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CURRENT INTERNATIONAL TRENDS IN SUBSTANCE ABUSE

In this issue, subject matter experts will examine new and/or evolving trends popping up on the international substance abuse landscape. Drug abuse continues to be a global challenge on many fronts: societal, economic, and health. The drugs of abuse are constantly changing to meet or create demand, with novel ones being developed or discovered and old ones being altered or intensified. Therefore, this edition of the Journal will focus on the issues related to this topic and hone in on specific areas of concern in the current substance abuse realm.

Included in this issue is a comprehensive, up-to-date, review of the literature related to the risks and harms associated with marijuana use. In this thorough and authoritative look, the author concludes that, based on a review of the current literature, marijuana does pose some

considerable risks to users. To date, the research evidence shows that marijuana use has a number of associated harms; although the research, in some areas, is inconclusive. The questions and answers posed in this review are important to the on-going policy debate in Canada, the author's home, and elsewhere in the world.

Designer drugs, a growing and difficult problem in the US and throughout the world, are created to be similar to, but not identical with psychoactive drugs that are illegal to possess or sell for human consumption - unless for medical purposes. In this study, the author details the history of these substances, what they are and why they exist, and their impact on the individual and society. The author also outlines possible policy implications and recommendations relating to these drugs.

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Designer Drugs: An Escalating Public Health Challenge

An Updated Review of the Research on the Risks and Harms Associated to the Use of Marijuana

Jordan Diplock, Dr. Darryl Plecas and Len Garis; Centre for Public Safety and Criminal Justice Research, School of Criminology and Criminal Justice, University College of the Fraser Valley

Introduction

Currently and in recent years, there is a continued debate over the personal use of marijuana in North America and around the world. The debate remains adversarial and is receiving a large amount of public attention in various media. It is commonplace for former supporters of the existing drug control policies to publicly announce their changes of opinion. In British Columbia, several former Attorneys General joined a growing number of activists looking for decriminalization and legalization (Mulgrew, 2012). In early 2012, the former US District Attorney, John McKay, who prosecuted Marc Emery, a Canadian, for selling marijuana seeds to American residents, has publicly denounced prohibition policies (CBC News, 2012). At the same time, the focus of the marijuana debate continues to be dominated by arguments about how prohibition does nothing more than put money into the pockets of organized crime, punish otherwise law abiding citizens, violate people's right to put whatever they want into their bodies, and throw good tax dollars after bad on a failed war on drugs (Harris, 2012). Decriminalization or legalization of marijuana, the advocates commonly argue, is really the only sensible solution.

What seems to have become increasingly lost in the debate over the personal use of marijuana, however, is a consideration of the negative effects that marijuana can have on users and how those harms can be addressed within any policy direction. It seems that we have moved past debating

whether the use of marijuana is potentially harmful enough to merit concern, to, it is not. In our view, though, such an assumption is premature. Indeed, as we established in a previous review of the literature (Diplock, Cohen, & Plecas, 2009), marijuana should not be viewed as a benign substance, but rather as one that, though unlikely to pose serious harm for most, will negatively affect a proportion of users. With that in mind, and in the interest of considering even more recent literature, the purpose of this current review is to update the original report on the harms associated with marijuana use. It is the hope of the authors that this information will begin to play a more prominent role in the discussions about future marijuana control policies. Similar positions have been put forward by authors in other parts of the world (for example see Roxburgh et al., 2010).

Research on the effects of marijuana and the cannabinoids on the various functions within the human body is growing rapidly. Since the original review (Diplock et al., 2009) focusing on research between 2000 and 2007, a greater number of researchers have focused on the potential for marijuana to be used medicinally to alleviate a number of negative health conditions (Leung, 2011). Furthermore, research on the biological mechanisms of marijuana's active constituents has also increased, particularly to help scientists determine how to best take advantage of the therapeutic benefits of the drug while avoiding the negative effects (Bifulco, 2009). No longer is the focus of research simply on asking how marijuana can negatively affect users. However, while these are valuable areas of research and their contributions will help us to better understand marijuana as a form of medicine, this type of research will largely be outside the scope of this review. This review, a synthesis of the best evidence from over ten years of research between 2000 and 2012, will add the most current research on the potential harms associated with marijuana use to the information presented in the original review. Of course, just as the body of knowledge has changed in the years since the previous review, it is also likely that future years will provide an even greater level of clarity around the true extent of harms. Just because research in one or more areas might not currently identify likely risks or harms, one should not interpret this as demonstrative evidence that no harm exists. It is the nature of research, for future

studies to build and improve upon the methodologies and results of past research, and therefore uncover things that were once unknown.

It is especially important to be mindful of the most current research on marijuana use because of the changing nature of both academic research and the drug itself. In other words, not only do methods for studying the effects of marijuana change and improve over time, but we must also be aware that marijuana may also be changing. The term “marijuana” does not refer to cannabis with a particular level of Δ^9 -Tetrahydrocannabinol (THC). Over time, the level of THC in marijuana has changed; typically, it has increased. However, because there have been very few studies on the changes in potency of marijuana over the years, it cannot be confirmed conclusively that marijuana users in the 1970s were typically consuming a different drug than today’s users. However, the information that does exist suggests that, on average, marijuana users today are exposed to higher levels of THC than in past decades. Research on potency trends of seized marijuana between 1980 and 1997 concluded that average THC levels of marijuana seized in the United States increased in levels of THC from less than 1.5% in 1980 to approximately 3% in the early 1990s, to over 4% in 1997 (ElSohly, Ross, Mehmedic, Arafat, Yi, & Banahan, 2000). By 2008, the average THC level of seized marijuana was over 11% (Mehmedic et al., 2010). While not observing large substantial increases in potency, McLaren, Swift, Dillon, and Allsop (2008) reported increasing trends in the United States, the United Kingdom, the Netherlands, and Italy. In Canada, the Royal Canadian Mounted Police [RCMP] (2008) reported that seizures of marijuana, in which only the buds are tested, had an average THC concentration of around 11% in 2008. Seizures in Europe of imported “herbal marijuana” typically had THC levels between 2% and 8%, but the potency of hydroponically-grown marijuana may be as high as double that (King, Carpentier, & Griffiths, 2005). Potter, Clark, and Brown (2008) found the median THC level from 2004 and 2005 samples of this more potent indoor-grown marijuana to be 13.9%. Common among all of the studies was that there was a high degree of variability, so it must be kept in mind that a regular user would likely be exposed to marijuana of various different concentration levels of THC. As the majority of marijuana production remains the industry of

criminals, many of whom use hydroponic operations and compete with each other to produce the most and the 'best' marijuana, there is no reason to believe that the quality of street marijuana has remained consistent over time.

Because marijuana is the most commonly used illicit drug in the world, with reports of approximately 125 to 203 million people having used the drug in the last year (United Nations Office on Drugs and Crime, 2011), there has been a great deal of research conducted on its effects on users. The use of marijuana results in a variety of changes within the user's body that can have a range of affects on the user's life (Copeland, Gerber, & Swift, 2006). The focus of this review will again be limited to the research evidence on potential harm associated with marijuana use in the areas of: (1) impairment; (2) academic and social development; (3) general physical health; (4) mental health; and (5) and continuing drug use. The discussion presented in this review will concentrate on the use of marijuana within the general population and the empirical evidence for how marijuana use effects the general population in the previously listed five areas.

Methodology

In the previous review by Diplock et al. (2009), the articles included were published between 2000 and 2007. The current review includes articles published between 2000 and 2012. Articles were identified by searching a number of databases, including Medline, PubMed, PsychINFO, and Google Scholar. Again, keywords related to each category were used to narrow the search and find appropriate articles.

Once an article was identified, it was assessed for appropriateness based on a review of the article's title and abstract. One potential limitation of this review was that only articles written in English were considered for this review. However, in order to expand the number of articles considered in this review, both original research studies and other literature reviews/meta analyses were included. In

order to ensure objectivity in the selection process, the inclusion or rejection of articles occurred without consideration of authorship or the conclusions or recommendations made by the authors. Given this, the articles considered in this review represented the continuum of current research on the harms that may be associated with marijuana use. Because of the scope of this topic and the amount of literature on marijuana use, the articles included in this review do not represent all available research on the effects of marijuana use. However, because many of the articles included in this review included extensive reviews of previous literature, the areas of focus for this review were well represented.

Finally, when considering the evidence presented in this review, it is critical to keep in mind that many of the studies based their results and conclusions on self-reported effects of marijuana use by the users themselves. While self-report studies are extremely valuable, they are susceptible to a variety of methodological problems, such as social desirability effects, errors in memory, exaggeration, and deception, which must be considered when evaluating results or conclusions (Palys, 1997). In addition, it is also extremely difficult to link or establish a direct causal relationship between drug use and other specific behaviours, as it is likely that behaviours or outcomes are the result of multiple factors, rather than exclusively one factor, such as drug use.

Marijuana-Related Impairment

This section reviews the findings of literature related to both short-term and long-term impairment. It is important to understand the short-term and long-term effects of marijuana use on cognitive and motor skills, as impairment may present a serious risk, particularly for younger users and those who may operate motor vehicles soon after use. Impairment will likely be a major source of concern around public safety in the event that the legal responses to marijuana use changes.

Short-Term Impairment

Impairment immediately after the consumption of marijuana may be a concern for users and the community at large. Recent research supports claims that marijuana impairs concentration, attention, planning, decision-making, and working memory (Crean, Crane, & Mason, 2011). Some effects, however, particularly those on attention, appear to be stronger in less experienced users, who have not built up tolerance to the drug, while heavy users may be more likely to experience impairments during short periods of abstinence (Crean et al., 2011). Since marijuana is a commonly used substance and research indicates that there may be close to 5% of drivers having THC in their system (Beirness & Beasley, 2009), these types of acute impairments may pose a risk to users and the general public.

Ilan, Smith, and Gevins (2004) determined that focusing attention and response accuracy were impaired immediately after smoking marijuana, even marijuana with less than 4% THC. Marijuana use resulted in difficulty maintaining a coherent train of thought and disruptions to selective filtering processes, both of which impaired memory (Ilan et al., 2004). Anderson, Rizzo, Block, Pearlson, and O'Leary (2010) found that marijuana had an impairment effect on attention, cognitive flexibility, and time estimation in their sample of both males and females. However, impaired attention was not found in a study of marijuana's effects on auditory focused attention tasks where participants responded to a tone by pressing a button as quickly as possible (O'Leary et al., 2007). Results of a double-blind test of marijuana's impairment of executive cognitive abilities by Vadhan et al. (2007) indicated that while marijuana caused an increase in the time used to make gambling decisions, the accuracy of decision-making was not impaired.

In their examination of brain functioning hours after using marijuana, Kanayama, Rogowska, Pope, Gruber, and Yurgelun-Todd (2004) found that heavy marijuana users did not present impaired abilities on simple spatial working memory tasks by compensating for deficits by employing regions of the brain not commonly used during such tasks. Smith, Longo, Fried, Hogan, and Cameron (2010) also found increased activation as well as increased blood flow to additional regions of the brain when marijuana users performed visuospatial working memory tasks. Howard and Menkes (2007) reported that acute marijuana intoxication was accompanied by impairment of brain function related to goal-oriented activities.

Although existing research indicates that short-term cognitive impairment can and does occur among marijuana users, the level of impairment is generally not serious. However, this does not suggest that there are no or few short-term risks of impairment associated with marijuana use. It is also important to note that most of the research to date has involved relatively small sample sizes, and with few exceptions, researchers are unable to control the dose of marijuana in their samples.

Despite the apparently minor levels of impairment reported in the existing research, there is evidence to suggest that marijuana use can have serious consequences for driving. Operating a motor vehicle can be a potentially dangerous activity at any time. However, doing so while impaired by marijuana significantly increases the risks of accident. Although studies revealed that recent marijuana use was a causal factor for only a small proportion of accidents, perhaps due to a lack of standardized roadside test instruments for marijuana impairment, short-term marijuana impairment does contribute to serious motor vehicle accidents (Bedard, Dubois, & Weaver, 2007; Blows et al., 2005; Laumon, Gadegbeku, Martin, & Biecheler, 2005). A meta-

analysis by Chen-li et al (2011) found that based on studies over the past twenty years, marijuana use by drivers significantly increases the risk of motor vehicle crashes. A Canadian study of fatally injured drivers conducted between 2000 and 2006 found that nearly 15% tested positive for marijuana use (Beirness, Baesley, Lecavalier, Boase, & Mayhew, 2009). Furthermore, research appears to support claims that driving after marijuana use is becoming more common (Bierness & Porath-Waller, 2009), with one recent study of university students in Toronto reporting that 35% of participants had driven under the influence of marijuana while only 5% reported driving while intoxicated by alcohol (McGuire, Dawe, Shield, Rehm, & Fischer, 2011).

Research has explored the relationship between marijuana induced cognitive impairment and operating a motor vehicle and found reasons for concern. Ramaekers et al. (2006) concluded that decision-making, planning, tracking, reaction time, and impulse control were all impaired by high-potency marijuana. Although the subjects were considered only light users, substantial impairment of executive and motor functioning for a period of at least six hours was found. Although the THC levels in the marijuana used in this study (13% THC levels) was higher than the averages reported by the 11% averages reported by Mehmedic et al., (2010) and the RCMP (2008), this study demonstrated that serious impairment lasting for many hours was common when consuming high potency forms of marijuana.

Field tests have found that impairment increases with the level of THC (Papfotiou et al., 2005; Khiabani et al., 2006), which presents further concern given the general trend of increased potency in available marijuana. Research by Ramaekers et al. (2000) concluded that even low levels of THC can moderately impair driving abilities, but driving is severely impaired when

either higher levels of THC marijuana is consumed or marijuana with lower levels of THC is consumed with even small amounts of alcohol. Considering the research examined for this section, there appears to be a strong consensus that marijuana use has a negative, and potentially harmful, effect on driving.

Long-Term Impairment

The question of whether long-term marijuana use can lead to serious negative effects on cognitive capabilities has recently received increased attention from researchers (Pattij, Wiskerke, & Schoffemeer, 2008). Researchers have examined the potential for impairment as a result of long-term use, even during periods of abstinence (Pope, Gruber, Hudson, Huestis, and Yurgelun-Todd, 2001; Tapert et al., 2007). From the results of these studies, it appeared that, although heavy marijuana users showed impaired cognitive abilities after a week of abstinence, for most users, there were no noticeable impairments after a period of twenty-eight days of abstinence (Pope et al., 2001; Tapert et al., 2007). There is no consensus on the extent of the risk of long-term cognitive impairment from marijuana (Pattij et al., 2008), but research findings suggest that heavier use and earlier onset of use cause greater long-term deleterious effects (Crean et al., 2011).

Research on long-term marijuana users found an increase in brain activity in more regions of the brain when performing a variety of cognitive tests when compared to non-users (Kanayama et al., 2004; Tapert et al., 2007). The researchers concluded that this finding was the result of the brain working harder and differently to overcome the deficits resulting from the marijuana use. In addition to working harder and differently, Schneider et al. (2006) discovered significantly increased blood volumes in various regions of the brain, even after a

period of abstinence of six to thirty-six hours. The researchers indicated that it remained unknown how these changes affected brain functioning and whether these changes were permanent, long-lasting, or temporary. However, these findings do suggest that there is a potential for some types of long-term brain impairment.

When considering early-onset users to late-onset users, even after twenty-eight days of abstinence, Pope, Gruber, Hudson, Cohane, Huestis, and Yurgelun-Todd (2003) found that early-onset frequent marijuana users had a greater likelihood of suffering a range of cognitive functioning impairments, in particular verbal IQ, compared to late-onset and non users. A review by Jacobus, Bava, Cohen-Zion, Mahmood, and Tapert (2009) found that even after a month of cessation, adolescents tend to show negative effects on attention, learning, processing speed, brain structure, brain function, and sleep. However, the abnormalities appear to be relatively mild, with effect sizes generally smaller than those found for alcohol and other drugs, and the majority resolve after three months of abstinence (Jacobus et al., 2009). Most researchers agree that adolescence is a period of neurodevelopmental vulnerability, and that heavy marijuana use at this time likely puts youth at risk of long-term changes to the brain (Gruber, Sagar, Dahlgren, Racine, & Lukas, 2011; Jacobus et al., 2009; Pattij et al., 2008).

The Effects of Marijuana Use on Academic and Social Development

As marijuana is the drug of choice for many young people, it is necessary to understand whether marijuana has any negative effects on academic performance and the transition from adolescence to adulthood. A number of studies suggest that marijuana is relatively easy for young people to access (Harrison, Erickson, Korf, Brochu, & Benschop, 2007; Johnston, O'Malley, Bachman, & Schulenberg,

2011). The evidence for both immediate impairment and the possibility of longer-term impairment support the notion that marijuana use may have negative consequences on the development of young users, which in turn could reduce their likelihood of having successful, productive, and happy lives.

