Psychiatria Danubina, 2016; Vol. 28, Suppl. 1, pp 49-58 *Conference paper*

UNDERSTANDING THE PREVALENCE OF 'LEGAL HIGH' MISUSE IN EARLY ADULTHOOD

Benedict Morris

Queens College, University of Cambridge, Cambridge, UK

SUMMARY

With the recent introduction of the Psychoactive Substances Bill in the United Kingdom, it is a useful time to retrospectively review the patterns of prevalence of the psychoactive products known as 'Legal Highs'. There has been emerging research and rapidly expanding political, public and media attention and awareness, yet comparatively little scientific discourse on the psychological aspects driving their consumption, beyond simply their legal status. This paper focuses on their usage patterns in the particularly vulnerable, but often-neglected period of young adulthood between the ages of 16-24, focussing on their prevalence, trends in pharmacology and psychological aspects of their usage and propensity for addiction. There is a greater skew of usage to young adulthood in legal highs than that seen in classical drugs of abuse. Although there are still significant research questions to be tackled, it is suggested that the interaction of legal high incentive value and their perception with aspects of enhanced risk taking in young adulthood, particularly impulsivity and sensation seeking, are of key significance, as opposed to any clear pharmacological mechanism for differing prevalence. While there is much further research to be performed on the contents and pharmacology of legal highs, the reasons for potentially lower levels of addiction are also discussed.

Key words: *Legal Highs - novel psychoactive substances – NPS - risk taking - young adulthood - addiction*

* * * * *

THE RISE OF LEGAL HIGHS

Defining legal highs

In understanding the term 'legal high', it is first essential to have a working definition for an often interchangeably used classification, that of *new psychoactive substances* (NPS). Article 3 of European Council decision (2005/387/JHA) is paraphrased by the European Monitoring Centre for Drugs and Drug Control (EMCDDA) as "a new narcotic or psychotropic drug, in pure form or in preparation, that is not controlled by the United Nations drug conventions, but which may pose a public health threat comparable to that posed by substances listed in these conventions" ('Action on New Drugs' 2016). Some, such as salva, are of natural origin, although a majority of newly detected compounds are now "designer drugs" based upon and designed to mimic other psychoactive parent compounds (Baumeister et al. 2015) via small structural modifications to the parent, such as XLR-11, a halogenated analogue of UR-144 which is itself a novel cannabinoid. A large number are rejected or appropriated experimental pharmaceuticals. The majority are believed to now be originating from laboratories based in Asia (Wasunna 2015). The scale of the output is hard to assess, although the increase to 101 new NPS detected by the European Early Warning System, up from just 14 in 2005 (EMCDDA 2015), is indicative of both heightened vigilance and an expansion in production.

Legal highs on the other hand are products marketed as a way of experiencing psychoactively altered states without the legal risks of obtaining their controlled cousins. While most legal highs are examples of NPS, many NPS are in fact regulated, such as p-methoxymethylamphetamine (PMMA), and therefore cannot be termed 'legal'. The distinction is important, as there is a risk of conflating the two when it comes to assessing resultant harms. However, in terms of available data, it is often necessary to consider NPS as representative, but not strictly identical to legal highs. Indeed, the composition of a legal high will often be changed week on week. For example, in Germany it was found whenone ingredient in a sample of the cannabis substitute "spice", JWH-018, was regulated it was simplyquickly replaced with another, JWH-073 (Lindigkeit et al. 2009). Legal highs often contain a mix of NPS, and despite being marketed as legal, it appears common that some ingredients are controlled. The sheer number of available products and variety of NPS however makes it near impossibility to perform regular testing orregulate any significant proportion of available products.

Where are they sold?

There are three main streams of supply to end-user. The first is through physical stores, either specialist 'head shops'or non-specialistretailers, which accounted for 34% of reported previous source in the 2014/15 Crime Survey for England and Wales, CSEW (Home Office 2015). Secondly, they are passed through traditional supply routesof dealers, friends, and non-formalised third parties; this is of particular importance for participants in the night-time economy or in cases where a first use is unplanned, as it removes the need for foresight in obtaining them. Data from the CSEW shows this is still the largest supply stream, however is significantly smaller than for classical drugs of abuse. The final mechanism is through online retailers, either the dark web, inaccessible through standard search

engines, or the open web. Arepresentative case study is www.globalweekends.co.uk. Their website was accessed through a Google search result for "legal highs". While their homepage included 12 uses of that phrase, the legal disclaimer in the terms and conditions stated "We sell them to customers who plan on using them to burn incense, use them for research or otherwise approach them as a product of intrigue. Nothing more." (Global Weekend Terms 2016).

By labeling as "not for human consumption" and instead ostensibly as 'plant feed' or similar,retailers currently avoid contravention of the UK Medicines Act and this warning is seen ubiquitously on the packaging of legal highs. The Act does mean that to avoid legal risk suppliers cannot give any information about dosing, side effects or interactions. By allowing user comments however, users can give personal experiences of substances, though it is unclear to what extent these are curated. This online expansion of sales is in tandem with the rising role of *psychonauts,* legal high users who aim to self-experiment and review available products.

Who uses legal highs?

The Crime Survey for England and Wales (CSEW) is a large, randomised general population survey of 35000 households in 42 representative areas (Home Office, 2015). While there are structural flaws, not least reliance on self-report, it currently provides the largest available UK sample of NPS prevalence data. It found two key fixed risk markers were age and gender. Reported prevalence in the last 12 months was 0.9%, in the survey range of 16-54 years, but 2.8% in those aged 16-24. Men were more likely than women to have used NPS in all age categories,with 3.9% vs. 1.9% lifetime usage. There was a particular density in young males, accounting for 46% of recorded users, although young females were also at heightened risk compared to other the older groups. A major variable risk factor is participation in the night-time economy. In the 16-59 bracket, the CSEW found that visiting night-clubs in the last month was associated with a 6 fold increase in previous year NPS use, while in the 16-24 bracket, there was a 3 fold increase. Of those aged 16-24 who had used NPS in the last year, 84.2% had used another illicit drug.

