A-DEBATE SCIENCE SUMMARY
March 2016

1. Introduction

This scientific summary is derived from the presentations and discussions that took place during the A-Debate (ALICE RAP Debate), ‘U-Turn on Addictions - Biological and social sciences to reframe drug policy’ convened in Barcelona, 17-18 February 2016. The ALICE RAP project (http://www.alicerap.eu/) is a €10 million, five year (2011-2016) action co-financed by the FP7 programme of the European Union to study the place of addictions and lifestyles in contemporary Europe. One thousand months of scientific endeavour in disciplines ranging from anthropology to toxicology have analysed the biological, economic, historical, medical, political and social factors behind addictive drugs and behaviours. The summary follows three main headings: biology and addictions, prevention and treatment, and governance.

2. Biology and addictions

There are many reasons why societies are concerned about alcohol, nicotine, and other psychoactive drugs (hereafter referred to as ‘drugs’). One obvious and important reason is because these drugs interfere with our biology and functioning.

Years of life lost due to drugs

There are many ways to document and describe this interference. One way is to use years of life lost (YLL), which also acts as a surrogate indicator of broader impact on functioning and well-being. YLLs are calculated by subtracting the actual age at death from the life expectancy given that age; if somebody dies aged 65 years, and the life expectancy for people his or her age is 80 years, then YLLs would amount to 15 years.

In the European Union in 2013, illegal drug use was responsible for 1.4 million YLL (1.8% of all YLL), alcohol for 6.1 million years of YLL (8.2% of all YLL) and tobacco for 13.6 million YLL (18.2% of all YLL).

Quantitative risk assessment

Another way to describe the interference of drugs on our biology and functioning is to use quantitative risk assessment. For example, the Margin of Exposure (MOE) for any drug gives an indication of whether individuals are exposed to (or use) a drug at a lower level of risk or not. Margins of exposure compare the ratio of a toxic dose of a drug (usually the benchmark dose BMDL10, the lowest dose which is 95% certain to cause no more than a 10% negative outcome incidence) with the dose consumed. A MOE of 100 means that the drug is being consumed at one hundredth of the toxic dose; a MOE of 1 means that the drug is being consumed at the toxic dose. Thus, the higher the MOE, the lower the level of risk. MOE for drugs can be calculated taking into account a range of hazard outcomes in health and other well-being domains, as long as suitable dose-response data are available (which is not the case for most drugs and many well-being indicators). Therefore, analyses to date are primarily restricted to lethal outcomes based on animal studies, which also act as a surrogate indicator of broader impact on functioning and well-being. Results for European adults are summarized in Figure 1. It is important to note that the MOE as described here applies where the harm from the drug is inherent in the drug itself; it does not account for the harms that arise from drug delivery systems, for example, smoked tobacco. The low MOE for alcohol (and thus high risk) is due to the high exposure levels (alcohol use) by European adults.
**Evolutionary drivers of drug use**

The supposed evolutionary novelty of exposure to drugs is often posited as one of the reasons that they cause so much harm (because our brains and bodies have yet to evolve to cope with these new substances). But multidisciplinary scientific evidence suggests otherwise: drugs are not evolutionary novelties. 5,6

In the story of life over the last 400 million years, one ongoing theme has been the battle between plants and the animals that eat them. Of many defence mechanisms, plants produce secondary metabolites, including cannabis, cocaine, morphine and nicotine, potent neurotoxins that evolved because they punished and deterred consumption by plant-eating animals. 5 Thus, from the the evolutionary ecological perspective, we find natural selection for drugs that discourage consumption of the plant (i.e. punishment of the consumer). We do not find natural selection for drugs that encourage consumption of the plant (i.e. rewarding the consumer), which would be the inferred outcome if selection were based only on the neurobiological and behavioral psychological theory of reward and reinforcement.