Marijuana and School Performance

There are many factors that contribute to academic achievement, such as general intelligence, interest/curiosity, motivation, lifestyle, and social relationships/networks. Since in adolescence the human brain is still in a developmental stage, it is possible that recreational marijuana use may disrupt 'normal' development (Gruber et al., 2011; Jacobus et al., 2009; Pattij et al., 2008), which may result in, among other things, poorer school performance. Lynskey and Hall's (2000) review of cross-sectional studies on marijuana and school-related issues concluded that marijuana appeared to have a strong relationship with absenteeism, lack of retention, and not graduating. Survey research by Bovet, Viswanathan, Faeh, and Warren (2006) revealed that students who were absent on the day of a school-based survey were more likely to use marijuana, alcohol, and cigarettes than students who were present. Research by van Ours and Williams (2009) found that marijuana negatively influences educational attainment, as users were more likely to drop out of school. This relationship was found to be particularly important for those users who began use prior to age 15 (Horwood et al., 2010). While marijuana appears to detract from academic achievement, recent research also indicates that academic issues, such as low grades, low participation in classroom activities, poor attendance, academic dishonesty, and incidents of discipline, are higher among those students who used marijuana at school than those who used, but did not use at school (Finn, 2012).

In an examination of the relationship between academic achievement and drug use in a wide range of students, Jeynes (2002) concluded that marijuana use, when examined alone, was statistically significantly related to lower standardized test scores in math, science, reading, and social studies. Average scores on the math comprehension test for marijuana users were further below the mean than

on any other test, while reading comprehension appeared to be affected the least. However, when marijuana was combined with alcohol or cigarettes, the results were much less robust. In effect, both regular smoking and alcohol intoxication explained much more of the variance, thus reducing the influence of marijuana on test scores. This may have been the result of the fact that it is rare for students to be under the influence of marijuana while at school (Jeynes, 2002). Similarly, Diego, Field, and Sanders (2003) found that grade point averages decreased as the reported frequency of marijuana use increased. Marijuana use had a larger negative correlation with grade point average as frequency of use increased ($r = -.400$) than alcohol ($r = -.355$) or cigarettes ($r = -.221$) (Diego et al., 2003). Research by van Ours and Williams (2009) reported that females were more susceptible to the negative effects of marijuana use on education, while Horwood et al. (2010) found that marijuana was likely to interfere with a male's likelihood of participating in post-secondary education than for females. While these studies suggest the existence of an association between marijuana use and academic achievement, the research cannot establish that there is a direct causal relationship. There may be pre-existing differences between those students who use marijuana and those who do not, which explains their rates of dropping out, particularly since tobacco use is also related to lower educational attainment, but is less likely to impair cognition (McCaffrey, Liccardo Pacula, Han, & Ellickson, 2010). While it is unknown what the factors are that explain the association between marijuana use and lower education attainment, van Ours and Williams (2009) discuss the potential for reduced health, decreased interest in studying, impairments to cognitive functioning, or a combination. Regardless of the underlying reasons for marijuana use to negatively affect educational attainment, the consequences on future earning can be harmful and therefore, deserve continued attention.

Since marijuana has been linked to impairment and a decrease in school performance, researchers have studied the effects of marijuana on IQ (Fried, Watkinson, James, & Gray, 2002). However, measuring the direct effects of marijuana use on IQ has been difficult as there is rarely a baseline measure of a subject's IQ prior to their initiation into marijuana use (Copeland et al., 2006). In one longitudinal study that did have baseline measures of IQ prior to the subject ever using marijuana, Fried et al.

(2002) reported a statistically significant decrease in IQ score among individuals who smoked five or more marijuana cigarettes per week. On average, these researchers measured a 4.1 point decrease between the time the subject was 9 to 12 years old (no prior use) and 17 to 20 years old (current and/or past use). However, when considering the degree of marijuana use, only those characterised as heavy users showed any decreases in IQ compared to slight users, former users, and non-users who all demonstrated increases in IQ (Fried et al., 2002). These results suggested that marijuana use has an effect on general intelligence, but is more severe for regular and chronic marijuana users.

Marijuana Use and Later Social Development

Success in adulthood is related to a wide range of developmental and social variables throughout childhood and adolescence. It has been hypothesised that many of these contributing dynamics could be negatively affected by the use of marijuana. For example, some people contend that one of the possible outcomes of marijuana use is chronic low motivation. In effect, the hypothesis is that marijuana use among young people contributed to the development of low motivation which has long-term effects on school and employment performance. In their research, however, Lynskey and Hall (2000) concluded that there was little evidence to support the low motivational syndrome hypothesis. Moreover, Eisen et al. (2001) reported that long-term (over 20 years), regular marijuana use among males was not associated with any specific negative socio-demographic effects such as alcohol or nicotine abuse or dependence, hospitalizations, and health-related quality of life.

However, other researchers have found several adverse associations between marijuana use and social development. A study of the relationship between marijuana use in high school students and later occupational attainment concluded that marijuana had differential negative associations with occupational attainment for males and females (Schuster, O'Malley, Bachman, Johnston, & Schulenberg, 2001). Similarly, Gren and Ensminger (2006) found that frequent adolescent marijuana use was associated with poorer academic achievement, a lack of stable employment, and family

dysfunction. These results suggested that using marijuana 20 or more times during adolescence was associated with being unemployed, unmarried, and becoming a parent while unmarried (Green & Ensminger, 2006). A study by Stuart and Green (2008), which used full matching to explore the effects of adolescent marijuana use on adult outcomes, also found that early marijuana use was associated to an increased risk of poverty, lower household income, and having had a period of unemployment. These effects were not observed for males, but heavy marijuana users of both genders were at increased risk of further serious drug use (Stuart & Green, 2008). Fergusson and Boden (2008) concluded that early marijuana use was associated to poorer educational outcomes, unemployment, increased likelihood of dependency on welfare, lower satisfaction with one's life and relationships, and lower income. Pedersen (2011) also found that marijuana users were more likely than non-users to later receive welfare, less likely to leave welfare, and receive welfare for longer durations.

When the findings from studies related to occupational attainment and school performance are considered together, it appears that marijuana use among young people can have a detrimental outcome on their future. However, these findings do not confirm a causal relationship between marijuana use and poor performance in school or life. Still, the evidence does suggest that, even in the absence of a direct causal link, the use of marijuana during adolescence, for many young people, is often accompanied by other factors, such as the development of delinquent peer associations or a general lack of commitment to prosocial activities and institutions, which can lead to problems with social development.

General Health Consequences of Marijuana Use

The use of marijuana introduces foreign substances into the body and produces a number of chemical changes in the user's brain and body. Given this, there is a large literature focusing on the physical effects of marijuana. To begin, there is little evidence to suggest that marijuana use poses a serious risk for an overdose death or its infrequent use is related to the development of long-term health problems (Copeland et al., 2006). This section focuses on the link between marijuana use and general health issues such as respiratory ailments, heart problems, threats to the immune system, potential

reproductive harms, and the risks for cancers. The section ends by exploring the effects of dependency and withdrawal symptoms.

Respiratory Ailments Related to Marijuana Use

The most common way of using marijuana is by smoking it. A direct consequence of this method of consumption is that smoke must enter the airways and lungs of the user. A past review by the authors (Diplock & Plecas, 2009) found a number of respiratory risks and harms related to marijuana use. Marijuana smoke contains many of the same poisons found in tobacco smoke (Lang 2007; Taskin, 2005), and this has led research to be focused on determining whether the respiratory outcomes of smoking marijuana are similar, less problematic, or worse than those associated with smoking tobacco (Copeland et al., 2006). One reason to believe symptoms may be worse in marijuana smokers is the way in which it is smoked, often unfiltered, with larger puffs, deeper inhalations, longer breath holding, and the use of the Valsalva manoeuvre (Lang, 2007). In their review of the research literature, Taylor and Hall (2003) argued that marijuana should be considered as damaging to the airways as tobacco. Aldington et al. (2007) argued that one marijuana cigarette had the potential lung obstructing effects of two to five tobacco cigarettes.

Taylor, Poulton, Moffit, Ramankutty, and Sears (2000) reported that respiratory symptoms were significantly more prominent in marijuana-dependent users than in non-users. The sample consisted of a group of 21 year old subjects from the 1970s who self-reported short histories of smoking marijuana (Taylor et al., 2000). The associated self-reported respiratory problems included wheezing, shortness of breath after exercise, nocturnal chest tightness, and early morning phlegm and mucus. These symptoms, which are typically indicative of chronic bronchitis, were also found to be associated with smoking marijuana in the research by Moore, Augustson, Moser, and Budney (2005). Overall, recent research suggests that most occasional marijuana smokers will not face serious negative respiratory

consequences, but that regular heavy use will likely cause accelerated declines in pulmonary functioning (Pletcher et al., 2012).

There is currently no consensus on whether marijuana smoking causes airflow obstruction. Taylor and Hall (2003) argued that there was a strong possibility that smoking marijuana was a contributing factor to the development of chronic lung disease. Further research by Tetrault, Crothers, Moore, Mehra, Concato, and Fiellin (2007) concluded that long-term marijuana smoking was also associated with an increase in airflow obstruction and obstructive lung disease. Aldington et al. (2007) argued that marijuana smoking may put users at risk of chronic obstructive pulmonary disease (COPD). However, Taskin (2009; 2010) argues that it is unlikely that marijuana smoking alone causes COPD, and research from Tan et al. (2009) reports that marijuana smoking may have an additive effect to COPD for those users who also smoke tobacco cigarettes, but that marijuana smoking alone was not associated to COPD.

Marijuana smoking does appear to have other effects on lung functioning. Marijuana use has been associated to higher lung volumes and hyperinflation (Hancox et al., 2010; Taskin, 2010). While the mechanism and consequences of these effects are unclear, they may be linked to other, serious though less common, conditions (Taskin, 2010). Research has found that marijuana smoking may be associated with serious respiratory conditions such as bullous lung disease (Hii, Tam, Thomson, & Naughton, 2008), collapsed lung (Beshay, Kaiser, Neidhart, Reymond, & Schmid, 2007; Gill, 2005), pulmonary fibrosis, byssinosis, and lung tumours (Phan, Lau, & Li, 2005). At this time there has not been enough research to provide estimates of the prevalence of these conditions.

Since many of the detrimental effects on the respiratory system are the direct result of smoking, there have been several studies examining whether vaporizers provide a less harmful way to consume marijuana (Earleywine and Barnwell, 2007; Hazekamp et al., 2006; Van Dam & Earlywine, 2010).

Based on self-reported respiratory symptoms after using vaporizers to inhale marijuana cannabinoids, Earleywine and Barnwell (2007) concluded that vaporizers did provide some measure of safety, especially as the amount of marijuana inhaled increased. Hazekamp et al. (2006) reached a similar conclusion. More recently, Van Dam and Earlywine (2010) conducted a small-sample pre-post test of vaporizers and found that the many respiratory symptoms were improved. The authors recommended that large-sample tests were needed to determine the viability of vaporizers as tools for harm reduction strategies (Van Dam & Earlywine, 2010).

While the use of vaporizers may eliminate or reduce some of the respiratory ailments for users, the THC in marijuana may pose another respiratory risk. As a response to the presence of THC, human airways experience cellular changes, especially to the mitochondrial energetic, which is responsible, in part, for the health of cells and their energy production (Sarafian et al., 2005; Sarafian et al., 2006). As expected, these changes were more significant with higher concentrations of THC and longer exposure times (Sarafian et al., 2005). In effect, as a result of THC in the lungs and airways, the risk of adverse pulmonary conditions is substantially increased (Sarafian et al., 2005; Sarafian et al., 2006).

Potential Harms of Marijuana Use on the Heart and Cardiovascular System

One direct outcome from using marijuana is an immediate increase in heart rate. It is estimated that marijuana use increases the heart rate 20% to 50% immediately following consumption (Copeland et al., 2006). This has led researchers to examine the short and long-term implications of marijuana use on the heart and the circulatory system. The majority of research in this area relies on case studies (Basnet, Mander, & Nicolas, 2009; Caldicott, Holmes, Roberts-Thomas, & Mahar, 2005; Lindsay, Foale, Warren, & Henry, 2005; Rezkalla, Sharma, & Kloner, 2003; Safaa, Markham, & Jayasinghe, 2012), which limits the generalizability of findings, but there are studies with larger sample sizes (Mittleman, Lewis, Maclure, Sherwood, & Muller, 2001; Vandry, Umbricht, & Strain, 2011). While effects on the heart and cardiovascular system can be very serious and may afflict marijuana users, it

must be kept in mind that there is little evidence to suggest that the outcomes discussed are typical or the norm for most users.

Based on their case study of a 34-year-old man who reported heart fluttering and near syncope after marijuana use, Rezkalla et al. (2003) suggested that marijuana was a likely contributor to the decrease in coronary blood flow and ventricular tachycardia experienced by their subject. Lindsay et al. (2005) described two cases; one in which a man with a history of heart problems suffered arrhythmia precipitated by marijuana use, the second described a young patient who suffered an onset of myocardial infarction. Based on these case studies, the researchers concluded that marijuana was a serious concern for those who may be predisposed to heart-related illnesses (Lindsay et al., 2005). Similarly, Caldicott et al. (2005) documented the case of a young patient who suffered a heart attack after marijuana use, despite having no other identifiable risk factors for a cardiac event. A case-study of a 17 year-old also found that marijuana may have played a role in reduced blood supply to the heart muscle (Basnet et al., 2009). Safaa et al. (2012) also identified coronary vasospasms resulting from reduced blood supply to the heart muscle as a potential risk of marijuana use based on a case study of a 40 year-old patient.

There have been other studies that have used larger samples to identify risks associated with marijuana use. A study by Mittleman et al. (2001) concluded that, although it was less common than other stressors, marijuana use was a trigger for myocardial infarction. In this study, the risk of onset of myocardial infarction increased approximately five-fold in the first hour after use (Mittleman et al., 2001). Marijuana is also a risk factor in clinically significant increases in blood pressure for some users after abrupt abstinence, particularly for those who already have hypertension (Vandrey et al., 2011). Mukamal, Maclure, Muller, and Mittleman (2008) reported that their findings suggested that marijuana use should be considered a particularly serious risk for those who have survived myocardial infarction and those with coronary heart disease.

When the research literature is considered, the conclusion is that marijuana use may, in rare instances, trigger a heart attack or other serious cardiovascular problems. Additionally, there have been instances in which a young person has experienced symptoms similar to Brugada Syndrome (Pratap & Korniyenko, 2012), a heart condition that is closely linked to sudden deaths. However, it is important to recognise that the evidence linking marijuana use to serious heart and cardiovascular effects may be confounded by the subject's participation in a wide range of other unhealthy habits and genetic predispositions. Still, there is evidence to conclude that marijuana can be harmful to the heart, and researchers, such as Aryana and Williams (2007), have voiced a belief that heart problems related to marijuana use may be more common than currently recognized. In addition, they warned that as the population of marijuana users aged, continued use may increase the risk for a number of adverse cardiovascular issues, such as tachyarrhythmia, acute coronary syndrome, vascular complication, and congenital heart defects (Aryana and Williams, 2007).

Consequences of Marijuana Use on Reproduction and Pregnancy

Research has explored the effects of marijuana use on sperm and egg development and the short and long-term outcomes for the foetus. This literature focuses on the relationship between drug use and implications for fertility and healthy, successful pregnancy. There is evidence to suggest that marijuana use can disrupt fertility and have other negative reproductive consequences.

Several studies have investigated the effects of marijuana use on male sperm fertility (Badawy et al., 2009; Rossato, 2008; Schuel et al., 2002; Whan, West, McClure, & Lewis, 2006). Scheul et al. (2002) found that the presence of THC in the reproductive fluids of both males and females could inhibit the ability of sperm to complete fertilization. Whan et al. (2006) also concluded that THC inhibited male fertility by binding to sperm cells and impairing sperm functions. More recent research suggests that there is a consensus that the THC and other cannabinoids in marijuana inhibit the sperm fertility

(Rossato, 2008). While all of the causal mechanisms have not been confirmed, one major contributor may be the fact that cannabinoids interfere with mitochondrial respiration and the production of energy for the sperm (Badawy et al., 2009; Rossato, 2009).

Marijuana use may also affect female fertility (Jukic, Weiberg, Baird, & Wilcox, 2007; Lee, Oh, & Chung, 2006). In females, marijuana was found to disrupt the endocrine system and produce an estrogenic effect, which can have detrimental effects on specific elements of the female reproductive system (Lee et al., 2006). It should be noted, however, that the effects were more the result of the contaminants of smoking the drug than the psychoactive chemicals (Lee et al., 2006). In addition, Jukic et al. (2007) determined that marijuana use negatively affected female reproductive hormones and could lead to delayed ovulation.

Overall, THC and other cannabinoids interact in a number of ways with the reproductive systems of both males and females. One recent review (Bari, Battista, Pirazzi, & Maccarrone, 2011) identified a number of risks marijuana use poses to the reproductive system. The authors indicated that males can experience a reduction in libido, problems with ejaculation, impaired sperm motility, reduced sperm counts, and impotence (Bari et al., 2011). Similarly, females can experience disruptions to the menstrual cycle, problems with ovulation, and impairment to the implantation and development of embryos (Bari et al., 2011). As the role of cannabinoids in human fertility is complex, even though researchers are currently exploring how these chemicals can be used to treat fertility problems in men and women, it is important to note that the use of marijuana may put users at risk of fertility problems.