While the CSEW is a useful guide, there is a clear dearth in the literature to fully estimate legal high prevalence. Of the surveys looking beyond classical illicit drugs, very few focus on legal highs, with most using NPS as their classification, though often including both terms. The CSEW neglects those living in shared accommodation such as university halls of residence, which might miss a large part of the vulnerable younger population. Many groups report far higher levels of usage, such as the Angelus Foundation, a charitable group working to increase awareness and harm reduction for legal highs in young people, who in a snapshot survey of university students at a single site found 19% had used legal highs and 36% had been offered them (Universities and Festivals 2016). While clearly more focussed and rigorous data gathering in the young adult population is sorely needed, it seems likely the problem is likely evenmore extensive then the suggested in the CSEW. Another issue is significant variation in what is classified as NPS between countries, presenting difficulties in comparing national levels of usage. This is demonstrated by 2015 The World Drugs Report, which includes ketamine as an NPS, despite being controlled in the United Kingdom (UNODC 2015). Better international standardisation is necessary to have truly comparable understanding of NPS use.

TYPES OF LEGAL HIGH

When exploring the neuropharmacological properties of legal highs in an attempt to explain their prevalence, a compound-by-compound approach is wholly impractical, due to the vast and rapidly expanding variety of NPS available. Nor would it be particularly useful; as discussed, legal highs often contain a mix of NPS, resulting in involuntary polydrug use, in varying doses and ratios, and changing contents. In terms of dosing and dose recommendations, this is potentially more of an issue in legal highs than in controlled drugs. This is because sellers of legal highs are prohibited from providing any information on them by the Medicines Act to maintain legal protection, and the substances they are taking are poorly understood, while dealers of controlled drugs have rather less incentive by their criminality to be concerned for contravening the act, and are selling substances that are, for the most part, extensively investigated to inform harm reduction strategies. This means that legal high users are relying at best on second or third hand advice from other users and the Internet, or at worst, sheer luck.

It is clear therefore that a group approach is needed when considering the NPS that make up legal highs. Baumeister et al. (2015) divides them into five categories based upon the properties of their 'parent compounds': those mimicking psychostimulants such as cocaine or amphetamine;the synthetic cannabinoids, mimicking the effects of cannabis; those modeled on benzodiazepines; dissociatives, similar to ketamine or phencyclidine and finally hallucinogens-analogues of LSD or psilocybin. Since so many NPS are designer drugs, this is a reasonable approach to classification, although not perfect by the authors' own confession. For example, it excludesthe small but growing use of opioid mimicking NPS and legal highs, such as the plant Mitragyna speciosa, more commonly known as kratom, with its main active ingredients, mitragynine and 7-hydroxymitragynine acting through μ-opioid receptor (Ward et al. 2011). His categorisations are however still useful for exploring the major classes of contents of legal highs and are used in Table 1. The interested reader is referred to Baumeister et al. (2015) for more extendedexamination.

Table 1. Selected Classes of Psychoactive substances, including examples and effects (non exhaustive) and features of note. Adapted from Baumeister et al. (2015), Morgan et al. (2008), ECMDDA (2015), Gurney et al. (2015), Pertwee et al. 2008 and Sousann & Kjellgren (2014)

Class	Psychostimulants	Synthetic cannabinoids	Benzodiazepines	Dissociatives	Hallucinogens
Sites of efficacy	Monoamine system, increase levels of monoamines (NA, DA 5-HT) through two mechanisms: • Decreased synaptic uptake: (inhibition of SERT, DAT and NAT) • Cytoplasmic vesicular reflux, via completion with monoamines	Cannabinoid Receptors 1 and 2 (CB1 and CB2) G-protein coupled receptors CB1 primary mediator of desired effects	Gamma-aminobutyricacid receptor (GABA) Via allosteric modification	NMDA and glutamate receptor via competitive antagonism	Serotoninreceptors, particularly 5-HT_{2A}
Classical examples	Cocaine Amphetamine MDMA	Cannabis – main active ingredient Tetrahydrocannabinol (THC)	Lorazepam Diazepam	Ketamine PCP	Psilocybin (the active ingredient in "magic mushrooms); LSD
NPS examples	BZP 2-AI Mephodrone	"Spice" (common name for multiple products) JWH-018 XLR-11 UR-144	Phenazopam Pyrzolam	Diphenidine Methoxetamine	Bromo-DragonFLY AL-LAD 5-MeO-DALT
Primary effects	Euphoria Disinhibition "High" State	Relaxation Anxiolysis Analgesia Sedation "High" State	Anxiolysis Muscle relaxant Sedation	"out of body" experience Euphoria "High" state	Psychedelic effects such as: • Hallucinations • Altered perception • Oceanic boundlessness
Side effects	Serotonergic syndrome Anxiety Psychosis Hyperthermia Mania Impulsivity	Anxiety Paranoia Seizures (NPS)	Respiratory depression Seizures on withdrawal	Psychosis Nausea Paranoia Anxiety	Few physical Anxiety Secondary harm from altered perception
Notable Features	Higher DA:5HT ratio give more amphetamine (stimulant like results) Lower ratios enhance entactogenicity (i.e. MDMA) NPS exist at more extreme ends of both ratios Popular in participants in night-time economy-MDMA, cocaine and amphetamine most commonly abused drugs apart from cannabis	CB1/2 receptors mediated physiologically by the endocannabinoids THC is a partial agonist. Furthermore, cannabis contains over 50 active ingredients, including cannabidiol, which antagonizes THC. (Pertwee et al. 2008) Huge range in specificities and affinities of novel cannabinoids (Gurney et al. 2014) Many designed as anxiolytics or analgesics, but little clinical use. Although cannabis does not cause classical physical withdrawal syndromes, aspects of dependency psychological dependency can form, such as craving and mood swings, which can persist after cessation (Soussan & Kjellgren 2014)	Also site of action of alcohol, co-administration can lead to potentia tion of effects Highly dependency forming in prolonged use. Pharmacologically useful in clinical context due to anxiolytic and sedative properties Many NPS rejected pharmaceuticals Classical examples widely available due to their wide legitimate use	Ketamine and PCP initially used as anaesthetic agents, but in the most part withdrawn due to their other effects Ketamine still used in some specialised contexts, such as animal use and roadside anaesthetic induction High propensity for addiction, with many studies showing difficulty in recovery, such as Morgan et al. (2008) where of 30, only 2 managed to cease usage due to the level of craving.	Can be divided into three broad groups by structure, phenethylamines, tryptamines and lysergamines Many classical examples synthetically developed and a great deal produced through innovation in structural modification by chemists of the time to produce analogues, with many of the ideas now used in production of designer drugs Drugs that are primarily hallucinogens seem to show very little propensity for addiction and physical side effects. Main risk is the danger of misadventure in altered psychological states Many drugs, such as MDMA have a hallucinogenic component however, it is possible NPS hallucinogens are less specific and have broader, more harmful effects.