Counterbalancing the development of plant neurotoxins, plant-eating animals have evolved to counter-exploit the plants’ production of drugs, including buffering against nutritional and energetic constraints on signaling in the central nervous system and exploiting the anti-helminthic properties of some drugs. 5 Present day examples of pharmacophagy are seen with Congo basin hunter gatherers, amongst whom the quantity of cannabis 7 and nicotine 8 consumed is titrated against intestinal worm burden - the higher the intake, the lower the worm burden. Moreover, when treated with the anti-worm drug, abendazole, the number of nicotine-containing cigarettes smoked is reduced. 8

In another example, the presence of ethanol within ripe fruit suggests low-level but chronic dietary exposure for all fruit-eating animals, with volatilized alcohols from fruit potentially serving in olfactory localization of nutritional resources (animals being more able to smell alcohol molecules when locating ripe food). 5 The same seems to apply to humans, since our ape ancestors gained a digestive dehydrogenase enzyme capable of metabolizing ethanol near the time that they began using the forest floor, about 10 million years ago. 9 The alcohol dehydrogenases in our more ancient and arboreal ancestors did not oxidize ethanol as efficiently as in humans today. This change suggests that exposure to dietary sources of ethanol increased in hominids during the early stages of our adaptation to a terrestrial lifestyle. Because fruit collected from the forest floor is expected to

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**Figure 1** Margin of exposure for daily drug use estimated using probabilistic analysis. Source: Lachenmeier & Rehm (2015).
contain higher concentrations of fermenting yeast and ethanol than similar fruits hanging on trees, this transition may also be the first time our ancestors were exposed to (and adapted to) substantial amounts of dietary ethanol.

**Heavy use over time as explanatory variable**

The evolutionary evidence suggests that humans have evolved to seek out and extract cholinergic agents from plants in order to combat invertebrate parasites such as helminths. This does not imply that humans evolved to specifically consume, for example tobacco, or that tobacco use is beneficial in the modern world. What is novel in the modern world is the level of availability and format of consumption. With alcohol, the evolutionary evidence implies that the genomes of modern humans began adapting at least 10 million years ago to dietary ethanol present in fermenting fruit— a source of ethanol that is remarkably similar in concentration and form (i.e., with food) to the low levels of ethanol consumption that might reduce the risk of ischaemic events.10 Again, what is different in the modern world is novel availability through fermentative technology enabling humans to consume beverages (devoid of food bulk) with higher ethanol content than fruit fermenting in the wild.

It is the sustained use of drugs over time, and, in particular, heavy use over time that leads to harm. In fact, the evidence suggests we can go further in noting that heavy use over time explains the consequences of what are called ‘addiction’ or ‘substance use disorders’, with heavy use causing end organ damage that results in more heavy use. The term ‘substance use disorder’, is often used as shorthand to identify individuals who might benefit from advice or treatment, but as a condition itself, ‘substance use disorder’ is a medical artefact for which biology provides no support, since ‘substance use disorder’ itself occurs in all grades of severity, with no natural distinction between ‘health’ and ‘disease’. 11, 12

Take one example, alcohol consumption. Chronic disease risk has a continuous exponential relationship with consumption.13 Alcohol consumption is close to log-normally distributed in populations, skewed towards heavy drinking.14 There is no natural cut-point above which “alcohol use disorder” or “alcohol dependence” definitively exists and below which, it does not.

Unmanaged heavy drinking can be associated with even further heavy drinking, often culminating in a more difficult to manage state due to end organ brain damage,15 with the brain damage a consequence of the heavy drinking.16, 17 “Alcohol use disorder” or “alcohol dependence” are defined as a score on a checklist of symptoms, and there is a smooth line exponential relationship between levels of alcohol consumption and the score on the checklist.18 Heavy drinking is a cause of the items on the checklist, including compulsion to drink more which is a consequence of brain damage, itself caused by heavy drinking. Thus “alcohol use disorder” is a diagnostic artefact and no more is needed to consider what is called “alcohol use disorder” other than heavy use over time.11,12 This does not imply that heavy use over time is the only cause of harm - there are other biological and contextual factors, for example, alcohol dehydrogenase polymorphisms19 and income levels20, which can impact harm independent of levels of alcohol consumption.