As have been identified with the use of other drugs, there may be harms associated to the use of marijuana by pregnant mothers, particularly to the unborn foetus. Kuczkowski (2007) reported that THC crosses the placental barrier, but that there was no confirmation that it had a teratogenic effect. In other words, there is no evidence that marijuana use by a pregnant mother contributes or causes birth

defects or malformations. Based on their review of the research literature, Fried and Smith (2001) concluded that the effects of prenatal exposure to marijuana were subtle with little evidence supporting growth or behavioural effects prior to age three. However, research by Wang et al. (2006) determined that impairment was present in foetuses exposed to marijuana. Moreover, research from El Marroun et al. (2009) indicated that intrauterine exposure to marijuana, even for short durations, can lead to a number of issues such as low birth-weight, reductions to body and head growth when compared to children born without exposure. Similar findings including preterm labour were reported by Hayatbakhsh et al. (2012).

There may be longer-term emotional and behavioural implications for children exposed to marijuana while in the womb. Day et al. (2006) concluded that there was a statistically significant association between prenatal exposure to marijuana and later use; however, these researchers also concluded that there were many other potential factors that could have contributed to later marijuana use among those exposed to the drug while in the womb. Findings from a study by Goldschmidt, Richardson, Willford, and Day (2008) indicated that children who were exposed to marijuana while in the womb had significantly lower school-age intellectual development. However, these findings reflected use by mothers of at least one marijuana cigarette per day during pregnancy (Goldsmith et al., 2008).

Maternal use of marijuana was not associated to later psychotic symptoms in offspring in a study exploring the potential of prenatal exposure to alcohol, tobacco, and marijuana (Zammit et al., 2009). However, El Marroun et al. (2011) found that intrauterine exposure to marijuana increased the risk of aggressive behaviour and attention problems in children at 18 months of age. This was only found for girls, and the authors indicated a need for further exploration (El Marroun et al., 2011). Also, Day, Leech, and Goldschmidt (2011) found that youth at age 14 who had been exposed to marijuana while in the womb were more likely to be involved in delinquent behaviour, partially due to the effects that prenatal exposure to marijuana had on increasing depressive symptoms and attention problems in childhood.

While the previous review was unable to identify many serious risks of maternal marijuana use (Diplock et al., 2009), it is now becoming more clear that exposure to marijuana while in utero may have negative implications for children. It is likely that the harms become increasingly likely with greater consumption of marijuana during pregnancy (Day et al., 2011; Goldschmidt et al., 2009), and therefore efforts to stop or at least reduce marijuana use by pregnant women would appear warranted (Hayatbakhsh et al., 2012). While more research is still needed to determine if there are even more risks of use during pregnancy, it is important for potential parents to understand that marijuana use during pregnancy can potentially affect a child's physical and neuropsychological development (Day et al., 2011; Goldschmidt et al., 2009; El Marroun et al., 2009).

Marijuana Use as a Potential Threat to the Immune System

THC and other cannabinoids from marijuana use may impair the immune system functions of various cells. If the immune system is compromised by the use of marijuana, there may be significant implications for the health of users (Copeland et al., 2006). The relationship between marijuana use and deficiencies in the immune system is based, in part, on the findings that THC inhibits the ability of T-cells and alveolar macrophages to protect the body from foreign pathogens (Tashkin, Baldwin, Sarafian, Dubinett, & Roth, 2002; Tashkin, & Roth, 2006; Shay et al., 2003). Alveolar macrophages are a main defence against infections in the lungs. A review of the research literature in this area by Copeland et al. (2006) suggested, however, that it might require high doses of THC to substantially impair immune system functioning. Recently, research has tended to focus on the effects of THC and other cannabinoids on alleviating symptoms related to serious medical conditions involving the immune system (Pacher & Gao, 2008; Tanasescu & Constantinescu, 2010). While it appears that these constituents of marijuana may have the potential for therapeutic uses as a result of their anti-inflammatory and immunosuppressive effects, there may also be risks of negative effects, such as serious infections, if used either medically or recreationally, particularly for those with previously compromised immune systems (Gargani, Bishop, & Denning, 2011).

Cancer Causing Effects of Marijuana

Because marijuana smoke contains many of the same harmful carcinogens as tobacco smoke, there is a possibility that marijuana use may be associated with the onset of various types of cancers (Tashkin et al., 2002). While there are cases in which cancers appear to be caused by substantial marijuana use (Graef, Choo, Warfield, Cullen, & Woolhouse, 2011), to date, research has been inconclusive about the link between marijuana use and cancer. There are many of the methodological difficulties in attributing cancer outcomes specifically to smoking marijuana (Mehra, Moore, Crothers, Tetrault, & Fiellin, 2006). For example, in many instances, marijuana users also smoke tobacco, there is the challenge of determining proper thresholds for marijuana use, and the research has typically included only small sample sizes.

Since the most common method of administration for marijuana use is smoking, lung cancers have received research attention. In their study, Hashibe et al. (2006) failed to find substantial evidence for an association between marijuana use and lung or upper aerodigestive tract cancers. A study by Berthiller et al. (2008) concluded that marijuana smoking did increase the risk of lung cancer, but since every subject in their marijuana smoking sample also smoked tobacco, the effects of confounding variables could not be ruled out. Aldington et al. (2008b) also reported that long-term marijuana smoking increased the risk of lung cancer, but this conclusion was challenged by Sewell, Cohn, and Chawarski (2008) on the basis of methodological issues and the interpretation of an association as causal.

Other research on other kinds of cancer has been equally inconclusive. Rosenblatt et al. (2004), in their large-sample study, concluded that marijuana was not associated to oral squamous cell carcinoma. Aldington et al (2008b) found no increased risk of head and neck cancer, although the duration use studied may have been too short for a long-term effect to appear in the data. Liang et al. (2009) reported that moderate use of marijuana may in fact reduce the likelihood of head and neck squamous

cell carcinoma. There was also no link between maternal or paternal marijuana use and risk of childhood acute myeloid leukaemia (Trivers et al., 2006).

There are many researchers who believe that the changes to a variety of cells in the body caused by marijuana use may contribute to the development of cancers including lung cancer, oral cancers, and breast cancer (Cho, Hirsch, and Johnstone, 2005; Mehra et al., 2006; Lee et al., 2006; Tashkin et al., 2002). Research on testicular germ cell tumours (TGCT), a rare form of cancer accounting for less than 2% of cancers in men, have found an association between this disease and marijuana use (Daling et al., 2009; Trabert, Sigurdson, Sweeney, Strom, & McGlynn, 2011). Daling et al. (2009) found that men with this condition were more likely to use marijuana than controls, indicating an association between marijuana use and this type of cancer. Trabert et al. (2011) reported a two-fold increased risk of TGCT association to regular marijuana use. While neither study could confirm the causal mechanism for the increased risk, both recommended further research on this topic (Daling et al., 2009; Trabert et al., 2011). Indeed, more research is needed to explore the potential for marijuana to be associated to a number of cancers, and also for any potential protective qualities of the cannabinoids against cancers to be explored.

Marijuana Dependency and Withdrawal

Despite the commonly held belief that marijuana use does not lead to addiction, existing research has often referred to a dependency on the drug (Copeland et al., 2006). Although many people use marijuana on a regular basis, Looby and Earleywine (2007) reported that fewer than half of all daily users exhibited the behaviours necessary to meet the established criteria for being classified as drug dependent. These criteria include tolerance, withdrawal, taking the drug for longer periods of time or larger doses than intended, inability to stop or reduce use, increasing the time spent obtaining the drug and recovering from its effects, ignoring other important activities, and continuing use despite undesirable consequences. Looby and Earleywine (2007) argued that dependence was not a necessary

result of frequent use, but that it may be a contributing factor. Their research suggested that negative effects of marijuana use, such as dissatisfaction with life, low motivation, and unhappiness, were more related to dependence on the drug than regular use (Looby & Earleywine, 2007). When considering the results of Looby and Earleywine's research with findings from Copersino et al. (2006) on withdrawal symptoms, strong support is established for the idea that a proportion of frequent marijuana users suffer negative effects resulting from a dependency.

Hasin et al. (2008) reported that withdrawal was prevalent among a sample of regular marijuana users. The commonly reported symptoms include weakness, hypersomnia, sleeping, yawning, depression, and feelings of anxiety or nervousness (Hasin et al., 2008). Bonn-Miller and Moos (2009) found that those in treatment for marijuana abuse who were more frequent users were more likely to experience anxiety after abstaining from use. Higher levels of anxiety and more frequent use were found to be significant predictors of relapse (Bonn-Miller & Moos, 2009). Levin et al. (2010) found that withdrawal symptoms were associated to failed attempts to quit use, as the drive to relieve the symptoms can cause users to relapse. Furthermore, withdrawal symptoms are prevalent even among marijuana users who do not exhibit other drug dependencies (Hasin et al., 2008).

In terms of factors that most likely contribute to the development of a marijuana dependency, Hall (2006) reported that initiation to drug use at an early age was the most significant factor. However, in terms of public policy, if THC levels are indeed increasing and continue to increase, there will likely be a growing number of users who find themselves dependent on the drug. This may prove to be more problematic if future research establishes additional and more serious negative health consequences of long-term use as users may experience more difficulty abstaining from use even in the face of exacerbating social and health problems. Researchers have suggested that marijuana dependency and withdrawal have serious clinical consequences, should be included in the DSM-V, and are a legitimate area for focused treatment (Hasin et al., 2009; Levine et al., 2010).

Marijuana Use and Mental Health

In addition to some potentially serious physical health problems, marijuana use has also been associated with mental health problems. While this topic had received a great deal of attention in research, the documentary film associated to the CBC's *The Nature of Things* titled *The Downside of High* (Mohun, 2010) brought the association between mental illness and marijuana into the public spotlight in Canada. The link between marijuana use and psychosis or later schizophrenia has possibly received the most attention in the research literature. However, there is research that associates marijuana use to other mental health issues including depression and anxiety.

Marijuana-Precipitated Psychosis and Schizophrenia

An association between marijuana use and the onset of psychosis has become a serious concern. Research suggests that 8% to 10% of all cases of psychosis may be triggered by the use of marijuana (Arseneault, Cannon, Witton, & Murray,; Linszen and Van Amelsvoort, 2007). Ferdinand et al. (2005) concluded that marijuana use was linked to psychosis independent of any previous mental pathology. Moore et al. (2007) argued that there was enough evidence to support a public warning that marijuana use increases the chances of suffering from a psychotic illness. The risk may be more pronounced for those who are already vulnerable for this type of mental affliction (Arseneault et al., 2004; Degenhardt and Hall, 2006; Linszen and Van Amelsvoort, 2007). In order to explain this relationship, Caspi et al. (2005) reported that there may be an interaction between the chemicals typically present in marijuana and a number of 'susceptible' genes in the user that contributes to the onset of marijuana-induced psychosis and schizophrenia. It is also likely that state of brain development during adolescence creates greater vulnerability to psychotic effects from marijuana use and perhaps even schizophrenia (Malone, Hill, & Rubino, 2010). Other recent research also suggests that earlier age of onset for marijuana use is associated to earlier expressions of psychotic symptoms in those who are predisposed (Dragt et al., 2010).

If marijuana use triggers psychosis, it might be a risk factor for schizophrenia (Arsenault et al., 2004; Arendt, Rosenberg, Foldager, Petro, & Munk-Jorgensen, 2005; Caspi et al., 2005). In a study to determine whether those who suffered from an episode of marijuana-induced psychosis were at risk of developing later schizophrenia, Arendt et al. (2005) found that marijuana-induced psychosis was an important risk factor for developing schizophrenia and that often symptoms began earlier than they did for those with no self-reported marijuana use. Solowij and Michie (2007) found similarities between the cognitive effects of marijuana use and the cognitive endophenotypes of schizophrenia.

One of the complications for fully understanding marijuana's association with psychosis and later schizophrenia is that people with mental illness may continue to use the drug. Grech, Van Os, Jones, Lewis, and Murray, (2005) investigated the effects of marijuana use in patients who had recently suffered from psychosis to determine whether symptoms were prolonged and worsened by the drug. From their findings, it appeared that those who continued to use marijuana were at a greater risk of having more symptoms and a continuous course of mental illness (Grech et al., 2005). It could not be confirmed from their study, however, whether marijuana made the symptoms worse or the degree to which marijuana directly contributed to the symptoms. Dekker, Linzen, and De Haan (2009) reviewed studies that asked patients suffering from psychotic symptoms why they used marijuana and what the effects were. The results indicated that while marijuana was used because it was perceived to improve relaxation, affect, and sociability, many patients reported negative effects (Dekker et al., 2009). A 10-year follow-up study of patients hospitalized for schizophrenia spectrum disorders revealed that continued marijuana use was associated with more severe psychotic symptoms independent of other factors (Foti, Kotov, Guey, & Bromet, 2010). It was also found that those suffering from more severe psychotic symptoms were more likely to use marijuana, which has important implications for treatment.

There are a number of hypotheses in the research literature about the nature of the relationship between marijuana use and psychotic symptoms (Degenhardt, Hall, & Lynskey, 2002; Hall, 2006;

Hall and Degenhardt, 2000; Smit, Bolier, & Cuijpers, 2004). The most common hypotheses were that: (1) marijuana use causes psychosis and schizophrenia without any existing predisposition; (2) marijuana use triggered the onset of these symptoms in people who were previously vulnerable; (3) marijuana use exacerbated the symptoms in those already suffering; and (4) those already suffering from these symptoms were more likely to self-medicate with marijuana. Based on the research, the strongest support was for the second and third hypotheses, with the self-medicating hypothesis failing to find any support.

The causal hypothesis remains debatable. Degenhardt and Hall (2002) found that cases of schizophrenia in the general population did not rise with an increase in reported marijuana use, thus weakening the case for the causal hypothesis. While multiple cohort studies that measure marijuana use and incidence of psychosis have found support for the general direction of a causal relationship, there is not enough evidence to claim that marijuana use causes schizophrenia or psychotic disorders that would not have otherwise occurred (McLaren, Silins, Hutchinson, Mattick, & Hall, 2010). While suggesting that marijuana use is neither necessary to cause schizophrenia or capable of doing so in and of itself, D'Souza, Sewell, and Raganathan (2009) argued that it may be a component cause, meaning that exposure to marijuana's cannabinoids, when combined with other factors, may cause a psychotic disorder. Further research is needed to more fully understand whether there is a causal relationship between marijuana use and psychosis, and to determine what the mechanisms are that may cause the cannabinoids to contribute to these types of mental illnesses. However, based on the research to date, psychosis and later schizophrenia as a result of marijuana use should be viewed as a potential risk for a small portion of marijuana users.

Depression and Anxiety among Marijuana Users

There is a larger body of research exploring the link between marijuana use and psychosis and schizophrenia than there is for other mental health issues associated with marijuana use. However,

research has explored marijuana's link to other mental health issues such as depression and anxiety. Diego et al. (2003) found that increased marijuana use among high school students, like the use of cigarettes and alcohol, was associated with increased self-reports of depression. However, Harder, Morral, and Arkes (2006) found that past-year marijuana use was not a significant predictor of future development of depression. Harder, Stuart, and Anthony (2008) found that depression may be a moderate risk for males who use marijuana, but that findings suggested that it did not contribute to depression in females. Similarly, research by Bonn-Miller, Zvolensky, Leen-Feldner, Feldner, and Yartz (2005) found that marijuana use was a predictor of anxiety symptoms, but not for depression. A study of marijuana use among high school students found that marijuana users had higher rates of both depression and anxiety, and that marijuana use was independently associated to measures of suicidality. Buckner, Joiner, Schmidt, and Zvolensky (2012) found a link between marijuana use and high social anxiety, which were also related to suicidality. Daily marijuana users with high anxiety had the highest levels of suicidality (Buckner et al., 2012). Furthermore, those dealing with problems associated to marijuana use may be more likely to exhibit social avoidance behaviours (Buckner, Heimberg, & Schmidt, 2011). Again, it remains a challenge to determine whether marijuana use is a cause of these symptoms, whether it exacerbates the symptoms in those who already exhibit them, or if the symptoms play a contributing role in marijuana use.

Marijuana's Role in Continuing Drug Use

The discussion of potential harms of marijuana use presented thus far indicated that marijuana poses a number of potential risks to the general population of users and some specific negative outcomes for a relatively small subgroup. The risk or actual harms associated with marijuana use can be seriously compounded by the use of other drugs, and can become overshadowed by the dangers associated with becoming addicted to 'harder drugs'. Moreover, there has long been the suggestion that marijuana can act as a 'gateway' for other drug use. It would appear that the probability that marijuana acts as a gateway to other illicit drugs is much higher than the other way around (Fergusson & Horwood, 2000). According to Fergusson and Horwood, when adjusting for other common covariate factors such as

childhood, family, and life-style factors, regular marijuana use (fifty or more times in a year) was strongly related to the onset of further illicit drug use. However, Morral, McCaffrey, and Paddock (2002) found that the opportunities presented by the lifestyle accompanying marijuana use were just as likely to predict the use of other illicit drugs as was the use of marijuana.