NB: SERT=serotonin transporter; DA(T)=dopamine (transporter); NA(T)=Noradrenaline (transporter); 5-HT=serotonin; MDMA=3,4-methylenedioxy-methamphetamine; BZP=Benzylpiperazine; 2-AI=2-Aminoindan; JWH-018=1-pentyl-3-(1-naphthoyl)indole; XLR-11=5"-fluoro-UR-144; UR-144, (1-pentylindol-3-yl)-(2,2,3,3-tetramethylcyclopropyl)methanone; PCP=Phencylidine; LSD=Lysergic Acid Diethylamine; AL-LAD=6-allyl-6-nor-LSD; 5-MeO-DALT=N, N-diallyl-5-methoxytryptapham

Pharmacological differences

While there is wide diversity in affinities between members of these groups, and particularly between the designer drugs found in legal highs and their parent compounds, this is not necessarily the key issue in understanding prevalence patterns. Propensity to be addictive is an important consideration, as this can lead to a greater proportion of older users compared to other substances, as seen for example in cocaine or heroin usage. It has been suggested low 5-HT: DA ratios show greater propensity to compulsive taking in animal models (Rothman & Baumann 2006). Since several NPS stimulants have higher DA: 5-HT ratios than their classical parents, particularly cathinones, this would suggest that, if judging purely by this measure, some NPS might be potentially more addictive.

Previous research, notably into cocaine, found that addictive potential is enhanced by the speed of reaching active concentration in the brain (Allain et al. 2015). Two properties significantly affect this; delivery root and lipophilicity of the substance, and hence its propensity to cross the blood brain barrier. There is user reported evidence of some legal highs being slower in activity than their parent compounds, for example PMMA, a MDMA analogue (Lapoint et al. 2013). Since legal highs have significant structural modifications to their parents, such as methylation or halogenation, and these can alter these properties. There is however unfortunately little or no data on overall trends in lipophilicity or lipophobicity in NPS. There is a clearer pattern of variation in delivery routes. While there are examples of NPS being delivered intravenously, including amongst some users of cathinones (Karila et al. 2015), the vast majority of legal highs are marketed as tablets, material to be smoked or ingested nasally. As discussed in Allain et al. (2015), this could potentially help temper addictiveness of some legal highs, which contain theoretically more chemically addictive agents.

Finally, it is worth noting again how variable both the doses and contents of legal highs can be. For example, Ayres and Bond (2013) found of 22 substances tested through a range of spectrometry, 32% did not contain the stated active ingredients; some containing class B controlled cathinones, the local anesthetic benzocaine and Benzofuran. Previously, Baron et al. (2011) found that of 7 tested products, only 1 contained the listed ingredients, and 5 contained the recently controlled benzylpiperazine and 1-[3-(trifluoromethyl)phenyl]piperazine. The majority were also cut with large amounts of caffeine. These results are qualified by the recency of regulation of the seingredients and could be the manufacturers attempts to dispose of stock. Ayres & Bond (2012) found that none of the products provided any clear instruction on dosing, despite being able to order up to 1kg quantities. This has implications both for safety and in changing the potential reinforcement and thus addiction formation in susceptible individuals. Since it is clearly not straight forward to reliably obtain the same substance, and dosing becomes a matter of trial and error, combined with the fact that ingredients can vary in the same product over time, there is significant potential for extinction and decreased reinforcement. With that being said, there are reports of dependency formation. In particular, there are reports of substitution of legal highs in recovering drug user populations, with some even reporting that they could obtain more potent drugs (Changing Lives 2014). The propensity to addiction, and how it might be controlled, is a critical area of hitherto neglected research.

THE VULNERABILITY OF YOUNG ADULTHOOD

Dual Systems Model

The transition from childhood to adulthood has long been associated with a propensity for risky behaviour of diverse types, including dangerous driving, unsafe sex, alcohol and, most saliently, drug misuse. Understanding the nature of this vulnerability is thus necessary in any explanation of legal high prevalence. Steinberg et al. (2008) proposes the *Dual Systems Model (DSM)* as an explanation for enhanced risk taking. They suggest that in this period of transition, there is a mismatch of the early maturing incentive systems, which heighten sensation seeking, and the later developing (and therefore still immature) cognitive control systems that restrict behaviour, leading to heightened impulsivity. It is also necessary to explore how other factors might interact with any potential change in propensity for risk. For legal high abuse, as well as assessing the evidence and potential mechanisms for this paradigm, it is also important to consider the factors that have been suggested to interact with it.

