (Grinspoon & Bakalar, 1981; Redman, 2011; Docimo et al., 2014). It is the most commonly used recreational drug worldwide, after cannabis (Karila et al., 2014) which is problematic from a public health perspective, as its use frequently leads to addiction (Adams, Gfroerer, Rouse, & Kozel, 1986; Ghodse, 2009).

f. LSD

Lysergic acid diethylamide (LSD) is a hallucinogenic drug, the use of which is known to alter cognition, particularly the user's perception of time (Vollenweider & Geyer, 2001). Its other effects include synaesthesia and hallucinations, both of which can occur even at very small doses (Grossenbacher & Lovelace, 2001). LSD is not considered addictive (Lüscher & Ungless, 2006) but it can have adverse acute effects. Emotionally distressing flashbacks are often reported, some of which may be experienced days, weeks or sometimes months following LSD use despite the quick absorption rate of the drug and its very short half-life (Smart & Bateman, 1967; Halpern & Pope, 2003).

g. Other Drugs

Opiates such as heroin are often mentioned in the polydrug use literature. Opiates are highly addictive drugs that reduce negative affect and pain and increase pleasure (Dickenson, 1991). They are often used as analgesics in pharmaceutical environments (codeine, oxycodone, etc.). The terms opioid and opiate are used almost interchangeably, but while opioids refer to all substances that act directly on opioid receptors in the brain, opiates only include opioids that are derived from the opium poppy plant (Dickenson, 1991).

GHB (γ-Hydroxybutyric acid) is a naturally occurring neurotransmitter but can also be acquired and synthesized in drug form. It can be used as an anaesthetic, but also finds use as anintoxicant and a date rape drug, often in the context of clubbing (Nicholson & Balster, 2001).

Ketamine is an NDMA receptor antagonist that acts as a dissociative and hallucinogen. At very high doses, users experience what is known as a 'K-hole' which is characterised by extreme dissociation and hallucinations (Muetzelfeldt et al., 2008).

III. Prevalence of Polydrug Use

Research on the prevalence of polydrug use has expanded in recent years as the range of cheap and easily-attainable drugs (both licit and illicit) has rapidly grown. Polydrug research can be performed for both large populations (e.g. for an entire country) and small populations (e.g. amongst rave-attendees). This review will examine both types and discuss the validity and usefulness of both.

A large section of the population could be considered polydrug users in the concurrent sense when alcohol and tobacco are included, as 86.6% of people report drinking alcohol at some point in their lifetime (NIH, 2015) and 19% of the population are self-reported smokers (ASH, 2015). A survey carried out in 1999 found that 68% of a 11,331 strong sample had taken alcohol and tobacco in their life, with 5.7% stating they took them both regularly (Choquet, Morin, Hassler, & Ledoux, 2004). This trend of high numbers of polydrug users continues when looking at simultaneous use too, in fact it has been reported that 20% of a 70,000-strong sample of teenagers had used alcohol and tobacco simultaneously (EMCDDA, 2011). Alcohol is of particular interest within this line of research, given that 37% of males and 23% of females between the ages of 16-24 consume twice the recommended safe level of alcohol (ONS, 2000) which could prove a very dangerous trend especially when other drugs are used concurrently.

There have been reports on wider drug use in specific large populations. For example, a study on illicit drug use in the UK found that participants were far more likely to have partaken in polydrug use than monodrug use and that hazardous drinking was more prevalent in polydrug users, demonstrating an association between illicit polydrug use and problematic levels of alcohol consumption (Smith, Farrell, Bunting, Houston, & Shevlin, 2010). Similarly, a large scale American study found that 1.1% of a 43,093-strong sample had either polydrug dependency or abused multiple drugs (Agrawal, Lynskey, Madden, Bucholz, & Heath, 2007). Specifically, they found that a large number of those identified were dependent on sedatives, tranquilisers and opiates (Daniulaityte, Carlson, & Kenne, 2006). Grant and Harford (1990) found that a sizeable population of Americans used alcohol and cocaine both simultaneously and concurrently, and identified socioeconomic factors that played a large part in predicting the extent to which the participants used the substances.

Polydrug use is highly prevalent in Spain, sample where an estimated 28.6% of individuals report using at least one drug and 13.9% report polydrug use, with a large majority of polydrug users consuming cannabis with either alcohol and/or tobacco (Font-Mayolas et al., 2013). This study noted that more females were polydrug users than males, which contradicts much research on gender disparity in polydrug use (Epstein, Botvin, Griffin, & Diaz, 1999). This may imply that the 'gender gap' in polydrug has diminished in recent years. Additionally, research in Latin America (specifically Argentina, Bolivia, Chile, Ecuador, Uruguay and Peru) has found that the overall lifetime rate of polydrug rate is 21% (Perez, Dowell, Cumsille, Reyes, & Colon, 2013), though data is limited, as this was the first study of its kind (surveying Latin America). They found that individuals who use alcohol and tobacco are less likely to use three or more substances than those who use more illicit drugs, such as cannabis, cocaine and paste cocaine.

Finally, MDMA use was significantly associated with polydrug use with both legal and illegal substances, a common finding in European and North American research that can now be applied to further populations thanks to this study.

A large majority of studies on polydrug use and abuse focus on more specific groups of individuals than the population of an entire nation. In particular, popular nightlife settings have become one area of focus (Calafat & Koller, 2003). Many recreational situations are conducive to SPU, explaining why a large portion of polydrug research focuses on the recreational context specifically (Boys, Lenton & Norcross, 1997; Barrett, Gross, Garand & Pihl, 2005; Grov, Kelly & Parsons, 2009). A problem with these smaller, targeted studies is that while they can provide insight into the patterns of polydrug use for these specific populations, they do not provide much information about polydrug use in wider populations.

Another study that looked at a specific slice of a larger population was a study looking into the 12-month prevalence for polydrug use including alcohol and prescription drugs in American undergraduate students. 12.1% of students were found to be polydrug users who abused drugs (McCabe, Cranford, Morales, & Young, 2006), which worryingly represents an increase from previous studies. Studies such as those performed by McCabe et al. allow for the compilation datasets about specific populations, and can be used to identify risk factors and predictors for polydrug use specific to these populations. Data about specific demographic groups also serve to increase our understanding about the behavioural changes that these groups experience as a

result of polydrug use in comparison to other polydrug using populations.