Since the majority of marijuana users do not continue on to other illicit drugs (Fergusson and Horwood, 2000), it is important to understand what factors distinguish between those who do and those who do not go on to use other illicit drugs. The policy and control responses are likely to be very different depending on whether the relationship is based on the effects of marijuana use or on the lifestyles that accompanied marijuana and other illicit drug use. Twin studies have established that marijuana use is a strong predictor of future illicit drug use regardless of the familial and environmental similarities between twins (Lynskey, Vink, & Boomsma, 2006). However, other research focusing on both monozygotic and dizygotic twins suggested that it is more likely that individual genetic traits explain the progression of marijuana to other drugs than does a triggering effect from the marijuana itself (Cleveland & Weibe, 2008). Agrawal et al. (2007) came to a similar conclusion that there is strong evidence of confounding factors such as genetics and lifestyle explaining the relationship between early marijuana use and later use of other illicit drugs, but the “gateway” effect could not be discredited. Recent data from a study by Van Gundy and Rebellon (2010) found that the link between adolescent marijuana use and adult use of other illicit drugs is more a factor of stress and other life-course variables than of a “gateway effect”. Degenhardt et al. (2010) also suggested that much of the progression to other illicit drugs was likely the result of other common causes, and that preventing the use of so-called “gateway drugs” will not likely lead to large reductions in the use of other illicit substances.

Overall, it is known that marijuana users are at an increased risk of continuing on to other illicit drugs. In fact, research suggests that it is rare for marijuana use not to have preceded the use of other illicit drugs (Van Gundy & Rebellon, 2010). However, this may be more the result of the user than the drug.

While it is most probable that pre-existing individual and environmental risk factors or lifestyle factors associated to marijuana use explain the “gateway effect”, there is not enough evidence to fully disprove the gateway theory. The hypothesis that pharmacological effects of marijuana use independent of other factors increase the likelihood of using other illicit drugs has yet to show strong evidence (Agrawal et al., 2007), although researchers continue to test this hypothesis (Fergusson, Boden, & Horwood, 2006; Lessem et al., 2006). Even with what is known, a better understanding of the potential causes or correlates for this association are needed to determine how changes to marijuana’s current legal status would impact patterns, rates, and additional harms of other drug use.

Conclusions

The discussion of the appropriate policy direction on marijuana use needs to be informed by up-to-date and unbiased research on the harms it may present to users. Based on a review of the current literature, it can be concluded that marijuana does pose some considerable risks to users. Concern over marijuana is merited by findings regarding its ability to create short-term impairment, specifically on driving ability. Academic performance and social development appear to be negatively affected by marijuana use, but the causal role that the drug plays in the lack of future success of young people remains unconfirmed. As expected, smoking the drug contributes to considerable harm to the lungs and airways. Even though the use of vaporizers removes the contaminants of combustion and reduces some major respiratory problems, THC exposure to the lungs appears to be unhealthy. The immune system is also compromised by the use of marijuana, specifically the ability of the lungs to defend against foreign pathogens. Although cancers, heart problems, and threats to human reproduction are not common among marijuana users, most experts contend that further investigation is required and the potential for risk should not be dismissed. The development of psychosis and later schizophrenia should also remain a concern for a small proportion of those who use marijuana. Dependency and regular, long-term use of the drug are also factors that likely exacerbate the potential for the majority of the harms previously identified in this review. Of course, these harms are often compounded by the fact that marijuana users have an increased likelihood of continuing on to other illicit drugs.

With a growing amount of research on the potential therapeutic benefits of marijuana and its constituent cannabinoids, there is a responsibility on those who advocate for its medical use to ensure would-be patients are adequately informed of the risks. As is the case with other drugs used for medical purposes, marijuana can have negative effects which could outweigh the benefits if used incorrectly. It is particularly important for messages to be crafted in such a way that the general public and potential recreational users do not misinterpret the potential medical benefits as evidence that marijuana use is completely risk-free. Similarly, if public policy moves toward decriminalization or legalization, the process needs to ensure that the policy rationale for the decision (i.e. increased taxation, reduced criminal justice costs, potential effects on organized crime, etc) does not send the message that the change to the legal status was based on the fact that the drug poses no risk.

Although very serious consequences from marijuana use are relatively rare, it should be acknowledged by all that the lives of a small proportion of the population will be seriously disrupted by marijuana use. The debate over the appropriate way to respond to marijuana use in society requires advocates both of decriminalization and of prohibition to concede that marijuana is neither harmless, nor is it particularly dangerous to the majority of users. With an understanding of the potential harms associated to marijuana use forming the basis of the debate, politicians, policymakers, and citizens can make responsible decisions about the legal status of the drug. By understanding that marijuana can and does cause harm to users, whether it is prohibited, decriminalized, or legalized, all concerned are in a better position to address those questions that must be answered in order to move forward. Among many others, those close to the debate need to consider the following questions: Are we willing to accept that some members of society will be harmed by marijuana use, and are taxpayers willing to pay associated costs? What lessons can be learned from the experiences with alcohol that might apply to marijuana? Are there other or better approaches than prohibition to manage the problems that marijuana use creates? Would changing the legal status promote increased marijuana use, reversing current decreasing trends? Would removing the prohibition of marijuana improve our ability to mediate the known harms, or would it result in even greater social harm?

To date, the research evidence shows that marijuana has a number of associated harms. In some cases, these harms are worse than those associated with regulated substances, such as alcohol or tobacco.

Based on the course of research, it is likely that future studies will further refine our understanding of the harms of marijuana use. It is possible that as time goes on, a greater number or more serious harms will be identified, or that answers to currently unanswered questions will reveal that there are relatively fewer risks than is now believed. Additionally, new research may discover ways to substantially limit the amount of harm caused by marijuana use. New information related to the harms of marijuana use should purposefully be brought into the discussion about how to deal with this issue. In any case, it is necessary that researchers disseminate their latest findings in a wide range of ways in order for the public to have the best information at their disposal about the harms and risks associated with using marijuana.

Author Information:

Jordan Diplock is a Research Analyst with the Royal Canadian Mounted Police. He is also a Research Associate in the Centre for Public Safety and Criminal Justice Research, and teaches part-time in the School of Criminology and Criminal Justice at the University of the Fraser Valley. He has co-authored numerous reports and articles relating to illicit drug production and use.

Darryl Plecas is the RCMP Research Chair and Director, Centre for Public Safety and Criminal Justice Research in the School of Criminology and Criminal Justice at the University of the Fraser Valley. He is also a member of the Board of Directors for the Canadian Centre on Substance Abuse. He has co-authored numerous reports and articles relating to illicit drug production and use.

Len Garis is the Fire Chief for the City of Surrey, B.C., President of the Fire Chiefs Association of British Columbia and Adjunct Professor in the School of Criminology and Criminal Justice at the University of the Fraser Valley and a member of the Institute of Canadian Urban Research Studies, Simon Fraser University. He has co-authored numerous reports and articles relating to illicit drug production and use.

Conflict of Interest Statement:

On behalf of my co-authors, Jordan Diplock (RCMP Research Analyst), Len Garis (Adjunct Professor at the University of the Fraser Valley), and myself (Darryl Plecas, RCMP Research Chair and Director, Centre for Public Safety and Criminal Justice Research, University of the Fraser Valley, and Board Member, Canadian Centre on Substance Abuse), I declare that we have no proprietary, financial, professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled “An Updated Review of the Research on the Risks and Harms Associated to the Use of Marijuana”.

Dr. Darryl Plecas

RCMP Research Chair

Director, Centre for Public Safety and Criminal Justice Research

University of the Fraser Valley

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Designer Drugs: An Escalating Public Health Challenge

Bertha K. Madras, PhD Professor of Psychobiology, Department of Psychiatry
NEPRC-Harvard Medical School

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Abstract

Designer drugs are created to be similar to, but not identical with psychoactive drugs that are illegal to possess or sell for human consumption. A recurring threat to public health, the designer drug sub-culture has exploded over the past decade. The rapid expansion can be attributed to a convergence of key technological advances combined with devious, aggressive marketing schemes. Globally accessible internet sites provide detailed information on the sensations produced by newly created drugs, how to synthesize them, and easy venues for buying the “research chemicals”, “bath salts”, “plant foods”, “incense”, and “plants” from websites. Frequently, these sites are impervious to legal sanctions, as it takes time to deliberate the evidence and move newly emerging drugs into a legally restrictive zone. This challenge is compounded by imperfect international agreements and a gradual dissolution of international resolve for combating drug use with supply side restrictions and laws. The designer drug industry is a niche business with a simple strategy to: (a) circumvent existing drug laws and promote their “products” as legal, (b) create new markets with rapid profits, (c) undercut producers and prices of common illegal drugs (e.g. cocaine, marijuana, and heroin), and (d) undermine routine clinical drug

testing. The consumer misperceives the drugs as legal, less hazardous than conventional street drugs, and more intriguing. They are more challenging to detect and easier to evade routine clinical drug testing. This overview summarizes legal, biological and psychoactive effects of two classes of designer drugs, cathinone-based psychostimulants packaged as “bath salts” and synthetic cannabinoids sold as “Spice” or “K2”. The essay concludes with a set of policy recommendations.

A. Introduction

Over millennia, humans serendipitously discovered that certain ingested plants were a source of unique rewarding sensations, beyond satiety. Some were mildly arousing (e.g. nicotine, caffeine), others enhanced mood or altered perception, reduced pain, intoxicated, or produced euphoria (e.g. alcohol, marijuana, hallucinogens, opiates, cocaine). In the past two centuries, consumption of these psychoactive substances expanded rapidly. Purification of the active chemicals, delivery by devices for maximum effect and global marketing contributed to this expansion. Modern chemistry has produced a vast array of variations of these plant products, paralleled by an unprecedented level of adverse biological, behavioral, medical and social consequences.

Designer drugs are created to be similar to, but not identical with psychoactive drugs that are illegal to possess or sell for human consumption - unless for medical purposes. It attracts those seeking “legal highs” and reflects the view that designating a drug as illegal attenuates use.

A recurring threat to public health, the designer drug sub-culture has exploded over the past decade. The rapid expansion can be attributed to a convergence of key technological advances combined with devious, aggressive marketing schemes. Globally accessible internet sites provide detailed information on the sensations produced by newly created drugs, how to synthesize them, and easy venues for buying the “research chemicals”, and “bath salts”, from websites. These sites are frequently impervious to legal sanctions, as it takes time to deliberate the evidence and move newly emerging drugs into a legally restrictive zone. This challenge is compounded by

imperfect international agreements, and a gradual dissolution of international resolve for combating drug use with supply side restrictions and laws.

A blunt snapshot of the global reach of this market can be gleaned from the European Union funded Psychonaut Web Mapping Project aimed at real-time identification of emerging new psychoactive substances (“legal highs”) through regular monitoring of the Internet: over 200 discussion forums, social media, online shops, websites and other Internet resources through YouTube, eBay, Google, and Google Insight (1). From these sites, more than 410 substances/products were recorded (121 herbal compounds, 153 chemical compounds, and 140 combinations). Not all became catalysts for a public health response and not all fell under the “illegal umbrella”. Detailed, valuable information emerged from these websites and forums, especially for substances with limited or nonexistent scientific publications. The rise of “Spice”, mephedrone, naphyrone, MDAI (5, 6-methylenedioxy-2-aminoindane), and MDPV (methylenedioxypropylvalerone) were tracked from single source countries until they spread widely. After they fell into the illegal zone of control, online searches decreased (1). This study dramatically highlights the cost-benefit of the internet, as a hub of information on designer drugs for consumers, but also as a propitious source of market trends for public health and law enforcement officials.

1. What are designer drugs?

Designer drugs are produced in laboratories, the majority resembling drugs legally restricted for distribution and possession. They share one common trait, producing psychoactive effects that can range from cannabis-like, psychomotor stimulation, dissociative anesthesia to hallucinogenic. Examples include mephedrone, methylone, MDPV, ethylphenidate, synthetic cannabinoids in “Spice” or “K2”, 2,5-dimethoxy-4-(n)-propylphenethylamine (2C-P), N-adamantyl-1-pentylindole-3-carboxamide (2NE1), methiopropamine, and methoxetamine. They are sold inexpensively as bulk powders, and are deceptively labeled “research chemicals”, “bath salts”, plant food” “incense”, “food”, or by other names and designated “not for human consumption”. The designer drug industry is a niche business with a simple strategy to: (a) circumvent existing drug laws and promote their “products” as legal, (b) create new markets with rapid profits, (c) undercut producers and prices of common illegal drugs (e.g.

cocaine, marijuana, and heroin), and (d) undermine routine clinical drug testing. The consumer misperceives the drugs as legal, less hazardous than conventional street drugs and more intriguing. They are more challenging to detect and easier to evade routine clinical drug testing. Standard strip tests do not identify most of these compounds. Nonetheless, most drugs or their metabolites are effortlessly isolated from biological samples, including hair samples, and can be identified in laboratories with standard or advanced analytical techniques (2, 3).

2. Sources and complexity

The range of substances available is wider than ever before, with the internet enabling a global marketing stream of choice and access. Primary sources are unregulated laboratories in Asia. For example, manufacturers in various cities in China (Wuhan, Changzhou, Shanghai, Hangzhou, Beijing) directly market a variety of designer drugs on the internet as “research products” or chemicals, “not for human consumption”, which can be allocated and sold in innocuous-looking packets. Designer drugs may evoke psychoactive effects similar to the parent drug, or elicit a more intense, amplified, unique or life-threatening response. Some are designed to mimic Schedule I or lower schedule drugs (e.g. THC or tetrahydrocannabinol, cocaine, cathinone, amphetamine, or methamphetamine, ketamine, LSD or lysergic acid diethylamide, methaqualone), while others create complex sensations because of their hybrid structures, and amalgamation of substances. Infrequently, new drugs are designed or discovered that have neither precedent in medicinal chemistry nor a long history of abuse (e.g. SalvinorinA), yet may possess equal or greater abuse potential or health hazards.

With the exception of barbiturates and benzodiazepines, psychoactive pharmaceuticals originated largely as modified plant products (e.g. ephedrine, THC, ergot, cocaine, morphine, cathinone). Designed by medicinal chemists in pharmaceutical companies, universities and small research companies for medications development, the vast majority were rejected because of their poor therapeutic potential, based on safety and efficacy trials. Others were created for basic research, to clarify the biological targets of plant products or to investigate mechanisms of chemical communication in the brain. For example, synthetic cannabinoids were instrumental in

mapping the targets of marijuana in the brain. The brain regions expressing marijuana sites of action were consistent with its array of psychoactive properties. The hippocampus, a brain region essential for learning and memory, harbored high concentrations of cannabinoid signaling receptors. Analogs of cocaine are another example of chemical modifications created for biological research. A radioactive analog of cocaine clarified the biological targets of cocaine in the brain (4). After being shelved in research laboratories, in dormant patents, or medicinal chemistry journals, these compounds are being revived as “designer drugs” by chemists (5). The majority of designer drugs are concocted by changing or inserting a few or more atoms into the core structures of legal or illegal drugs, by mining old sources (chemical journals, patents), or by creating new entities based on existing structures. Although these modifications can drastically transform the psychobiology of the parent drug, a slight or major structural variation can temporarily evade legal definitions, penalties and consequences. By this strategy, designer drugs are manipulated into a legal “grey zone”.

A challenge to the scientific and the consumer community is the complexity of unregulated production of these chemicals. Laboratory analyses of 124 different “K2” cannabinoids products and other “bath salts” submitted to the Arkansas Designer Drug Research Consortium identified the inclusion of over 240 distinct chemicals in 46 different combinations of compounds, including the cathinones MDPV, 4-methylmethcathinone (methyone, 4-MMC), 3,4-methylenedioxymethcathinone (mephedrone), as well as caffeine, lidocaine, methamphetamine, levamisole, benzocaine, and synthetic cannabinoids (Dr. JH Moran, Arkansas Dept of Health, reported at the annual CPDD meeting, June 2012). Without quality assurance and deceptive labeling practices, compounds vary from product to product, from batch to batch and even contain “hot spots” within each packet. This array of untested poly-pharmaceuticals place users at great risk to their health, baffle emergency department physicians, and render the medical community defenseless in identifying the most significant threat to patients’ health and selecting effective antidotes.

B. Legal History and Status

Drug traffickers circumvented drug laws by developing analogs of banned opioids as early as the 1920's. During the 1960's a rash of new psychoactive drugs were introduced to American culture. The movement to normalize use and the resulting pandemonium catalyzed the formation of the Drug Enforcement Administration (DEA) in the United States in 1973, establishing a single unified federal agency to regulate drugs with high abuse potential. The resistance to drugs and a shift in perceptions took years to penetrate public opinion, when drug use became viewed as reducing natural potential, and the consequences of drugs in family members, schools, and the workplace, begin to take a toll. Drugs were placed into 5 categories known as schedules. Schedule I substances have a high potential for abuse, no currently accepted medical use in treatment in the United States, and a lack of accepted safety for use of the drug under medical supervision. These drugs include. heroin, lysergic acid diethylamide (LSD), marijuana (cannabis), peyote, methaqualone, and MDMA or ecstasy. Legal psychoactive drugs classified as Schedule II drugs have accepted medical use, and a high potential for abuse which may lead to severe psychological or physical dependence. Examples of these drugs are opioids (methadone, oxycodone, hydromorphone, meperidine, fentanyl), stimulants (cocaine, amphetamine, methamphetamine, methylphenidate), and barbiturates; Drugs in Schedule III (hydrocodone, buprenorphine, codeine, ketamine and anabolic steroids), Schedule IV (propoxyphene, benzodiazepines), and Schedule V (low dose narcotics for cough, diarrhea, or pain) have decreasing abuse liability, but accepted medical uses. Encroachment of regulations by non-medical use of scheduled drugs reflects a growing challenge to the medical and law enforcement community. Prescription medications, primarily opioid analgesics, may be legally obtained by a single physician, by "doctor-shopping" (obtaining multiple prescriptions from multiple physicians, even crossing state lines to accumulate supplies), from friends and family (without payment) and used inappropriately by intended or unintended persons for psychoactive purposes or chemical coping. Marijuana can be "recommended", but not prescribed by a physician in states that have approved its use, even though it is not approved by the Food and Drug Administration (FDA) and remains an illegal drug, classified in Schedule I by the Federal government. The majority of designer drugs are similar in chemical structure to illegal or legal drugs currently under federal and/or international control. Emergency scheduling has inserted a number of them into Schedule I, on the basis of accumulating evidence that they are health hazards.