The ventral striatum and medial Pre frontal cortex (mPFC) have long been implicated in immediate reward control through lesion studies, and increasing pre frontal activity detected in inhibition tasks. This has been supported by evidence of an inverse correlation found between superior frontal cortex thickness and impulsivity, such as Schilling et al. (2013), a large multinational MRI study with 1620 adolescents. This region undergoes growth during adolescence, a process sometimes termed frontalisation. Asynchronous development of the *bottom up* systems driving motivational state, and later developing *top down* cognitive control and motivational suppressive mechanisms (Casey & Jones 2010) would provide support for the DSM. This has emerging neurodevelopmental evidence, including decreasing grey matter density in mid adolescence in the PFC (Blakemore & Robbins 2012). The decrease in density is indicative of increasing levels of myelination and development of this brain area and associated development of these systems, although the evidence is often limited by small samples. The challenge of establishing causative links in a period of remarkable neural change remains.

Impulsivity

Impulsivity can be conceptualised as the driving force for behaviour initiation and is of particular importance in risk taking. A useful, if simple definition is, "the tendency to act prematurely without foresight" (Dalley et al. 2011). It has long been accepted that impulsivity varies through lifetime, in particular decreasing through adolescence and early adulthood. In substance abuse, impulsivity can be both a predisposing factor and consequence of substance taking. Both present potential increased risk in early adulthood, thus contributing to the increase legal high usage. In measuring impulsiveness however, there is significant difficulty; objective testing measures do not necessarily correlate, such as between stop signal reaction time tasks and delayed discounting tasks (Dalley et al. 2011). This lack of correlation has led to the suggestion that the impulsivity construct is actually made up of multiple components, often formalised into choice impulsivity and rapid response impulsivity, with separate neurological substrates. While there is compelling evidence of the importance of a spectrum of impulsive traits as an endophenotype for transition to addiction (Belin et al. 2016), in considering drug use prevalence, choice impulsivity is of greater importance and so will be the focus of consideration.

Sensation seeking

Sensation seeking has been strongly associated with impulsivity but is an independent personality trait. It can be usefully thought of as the affective experiential pullin risky behaviour, presented by an object or action, as opposed to the decision-making push that is impulsiveness - in other words, the propensity to seek out "exciting, pleasurable and novel activities" (Schulman et al. 2015). Unlike the development of impulsive control, sensation seeking is correlated with the onset of puberty, not age. Current evidence suggests that the surge in hormone levels within the brain leads to a sensitisation of the reward systems, in particular the limbic system (Peper & Dahl 2013). Later desensitization of the system (Smith et al. 2013), would lead to decreased sensitivity, giving the corresponding "inverse U" pattern of reward sensitivity. The peak of the "U" is usually determined as near mid adolescence with decrease well into adulthood. Ersche et al. (2010) examines respective levels of sensation seeking and impulsivity in 30 pairs of siblings where one of the pair was stimulant dependent, and 30 controls. They found increased impulsivity in both siblings compared to the controls, but no difference between the controls and non stimulant dependent siblings in sensation seeking, suggesting that for stimulant abuse at least, it is unlikely to be an endophenotype for addition, but rather a trait. This study is, however, limited in both size and scope, as it only considers dependency as opposed to use. A larger more recent study considering young adults specifically (McCabe et al. 2015) found an association with not just addiction but also more casual use. This vulnerability was dependent on levels of moderation by premeditation, suggesting sensation seeking might be of greater importance in young adult drug misuse and saliently its initiation, since it is a period during which premeditation, or impulsivity is underdeveloped.

Experimental evidence for the DSM

In assessing impulsivity experimentally, Self-report tools, such as the Barratt Impulsiveness Scale (BIS) are commonly used. Some studies use only part of the scale, such as Steinberg (2010), which used only 3 of 6 subsets as part of an experimental battery, since they felt these fit best their definition of impulsivity, and the others risked confounding their data. This highlights a wider problem within the study of impulsiveness generally; when there is still significant variation between working definitions, assessing and comparing data and making use of clinical tools must be performed with caution, since there is a risk of forming incorrect inferences from the data. Steinberg (2010) found a linear decrease in BIS reported impulsivity, while in a separate section, it found self reported reward-seeking fit to a curvelinear "inverted U" decrease. Self-report however does not provide conclusive evidence. Variations could be due to other factors, such as other age effects, including changes in honesty due to embarrassment or even consciously or subconsciously responding as influenced by previously encountered described expectations for their age group. Thus while survey based tasks are practical to administer and useful in that they are illustrative of trends, corroboration by experimental task is needed.

The Iowa Gambling Task (IGT) can be used as a measure of risk taking. Subjects are instructed to try to maximise their return in a choice of gambling decks, with best return offered by lower reward, but smaller punishment decks. Various lesions have been demonstrated to alter test behaviour. When it is performed on those with vmPFC lesions for examl, there is a tendency to persist on risky packs, which offer high reward but net loss (Blakemore & Robbins 2012). In order to measure how decision-making changed through adolescence, Caufmann et al. (2010) used a modified version of this test. Decks are chosen in each of multiple rounds of testing, and the subject selects whether to 'pass' or 'play' each turn. The Percentage good plays, (the percentage of net advantageous deck cards played), and percentage bad plays (percentage of net negative deck cards played), is calculated. Rates of change between the two are used to represent approach behaviours and avoidance behaviours respectively. They found a linear increase in avoidance behaviour concordant with findings for PFC development through adolescence (Schilling et al. 2013). Approach behaviour showed an 'inverted U' pattern, with an apex in late adolescence, decreasing through early adulthood despite overall performances above age 14 being similar. Thus,

the research supports separate time course and development process in inclination to play from advantageous decks and resistance to play cessation in negative decks, and so there is a period of vulnerability where reward seeking is more dominant than the developing risk aversion. By extension, this reward bias provides some potential explanation for the pattern of legal high abuse, and its concentration in this group. Further isolating the neurological substrate of this variation would help confirm the influence of these two factors.