A study on younger American students (12th graders) found that more than 33% of the sample took part in CPU, and as many as 33% had taken part in SPU. Additionally, a higher percentage of students were found to be involved in polydrug use than non-alcohol and non-cannabis monodrug use (Collins, Ellickson, & Bell, 1998). In Denmark, it was found that 41.8% of a large sample of children between the ages of 12 and 16 were polydrug users in the sense that they had taken multiple drugs (studied substances were alcohol, tobacco, cannabis, ecstasy, amphetamines, opiates and cocaine) within the last four weeks (Smit, Monshouwer, & Verdurmen, 2002). Most of the students only used alcohol and cannabis, though around 21,000 participants reported combining alcohol, cannabis or tobacco with at least one hard drug. Additional evidence (see Table 1) suggests that adolescents are indeed prolific polydrug users (Wu, Schlenger, & Galvin, 2006). In fact, 99.3% of participants in this study that reported using any "club drug" also reported using alcohol, with 97% also using cannabis at some point in their life.

A report on polydrug use across three clubs in Belgium found that participants who reported using an illicit drug said they 'regularly combined alcohol and an illicit drug, and one in four users regularly combined different illicit drugs' (EMCDDA, 2011). Polydrug use has similarly been reported in clubbing populations worldwide. Approximately 20% of youths aged 16-23 (in an American sample) reported having concurrently used more than one drug out of a choice of MDMA, LSD, ketamine, GHB and Flunitrazepam, and female clubbers were overrepresented among polydrug users (Wu, Schlenger, & Galvin, 2006). In the UK, club- goers were far more likely to report illicit drug use and polydrug use than bar-goers (Measham & Moore, 2009), which implies that there may be "culturally, spatially and pharmacologically distinct local leisure scenes operating within the contemporary night time economy" (Measham & Moore, 2009). Significant portions of those using so-called 'dance drugs' (MDMA, amphetamine, LSD) have been found to mix these drugs with other substances in both Western Australia (Boys, Lenton, & Norcross, 1997) and Canada (Barrett, Gross, Garand, & Pihl, 2005), showing that increased rates of polydrug use at raves and clubs is a phenomenon that can probably be generalized across much of the developed world.

Ives and Ghalani (2006) proposed that the 'normalization' of drug culture was one of the main reasons that people indulged in SPU and quoted the behaviours of those in the rave scene of the 90s as an example of this. A study into the drug habits of an annual rock festival found that 35.5% of the attendees were using three or more drugs simultaneously at the event, supporting that raves and concerts are conducive to polydrug use (EMCDDA, 2002).

MDMA features prominently in polydrug research, being the most commonly used drug in cases of polydrug use at clubs and other dance-related situations (86.6% of MDMA users reported combining MDMA with another drug; Grov, Kelly & Parsons, 2009). This studyfound that the most common combinations of drugs used at clubs were MDMA and Ketamine, MDMA and cocaine, and MDMA and GHB. Other frequently cited drug combinations included cocaine and cannabis, MDMA and cannabis, LSD and cannabis, and cocaine and alcohol.

Opiates also commonly feature in polydrug use. Pharmaceutical opiate misuse is a serious issue for many individuals in the western world, as opiates are highly addictive and readily accessible.

A study on the illicit use of opioid drugs in Ohio (Daniulaityte, Falck, Wang, & Carlson, 2009) found that 81% of participants reported lifetime misuse, and 31% reported current misuse of opioid drugs. The study also suggested that opioid misuse was most often just a part of a wider polydrug use behaviour pattern, as common predictors for opioid misuse included the illicit use of pharmaceutical tranquilisers and pharmaceutical stimulants. College students are also noted to be a population at risk of pharmaceutical opioid abuse, with prescription pain medicine often being misused for both recreational purposes and self-medication (McCabe, Teter, & Boyd, 2005).

Alcohol use seems to increase directly in parallel with the use o other psychoactive substances, particularly MDMA, cannabis and amphetamine (Parrott, Morinan, & Moss, 2004, p.120). Due to this relationship, the most intensive patterns of alcohol abuse are reported by younger illicit polydrug users (Parrott, Milani, Parmar, & Turner, 2001). However, O'Malley and Johnston (2015) found that heavy alcohol use did not precipitate the use of other psychoactive substances, suggesting that non-alcoholic psychoactive substances may pre-empt heavier rates of alcohol use, and not vice versa.

A longitudinal study (Brecht, Huang, Evans, & Hser, 2008) examining ten-year trajectories for heroin, cocaine, alcohol, cannabis and methamphetamine polydrug users found that in the cases of primary heroin and meth use, drug usage rates have declined over time, but rates of alcohol and cannabis use have remained fairly constant. Additionally, usage of non-primate heroin, cocaine and meth was found to be generally low. This study was specifically carried out to investigate the validity of research that has focused on drug-use trajectories for one drug specifically, without assessing for polydrug use. They found that group descriptions of primary heroin, cocaine, or meth use trajectories over time may present valid information about drug use patterns in general. A study on drug use patterns in participants who used either primarily heroin or amphetamine found that as age increases, rates of drug use decrease (Hall & Darke, 1995). Research identifying trends in drug use over time is generally important because it may aid in the development of health-focused interventions against substance abuse.

A 2015 report on trends in drug use did indeed find that between 10% and 48% of all drug-related emergency presentations involved cannabis and in addition to that, 90% of those presentations included another drug alongside cannabis, indicating that polydrug use may be a significant health risk (EMCDDA, 2015a) and that interventions are required to reduce the negative impact that it has on individual health. It is not a surprise that cannabis is present in most polydrug related health cases, as cannabis is the most common illicit drug in the world (Hall & Degenhardt, 2007). Despite this fact, it has been noted that much of the literature pertaining to cannabis use ignores findings that cannabis users are very often prolific polydrug users (Parrott, Morinan, & Moss, 2004, p.92). Smith, Farrell, Bunting, Houston and Shevlin (2010) carried out research into the most frequent patterns of polydrug use when cannabis was involved (see Figure 1) and found that cannabis is most often combined with MDMA, but also commonly with amphetamines and cocaine. It is important to note, however, that this study found that cannabis was most often used singularly, with only 6.3% of cannabis users reporting polydrug use.

IV. Predictors of Polydrug Use

Much research has focused on factors that may predict polydrug use onset. It is important to realize that these factors differ significantly between drugs due to individual differences between

'prototypical' users of different classes of drugs. For example, research on undergraduate students at a university in the Midwestern United States found that SPU was most common within white students, male students, and students who had reported early initiation to alcohol use (McCabe, Cranford, Morales, & Young, 2006). Other studies have suggested the existence of many other polydrug use predictors, and it is to the findings of these studies that we shall turn next.