1. Law enforcement and amendments

Advocates of stringent legal restrictions and policies for drugs view drug issues through a prism of concerns for human health, welfare, social and safety. The DEA has drawn legal distinctions among substances, but these boundaries are frequently breached by substance abusers. Law enforcement is in a perpetual race to outflank designer drug producers and dealers. As the federal government cannot prosecute until drugs are marketed, the Comprehensive Crime Control Act of 1984 amended the Controlled Substances Act (CSA) to allow the DEA Administrator to temporarily schedule an abused, harmful, non-medical substance in order to avoid an imminent hazard to public safety while the formal rule-making procedures are in process. This change required that a controlled substance be a single chemical of known structure, but this criterion could be circumvented readily by slight chemical modifications. Regulation of new “designer drugs” was catalyzed by the reported deaths from consumption of 4-methylfentanyl or “China White”, an opioid approximately 30 times more potent than the extremely potent fentanyl (6). In response, Congress enacted the Controlled Substance Analogue Enforcement Act of 1986, which defined a “controlled substance analogue” as a chemical structure “substantially similar” to the chemical structure of a controlled substance in schedule I or II, with psychoactive properties (i.e. stimulant, depressant, hallucinogen), similar to the controlled substance in Schedule I or II. Yet, the “substantially similar” clause proved to be ineffective in protecting the public, with the appearance of synthetic cannabinoids which are structurally quite distinct from THC or Δ^9 -tetrahydrocannabinol yet engendering similar psychoactive effects (6).

In 2011, the Synthetic Drug Control Act (H.R. 1254) amended the earlier CSA with a new provision to schedule “cannabimimetic agents,” as functional compounds that act at the cannabinoid receptor1 (CB1). With this strategy, the Act attempted to preempt distribution of new molecules, regardless of structure, that would have the same end point - a pharmacological response similar to THC at the cannabinoid receptor1. The law also incorporated new restrictions on substituted cathinones and hallucinogenic phenethylamines, anticipating that the chemistry literature would be excavated to identify and circumvent weaknesses inherent in the “controlled

substance analogue” law. The net effect is to raise the barriers to “legal highs” and expand the “red zone” of federal law by anticipating a broader range of chemicals that can be abused, by adding psychoactive properties *and* biological targets (e.g. receptors) as criteria for scheduling a compound.

As of 2012, the DEA currently has emergency powers to temporarily schedule a drug for 36 months, a much longer time period to accumulate enough evidence to deposit the drug permanently in a “red zone”. When poison control centers, physicians’ offices, emergency rooms or morgues, become flooded with designer drug crises, the legal “grey zone” can now rapidly morph into an illegal “red legal” zone. In October 2011, the United States Drug Enforcement Agency (DEA) asserted itself and brought the full weight of the federal government to controlling distribution of newly emerging designer drugs. Exercising its emergency scheduling authority, the DEA controlled three synthetic stimulants (mephedrone, 3, 4-methylenedioxypropylamphetamine (MDPV) and methylone) that had been marketed as “bath salts” and “plant food”. Specific health crises related to synthetic marijuana also aroused a rapid DEA response (7). The American Association of Poison Control Centers reported that they received 6,959 calls related to synthetic marijuana in 2011, up from 2,906 in 2010 (8). On March 1 2012, the DEA extended, by six months, control of five chemicals that are designed as “fake marijuana” products (JWH-018, JWH-073, JWH-200, CP-47,497, cannabicyclohexanol. In June 2012, 26 synthetic drugs, including 15 different synthetic cannabinoids, were placed under the Controlled Substance Act. These actions made possession and sale of these chemicals, or the products that contain them, illegal in the United States. The DEA deemed the emergency actions necessary to prevent an imminent threat to the public safety. The temporary scheduling action on specific compounds will remain in effect for one to three years while the DEA and the United States Department of Health and Human Services (DHHS) further study whether these chemicals should be permanently controlled.

The DEA is not the only government agency responding to an increasing number of reports from poison control centers, hospitals and law enforcement regarding products containing one or more of these chemicals. More than

43 states and the US Armed Forces have taken action to control or ban these or other synthetic stimulants, with counties and municipalities also using local ordinances to restrict distribution. The long-term physical and psychological effects of these products are unknown, but potentially severe. They have become increasingly popular, targeting our most promising and yet vulnerable populations - teens and young adults. They are sold at a variety of retail outlets, in head shops and over the Internet. Without approval by the Food and Drug Administration for human consumption or for medical use, there is no oversight of the manufacturing process, safety, purity or other standards routinely imposed by the FDA. DEA Administrator Michele M. Leonhart has stated that, “These chemicals pose a direct and significant threat, regardless of how they are marketed, and we will aggressively pursue those who attempt their manufacture and sale.”

2. Rationale for Legal Restrictions

Opinions vary widely on how nations should respond to drug threats and challenges to public health. Some nations have moved to categorize drugs in terms of their potential harm, with the possibility of deregulating designer drugs that, in some opinions, are deemed safe. Some individuals have claimed that designer drugs are an appalling response to, and an unintended adverse consequence of, regulating conventional psychoactive street drugs (e.g. marijuana, cocaine, LSD). By designating conventional drugs as illegal, they claim a more dangerous designer drug market was unleashed to circumvent the illegal status of drugs with a longer history and known biological profiles. Yet, designer drugs have been synthesized and marketed for decades, with or without controlled substance laws. Wherever there is a niche market, someone, somewhere will try to permeate it for profit. Public health and safety drive the views expressed below. The hazards of these drugs and the rationale for regulating and controlling access to them are based on a number of considerations:

(1) *Emergency room mentions of designer drugs (and deaths), from Poison Control Centers, and from single case reports from physicians has escalated in recent years. These occurrences represent a significant public health and safety issue that requires regulatory intervention (Table 1).*

(2) *The acute biological and behavioral effects and long term consequences are unknown: erring on the side of caution is sound public health policy.* Detailed biological effects and targets of many drugs have not been identified, nor do we know how they will react in the presence of other drugs in the body, or what potentially toxic contaminants are in the marketed mixtures. Currently, treatment of overdose crises or addiction is based on guesswork, or extrapolation by analogy to drugs with similar psychoactive effects. For the majority of these drugs, approved pharmacological antidotes do not exist and their projected biological targets can be far off the mark. For example, the sites of action of the unusual chemical SalvinorinA, a powerful hallucinogen produced by the plant *Salvia Divinorum*, baffled the scientific community. It bore no chemical resemblance to any of the known hallucinogens that target principally serotonin receptors (subtype 5-HT_{2A}) in the brain, and was missing the element nitrogen, thought to be essential for hallucinogenic effects. A screening procedure finally identified a most unlikely primary target - the kappa opioid receptor. The kappa opioid signaling system normally can reduce pain, but can also produce unpleasant sensations or dysphoria (9). The chemical structure of SalvinorinA was so remote from conventional kappa drugs that this discovery sent shockwaves through the scientific community (Figure 1). How can a non-nitrogenous hallucinogen, that bears little resemblance to any known hallucinogen and has no biological effect on the targets of the majority of hallucinogens, serotonin receptor subtypes, be attracted by opioid receptors in the brain?

This is a dramatic example of how a newly discovered or a slightly altered drug can affect brain function unpredictably. Many of these drugs have not been extensively tested in controlled laboratory conditions; the responses they elicit in humans are gleaned largely from single case reports, from anecdotes, surveys, emergency department mentions, without the advantages of controlled clinical trials. How do they act? What are their

biological targets? What are the effects if a dose is increased by a factor of 3- or 10- or 100-fold? What if three or ten compounds are sold in the same mixture? Are their effects additive or synergistic or antagonistic? How long do they persist in the body? Do they interfere with sleep, cognition, memory, coordination, spatial, time, sensory perception? Do they produce hallucinations or psychosis? Are these drugs acutely toxic to brain cells or to other organs? Are they addictive? Are there long term adverse effects after repeated use? Are unwanted side effects irreversible? Do they interfere with cardiovascular, lung, kidney, endocrine, liver, immune or reproductive functions? Can they synergistically interact with other drugs (e.g. alcohol or medications) to create a health crisis? Do they interfere with absorption or metabolism of foods, medications or other safe, ingested materials? What would transpire if governments decided that some designer drugs have relatively low potential for harm and permit sale by regulated manufacturing processes? Would regulatory oversight of chemical synthesis absolve governments from public protection?

Another problem is the terminology “relatively safe”. What criteria are to be applied to designate a psychoactive designer drug “harmful” or “safe”? Is harmful to be defined as: an acute illness? addictive potential? overdose crisis or death? impaired or loss of cognitive function? cardiovascular effects? hallucinations or delusions? loss of interest in responsibilities, school, work, parenting, other activities? Is harmful only to be scrutinized during an acute phase?

Time, or rather, an extended period of time is needed before scientific evidence and public perception/use patterns are in synchrony. One example of lag time between initiation of use and evidence for unacceptably high consequences is observed with early initiation of drugs. Early adolescent drug use is associated with a much higher prevalence of addiction, cognitive impairment, and other adverse consequences in adulthood (11, 13, 14). This pattern is consistent for early adolescent use of marijuana, alcohol, cocaine, amphetamines, nicotine, heroin, inhalants, and benzodiazepines. As designer drugs are analogs of this drug array, conceivably early initiation of

the majority of designer drugs will confer the same high risks for youth. Yet, prospective studies will require years or decades before an association is discerned.

Another example is the lag time between the rise of smoking as a socially acceptable behavior, and the decades of research that established smoking as a health hazard. Smoking tobacco had been practiced sporadically for at least 1,000 years in the Americas, but it was only after mass production of cigarettes - to over 300 billion cigarettes each year in the US – that use rates rose rapidly from the turn of the century to peak just past the mid-20th century. Recall that during this period of “immature evidence”, the classic movie “Casablanca” was filmed in a fog of cigarette smoke. By the mid-20th century, the scientific evidence that smoking was the leading cause of lung cancer and a major cause of cardiovascular disease was overwhelming. The lag time between early acceptance of smoking as a harmless, or even a beneficial, glamorous social norm, and indisputable evidence for health problems was 50 years. When the Surgeon General of the United States publicized this major health risk in a detailed scientific report (1964), he catalyzed a striking change in national awareness and behavior (10). But during the 60 years that had lapsed, thousands of premature deaths and illnesses beset individuals and their families.

Marijuana consumption is another example of a divergence between public perception and scientific evidence. Marijuana has a much longer recorded history than tobacco. Yet, evidence for its adverse consequences, on cognition, addiction, psychiatric status, fertility, pulmonary, cardiovascular system, life-span, has taken decades to accumulate. Even so, the scientific data only rarely penetrates the mainstream media and public awareness. Only recently (August 2012) did marijuana receive significant negative press and public attention, with the publication of a report describing its IQ lowering effects in young initiators (11). Yet marijuana use continues to climb and states continue to approve marijuana as “medicine”, to decriminalize it, by ballot initiatives or legislative acts.

(3) *Quality control does not exist. The public should be informed of criteria for “quality control” and why designer drugs do not achieve these criteria.* As research chemicals are prepared in clandestine laboratories, there is no regulatory oversight on quality control. In contrast, the list of regulations that govern approval and oversight of production of medications by the FDA is daunting and lengthy. Requirements include evidence that the synthesis is reproducible and each batch is identical, the dose range is known and safe, the shelf life is known and a safe date of expiration is known, the purity is “pharmaceutical grade” as even a 1% or less toxic impurity can have devastating effects, that each batch be tested for microorganisms, fillers are non-toxic and as pristine chemically as the drug itself, and the drugs are tracked by a chain of custody. Designer drugs do not fulfill any of these criteria and there is no assurance that these compounds correspond to the ones “marketed” or come close to achieving the standard of purity legally required for pharmaceuticals. Even if the company that markets the “research chemical” advertises purity levels or offers documentation of purity, there is no guarantee that these documents accurately reflect the quality of the purchased material, without legalization and regulatory oversight. Obviously, designer drugs are not subject to the same pre-clinical and clinical trials required for approval as a pharmaceutical agent. With years of chemical, biological, metabolic, behavioral, toxicological testing in animals and years more of randomized, controlled, multi-centered clinical trials in thousands of subjects, and hundreds of millions of dollars expended for this costly research, the drugs that have passed through this “firewalk” and finally are approved for human use by the FDA, have a measure of safety and efficacy that no designer drug can claim. With or without regulatory oversight, individuals’ adverse responses to the drugs generally emerges only during crises, with critical information gleaned from emergency rooms, physicians, and surveys rather than from controlled clinical trials.

3. Current illegal drugs and designer drugs

Some claim that current restricted illegal drugs are relatively “safe” compared with designer drugs and should be legally available. If viewed in the context of the prevalence of addiction to marijuana, psychostimulants, opioids, the incidence of adverse medical, educational, occupational, safety and social consequences, this view is unsupportable. From the perspective of prevalence of use, of adverse consequences and the potential for effective preventive measures, a choice between two preventable risks to human health and safety is not sound public health policy (12-14).

(1) During the 1960’s, a time period when choices between current Schedule I (e.g. marijuana, LSD) and “designer drugs” did not exist (the Controlled Substance Act passed in 1973), a wide range of designer drugs, including hallucinogens flooded the market and were absorbed by the culture. The incentives then were the same as they are today, to offer users novel sensations and experiences, expand markets to new users, undermine the profits of “conventional producers”, profit from chemical, and not agricultural production, and evade legal sanctions.

(2) The drugs that currently are the leading cause of morbidity (illness and overdose) and mortality (overdose deaths) in the US are not Schedule I drugs, the most restrictive category, but legal prescription opioids. In this case, the legal status of opioids has not curtailed overdose deaths, but the designation as a scheduled prescription opioid most likely reduces its non-medical use.

(3) The potencies of conventional drugs (e.g. marijuana) have increased considerably over the past decade; increasing potency has paralleled increasing emergency room mentions and increased addiction prevalence. There are no guarantees that the production, strength and the current “safety” profile of Schedule I drugs will remain stable or “safer” than designer drugs.

- (4) Drug control clearly has a significant impact on reducing overall use, on public perception of drugs and on their risks. There is evidence that the legal status of designer drugs drives use among those attracted to experimenting with designer drugs and discourages users seeking only “legal drugs” (15,16).
- (5) Intoxicating, psychoactive drugs that are marketed legally, (e.g. inhalants, alcohol, nicotine, or prescription opioids), can also result in massive public health problems and premature deaths (17).
- (6) Some politicians, drug use advocates and scientists claim that emergency and permanent scheduling of drugs are burdened with an unintended consequence: interference with research on the potential benefits of these drugs. Yet a search of the National Institutes of Health database and the medicinal chemistry literature reveals robust research with Schedule I drugs, their derivatives, and with novel, unscheduled drugs. A fraction of these will evolve into medications, while others may be diverted into the squalor of street drugs. At times, some unintended consequences materialize from scientific curiosity and motivation to develop effective medications. The majority of designer drug structures and routes of synthesis were gleaned from manuscripts published in high quality journals and from patents. Medicinal chemists and pharmacologists seeking biological clarity or improved therapeutics agonize over the appropriation of their creative science by clandestine chemists, which use the inventions of those motivated to improve health and seek understanding, to market hazardous chemicals that compromise health.

C. The Designer Drugs

Current designer drugs can be classified by their chemical structure, by their psychoactive properties, by their known biological targets, or by their source (plant, synthetic, or combined) (Figure 2).

1. Stimulants: The “Bath Salt” Cathinones

The drugs most found in “bath salts” are substituted cathinones (synthetic derivatives of the stimulant chemical in Khat). “Bath salts” are disguised as plant foods, insect repellent, bath salts, stain removers, and sold under brand names such as Bliss, Blue Silk, Cloud Nine, Drone, Energy-1, Ivory Wave, Lunar Wave, Meow Meow, Ocean Burst, Pure Ivory, Purple Wave, Red Dove, Snow Leopard, Stardust, Vanilla Sky, White Dove, White Knight, and White Lightning. The products are sold as powders in small plastic or foil packages of 200 and 500 milligrams. The chemical compositions vary widely, as do purity and safety. Prior to current and ongoing DEA classification of these drugs in Schedule 1, distributors continue to package and market them deceptively.