Hedonic titration and reward

While enhanced impulsivity in the context of sensation seeking forms an important explanation for risk taking and initiation of substance use in young adults, it is not on its own sufficient to fully explain patterns of legal high usage. The 'licit' substances of alcohol and nicotine offer a more reliable risk and less uncertainty to users than legal highs. Simply, sensation seeking alone cannot explain why some young people choose more risky, but more intense substances. Clearly, the nature and magnitude of sensation is important. There is emerging evidence of age differences in pleasure seeking (hedonic) behaviour. In Reedier et al. (2009), participants were asked to track their hedonic behaviour, sampled via mobile phones. The findings suggest that there was a tendency to maintain pro-hedonic behaviour, but not increase it in older participants. Younger participants were however more likely to attempt to seek out even more pleasurable experiences, though had a less positive average affect. A further finding was that younger participants were more likely to engage in contra-hedonic behaviour. Contra-hedonic behaviour seems counterintuitive, contrary to the pleasure principle, 'Das Lustprinzip' of Freud, where pleasure seeking drives behaviour. However recent utility-based argument has suggested affective self-regulation is advantageous with negative affect helping in conflict, for example. Excessive positive effect can decrease efficiency in tasks (Tamir et al. 2013). Furthermore, positive affect can accompany negative, such as viewing horror films (Andrade & Cohen 2007), and this too can partly explain contra-hedonic behaviour. Clearly, there are changes in hedonic titration with age, with a tendency in younger people towards more extreme mechanisms of regulation, instead of maintaining behaviour. This can help explain why young adults in particular might stray from the known hedonic value of licit substances into the novel, varied and potentially far more intense hedonic experiences of legal highs, to which they are vulnerable due to increased risk taking. Further, the propensity to enhance hedonic experience helps explain vulnerability in young participants in the night-time economy, already a pro-hedonic context.

The mechanisms for the increased reward sensitivity demonstrated by the IGT, and for pleasure are still unclear. Dopamine has long been implicated as a neural substrate, notably by Roy Wise (1978). Later research has challenged his initial proposal that it is the substrate for all aspects of reward and, particularly, the 'hedonic substrate'. This is now considered to be more closely tied to other systems, particularly the opioid, GABA and endocannabinoid (Berridge & Kringelbach 2015), without perhaps a single 'hedonic nectar'. Dopamine is still strongly implicated in incentive salience, 'wanting' behaviour, with the dopamine surges in stimulant abuse correlating far better with subjective reports of 'wanting' as opposed to 'liking' (Evans et al. 2006). There is evidence of significant remodelling and potential hyperactivity of the dopamine system in adolescence, particularly in the PFC and areas associated with reward and decision-making (Wahlstrom et al. 2010). Much more work is needed to elucidate exact neural correlates with the developmental effects and, in particular, distinguish what proportion of changes in reward sensitivity in adolescence relate to hedonic value and what proportion incentive salience.

Emotion

The issue with much of the evidence presented thus far, and indeed the main criticism of the DSM, is that it is very much evidenced by laboratory based scenarios, which differ significantly from "real world" decision making, where there is uncertainty rather than known risk, especially in legal highs. Decisions are also taken in less emotionally "hot" contexts (Schulman et al. 2015). Emotion can be considered the "internal subjective states that influence the direction of subjects" (Ernst 2014). Since the initial proposition of the DSM, research has explored not just the raw impact of emotion, but its interaction with any potential predisposition in adolescence. Although the IGT has an emotional component, featuring reward and punishment, it doesn't measure the effect of background emotion. One approach has been to use emotional go/no-go tasks. In the standard go/no-go task, reaction time is measured to a "go" signal, with participants instructed not to respond to another "no-go" signal. In the emotional adaptation, the stimuli are non emotionally neutral, such as smiling faces. The results of these tasks have been mixed, and more work is required to categorise the differences in performance, if there are indeed any, as well as establishing their relevance to risky behaviour (Schulman et al. 2015). None the less, evidence of amygdala involvement has led many to conclude there is over focus upon the PFC and in fact instead of a dual model, there should be a triadic model, incorporating emotion, as well as motivation and regulation, with constructs such as emotional lability mapping onto the these three (Ernst et al. 2014). While intriguing, and worthy of further study (and more extensive discussion than the scope of this paper), the research is less developed than for the DSM, which still appears to offer the best evidenced predictive tool and explanation.

When considering legal highs, as well as the potentially emotionally rich backgrounds in which they are often consumed, there is also the packaging. Although invariably stating "not for human consumption," potentially emotionally negative, this might well be outweighed by the colourful, deliberately graphically exciting packaging. Research in cigarette use has shown significant reductions in attractiveness and positive association with plain packaging compared to colourful, with the effect potentially enhanced in young people (Moodie et al. 2012). More evidence is needed to draw further conclusions for legal highs.

Peer influence

While risk taking is well characterised as heightened during adolescence and early adulthood, emerging focus is on the role of peers in risky decision-making, and particularly whether this potential modifier is influenced by age. Gardner and Steinberg (2005) offered probably the most extensive and cited studies. In their experimental paper, they measured peer influence in three cohorts, adolescence (13-16), young adults, (16-22) and adults (24+), by comparing solitary response against that accompanied by 2 peers in scenario based questionnaires and a computerised game, 'Chicken', designed to measure risky decision making through a driving based task, in which virtual earnings increased with time, however at a random point these earnings would be lost if the car had not been stopped by the participant, thus granting an index of risk taking. They found risk taking decreased with age, but increased with peer presence. The magnitude of this increase was greater in adolescence, decreasing through young adulthood and was insignificant by adulthood. There was also increased risky decision-making preference on the questionnaire. The study suggests peers presence enhances adolescent vulnerability to risky decision-making.