Gender seems to predict polydrug use, despite the factors leading to this association not being well-understood. Collins, Ellickson, and Bell (1998) found in their study on young American college students that females were less likely to take part in polydrug use than males even after controlling for other predictors, but also concluded that polydrug use involving hard drugs exhibited no gender differences.

Instead, Collins et al. cited environmental factors to explain the lack of gender differences for hard drug use, proposing that females often enjoy social protections (e.g. stronger social circles, lower rates of deviance) that apply to some forms of drug use but not others. Smit, Monshouwer and Verdurmen (2002) described males as having a 'specific' risk for polydrug use for both "soft" (alcohol and cannabis) and hard drugs. Other research has supported that gender differences in polydrug use are on the decline, for example in the case of simultaneous alcohol and cigarette use (Hoffman, Welte, & Barnes, 2001). It can be concluded the role of gender in determining the probability of polydrug use may depending on which particular pattern of polydrug use is being examined.

A study on Australian adolescents below the age of 18 found that the greatest predictors of both limited (using only alcohol, nicotine and cannabis) and extended polydrug usage were perceived peer drug use and psychological distress, with psychological distress being more significantly related to extended drug use (White et al., 2013). It seems reasonable that peer behaviour would predict drug use, as adolescents are highly impressionable and may use drugs more frequently under social pressures (Kelly et al., 2010). The role that psychological distress may play in predicting polydrug use is more intriguing. Indeed, Smith, Farrell, Bunting, Houston and Shevlin (2010) have reported that poor mental health can predict polydrug usage. Going forward, it will thus be important for drug use interventions to focus on psychological problems that adolescents commonly face, including anxiety and depression.

Psychopathology has been found to predict polydrug use in general, and not just in adolescents. For example, it has been noted that individuals with previously-existing mentalhealth conditions are less likely to use a combination of MDMA and alcohol, but are actually more likely to use a combination of MDMA and opiates (Schifano, Furia, Forza, Minicuci, & Bricolo, 1998) which could suggest that combining MDMA and opiates may help the individuals cope with mental illness in ways not yet understood.

Another study on young students from grades 7 to 10 (Brière, Fallu, Descheneaux, & Janosz, 2011) found that alcohol and cannabis use at a young age predicts polydrug use with the two substances at later grades and beyond. Additionally, the study found that simultaneous alcohol and cannabis use is predicted by multiple psychosocial risk factors, including depressive symptoms, low school grades, delinquency, parental conflict and drug use by peers. SPU may thus be influenced by both internal and external factors that shape an individual's lived experience.

It has been hypothesized that college- related stress could be a contributing factor to polydrug usage, with

stress leading students to use drugs to emotionally cope with academic and social demands (Quintero, 2009). However, other evidence suggests that it is this drug use itself that contributes to perceived stress in college-aged polydrug users (Pierceall & Keim, 2007). Self- reported stress in college students also appears related to risky decision-making and reduced social competence, potentially maintaining cannabis, alcohol and general polydrug use (Fishbein et al., 2006). If it is true that stress increases polydrug usage, there are implications for monodrug users who use MDMA, as it increases stress exponentially (Parrott, Sisk, & Turner, 2000; Parrott, 2009). Additionally, polydrug users are more likely than monodrug users to report using drugs to deal with unpleasant emotions such as stress (Kelly & Parsons, 2008), further supporting the the hypothesis that stress may pre-empt polydrug use.

Factors related to family life can have an effect on the likelihood that an individual will become dependent on multiple drugs. A study carried out by Humes and Humphrey (1994) analysed families which either had a polydrug-dependent daughter or a normal daughter. They found no differences in the behaviours from the daughters, but did find differences in the parents. The parents of the polydrug-dependent daughters exhibited greater affirmation and condemnation of their daughter's autonomy, and in those families both the parents and the daughters themselves blamed the drug-dependent daughter for the family's problems. These findings confirm general socio-developmental (Hussong, Jones, Stein, Baucom, & Boeding, 2011) and psychoanalytic (Stanton et al., 1978) theories of drug abuse as a form of derailed individuation from the family unit.

Alcohol dependence has been identified as being a factor in polydrug use. Research has found that when compared to a population of drinkers without an alcohol-related psychiatricdiagnosis, alcohol dependents and alcohol abusers have higher rates of polydrug use (69% and 72% respectively, compared to 45%), a trend which was associated with high levels of behavioural undercontrol and negative emotionality (Martin, Kaczynski, Maisto, & Tarter, 1996). This finding is further supported by research showing that alcohol abuse/dependence is associated with depression (Fergusson, Boden, & Horwood, 2009) though Fergusson et al. hypothesized that alcohol dependence may also directly cause depression symptoms.

A common theme throughout drug prevalence research is that of the "gateway drug," referring to substances whose use may easily lead into more serious drug abuse problems. In the early 1980s, the term 'gateway drugs' usually included alcohol and cigarettes, as these drugs were often identified as being the precursors to illicit drug use. Since then, cannabis has come to be included in this category (Kandel, 2002). Indeed, at least one study study has concluded that alcohol, cannabis and tobacco use may directly contribute to the emergence of a new substance use pattern (Olthuis, Darredeau, & Barrett, 2012; see Figure 2). Furthermore, Olthuis et al. found that illicit drug initiations vary by which other pre-existing drug use patterns they are most tightly associated with. For example, heroin initiation was accompanied by cigarette use in 87.5% of occasions, compared to alcohol and cannabis, both only present at 62.5% of initiation events. It is, of course, also important to isolate predictors for initiation of each of these substances. The use of cannabis, commonly considered in modern times to be a "gateway" drug, is predicted primarily by drug availability, peer group pressure and low self-esteem (Sydow, Lieb, Pfister, Höfler, & Wittchen, 2002). Identifying early predictors of 'gateway drug' use could be very useful in developing preventative measures against

the initiation of dangerous polydrug use behaviours.

Various other predictors exist for polydrug abuse, and some will be described very briefly here. For example, users of anabolic- steroids were found to be more likely to use multiple other drugs, with the frequency of steroid use correlating positively with both cocaine and heroin use (Heath, Escobedo, & DuRant, 1995). Legislation can be a factor in determining whether an individual has easy enough access to a drug, as accessibility is a large predictor in polydrug use (Hser, Maglione, Polinsky, & Anglin, 1998). Legislation illegalizing mephedrone played a significant role in lowering general levels of its usage due to a decrement in the quality of mephedrone available and an increase in its price (Polwin, 2013). A large-scale report on polydrug use found that some of the main factors that can predict polydrug use include truancy rates and family risk (EMCDDA, 2011). The misuse of methylphenidate was also related to misuse of both prescription and non-prescription drugs concurrently (Barrett, Darredeau, Bordy, & Pihl, 2005).