The structure of phenethylamine, a trace amine found in the brain, is the backbone for most of the stimulant-type designer drugs (Figure 2). These compounds are easy to prepare and can be chemically fashioned in a myriad of ways to produce stimulants (amphetamine), stimulant-like hallucinogens or “entactogens”. Variants currently in the research domain or in the illicit drug market are a small fraction of the possible drugs that can be conceived of and synthesized. Cocaine- and amphetamine-like psychostimulant drugs of abuse, mephedrone, methylene, and pyrovalerone analogs, including MDPV, and naphyrone are some of the chemicals packaged as “bath salts”. These drugs are typically self-administered by injection, smoking, insufflating, gingival delivery, via intramuscular or other routes (18). The products have been widely available in the United Kingdom for several years, but emerged in the United States in the past three years. Nationwide, typical male and female abusers of these substances range from teenagers to those in their 40s. Users often have an extensive history of drug abuse. Some abusers describe the effects as similar to methamphetamine, ecstasy, and cocaine, and have referred to the substances as “complete crank” while others use the term “fake cocaine or “fake MDMA” (16, 18, 20, 21, 26).

These putative inhibitors of transport of brain monoamines all produce psychostimulation, possible “empathic responses” and cardiovascular effects, consistent with alterations in dopamine, serotonin and norepinephrine biology. They can also produce extreme agitation and life-threatening cardiovascular crises, which accounts for the steep rise in emergency department mentions. A paucity of information exists on the biological, physiological and toxicological effects of these drugs, especially their long term effects after heavy and prolonged use.

Collectively, the subjective effects of synthetic cathinones have been reviewed (18, 19). The spectrum of psychoactive effects include aggression, dizziness, memory loss, seizures, blurred vision, anxiety, hallucinations, depression, dysphoria, euphoria, fatigue, increased energy and decreased concentration, panic and paranoia. Other reported effects are palpitations, shortness of breathe, chest pain, dry mouth, abdominal pain, anorexia, vomiting, erectile dysfunction, discoloration of the skin, and muscular tension. Clinical symptoms reported by healthcare providers involve the majority of organ systems: psychiatric, neurological, gastrointestinal cardiac, pulmonary, renal, eyes, ear, nose, and throat. There is no consistent information on the addictive potential of these drugs, but based on the structures, their resemblance to amphetamines and cathinones, and modes of action, it is likely that most will have addictive potential. In several surveys of mephedrone users, 50% considered it to be addictive, nearly half reported continuous use for more than 48 hours, and more than 30% reported fulfilling three or more criteria for abuse/addiction, according to DSM-IV (20). A different survey (n=1,006) found that 17.5% of users reported symptoms of addiction, with the highest frequency of daily use falling in the 11-15 year old age range (21).

1a. Mephedrone

Mephedrone or 4-methyl-*N*-methylcathinone is a synthetic compound first synthesized in 1929 and rediscovered in 2003. Its root structure overlaps with cathinone from Khat plant, and has structural features in common with

amphetamine and phenethylamine (PEA), a chemical signal produced by the brain that activates a trace amine receptor1 (22). Mephedrone reportedly became available via internet sales in 2007, and has become prevalent in many European countries, in Asia, Australia, New Zealand, Israel, the US and Canada. Unconfirmed reports of deaths, a high number of emergency room mentions and addictive potential associated with its use has resulted in its classification as an illegal substance by United Kingdom (April 16, 2010) and the EU in 2010 (23). On the one hand, distribution and use of mephedrone continues and users may be replacing MDMA with mephedrone (24-27). On the other hand, an analysis of presentations to the emergency department of patients with acute toxicity related to the use of mephedrone demonstrated that there was a peak in presentations prior to and a significant fall in presentations following legal restrictions on mephedrone. This suggests that mephedrone control may have been effective in reducing the acute medical crises associated with the drug (15).

Psychoactive effects of mephedrone. Possible leads on mephedrone's biological activity, and toxicology, are derived from human self-reports, emergency department mentions and preclinical research. The majority of reports claim that mephedrone is a psychostimulant, with effects similar to those of cocaine, amphetamines and MDMA (ecstasy), after ingestion, i.v. injection, rectal administration, or insufflation as a powder, pill or capsule. Insufflation is the most common routes of administration (25-29). Although 56% of users reported adverse consequences in one survey (19, 21), respondents also reported intense stimulation, alertness, euphoria (consistent with cocaine or amphetamine effects), empathy and increased intensity of sensory experiences (consistent with MDMA effects), mild sexual arousal and perceptual distortion at high doses (28). In an acute study that compared 20 mephedrone users (a) during intoxication, (b) drug free and with (c) non-using controls, mephedrone users had impaired prose recall, higher scores in schizotypy and depression, primed a marked 'wanting' for the drug, induced stimulant-like effects, impaired working memory and enhanced psychomotor speed, in an average mephedrone session lasting nearly 8 hours (30).

Emerging as a drug of choice for some, mephedrone, has addictive potential. Users reported binge use, an inability to abstain, and use until supplies are depleted or symptom severity requires medical attention. Recent surveys found that 15-20% of users reported using weekly or more frequently in England (20, 21). Most disconcerting is the finding that 13-15 year olds had the highest percentage of daily use. Intranasal use is associated with higher self-reports of mephedrone as an addictive drug. More than half reported that the duration of the “high” and the quality of the “high” was better with mephedrone than cocaine. These behavioral patterns converge on mephedrone as an addictive drug, with a profile similar to responses engendered by high doses of cocaine, amphetamine or MDMA (29). In a survey of high schools and colleges, 17.6% of users reported addiction or dependence on mephedrone (21). Recent reviews of mephedrone documented in detail the known prevalence of use in the UK, and its acute and toxic effects of the drug (3, 19). Collectively, the reports provide compelling reasons to regulate and then clarify the biological and long term effects of mephedrone and related drugs.

Adverse consequences of mephedrone: psychoactive, cardiovascular and addictive properties. The adverse effects of mephedrone are derived from analyses of emergency department mentions, single case reports, and self-reports from interviews. At least 56% of users report adverse consequences (19-21, 31-36). These range from inability to concentrate, inability to focus visually, memory problems, nasal irritation, nose bleeds, loss of appetite, nausea, vomiting, tremors, headaches, hyponatremia with encephalopathy, psychiatric symptoms, crushing chest pain, urination difficulties, changes in body temperature (hot flushes and sweating), discoloration of extremities, tremors, convulsions, insomnia, nightmares, hallucinations, delusions, and immunological toxicity. In several reports relating to mephedrone toxicity (34-36), subjects were identified with mephedrone complications including psychoactive and cardiovascular toxicity. Of mephedrone patients, 51% were admitted, reflecting symptom severity. Adverse symptoms include agitation, aggression, anxiety, parasthesia, palpitations, shortness of breath, confusion, collapse, paranoia, hallucinations, aggression, peripheral vasoconstriction, pain, and seizures. Heart rate, sinus tachycardia, and blood pressure were elevated, in some cases to extreme levels,

while temperature was low to normal. Most of these symptoms were associated directly with mephedrone. In a series of analytically acute mephedrone toxicity presentations to an ED, the clinical features were consistent with an acute sympathomimetic toxicity including hypertension, tachycardia and agitation (3, 15, 37-39). These findings are similar to the pattern of toxicity seen with other sympathomimetic drugs such as MDMA, amphetamine or cocaine. At least 60 cases of mephedrone-suspected deaths have been reported in the UK. In one confirmed case of mephedrone fatality, stomach levels were 115 mg and blood levels reached 5 mg/L, equivalent to 28 μ M (40). These blood levels are rarely seen with any legal or illegal psychoactive drug!

Possible mechanisms of action. Similar to related cathinones and amphetamine-type drugs, mephedrone affects signaling of dopamine, serotonin and norepinephrine in the brain. These three chemical messengers (also known as biogenic amines, monoamines, or neurotransmitters) transmit signals between nerve cells in the brain and in other organs. They are critical for a wide range of functions in the brain and peripheral tissues, including reward, mood, learning and memory, alertness, motor activity, sleep, sexual behavior, hormone release, heart rate, pain perception, blood pressure, platelet aggregation, and others. Mephedrone and its related analogs affect the brain levels of these transmitters by interfering with mechanisms that are critical for regulating their concentrations. These designer drugs target transporters – complex proteins located on or in nerve cells that control, with exquisite precision and in millisecond time frames, the amount of transmitter available for signaling. Mephedrone and similar cathinones bind to these transporters, either blocking them or “tricking” the transporter to carry them into the nerve cells (41-49). The net effect is to release vast quantities of monoamines; the inundation conceivably produces the euphoria that promotes “liking” and “wanting” the drug.

In preclinical research, mephedrone lowered body temperature and heart rate, increased locomotor activity and intracranial self-stimulation in rodents, elicited conditioned place preference (a measure of rewarding properties) and produced psychomotor stimulant effects similar to methamphetamine in nonhuman primates (41-49).

Mephedrone blocked dopamine and serotonin transporters, elevating monoamines to levels observed with MDMA and other amphetamines.

1b. Methylone

Biological, psychoactive effects of methylone. Methylone has minor structural changes similar to scheduled drugs, e.g. cathinone (Figure 2). It acts on monoamine transporters (dopamine, norepinephrine, serotonin), blocking the transport of these critical transmitters in the brain, serving as a substrate for the transporters, and promoting the serotonin. These biological effects are similar to amphetamine-like psychostimulant drugs and Ecstasy (42-44, 49) and produces locomotor activity, in accord with its effects on dopamine (44).

Adverse effects of methylone. Increasing case reports exist on the morbidity and mortality associated with methylone. One example described “a case of a healthy 24-year-old who ingested a capsule containing methylone and butylone sold as "Ecstasy" at a concert. The patient presented to the emergency department comatose, with high fever, rapid heart rate, high blood pressure, and seizure-like activity. Despite maximal medical care, she suffered multi-system organ failure and died. Laboratory analysis identified only methylone and butylone in a capsule found in her belongings and in her urine (50).” More reports of medical crises and fatalities attributable to methylone are beginning to appear in the biomedical literature (50-53).

1c. 3,4-Methylenedioxypropylamphetamine (MDPV)

Propylamphetamine was developed in the 1960's as a treatment for chronic fatigue and obesity, but it was removed as a therapeutic drug because of its abuse liability. A drug patent reported its potency as higher than methylphenidate. MDPV is a psychostimulant analog of cathinone, but derived from propylamphetamine. It became a

drug of abuse in 2008, marketed in the US as “bath salts” and as an intoxicant with effects similar to cocaine, amphetamine, or MDMA. A growing body of scientific, emergency room mentions and other sources of information on MDPV’s acute psychoactive effects, toxicity and pharmacology (e.g. the DEA, the Psychonaut Web Mapping Research Project MDPV report) created the necessary support for the UK and DEA decision for emergency scheduling (1,2,7,8,18,23,54-61). Yet, the internet persists as a major source for purchase. MDPV reportedly has similar biological effects as mephedrone, cocaine, methamphetamine, and methylphenidate, producing stimulation, increased energy, mild empathogenic effects. Taken by insufflation, orally, intravenous, smoking, or other routes, the drug can produce a profound health crises of 6-8 hour duration. Its acute psychoactive effects can range from severe paranoia, hallucinations, psychosis, suicidal ideation, self-mutilation, aggressive, violent or self-destructive behavior. It also affects other organ systems, reportedly producing rapid heart rate (tachycardia) hypertension (high blood pressure), heart arrhythmias, high body temperature, sweating, insomnia, stomach cramps, grinding teeth, increased body temperature, chills, sweating, headache, bloodshot eyes, kidney pain, ringing in ears or dizziness, breathing difficulty, agitation and panic attacks. In an acute emergency, seizures, stroke, brain swelling (cerebral edema), heart attacks, collapse of the cardiovascular system, and death can occur (54-61). High frequent doses reportedly cause intense, prolonged panic attacks in intolerant users, psychosis from sleep withdrawal, craving and addiction. In preclinical studies. MDPV maintained self-administration and lowered the threshold for intracranial self-stimulation, properties characteristic of other highly addictive drugs in humans, such as methamphetamine (62).

1d. Naphyrone or naphthylpyrovalerone

Naphyrone was produced in a medications development program (63) in an effort to discover new treatments for psychostimulant addiction. Lipophilic analogs of pyrovalerone were designed to reduce its rapid entry into brain and associated abuse liability. It was then diverted and sold in the illicit drug market as “pond cleaner” as a psychostimulant substitute for mephedrone (NRG-1, infrequently containing naphyrone) or as “glass or jewelry

cleaning agent” (64). In July 2010, it was placed under control in the UK as a public health hazard (1). Naphyrone inhibits dopamine, norepinephrine and serotonin transporters in the nM range in vitro (43, 63), but there is scant other biological or behavioral data in peer-reviewed journals. A single case study reported that a 31-year-old man ingested a dose of naphyrone (100 mg), which produced acute sympathomimetic toxicity with restlessness, insomnia, anxiety, and hallucinations lasting for two days. Naphyrone was detected in the patient's plasma by gas chromatography with mass spectrometry after drug intake (65). In another case study, a user bought what he reportedly thought was the legal compound naphyrone (NRG-1) but in fact was MDPV and butylone. After ingesting a massive 1 gram dose, he developed palpitations, sweating and insomnia (66).

Summary. Not all cathinones are the same, with each conferring a different set of health risks. Nonetheless, use of cathinone analogs is increasing rapidly, especially among youth and in the face of mounting evidence that they engender unacceptable risks and adverse consequences: (a) emergency department mentions, (b) persistence of effects after 24 hours, (c) addictive potential, (d) psychiatric and cardiovascular effects, and (e) deaths. We urgently need a national and international response that imposes further legal restrictions, expands public education efforts, and education of health care professionals.

2. *Cannabinoid designer drugs: “Spice”, “K2”*

The annual Monitoring the Future (<http://www.monitoringthefuture.org/>) survey of high school students, for the first time in 2011, surveyed the use of “Spice or “K2”, but only in 12th graders. *An astonishing 11.4% had used some form of synthetic cannabinoids in the past year!*

2a. *Cannabinoid biology*

There are three types of cannabinoids: (1) Phytocannabinoids - are cannabinoids produced by plants. The marijuana plant produces over 70 phytocannabinoids. Δ^9 -TetraHydroCannabinol or THC is found at much higher concentrations than any other cannabinoid in the common *Cannabis Sativa* plant, one of several plants that produce cannabinoids. (2) Endocannabinoids - are produced by the brain and other organs. The body produces seven or more endocannabinoids, two of which are widely distributed and function in cannabinoid signaling: anandamide (2-arachidonoyl ethanolamide) and 2-AG (2-arachidonoylglycerol), which resemble, but are not identical to cannabinoids of plant origin. (3) Synthetic cannabinoids - were developed over the last 30 years as research tools to investigate cannabinoid systems in the brain and other organs and to explore the feasibility of developing cannabinoid medications (Figure 3).

What are the functions of endocannabinoids? Cannabinoid communication or signaling system has three major components: (1) a chemical message or neurotransmitter (e.g. endocannabinoid), (2) a receptor that interprets the message, and (3) an enzyme that degrades the message. The system has ancient evolutionary origins, with components discovered in a range of vertebrates, and possibly some invertebrates. Endocannabinoids activate two types of proteins, the CB1 and CB2 cannabinoid receptors. These receptors have a myriad of functions in the body that influence functions of the brain, heart, testes, uterus, prostate gland, vascular tissue, immune cells, adrenal gland, and the intestinal tract. The CB1 receptor is the target of THC, the most active constituent of the marijuana plant, whereas the CB2 receptor, a weak target of THC, functions primarily in peripheral tissues, and specifically in the immune system. With the discovery of these receptors and the host of endocannabinoid functions throughout the body, medicinal chemists produced thousands of synthetic cannabinoids, seeking to discover cannabinoids that possess therapeutic, but not psychoactive properties (67, 68), or to probe the cannabinoid signaling system to clarify their role and how marijuana produces profound psychoactive effects. With this large array of synthetic cannabinoids, and the precedent established by designer opioids, stimulants and hallucinogens, it was predictable that some cannabinoids would be extracted from legitimate research/development documents and diverted to the clandestine marketplace.

2b. Synthetic “designer” cannabinoids

Trafficking of synthetic cannabinoids was first reported in the United States in a December 2008 encounter, in which a shipment of “Spice” was seized and analyzed in Dayton, Ohio. Sold as “legal” alternatives to marijuana, synthetic cannabinoids originally were confined to a few compounds, (e.g. JWH-018 or 1-pentyl-3-(1-naphthoyl)indole), but others rapidly followed. JWH-018, JWH-073, JWH-200, CP-47,497, and cannabicyclohexanol have been found alone or laced on products that are marketed as herbal incense. The popularity and abuse of these substances and associated products has spread rapidly since 2008. Prior to being temporarily placed in Schedule I on March 1, 2011, “K2” and “Spice”, they were marketed under the guise of “herbal smoking mixtures”, “incense”, “herbal blends”, “air freshener” and designated “not for human consumption”. Promoted as legal alternatives to marijuana, they became widely available over the Internet, and sold in gas stations, convenience stores, tobacco and head shops to all populations (69, 70).

Some synthetic cannabinoids are relatively old compounds dating to the 1960’s and 1970’s, while others are of more recent vintage. Warnings regarding the dangers of synthetic cannabinoids and associated products have been issued by numerous state public health departments and poison centers and private organizations. Detailed product analyses show wide variations in the amount and type of synthetic cannabinoid laced on the plant material.