The obvious question in understanding the implication of this is whether it matters if the peer is actively encouraging, '*peer pressure'*, as in Gardner & Steniberg (2005), or presence and observation of a peer is sufficient. Chein et al. (2011), an MRI study studied passive presence. They found increased risk taking in adolescent, but not young adult or adult groups, with associated increases in activity in the VS and OFC. Later research, focussed on the (18-20) age bracket, found no significant difference between the passive peer and no peer groups, but enhanced risk taking response in the active peer encouragement scenario (Reynolds et al. 2014). However, this was limited in that it did not control the contents of encouragement or record the interactions. Further studies will be needed to clarify this research picture.

Risk perception

A tenet commonly found in "folk" adolescence psychology, is that there is a propensity in the period from puberty to adulthood for underestimation of risk. This would lead to consequent increases in the propensity for risky behaviour and would provide some explanation for patterns of risk taking. The evidence is however extensively and firmly against any difference. Indeed, some studies have found that between puberty and adulthood, risk valuation is temporarily increased (Halpern-Felsher et al. 2002). There is however growing evidence that age is associated with the effect of peers on risk evaluation. Subjects show decreasing propensity for social conformity to risk evaluation with age, examined by frequency of changing their risk assessments based upon those of others, with teenagers more susceptible to those of their own age than adults (Knoll et al. 2015).

CONCLUSIONS

Implications for the management of legal high misuse

It is clear that currently in the United Kingdom, the misuse of legal highs has been a growing problem and it is also clear that that problem is most salient in young people. In reviewing the evidence to date, it seems that although still deeply limited, the explanation for this pattern of prevalence does not lie primarily in the pharmacology of the contents. The clearest implication of the pharmacological evidence is that the potential danger presented by legal highs to users and in particular young people is very great. The current situation where substances can be sold without information on safe consumption, or indeed any information on concentrations, coupled with the questionable nature of the contents and the inconsistencies within supply create a dangerous cocktail, masked under the façade of purported legality. This has clear implications for the clinician too, in that treatment of unknown and regularly polysubstance presents a significant potential medical challenge, and although assessing the total level of harms is near impossible, there are enough reports and signs that there is a clear urgency to address the problem.

There is not enough evidence to draw significant conclusions regarding the pharmacokinetic properties of the NPS within legal highs compared to their classical cousins and parents to support the suggestion that there is a reduction in habit forming or addictive potential, leading to lower adult prevalence. It seems therefore that of greater importance is the interaction of the still-developing decision-making mechanisms in young adulthood and the availability of legal highs. It is likely not an intrinsic difference in risk evaluation that presents an issue, but instead how these risks are acted upon. The particular risk factors differ from the older population, with the unmasking of sensation and reward seeking by reduced regulation of impulsivity seeming to be key, with both the evidence of these risk factors and the prevalence pattern fitting well the predictions of the DSM. This is complemented by further interaction with

emotional systems and peer influence. Legal highs are marketed in a way which presents a potentially enhanced emotional appeal and often sold to young people in high risk contexts, surrounded by their peers, by whom they seem to be likely more influenced, although whether this is purely via active encouragement or also passive mechanisms is unclear.

Limitations and future research questions

As is often the case, conclusions reached must be coupled with significant "health warnings". The literature available is still limited, and in particular not enough studies have examined legal highs, as opposed to NPS, thus presenting a challenge to draw "real world" conclusions about these products and requiring informed extrapolation. Although not exclusively, many of these prevalence patterns sited are from United Kingdom data, and certainly are at risk of being western-centric. How these conclusions would transfer to non-western cultures is unclear and with many of these substances produced in Asia, and many naturally obtained examples widely available there (Wasunna et al. 2015), this is an important area of future exploration. Similarly, the picture in the United Kingdom will imminently be changing, with the Psychoactive Substances Bill. Perhaps this is the ideal time to take stock of the current situation, and while this might shift research interests, there is such a spectrum of drugs policy that there is still a clear need to build on research to date.

Perhaps most urgently in a world where legal highs are still widely available, there is a need for a far larger and better-planned effort to characterise and review the contents of legal highs, of significantly larger scale than, for example Ayres & Bond (2012) or Baron et al. (2011) of different purported classes, and then attempt to draw structural trends in the pharmacokinetics of these products. Only then can safer conclusions be applied to potential management strategies. While the literature on risk taking in young adults, and young people is more extensive, further work is needed in crystallising the neurological substrates, both through receptor systems and neuroanatomically. This will require both new studies in human subjects, but also perhaps application of new eroptogenetic techniques in animal models to more accurately isolate neural substrates and mechanisms. While some exciting work is emerging in this field, for example Zalockusky et al. (2016), more extensive work and in particular, application of these techniques in animal models of adolescence could prove fruitful. Literature is also sparse in converting broader trends about decision-making into drug initiation, and specifically for legal highs. As a first step, using legal high packaging as a stimulus in decision making tasks, such as in an emotional go/no go task, or at least risk taking surveys themed more on substance misuse and legal high taking could have a useful contribution to the literature. Peer influence is a potentially key consideration in substance abuse more widely but the picture is still somewhat unclear. A large, multicentre effort to determine links between active and passive peer influence and effect of age is needed to clarify this central question. Again, designs more focussed on substance taking would fill a notable literature gap. Of interest both in legal highs, but also potentially in tobacco control, would be work to categorise the emotional response interaction of packaging in young people. Simple tasks categorising attractiveness to more detailed studies using MRI, (for example decision tasks) could provide useful evidence in any regulatory efforts. Finally, although the prevalence pattern is clearly weighted towards young people, survey tools are wholly inadequate. There is a clear, critical need for better design, or new surveys to more accuratelyinvestigate younger people than CSEW, including those living in shared accommodation, coupled with more extensive work with participants in the night-time economy.