V. **The Pharmacology of Polydrug Use**

It is widely known that drugs can have very significant effects on bodily functioning, both acute and chronic. Polydrug combinations may potentiate these effects, and much data exists describing polydrug use pharmacology and physiology. This review will look at some of the pharmacological effects induced by certain combinations of illicit drugs, prescription drugs and even some foods.

According to the EMCDDA's 2015 report on the trends and developments in drug use in 2015, veteran polydrug opioid users have experienced an accelerated aging process due to their years of drug use (EMCDDA, 2015a). It has been documented that polydrug dependence can have effects on aging, including an increased risk of hepatic (liver) and renal (kidney) dysfunction, both of which have serious implications for the long-term health of polydrug users (Reece, 2007). Additionally, opiate dependence has been linked to early emergence of other markers of aging, such as erosive periodontitis and hair greying (Reece, 2010).

The neurochemical effects of opiates on the human body are more pronounced in polydrug users. Polydrug users have been found to have abnormal brain metabolism and as a result, an irregular cerebral phospholipid balance (Kaufman et al., 1999). Similar results have been found for cocaine users (MacKay, Meyerhoff, Dillon, Weiner, & Fein, 1993). Since phospholipid integrity is important for the maintenance of associated cortical cholinergic structures, cognitive and motor skills may both be impaired in cases of irregular phospholipid balance (Casacchia, Meco, Corona, Castellana, & Cusimano, 1981). However, these physiological irregularities were not found in long-term patients in a methadone maintenance treatment (MMT) program, implying that MMT may be associated with neurochemistry recovery, and that drug use must be ongoing for brain neurochemistry to be altered. Drug interventions for cocaine- dependent individuals could thus potentially reverse the neurochemical effects of chronic cocaine use similarly to opiate interventions.

The co-use of cocaine and heroin (colloquially known as ‘speedball’) does not produce a novel set of subjective effects, and yet it is still common in practice (Leri, Bruneau, & Stewart, 2003). Both drugs have an effect on the same biological systems, but typically manifest some opposing effects within these systems. For example, heroin is known to reduce norepinephrine release, while cocaine blocks norepinephrine reuptake and promotes its activity (Pitts & Marwah, 1987; Maldonado, 1997). Evidence has also been published documenting a synergistic

elevation in extracellular dopamine concentration at the nucleus accumbens, a brain area that plays a central role in drug addiction and positive reinforcement, following thesimultaneous administration of both heroin and cocaine (Smith, Hemby, Co, & Dworkin, 1999).

The combination of cocaine and alcohol is common, and has a unique effect *in vitro* (Hearn et al., 1991). In the presence of alcohol, cocaine is metabolised into cocaethylene in the liver. Cocaethylene is similar to cocaine in its ability to blockade dopamine reuptake, but is a more potent mediator of lethality than cocaine alone (Hearn, Rose, Wagner, Ciarleglio, & Mash, 1991).

Alcohol produces behavioural disinhibition, and thus it stands to reason that a cocaine and alcohol simultaneous polydrug user would be more likely to consume an excessive quantity of both drugs, introducing more cocaethylene into the body and potentially putting the user at risk of death.

Chemotherapy patients often suffer from vomiting as a side effect of the intense regime of drugs they are required to take. It has been found that cannabis can reduce the emetic effects of chemotherapy drugs, leading many patients to use cannabis to reduce nausea and vomiting (Parrott, Morinan, & Moss, 2004, p.225). These findings have persisted for decades (Sallan, Zinberg, & Frei, 1975), leading influenced many researchers to support the use of medicinal cannabis, especially for chemotherapy patients (Doblin & Kleiman, 1991). Indeed, the use of cannabis as an anti-emetic provides a strong case for its approval in a medical setting.

MDMA and methamphetamine are two drugs that are sometimes used in combination for their synergistic stimulant effects, but combining the drugs may have more serious effects than use of either drug alone in the long-term, both in terms of behavior (See Table 2) and neurochemical alterations (Clemens, Cornish, Hunt, & McGregor, 2007). The combination of MDMA and methamphetamine appears to induce oxidative stress and the production of free- radicals in cell bodies, particularly when a large quantity is consumed in a short time period. Other consequences of this form of polydrug use include significant depletion of serotonin, dopamine and noradrenaline across multiple brain regions (Clemens, Cornish, Li, Hunt, & McGregor, 2005). Additionally, concurrent MDMA and methamphetamine use may lead to increased symptoms of social anxiety, even in the absence of marked neurochemical depletion (Clemens et al., 2007).

Cross-tolerance may lead some individuals to initiate polydrug use (Parrott, Morinan, & Moss, 2004, p.46). Many stimulant users become tolerant to their drugs of choice and therefore start to mix and combine stimulants with other drugs to more easily acquire an "increasingly elusive hit" (Parrott, Morinan & Moss, 2004). Polydrug users who use hallucinogens may also suffer from cross-tolerance effects. Indeed cross-tolerance has been demonstrated between LSD, psilocybin (Isbell, Wolbach, Wikler, & Miner, 1961) and mescaline (Wolbach, Isbell, & Miner, 1962), prompting hallucinogen users to pursue higher doses over time to acquire the same effect.

Prescription drugs often have complex drug profiles that require a great deal of caution in care on the part of medical professionals. Due to the vast quantity of prescription drugs currently available, only a few common drugs will be considered in this review. One commonly prescribed class of drugs are the antidepressants. Tricyclic antidepressants (TCAs) affect neuronal signalling at multiple levels, inhibiting the uptake of both dopamine and serotonin and inhibiting acetylcholine release, among other effects. As a result, TCAs exhibit

many possible interactions with other drugs that can either be beneficial to the patient (e.g. in the case of SSRIs, lithium, L- tryptophan) or problematic for health (e.g. in the case of antiepileptics, which may counteract the effects of TCAs). Patients and doctors alike thus must be careful to monitor the substances that are being concurrently introduced into a patient's body (Anderson & Reid, 2004).