Biology. All designer cannabinoids mimic the psychoactive effects of marijuana, with some considerably more potent than marijuana at the cannabinoid CB1 receptor. Their metabolites may differ biologically from marijuana (7, 70). Users perceive synthetic cannabinoids as another form of marijuana, but in the absence of detailed research, there exists serious safety concerns, because the adverse side effects are pronounced with synthetic

cannabinoids: agitation, hallucinations, psychoses, seizures, hypertension, panic attacks. For example, some of the metabolites of these compounds do not activate CB1 signaling, but prevent it, causing the opposite effect of endocannabinoids or marijuana. Some are active at the CB2 receptor which could significantly affect the immune system. In preclinical studies, drug discrimination procedures test whether a drug produces the same physical or subjective perceptions similar to those produced by a known drug of abuse. Drug discrimination studies in monkeys suggest that controlled synthetic cannabinoids (JWH-018, JWH-073) have similar subjective effects as THC (71). In the test tube and animal studies, the pharmacological effects of JWH-018, JWH-200, JWH-073, CP- 47,497 and cannabicyclohexanol are similar to those of THC. The CB1 receptors are thought to be responsible for the euphoric and psychoactive effects of THC and related cannabinoids (72). As with THC, JWH-018, JWH- 200, JWH-073, CP-47,497 and cannabicyclohexanol have agonist properties at the CB1 receptor.

Acute effects. Numerous anecdotal self-reports, case reports and series indicate that these substances are abused by humans for their hallucinogenic effects. The abuse of synthetic cannabinoids has been associated with both acute and long-term public health and safety concerns. As of December 31, 2011, the American Association of Poison Centers has reported receiving 9,992 calls corresponding to products purportedly laced with synthetic cannabinoids. The calls represented exposed individuals from all 50 states and the District of Columbia, Puerto Rico, U.S. Territories, foreign countries, and a overseas/US military/ diplomatic. Several of these exposures were confirmed to involve JWH- 018, and JWH-073. With evidence of abuse and adverse health effects on a national scale, state public health and poison centers have issued warnings of herbal incense products containing these synthetic cannabinoids (7, 69, 70).

Systematic reviews of this class of agents reveal both acute and long term effects (69, 70). Acutely, a few case studies report that Spice produces pleasant and euphoric sensations to anxiety, psychomotor agitation, cognitive impairment, palpitations and in a single case, generalized convulsions (73). Although symptoms vary with

individuals, typical effects can include marijuana-type symptoms, relaxation and sedation, euphoria, while others report agitation, illness, eye soreness, and impaired short-term memory and concentration.

Case reports describe presentations to emergency departments of individuals exposed to synthetic cannabinoids with severe symptoms that include anxiety and panic attacks, tremors, generalized convulsions, psychosis, heart palpitations and elevated pulse, severe gastrointestinal distress, tremors, blurred peripheral vision, nausea, and persistent vomiting with retching (70). Such abuse also includes instances of persons suspected of driving under the influence of these synthetic cannabinoids, including one incident where an automobile was driven through a residence. In that case the driver claimed to have no memory of the event while a toxicology analysis confirmed that the driver had smoked a product containing JWH-018, but not any other drugs (7). Other symptoms of severe acute toxicity that can endure for as long as 10 hours may include delirium, impaired coordination, sleeplessness, seizures, palpitation, agitation, headache, paranoid hallucinations, confusion, mood disorders, and psychotic symptoms that can persist long after the last dose. Serious effects of these synthetic cannabinoids can also be manifest as tachycardia (rapid heart rate), loss of consciousness, diarrhea, nausea, and vomiting. There are also three reports of myocardial infarction (heart attack) in healthy adolescents (74) but this was not confirmed by detailed chemical analysis of the ingested material. Severe toxicity, with seizures, vomiting, agitation after smoking Spice has been documented (75).

Long-term effects. The pharmacological profile of JWH-018, JWH-200, JWH-073, CP- 47,497 and cannabicyclohexanol strongly suggests that they possess physiological and psychological dependence liability similar to that of the Schedule I controlled substances marijuana and THC. Physical and psychological withdrawal symptoms are manifestations of biological adaptation in the body. Some reported withdrawal symptoms included elevated blood pressure, restlessness, drug craving, nightmares, sweating, nausea, tremor and headache, palpitation, insomnia, headache, diarrhea, vomiting (69, 70, 76). Because these substances act through the same molecular target as THC, the main active ingredient of marijuana, it can be reasonably expected that

their physical dependence liability will be similar. Long-term, regular use of marijuana can lead to physical dependence and withdrawal following discontinuation as well as psychic addiction or dependence.

Adding to these concerns are reports of new-onset of psychosis in otherwise healthy males reportedly smoking synthetic cannabinoids frequently and reports of the drugs exacerbating psychotic episodes (77-79).

2c. Legal status of synthetic cannabinoids

On March 1, 2011, several of these synthetic cannabinoids were temporarily placed into Schedule I by the DEA, imposing criminal sanctions and regulation of their manufacture, distribution, possession, importation, and exportation and this was extended into 2012 (7). As of early 2012, at least 48 states have banned one or more of this class of drugs. They are legally available for research purposes. The evidence underpinning this decision was based on health and safety considerations. If taken in sufficient amounts, the toxic effects were similar to those induced by high doses of marijuana (anxiety, tachycardia and hallucinations) but also include seizures, tachyarrhythmias, extreme anxiety. The precipitation of psychotic episodes has also been reported following abuse of these substances or products containing these substances.

There is no currently accepted medical use for any of the five described synthetic cannabinoids, and, outside of a limited research setting, no medical practitioner is currently licensed by law to administer them. HHS states that JWH-018, JWH-073, JWH-200, CP-47,497 and cannabicyclohexanol are cannabinoids with a potential for abuse similar to the Schedule I substances marijuana and THC. These synthetic cannabinoids appear to be marketed solely for abuse of their marijuana-like activity and because, prior to the March 1, 2011, they were not controlled under the CSA. As such, commerce involving these synthetic cannabinoids can only be for the purposes of abuse and escaping the regulatory and criminal penalties of the CSA that pertain to marijuana.

The increased abuse of these synthetic cannabinoids in the United States is supported by an increasing number of encounters by law enforcement. Over the past year in the United States there has been a significant increase in availability, trafficking and abuse of these substances as evident from the increasing number of encounters reported by forensic laboratories. Product manufacturing and synthesis laboratories have been discovered, and laboratories have been found manufacturing products by lacing plant material with synthetic cannabinoids. Two suicides, one also involving a murder, have been linked to the abuse of synthetic cannabinoids (law enforcement communication to DEA, 7).

Summary. “Spice” and “K2”, especially as they are widely used by high school and college students, are emerging public health challenges (80). Their rapid rise in popularity, ready access from multiple sources, production of acute psychological distress, toxicity and potentially long term harmful effects, ability to evade standard drug tests, require an integrated national response. Healthcare professionals, law enforcement, testing capabilities, a massive public education campaign and strategies for deterrence in healthcare systems are needed to respond to this emerging threat.

3. Hallucinogens and other emerging designer drugs: A brief overview.

A number of hallucinogens and other psychoactive drugs have evolved into street drugs: (1) phenethylamines (similar to mescaline), rigid analogs of phenethylamines and benzylphenethylamines (e.g. 2C-Bfly, Br-fly, Br-dragonfly); (2) SalvinorinA, *which the 2011 Monitoring the Future survey showed past year use rate of 5.9% among 12th graders!* (3) tryptamines; (4) the dissociative anesthetics methoxetamine, ketamine, and PCP. Phenethylamine derivative potencies (e.g. amphetamines, mescaline) have been increased by locking the structure more rigidly to produce compounds designated as “fly” (Figure 4). Some are extremely potent and one (Br-dragonfly) is associated with an overdose death (89).

DMAA (1,3-dimethylamylamine), a common ingredient in “party pills” and some weight loss and sports performance supplements was regulated in Europe. DMAA has been linked to a range of health concerns, including increased blood pressure, headaches, vomiting and severe cases of cerebral hemorrhage or stroke (81).

A systematic survey of these drugs is outside the scope of this manuscript. Readers can glean an appreciation of the magnitude of the problem, the challenge of law enforcement in tracking all the possible compounds that can be made, and their behavioral, psychological and biological effects in an excellent review (6), and in other sources (81-91).

D. Policy Recommendations

In 1982, seven young heroin addicts in Santa Clara County, California, were diagnosed with severe and unremitting cases of Parkinsonism after a street purchase and injection of, what they presumed was synthetic heroin (the meperidine analog MPPP or 1-methyl-4-phenyl-4-propionoxy-piperidine). Their bodies were frozen, bent over and immobilized, as if they were elderly, late-stage Parkinson’s disease patients. Three that had been followed survived from 3-16 years. The clandestine chemist that produced MPPP allegedly had ripped the pages that describe the synthesis of meperidine and MPPP out of a medicinal chemistry journal from a university library, as the journal was found with these pages missing. Allegedly, the incompetent chemist had changed the synthetic procedure to accelerate production (by heating the mixture to a higher temperature than in the original “recipe”) and did not test the final product for purity. The product was contaminated with a chemical neurotoxin, MPTP (1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine) which destroys the same dopamine nerve cells that degenerate in Parkinson’s disease. Parkinson’s disease is a neurodegenerative disease of mostly elderly people, characterized by tremor, rigidity, slow movements, and impaired balance. In collaboration with the National Institutes of Health, the neurologist Dr. J. William Langston tracked

down MPTP as the cause (92). In 2008, another drug, methylcathinone was implicated, but not yet proven, as a new source of drug-induced parkinsonism in central Europe (93).

These two, egregious examples of the hazards of street drugs can be expanded into a multitude of cases. In an era of modern chemistry, modern communications, and modern marketing, can we interrupt the progression of drug-related public health problems? With resolve and effective strategies, the guardians of public health can triumph in this seemingly perpetual race against the distributors, who devalue or are indifferent to the well-being of consumers. Resolve, effective, rapid responses and public awareness are critical.

1. Designer drugs: an international problem requiring international cooperation.

- Coordinate international monitoring activities involving health professionals, researchers and law enforcement to glean and identify emerging drugs, sources, consequences via the internet, using automated web-crawling systems that require minimal diversion of resources.
- Collate and categorize synthetic drug information on a website to share with relevant agencies, including prevention and treatment communities, state departments, law enforcement, and internet monitoring sites. Develop a uniform set of international guidelines on what criteria should trigger emergency regulations.
- Based on these guidelines, identify gaps in information needed for legal restrictions on specific drugs or categories.
- Coordinate international law enforcement policies on marketing and sales of designer drugs. Easy access to these chemicals sources should be restricted by international laws, agreements, and local enforcement.

- Routinely monitor websites for traffic to and from producers.

2. National response

- Implement a comprehensive internet site for real-time entry, by health care providers, school officials, emergency departments, poison control centers law enforcement, of emerging threats and medical crises; ensure quality by designating credentialed individuals for data entry; create national awareness of its existence.
- Implement nation-wide, state-wide and local surveys of designer drug trends in schools, workplace (e.g. National Survey on Drug Use and Health, Monitoring the Future).
- Implement nation-wide, state-wide and local surveillance of healthcare centers (primary care, clinics, hospitals), with uniform questionnaires, case records and samples for biometric monitoring.
- Implement a national, standardized testing facility of samples to decipher chemical identity and chemical signatures (e.g. Department of Defense model).

3. Prevention and deterrent programs

- Create a single web-site that collates ongoing information and translates it to the public.
- Create a mechanism for press releases and releases into internet sites including social media (e.g. Twitter, Facebook, others) to alert the public on emerging drugs and their hazards.
- Create a prevention team that prepares internet accessible presentations for parents, teachers, community groups, universities, and schools.

- Create a method for raising awareness of and distribution of this information, to penetrate schools and universities, parents, teachers, and student populations.
- Develop a rapid response team including expertise in chemistry, biology, emergency room medicine, law enforcement, and media to respond to surges of specific drugs in local microenvironments. Each specialist should provide alerts and bulletins to colleagues for widespread distribution and public education.
- Incorporate designer drugs into standard Screening, Brief Interventions, Referral to Treatment (SBIRT) questionnaires.

4. Law enforcement

- Coordinate international regulations.
- Develop guidelines for “cut-off” of the amount of information necessary for emergency scheduling.
- Strengthen and enforce precursor laws.
- Monitor international research laboratories and enforce laws, as applicable.
- Identify rogue laboratories, their locations, and disseminate the information to the public.

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Figure Legends

Figure 1. Comparison of the structure of a conventional kappa drug (butorphanol) and the active ingredient of *Salvia divinorum* (SalvinorinA). Both target the kappa opioid receptor in the brain with butorphanol an analgesic (pain-killer) and SalvinorinA a hallucinogen. SalvinorinA is the first known compound acting at the kappa opioid receptors that is not an alkaloid (no amine nitrogen in its structure). The amine nitrogen in butorphanol is shown with an arrow). Photo of the mint plant *Salvia divinorum* that produces SalvinorinA.

Figure 2. Phenethylamine, the core structure of many designer drugs, is a neuromodulator produced by the brain which activates the Trace amine Receptor 1 or TAAR1 (22). Designer drugs are similar to amphetamines (amphetamine, methamphetamine, 3,4-methylenedioxymethamphetamine or MDMA) and to the phytochemical cathinone, the active constituent of the Khat plant. Even subtle modifications can yield profoundly different behavioral, neurochemical, and neurotoxicological effects. For example, methamphetamine and methcathinone induce persistent dopaminergic and serotonergic abnormalities, while MDMA and mephedrone only induce serotonergic abnormalities.

Figure 3. Structures of phyto-, endo- and designer cannabinoids. Note how different the brain's own endocannabinoid anandamide, differs from the plant product (THC) and the synthetic cannabinoids (JWH-018). Even subtle modifications can yield profoundly different and unpredictable behavioral, neurochemical, and neurotoxicological effects.

Figure 4. Emerging designer hallucinogenic drugs: the rigid structures of the “flies”.

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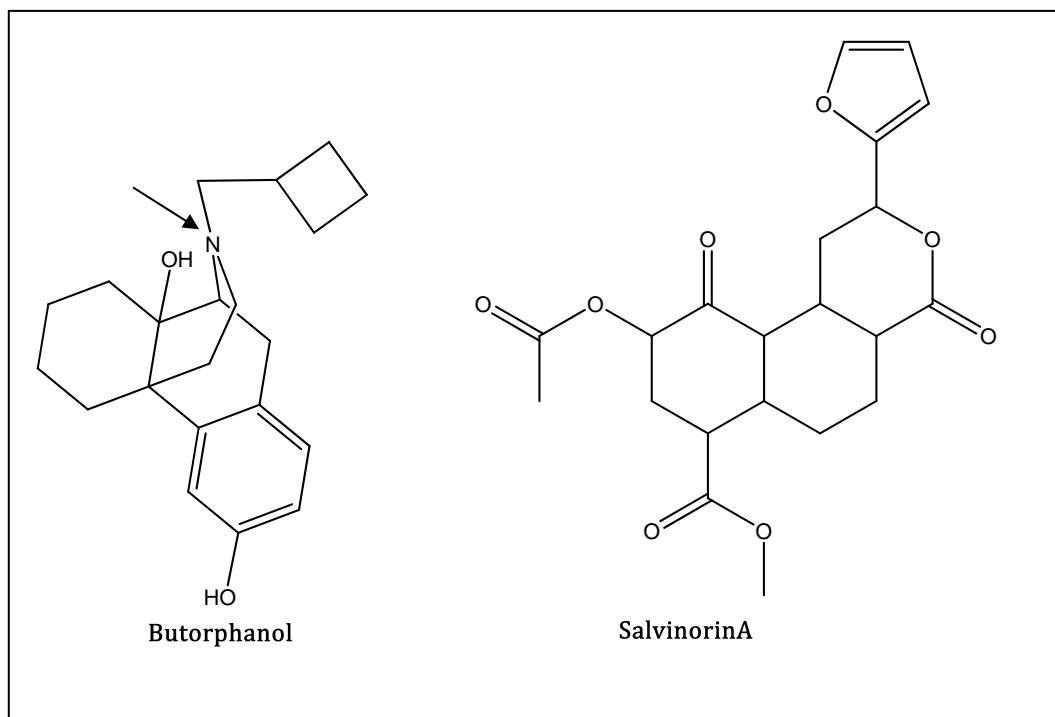