The Psychoactive Substances Bill will attempt to control the rise of legal high availability and misuse in the United Kingdom, switching from a system where broadly NPS are "innocent until proven guilty" (with exceptions for attempts to control various compound families), to a system where psychoactive substances are controlled, unless an exception is granted. Licit highs are exempted. Only time will show the effect this has on prevalence. Certainly, re-branding will be necessary, for 'legal high' will have become somewhat of a misnomer. Supply routes will also change; many "head shops" have already closed and notably several online suppliers have launched "closing down" sales in the lead up to the now delayed implementation day. However, it would be premature to declare the problem solved. Other countries have found that usage of NPS has merely been diverted from legal highs to other sources. The 'dark web' holds great potential for an underground market, as does expansion of the role of illicit dealers. Others have found difficulty in analysis, since there simply aren't field-testing kits available to enforcement agencies for all potential compounds, or proof of psychoactivity. Close monitoring is required to ensure that any reduction in legal highs really does have an impact on substance misuse levels and awareness campaigns must be focussed intensely at the clearly vulnerable but oft neglected young adult population. A ban on its own perhaps might increase the ascribed risk of substance misuse, but could also increase harmfulness. It remains very much to be seen whether this deterrence can be transferred into lower substance misuse and reduced harm in this population.

Acknowledgements: None.

Conflict of interest: None to declare.

References

1. Allain F, Minogianis E-A, Roberts DCS & Samaha A-N: How fast and how often: The pharmacokinetics of drug use are decisive in addiction. Neuroscience and Biobehavioral Reviews 2015; 56:166-79. http://doi.org/10.1016/j.neubiorev.2015.06.012
2. Andrade EB & Cohen JB: On the Consumption of Negative Feelings. Journal of Consumer Research 2007; 34:283-300. http://doi.org/10.1086/519498
3. Angelus Foundation (n.d.): Universities and Festivals. Retrieved March 14, 2016, from http://www.angelusfoundation.org.uk/universities-and-festivals/
4. Ayres T, Ayres T & Bond J: A chemical analysis examining the pharmacology of novel psychoactive substances freely available over the internet and their impact on public (ill) health. Legal highs or illegal highs? BMJ Open 2012; 2:1–8. http://doi.org/10.1136/bmjopen-2012-000977
5. Baron M, Elie M & Elie L: An analysis of legal highs: do they contain what it says on the tin? Drug Test Anal 2011; 3:576–581. http://doi.org/10.1002/dta.274
6. Baumeister D, Tojo LM & Tracy DK: Legal highs: staying on top of the flood of novel psychoactive substances. Therapeutic Advances in Psychopharmacology 2015; 5:97–132. http://doi.org/10.1177/2045125314559539
7. Belin D, Belin-Rauscent A, Everitt BJ & Dalley JW: In search of predictive endophenotypes in addiction: insights from preclinical research. Genes, Brain, and Behavior 2016; 15:74-88. http://doi.org/10.1111/gbb.12{Bibliography}265
8. Berridge KC & Kringelbach ML: Pleasure Systems in the Brain. Neuron, 2015, May 6. http://doi.org/10.1016/j.neuron.2015.02.018
9. Blakemore S-J & Robbins TW: Decision-making in the adolescent brain. Nature Neuroscience 2012; 15:1184–1191. http://doi.org/10.1038/nn.3177
10. Casey BJ & Jones RM: Neurobiology of the adolescent brain and behavior: implications for substance use disorders. Journal of the American Academy of Child and Adolescent Psychiatry 2010; 49:1189–201; quiz 1285. http://doi.org/10.1016/j.jaac.2010.08.017
11. Changing Lives: Novel Psychoactive Substance use amongst clients accessing Changing Lives services in Newcastle upon Tyne, 2014.
12. Chein J, Albert D, O'Brien L, Uckert K & Steinberg L: Peers increase adolescent risk taking by enhancing activity in the brain's reward circuitry. Developmental Science 2011; 14:F1–10. http://doi.org/10.1111/j.1467-7687.2010.01035.x
13. Dalley JW, Everitt BJ & Robbins TW: Impulsivity, Compulsivity, and Top-Down Cognitive Control. Neuron 2011; 69:680–694. http://doi.org/10.1016/j.neuron.2011.01.020
14. Ernst M: The triadic model perspective for the study of adolescent motivated behavior. Brain and Cognition 2014; 89:104–111. http://doi.org/10.1016/j.bandc.2014.01.006
15. Ersche KD, Turton AJ, Pradhan S, Bullmore ET & Robbins TW: Drug addiction endophenotypes: impulsive versus sensation-seeking personality traits. Biological Psychiatry 2010; 68:770–3. http://doi.org/10.1016/j.biopsych.2010.06.015
16. European Monitoring Centre for Drugs and Drug Addiction (n.d.): Action on New Drugs. Retrieved 3 15, 2016 from European Monitoring Centre for Drugs and Drug Addiction: http://www.emcdda.europa.eu/activities/action-on-new-drugs
17. Evans AH: Compulsive Drug Use Linked to Sensitized Ventral Striatal Dopamine Transmission 2006; 59:852-858. http://doi.org/10.1002/ana.20822
18. Gardner M & Steinberg L: Peer influence on risk taking, risk preference, and risky decision making in adolescence and adulthood: an experimental study. Developmental Psychology 2005; 41:625–35. http://doi.org/10.1037/0012-1649.41.4.625
19. Global Weekends: Terms. Retrieved February 9, 2016 from Global Weekends: www.globalweekends.co.uk/terms
20. Gurney SMR, Scott KS, Kacinko SL, Presley BC & Logan BK: Pharmacology, toxicology, and adverse effects of synthetic cannabinoid drugs. Forensic Science Review 2014; 26:54–76.
21. Home Office: Drug Misuse: Findings from the 2014/15 Crime Survey for England and Wales. Retrieved February 9, 2016, from https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/462885/drug-misuse-1415.pdf
22. Karila L, Megarbane B, Cottencin O & Lejoyeux M: Synthetic Cathinones: A New Public Health Problem. Current Neuropharmacology 2015; 13:12–20. http://doi.org/10.2174/1570159X13666141210224137
23. Knoll LJ, Magis-Weinberg L, Speekenbrink M & Blakemore S-J: Social Influence on Risk Perception During Adolescence. Psychological Science 2015; 26:1-10. http://doi.org/10.1177/0956797615569578
24. Lapoint J, Dargan P & Hoffman R: Individual Novel Psychoactive Substances. In P. Dugan & D. Wood (Eds.), Novel Psychoactive Substances: Classification, Pharmacology and Toxicology (p. 164). Academic Press, 2013.
25. Lindigkeit R, Boehme A, Eiserloh I, Luebbecke M, Wiggermann M, Ernst L & Beuerle T: Spice: a never ending story? Forensic Science International 2009; 191:58–63. http://doi.org/10.1016/j.forsciint.2009.06.008
26. McCabe CJ, Louie KA & King KM: Premeditation moderates the relation between sensation seeking and risky substance use among young adults. Psychology of Addictive Behaviors, 2015. http://doi.org/10.1037/adb0000075
27. Millstein SG & Halpern-Felsher BL: Judgments about Risk and Perceived Invulnerability in Adolescents and Young Adults. Journal of Research on Adolescence 2002; 12:399-422. http://doi.org/10.1111/1532-7795.00039
28. Moodie C, Stead M, Bauld L, McNeill A, Angus K, Hinds K, Kwan I, Thomas J, Hastings G, O-E A: Plain tobacco packaging: a systematic review. London: Public Health Research Con. London: Public Health Research Consortium, 2012.
29. Morgan CJ, Rees H & Curran HV: Attentional bias to incentive stimuli in frequent ketamine users. Psychological Medicine 2008; 38:1331–1340. http://doi.org/10.1017/S0033291707002450
30. Pertwee RG: The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. British Journal of Pharmacology 2008; 153:199-215. http://doi.org/10.1038/sj.bjp.0707442
31. Reynolds EK, MacPherson L, Schwartz S, Fox NA & Lejuez CW: Analogue study of peer influence on risk-taking behavior in older adolescents. Prevention Science: The Official Journal of the Society for Prevention Research 2014; 15:842–9. http://doi.org/10.1007/s11121-013-0439-x