Another category of antidepressant, the selective serotonin reuptake inhibitors (SSRIs), have also exhibit potentially problematic interactions with other drugs. The main effect of SSRIs is to increase the amount of serotonin present in the synaptic cleft at any given moment by inhibiting serotonin reuptake. Too much serotonin in the system can cause serotonin syndrome, which is characterised by headaches, agitation, hypomania, hyperthermia, vasoconstriction, tachycardia, nausea, myoclonus and tremor (Boyer & Shannon, 2005). Some forms of polydrug use can increase the risk of developing serotonin syndrome and thus should be avoided, such as taking both SSRIs and MAOIs at the same time (Anderson & Reid, 2004). A study of five cases of serotonin syndrome in elderly depression patients found that many had been taking St. John's Wort in addition to their usual SSRI medication (Lantz, Buchalter, & Giambanco, 1999), implying that the two substances have an additive effect and can prove dangerous.

Cholinesterase inhibitors that are used for treating dementia are antagonised by multiple other drugs, such as procainamide (an antiarrhythmic medication), aminoglycosides (antibiotics) and antimuscarinic drugs (anti- Parkinson's drugs). Interactions between these drugs may thus be problematic for dementia patients. Yet, as dementia is frequently co-morbid with many others conditions such as cardiovascular disease and Parkinson's disease, dementia patients consume an average of 5.1 medications per day (Fu et al., 2003; Anderson & Reid, 2004; Schubert et al., 2006; Riedel et al., 2010). With dementia being such a complex and difficult to treat disease, further work is needed to elucidate which factors can predict the optimal treatment regime for an individual patient.

Certain types of food can contain 'drugs' that interact with other drugs or medications, and these interactions may prove problematic for health. It is, for example, widely known that MAOIs interact with tyramine-containing foods (including cheese, chocolate, alcoholic beverages and most fermented foods), causing hypertension (Simpson & White, 1984). The effects of this interaction are potentially so serious that diet counselling is advised prior to undergoing drug therapy with MAOIs (McCabe, 1986).

The interaction between alcohol and grapefruit juice, discovered inadvertently in a study that assessed for the effects of alcohol on the hemodynamics of Felodipine, appears to cause the bioavailability of certain compounds such as Felodipine to greatly increase (Bailey, Edgar, Arnold, Spence, & Bayliff, 1990). It since been determined that grapefruit juice has clinically relevant interactions with other drugs such as cyclosporine, midalozam, terfenadine, saquinavir and many other drugs that have low oral bioavailability. These findings have implications for patients who are administered these drugs during transplant surgeries, during surgeries requiring anaesthesia and for patients who sleeping problems, allergies, HIV/AIDS and a variety of other conditions. Research on grapefruit juice interactions, though limited in utility, demonstrate that drug interactions can occur on a daily basis and inadvertently, though the extent to which they can affect an individual depends on their individual susceptibility, their drug regime and the specifics of their diet.

VI. The Psychopharmacology of Polydrug Use

Psychopharmacology is a major area of polydrug use research that examines issues related to behavior, cognitive function and mental health. This section of the review will highlight and discuss some studies that have explored the psychopharmacology of polydrug use.

Polydrug use in the UK is significantly associated with mental health problems (See Table 3), in particular with lifetime suicide attempts (Smith, Farrell, Bunting, Houston, & Shevlin, 2010), which can occur independently from substance abuse or dependence (Borges, Walters, & Kessler, 2000). In a sample of 533 opiate addicts (Kleber, Eyre, Rounsaville, Murphy, & Eyre, 1983), risk factors for suicidality identified included a history of alcohol, sedative and amphetamine abuse, implicating polydrug use. Similar results were found by Darke and Ross (2001) who determined that participants who had attempted suicide had a history of wider polydrug use, and by Rossow and Lauritzen (1999), who concluded that polydrug use had similar effects on the likelihood to attempt suicide as poor social functioning and HIV risk-taking behavior. It will be important to identify whether these trends are a result of polydrug use itself or a consequence of the environments that tend to coincide with polydrug use. Many drugs often used by polydrug users (particularly MDMA) are linked with suicidality when used in isolation, and thus future studies may wish to isolate the factors that lead to suicidal outcomes in these users.

Polydrug use can also influence drug dosage. Barrett, Darredeau and Pihl (2006) found that when alcohol was used with cocaine or methylphenidate, it was ingested in greater quantities than when used in their absence. Conversely, drug users reported drinking less than nonusers on a drinking day in a self-report study carried out to investigate polydrug use among alcohol-dependent individuals (Staines, Magura, Foote, Deluca, & Kosanke, 2001).

Martinotti et al. (2009) carried out a study on substance-dependent individuals and compared the incidence of social factors, childhood trauma, personality, suicidal behaviour, and comorbid Axis I diagnoses between monodrug and polydrug dependents. Almost half of the sample were found to be polydrug dependents, most of whom relatively young, likely to be unemployed and/or divorced and scored highly on scores of childhood neglect, psychoticism, aggression and impulsivity compared to monodrug dependents. Thus, the socio-demographic, developmental and personality factors that distinguish polydrug use in isolation from monodrug use suggest that polydrug use and/or dependence is often associated with adverse circumstances early in life.

Polydrug use can also have highly negative effects on cognition. Polydrug use has been linked to deficits in concept tracking, rule shifting and learning and other forms of prefrontal cortex-mediated processing (Brandt & Doyle, 1983). Chronic primary-cocaine polydrug dependence is associated with lower scores on working memory tests, attention tests and concept formation (Rosselli & Ardila, 1996). Working memory also appears to be impaired in cannabis polydrug abuse (Fletcher et al., 1996). Impairments to cognition in polydrug use serves to further highlight the significant negative repercussions that using combinations of drugs simultaneously can have at the individual level. Furthermore, many studies have focused specifically on adolescent polydrug users, as the still-maturing brain may be highly susceptible to the effects of extraneous substances on its optimal development (Dubman, Yucel & Hall, 2007).

Speedball (simultaneous use of cocaine and heroin) use is often utilised by

heroin- dependent individuals, as the combination can potentiate the alleviating effects of cocaine on heroin withdrawal symptoms, and the motivational effects of cocaine may also mediate dependence on and withdrawal from opioid drugs (Leri, Bruneau, & Stewart, 2003). The "speedball" combination is highly dangerous, and has serious implications for mental health: an investigation into differences in psychopathology between cocaine and speedball users found that the latter displayed far greater problems with depression, anxiety and related symptoms (Lott, Pena, Corrigan, Malow, & West, 1992).