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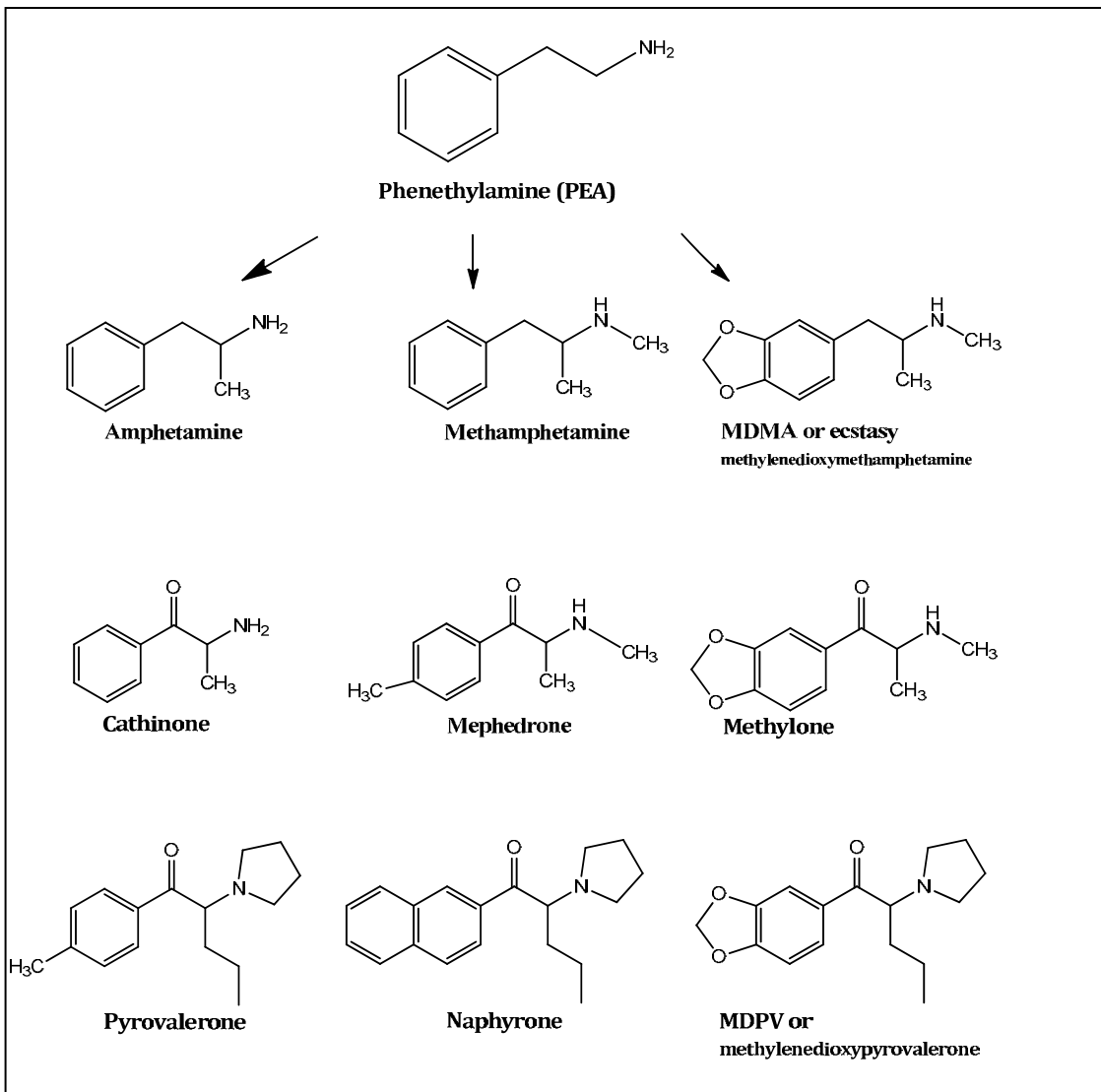


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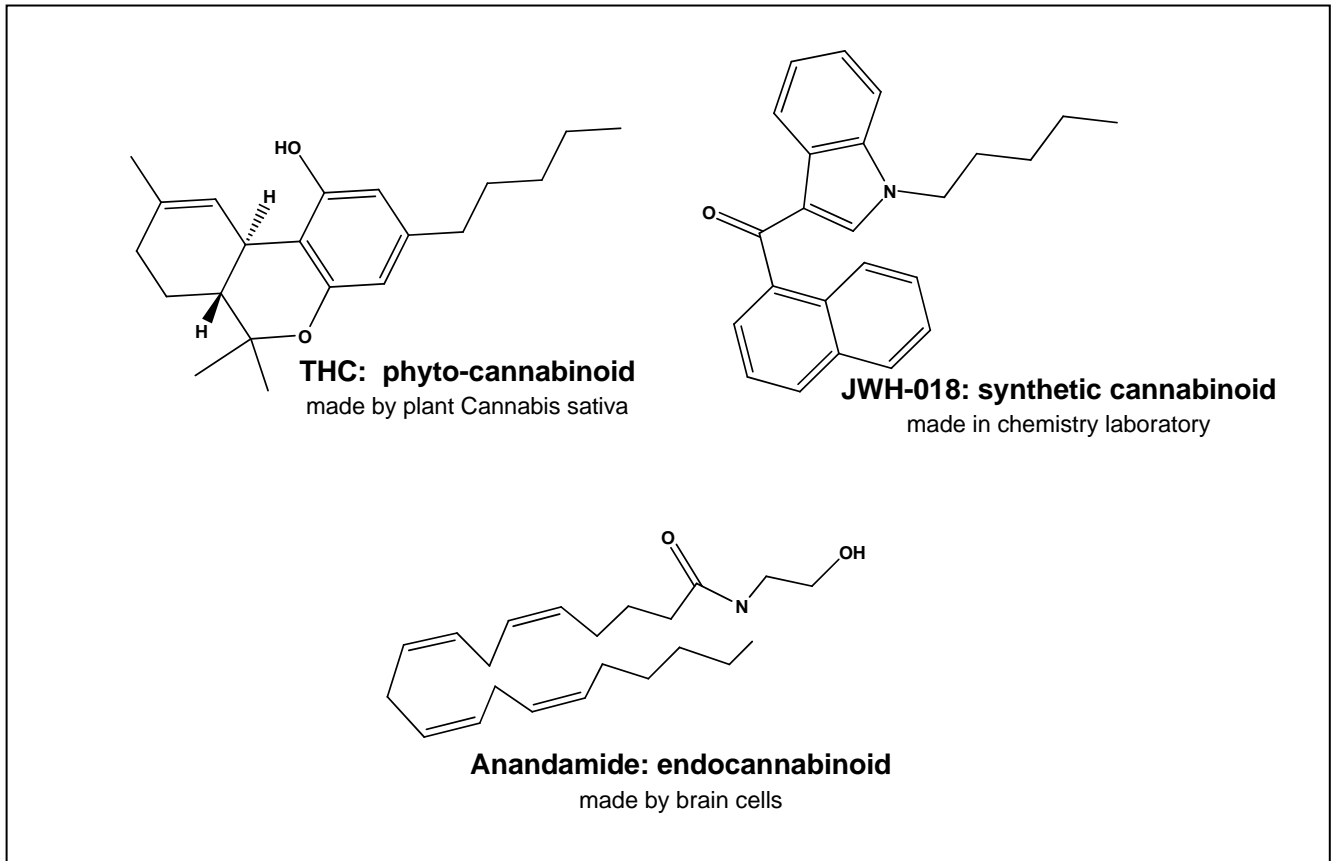


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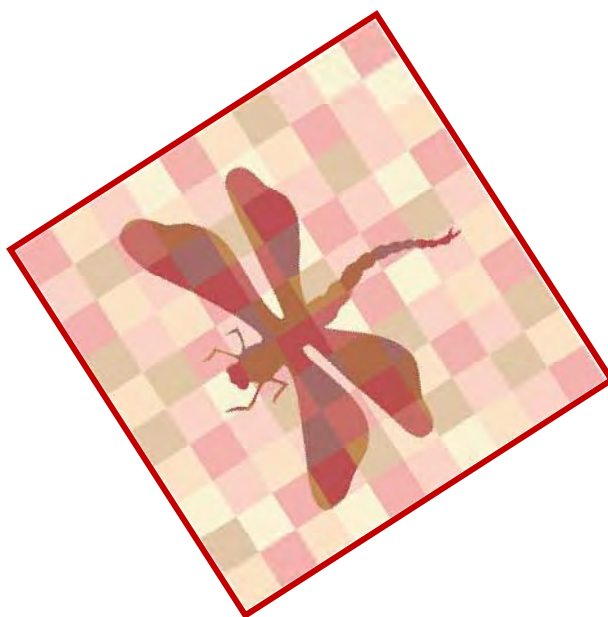
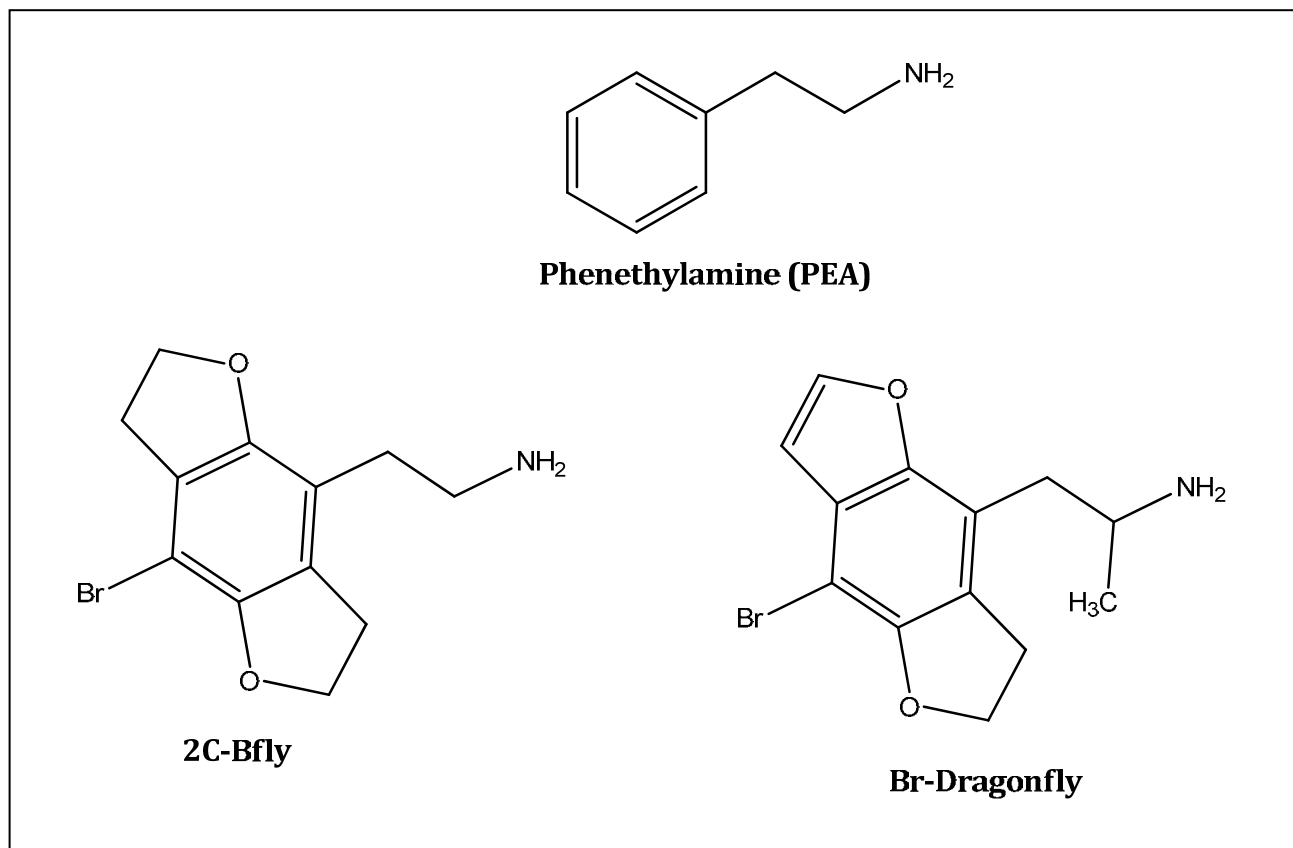


Table 1 – Page 1

<p>“Bath salts” (50-500 mg packets)</p> <p>Primary constituents:</p> <p>-MDPV (~5-20 mg+);</p> <p>-Mephedrone (500 mg-2 g/session);</p> <p>-Other cathinones:</p> <p>Butylone, methylone, Dimethylcathinone, ethcathinone, ethylone, 3-, or 4-fluoromethcathinone, Methcathinone, methdrone, ephedrone, pyrovalerone, naphyrone</p>	<p>Panic attacks, anxiety, agitations, paranoia, hallucinations, psychosis, aggressive behavior, violence behavior, excited delirium, self-destructive behavior, self-mutilation, suicidal ideation, memory loss, insomnia, anorexia, depression, (Reviews: 18, 19, 20, 30-40, 50-61)</p> <p>Suspected Parkinson’s disease (93)</p>	<p>tachycardia (rapid heart rate), hypertension (high blood pressure), vasoconstriction (blood vessel contraction), arrhythmias (irregular heart beat), hyperthermia (high temperature), sweating, pupil dilation, epistaxis (nose bleed), muscle tremor/spasms, hyper-reflexia (over responsive reflexes), rhabdomyolysis (muscle destruction), seizures, respiratory distress (breathing difficulty), myocardial infarction (heart attack), cardiovascular collapse (blood circulation failure), stroke (brain circulation failure), cerebral edema (brain swelling), coma, death (Reviews: 18, 19, 20, 30-40, 50-61, 64-66)</p>	<p>Unknown</p>	<p>> 1,500 mephedrone users surveyed considered it addictive (16)</p> <p>- of 100 mephedrone users nearly 50% reported continuous use for > 48 hours (26)</p> <p>-of 1,006 students, daily use reported by 4.4% (all less than 21 years old); 17.5% of users reported addiction (21)</p>	<p>-UK: High school and college students; 20% used on occasion; 4% used daily; all daily users under age 21 (21)</p> <p>-Finland: 8.6% of suspected DUI tested positive for MDPV. 84% were functionally impaired (18)</p> <p>-UK: 33% of club-goers used past month; 14% weekly; (20, 26)</p>
<p>“K2” or “Spice”</p> <p>Primary constituents:</p>	<p>Exacerbation of recurrent psychosis, psychosis relapse, new onset psychosis. Seizures</p>	<p>Tachycardia, tachyarrhythmia, cardiotoxicity, chest pain, nausea, vomiting, dilated</p>	<p>New onset psychosis, psychosis relapse; psychotic</p>	<p>Dependence (76)</p>	<p>-12th grade 11.4% (past year (Monitoring the Future, 2011);</p>

Table 1 – Page 2

JWH -018, JWH-073, JWH-200; HU- 210; CP- 47,497, others	Anxiety Agitation Irritability Memory changes Sedation Confusion Palpitations, compromised cognitive abilities (69-70; 73-75; 77- 79)	pupils, brisk reflexes, appetite change, seizures, hot flushes, burning eyes, dilated pupils, drug mouth, tremors, myocardial infarction (76-70; 73-75)	episodes, anxiety, irritability (review: 69) Much remains unknown By analogy to marijuana, reduced brain volume,		-Ever use of “K2” reported by 8% of sample of college students (80)
Salvia Primary constituent: SalvinorinA					12 th grade 5.9% (Monitoring the Future, 2011)
“Fly”		Death (88, 89)			
Methoxetamin e, ketamine	Dissociative/catatoni c state; Cerebellar toxicity (82-83, 85- 86)	Tachycardia, hypertension (85); deaths (86)			
1,3- dimethylamyla mine (DMAA)	Cerebral hemorrhage in 3 cases (81)				
“Whack” “Ivory Wave” 2-DPMP and D2PM	Agitation, anxiety, insomnia, psychosis, hallucinations, paranoia; in 26 cases, 96% had neuropsychiatric symptoms (84, 87)	Chest pain, hypertension, tachycardia, dystonia, rhabdomyolysis, (84)	Prolonged clinically significant neuropsychi atric symptoms (84)		1% past year use in night club survey (84)

Biography

Dr. Bertha K. Madras is Professor of Psychobiology, Department of Psychiatry at Harvard Medical School (HMS), and is cross-appointed at the Massachusetts General Hospital. She served as Deputy Director for Demand Reduction (prevention, intervention, treatment) in the White House Office of National Drug Control Policy (ONDCP), a Presidential appointment confirmed unanimously by the US Senate. At Harvard, her multidisciplinary research focuses on neuropsychiatric diseases and addiction biology, documented in over 150 manuscripts and as co-editor of books “The Cell Biology of Addiction”, “Effects of Drugs in the Human Nervous System”, “Imaging of the Human Brain in Health and Disease”. At ONDCP, she incorporated Screening, Brief Intervention, Referral to Treatment (SBIRT) into the national drug control strategy, spearheaded SBIRT CPT®, other billing code approvals, Medicaid reimbursement, SBIRT adoption by Health Resources and Services Administration, the Veterans Administration, recruitment of Federal healthcare insurers, a UN declaration of endorsement, and other initiatives. In service to the public, she directed creation of a Museum exhibit, a CD (licensed by Disney Corp), “Changing your mind: drugs in the brain” for the Boston Museum of Science. She has given hundreds of presentations worldwide, on how drugs affect the brain and consults to government, organizations and industry. She holds 19 patents, is a recipient of a NIDA Public Service award, a NIH MERIT award, American Academy Addiction Psychiatry Founders’ Award, and Marian Fischman Award. A brain imaging agent strategy she developed was cited by The Better World Report, 2006, as one of “25 technology transfer innovations that changed the world”. Her experiences in translational neurobiology, government and public service afford her a unique perspective on science and public policy.

Conflict of Interest Statement

I declare that I have no proprietary, financial, professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled

“Designer Drugs: An Escalating Public Health Challenge”

Signed electronically

Bertha K. Madras, PhD, September 10, 2012