32. Riediger M, Schmiedek F, Wagner GG & Lindenberger U: Seeking pleasure and seeking pain: Differences in prohedonic and contra-hedonic motivation from adolescence to old age. Psychological Science 2009; 20:1529-1535. http://doi.org/10.1111/j.1467-9280.2009.02473.x
33. Rothman RB & Baumann MH: Therapeutic potential of monoamine transporter substrates. Current Topics in Medicinal Chemistry 2006; 6:1845–59. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/17017961
34. Schilling C, Kühn S, Paus T, Romanowski A, Banaschewski T, Barbot A, Gallinat J: Cortical thickness of superior frontal cortex predicts impulsiveness and perceptual reasoning in adolescence. Molecular Psychiatry 2013; 18:624–30. http://doi.org/10.1038/mp.2012.56
35. Shulman EP, Smith AR, Silva K, Icenogle G, Duell N, Chein J & Steinberg L: The Dual Systems Model: Review, Reappraisal, and Reaffirmation. Developmental Cognitive Neuroscience 2015; 17:103–117. http://doi.org/10.1016/j.dcn.2015.12.010
36. Smith CD & Robert S: "Designer drugs": update on the management of novel psychoactive substance misuse in the acute care setting. London, England. Clinical Medicine 2014; 14:409–15. http://doi.org/10.7861/clinmedicine.14-4-409
37. Soussan C & Kjellgren A: The flip side of "Spice": The adverse effects of synthetic cannabinoids as discussed on a Swedish Internet forum. NAD Nordic Studies on Alcohol and Drugs 2014; 31:207–219. http://doi.org/10.2478/nsad-2014-0016
38. Steinberg L: A dual systems model of adolescent risk-taking. Developmental Psychobiology 2010; 52:216–24. http://doi.org/10.1002/dev.20445
39. Steinberg L, Albert D, Cauffman E, Banich M, Graham, S & Woolard J: Age differences in sensation seeking and impulsivity as indexed by behavior and self-report: evidence for a dual systems model. Developmental Psychology 2008; 44:1764. http://doi.org/10.1037/a0012955
40. Tamir M, Ford BQ & Gilliam M: Evidence for utilitarian motives in emotion regulation. Cognition & Emotion 2013; 27:483–491. http://doi.org/10.1080/02699931.2012.715079
41. United Nations Office on Drugs and Crime: World Drug Report, 2015. Retrieved February 9, 2016, from http://www.unodc.org/documents/wdr2015/WDR15_ATS_NPS.pdf
42. Wahlstrom D, Collins P, White T & Luciana M: Developmental changes in dopamine neurotransmission in adolescence: Behavioral implications and issues in assessment. Brain and Cognition, 2010. http://doi.org/10.1016/j.bandc.2009.10.013
43. Ward J, Rosenbaum C, Hernon C, McCurdy CR & Boyer EW: Herbal medicines for the management of opioid addiction: safe and effective alternatives to conventional pharmacotherapy? CNS Drugs 2011; 25:999–1007. http://doi.org/10.2165/11596830-000000000-00000
44. Wasunna B, Thomas E & Morgan S: Development of legal highs. Journal of Psychiatric Intensive Care 2015; 11:128–137. http://doi.org/10.1017/S1742646415000011
45. Wise RA: Catecholamine theories of reward: A critical review. Brain Research, 1978. http://doi.org/10.1016/0006-8993(78)90253-6
46. Zalocusky KA, Ramakrishnan C, Lerner TN, Davidson TJ, Knutson B & Deisseroth K: Nucleus accumbens D2R cells signal prior outcomes and control risky decision-making. Nature 2016; 531:642–646. http://doi.org/10.1038/nature17400

Correspondence:
Benedict Morris, MD
Queens College, University of Cambridge
Cambridge, UK
E-mail: bpmm2@cam.ac.uk