Polydrug use can also exacerbate the problems caused by individual drugs. For example, the psychobiological decrements associated with cannabis use can be potentiated by concurrent alcohol use (Chait & Pierri, 1992; Ramaekers et al., 2010), among other drugs (Parrott, Milani, Parmar, & Turner, 2001). In the case of alcohol and cannabis, Ronen et al. (2010) found that the combination produces an intense subjective experience of sedation, hunger and "feeling high" greater than that for each drug used in isolation, suggesting an additive effect as the primary motivation for co-use of cannabis and alcohol. The combination of alcohol and cannabis has also been found to increase rates of both alcohol dependence and depression, mirroring trends that suggest younger populations use alcohol and drugs in part as a form of self- medication or to cope with distress (Midanik, Tam, & Weisner, 2007).

Similarly, recreational cocaine polydrug use potentiates the impairment that cocaine has on cognitive flexibility (Colzato, Huizinga, & Hommel, 2009), which has implications for users' performance on tasks that require rapid behavioral responses, and thus for their quality of life. Decrements in cognitive abilities such as flexibility have been linked to an increased risk of substance abuse in the past (Giancola & Tarter, 1999), and thus cocaine polydrug use and cognitive decrements may interact cyclically, with each reinforcing the other. Primary cocaine polydrug use has also been found to cause the development of abnormal brain perfusion (Mendelson et al., 1991) which could be related to observed cognitive deficits.

LSD use is characterised by hallucinations and, for an extended period following use, what is colloquially known as "LSD flashback syndrome." Markel, Lee, Holmes and Domino (1994) studied the case histories of two LSD abusers who had comorbid major depression and were treated with SSRIs, and found that antidepressents use seemed to exacerbate LSD-induced flashbacks. It is thought that the culprit for this interaction is the similarity in physiology between LSD and serotonin. This research has important implications for patients with depression who also have a history or a proclivity to take LSD, though the cited study only examined reports from two patients, which does not represent a large enough sample to be able to generalise the results to larger populations.

Parrott, Sisk and Turner (2000) found that polydrug use in MDMA users most likely contributes to the adverse psychobiological profiles observed in MDMA-using populations. These results were supported by another study which examined MDMA polydrug abuse and comorbid depression, psychotic disorders, cognitive disturbances, bulimic episodes, impulse control disorders, panic disorders and social phobia (Schifano, Furia, Forza, Minicuci, & Bricolo, 1998). Other problems experienced by heavy MDMA polydrug users include phobic anxiety, obsessive compulsive disorder and sexual problems, including loss of interest or pleasure (Parrott, Milani, Parmar, & Turner, 2001). A possible explanation for these effects was proposed by Gouzoulis-

Mayfrank & Daumann (2006), who hypothesized that since stimulants (e.g. amphetamine, cocaine) are commonly used alongside MDMA, this form of polydrug use can worsen the already neurotoxic effects of MDMA and act synergistically to worsening the drug's long-term neurobiological effects.

Interestingly, Parrot, Sisk and Turner (2000) also found that cannabis partially blocks MDMA's neurotoxic effects due to its neuro- protective qualities while also potentiating different psychological problems and cognitive failures. As an example of the latter scenario, MDMA polydrug users exhibit impairment on tasks known to be sensitive to temporal functioning (Fox et al., 2002). It is evident, then, that MDMA interacts in a complex manner, producing both positive and negative long-term effects for the user. Simultaneously users of both MDMA and cannabis also appear to have altered neuronal integrity in the Brodman Area 45, an area involved in verbal memory processing (Cowan, Joers, & Dietrich, 2009). Indeed, the cited study found an inverse association between cannabis use and Brodman Area 45 N-acetyl aspartate (NAA) levels in MDMA users.

The combination of MDMA and methamphetamine, both of which are classified as stimulants, may potentiate the effects of both drugs simultaneously, at least in rats (Clemens et al., 2004). For example, hyperthermia is exacerbated in MDMA/methamphetamine compared to MDMA alone, as is stereotypy (persistent repetitive behaviors). Changes to social behavior were also observed following the consumption of both drugs, with rodent models exhibiting greater social-anxiety-related behaviors and decreased social interaction. This is a peculiar finding, as MDMA alone is known to increase social interaction in rats (Thompson, Callaghan, Hunt, Cornish, & McGregor, 2007), suggesting that the introduction of methamphetamine alongside MDMA may reverse the social potentiation induced by MDMA alone. One potential explanation for this finding is that the introduction of methamphetamine depletes the activity of DOPAC, which is known to participate in the destruction of dopamine storage vesicles in the substantia nigra (Clemens et al., 2004; Hastings, Lewis, & Zigmond, 1996). This particular effect of methamphetamine may have numerous behavioural and psychobiological consequences that could lead to a reversal of social potentiation induced by MDMA.

When used in combination, CNS depressants such as alcohol, barbiturates and opiates may place users at a heightened risk of language and perceptual-motor dysfunction (Grant et al., 1978). Grand and Judd, 1976, also observed that cerebral dysfunction associated with neuropsychological impairment in poly- depressant drug use may persist beyond 5 months following abstinence, indicating that this behavior may have serious long-term consequences for cognitive function.

Seizures can also result from polydrug use. Brust (2006) identified that taking one drug while recovering form the effects of another may have many adverse effects on the body, including the initiation of seizures. Seizures are intensely dangerous, and have been identified as a cause of death resulting from MDMA use (Schifano et al., 2003). Seizures may also result from the use of anticonvulsants to treat alcohol dependence, as alcoholics are prone to erratic drug-taking behaviour and the possible interactions between anticonvulsants and non-alcohol drugs can greatly heighten seizure risk (Hillbom & Hjelm- Jäger, 1984).

Polydrug use is associated with a variety of forms of risky behavior. Heavy polydrug users have been found to be more likely to engage in risky sexual behaviour

and to have more sexual partners (Patterson, Shemple, Zians, & Strathdee, 2005). Additionally, in a sample of HIV-positive men who have sex with men (MSM), most had a pattern of primary methamphetamine polydrug use and tended to be more impulsive than light polydrug users. These findings were supported by Stall et al. (2003) who found that MSM weremore likely to exhibit problematic polydrug use and develop associated mental health conditions.

Other risky behaviours that are associated with polydrug use include criminal behavior, which along with alcoholism was concluded to be a result of chronic polydrug use (Wu, Schlenger and Galvin, 2006). Similarly, polydrug use causes an increase in violent behaviour in adolescents (Dornbusch, Lin, Munroe, & Bianchi, 1999). Gender differences were evident in this data, as might be expected, with males tending to be more violent than females, but even after controlling for gender, polydrug use was still found to be a factor associated with an increase in violent behaviour among adolescents and adults alike. Similar results were found in a study carried out by Degenhardt and Topp (2003) who concluded that crystal methamphetamine polydrug use was related to violent behaviour, even in small doses. Finally, early onset polydrug use has been identified as a risk factor for using injection drugs later in life (Trenz et al., 2012).

A novel way that a polydrug interaction can be utilised by the health profession is exemplified in the rise in the use of drugs such as disulfiram or naltrexone to treat alcohol dependence. When disulfiram is taken with alcohol it causes an accumulation of acetaldehyde in the body, which in turn causes symptoms of nausea, vomiting, flushing, palpitations, headaches and hypotension (Anderson & Reid, 2004) and leads to alcohol aversion. Disulfiram treatment along with psychotherapy has been found to be a useful tool in treating dependence in

both alcohol-dependent individuals and cocaine-dependent individuals who use alcohol (Carroll, Nich, Ball, Mccance, & Rounsavile,
1998). When naltrexone is taken with alcohol, it reverses its opioid effects and significantly reduces both alcohol cravings and binge drinking (Volpicelli, Alterman, Hayashida, & O'Brien,
1992).

VII. Future Directions

Polydrug use does not seem to be decreasing in prevalence. In fact, problematic polydrug use increasing across many regions of the world (Klee, Faugier, Hayes, Boulton, & Morris, 1990; Choquet, Morin, Hassler, & Ledoux, 2004; Wish, Fitzelle, O'Grady, Hsu, & Arria, 2006; Brecht, Huang, Evans, & Hser, 2008) and it is therefore not surprising that so much research has already been undertaken to investigate which factors may predispose individuals to engage in polydrug use.

Dosages, frequencies and durations of use all represent factors in need of further exploration on the polydrug use literature (Grant & Harford, 1990), and it would thus be prudent to invest time and money into researching the relationships between these variables and their association with other variables (e.g. psychiatric diagnoses, lifetime polydrug use, lifetime health service utilisation, socioeconomic factors). Such research would be greatly useful towards developing interventions that reduce frequency of polydrug use and educate specific populations about the risks that it entails. Animal studies have been utilized in this respect, particularly studies in which rats have been administered various combinations of drugs and their effects studied in a controlling setting (Ranaldi & Munn, 1998; Izco, Orio, O'Shea, & Colado, 2006). This method could prove useful towards examining understudied individual

difference variables such as drug dosages and frequencies of use

Much polydrug research, and indeed drug research on the whole, relies on self-report questionnaires and interviews, which can be problematic in terms of data reliability, particularly since drug users have a tendency to give socially desirable answers. Self-report data can thus be unreliable, particularly with respect to polydrug use initiation and the frequency/severity of use, both of which represent crucial domains for the development of effective interventions. Additionally, much research is carried out via sampling individuals who possess a fixed home address/landline (AIHW, 2011) which can leave high-risk individuals such as those in transient accommodation to be exempt from the sampling process and thus cause an underestimation of the rates of polydrug use in this group. To this extent, assessing drug use through methods that cannot be falsified may be utilized to great effect. One example of an unfalsifiable method is the analysis of hair samples to identify chronic MDMA use (Pichini et al., 2006).

There is also a need for further research on the psychopharmacological effects of mixing illicit drugs with prescription drugs. The research that does exist seems is generally limited either by sample size or by paucity of other experimental data to support findings (Markel, Lee, Holmes, & Domino, 1994). Given that many prescription and illicit drugs produce a wide range of pharmacological and psychological effects, yet most relevant research included within this review has pertained uniquely topharmacology, it will be important to more thoroughly investigate the psychopharmacological effects of prescription and illicit drug mixing. Future studies could aim to assess for differences across a variety of predictor variables for groups administered either one or two drugs at once (one illicit, one prescription) or a placebo control. Two-way ANOVA hypothesis testing would then permit researchers to easily differentiate psychopharmacological effects that are due to drug interactions (polydrug use) from individual drug effects (monodrug use).

Interventions and legislation are often discussed in the context of polydrug use. Recent furor surrounding the United Kingdom's Psychoactive Substances Bill ('Psychoactive substances act 2016 — UK parliament', 2016) has proved that at least in the UK, the societal implications of drug use is a topic that provokes much debate. It appears that in these cases, for both the public and for government officials involved, education is the best route by which to improve societal understanding of the effects of drug use, including polydrug use. To this end, research into the effects of polydrug and monodrug use alike must become both extensive and accessible to the public. Drug use interventions in the past have proved complex, and no single strategy represents a cure-all for dependency or abuse in a polydrug context (Ives & Ghelani, 2006). Thus, the investment of both time and money into developing multiple types of intervention strategies, each tailored to a different at-risk population, is strongly recommended moving forward.

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Appendix

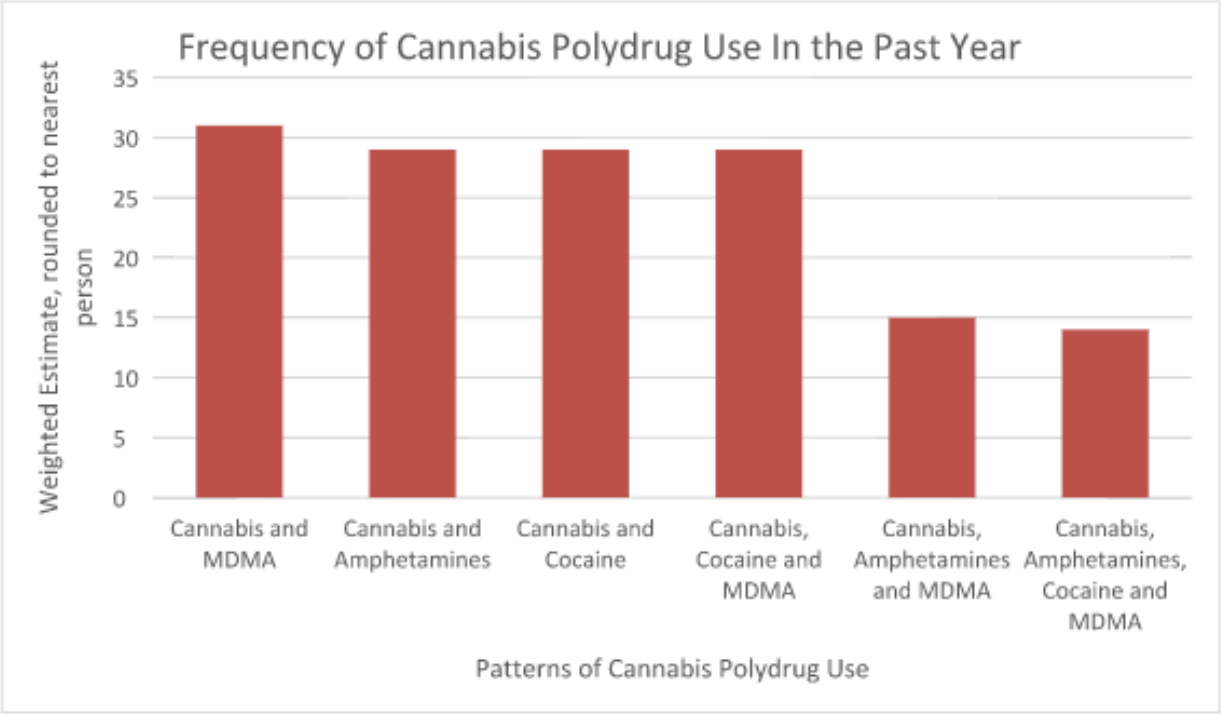

Figure 1: Most frequent patterns of response of illicit drug use in the past year (N=8358). From Smith, Farrell, Bunting, Houston, & Shevlin (2010).

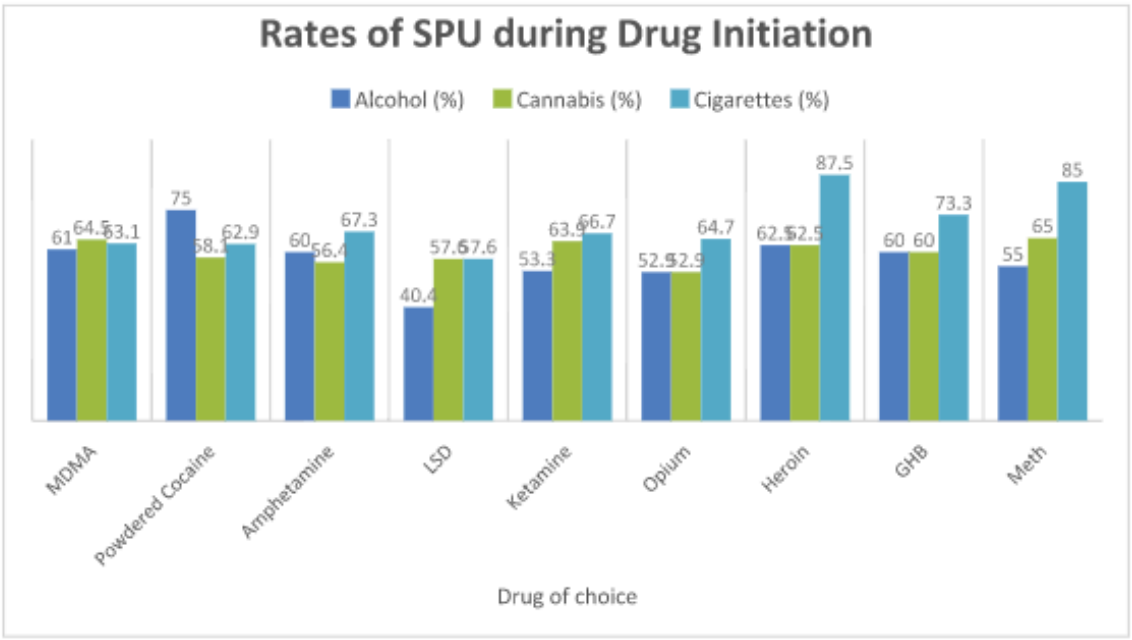

Figure 2: Simultaneous polysubstance use during substance use initiation (i.e. first-ever use). From Olthuis, Darredeau and Barrett (2012)

	ANY	METH	MDMA	LSD	KETAMINE	GHB	FLUNITRAZEPAM
ALCOHOL	99.3	99.5	99.5	99.4	100	100	97.8
CANNABIS	97	98.1	97.4	98.4	100	100	99.2
INHALANTS	43.5	56.1	45.1	51.6	71	83.5	57.8
COCAINE/CRACK	53.3	75.9	56.4	61.1	69.2	35.3	78.6
HALLUCINOGENS	96.2	85.7	100	100	98.5	100	87.7
HEROIN	6.4	13.6	7.7	8.4	22.9	20.1	16.6
STIMULANTS	38.3	100	36.5	40.5	54.8	9.4	57.9
SEDATIVES	7.2	15.4	7.9	8.8	18.8	17.5	28.1
TRANQUILISERS	37.5	51.5	40.4	44.2	83.4	94.7	100
PAIN RELIEVERS	57	72.8	59.6	62.9	87	87	81.3

Table 1: Lifetime prevalence (%) of alcohol and drug use among club drug users aged 16-23 (unweighted N = 19.084). From Wu, Schlenger & Galvin (2006).

	COUNT	DURATION (SECONDS)
CONTROL/VEHICLE	84.33 (3.82)	93. 77 (8.25)
MDMA	73.83 (4.16)	68.51 (5.96) *
METHAMPHETAMINE	68.83 (5.96) *	53.61 (7.21) ***
MDMA/METHAMPHETAMINE	60.42 (5.04) **	52.51 (7.34) ***

Table 2: Number and duration of social interaction events 7 weeks after chronic drug administration, values represent mean (S.E.M.).
*Asterisks indicate differences at the *p < 0.05, **p < 0.01 and ***p < 0.001 levels of significance. From Clemens, Cornish, Hunt and McGregor (2007).*

	WIDE RANGE POLYDRUG USER	MODERATE RANGE POLYDRUG USER
GENERALISED ANXIETY DISORDER	2.26 *	1.82 *
MIXED ANXIETY AND DEPRESSIVE DISORDER	1.22	1.71 *
SUICIDE ATTEMPT IN LIFETIME	2.50 *	1.73 *
DEPRESSIVE EPISODE AT PRESENT	1.39	1.98 *

Table 3: Odds ratios and 95% confidence intervals between mental health/demographic predictors and latent class membership of classes 1 (wide range polydrug user) and 2 (moderate range polydrug user) compared to baseline non-polydrug users. From Smith, Farrell, Bunting, Houston and Shevlin (2010).