There is ongoing discussion as to whether or not sugar is an ‘addictive’ substance in the same bucket as alcohol and other drugs.21 Moving out of the addiction frame to the heavy use over time frame provides an alternative insight to this. As with alcohol (and, high blood pressure22), chronic disease risk associated with plasma glucose levels is a continuous exponential relationship.23 The distribution of blood glucose levels is close to log-normally distributed in populations, skewed towards high levels.24 There is no natural cut-point above which diabetes definitively exists and below which, it does not. Similar to the alcohol model (heavy use of alcohol over time results in brain damage, which leads to further heavy use of alcohol over time), there is evidence that heavy use of sugar over time damages hippocampal function25, which leads to further heavy use of sugar over time.26 Thus, in the heavy use over time frame, sugar can be placed in the same bucket as alcohol and other drugs, and managed with similar public health regulations.
3. Prevention and Treatment

Prevention
Combinations of factors from three levels, molecular/cellular (e.g., genes), individual (e.g., knowledge and skills – health literacy) and the environment (e.g., social norms) drive heavy drug use, with components from all three levels exacerbating harm, independent of the amount of drug use (for example, alcohol dehydrogenase at the molecular level, income at the individual level, and stigma at the environmental level).  

One of the implications of the biological approach is that, given the active and functional relationship we have with drugs, it is not surprising that exposure to drugs facilitated by affordability (high availability and low price) and commercial communications result in heavy use over time. Advertising increases use for both novice users and heavy users, operating at the level of measurable brain responses.

Given the multiple drivers acting across all three levels (molecular, individual and environmental), it is little wonder that prevention amongst youth has not had the impacts that we would like. This is also due, to a large part, to insufficient resourcing for prevention, insufficient research and appraisal of the impact of preventive activities, and insufficient implementation of evidence-based effective programmes. One solution to help rectify these deficiencies is to create a central, transparent and evidence-based approval process for behavioural interventions, a European Prevention Agency.

Treatment
No matter what prevention or policies are put into place, a number of people will still run into problems with heavy drug use over time and will need and benefit from treatment. Unfortunately, there are three problems here. First, the gap between need and treatment is large. Using United States data, for example, less than 1 in 5 of individuals with a lifetime ‘diagnosis of alcohol use disorder’ have ever received treatment and less than 1 in 4 of individuals with a lifetime ‘diagnosis of drug use disorder’ have ever received treatment. Second, considerable marginalization and stigmatization happen in the path to treatment, and these are often exacerbated by treatment. And, third, even if people get into treatment, pharmacotherapy for heavy use of alcohol and drugs is generally under-developed and under-performing in terms of impact.

Drug delivery systems
Harm from drugs also results from modes of drug delivery, as in the case of nicotine. Whilst nicotine itself is not a harm-free drug, over the last one hundred years, the harm has largely derived from its mode of delivery - smoked tobacco. Technological developments have now led to electronic nicotine delivery systems (ENDS) (e-cigarettes) as widespread alternatives to smoked tobacco, with current best estimates showing e-cigarettes to be 95% less harmful to health than smoked cigarettes. Margins of exposure analyses of ENDS find that the main toxicants found in tobacco and trace nicotine impurities are below levels likely to cause harm, suggesting that, at least from this perspective, e-cigarettes are likely to be less harmful than smoked tobacco. MOE analyses find that it is nicotine that is the primary toxic drug in e-cigarettes. Nicotine levels can be set, regulated and monitored. Concern has been raised that ENDS are additive or gateway products to smoked tobacco, rather than replacement products. However, the evidence does not support this.

4. Governance

Governance
Governance can be considered as the processes and structures of public policy decision making and management that engage people across the boundaries of public agencies, levels of government, and/or the public, private and civic spheres in order to carry out a public purpose that could not otherwise be accomplished. An analysis of 28 European countries finds that only one-quarter of the countries can be considered as having a comprehensive policy for all drugs, within a broad societal well-being approach. For almost all European countries, there are opportunities for improving governance both for legal and illegal drugs, while pursuing a societal well-being goal.
Missed opportunities
There are a number of reasons for the missed governance opportunities. First, it is not generally clear what is being governed. Concepts of addiction have varied enormously over both time and place within Europe, with considerable heterogeneity between drugs (alcohol, tobacco and illegal drugs) and levels of governance (international, national and local). Using heavy use over time as the frame for action would simplify and facilitate convergence of our approaches to drug governance as we move forward across different jurisdictions. Second, a panoply of stakeholders is active in addictions governance, and the relationship between evidence and policy will be driven by the stakeholder group which has power and influence at the time - and this will also vary by time and place. Third, concepts and power are reflected in and further driven by variations in media constructs, which also vary over time and place. And, fourth, corporate power through multiple channels of influence can hinder adequate governance - there are insufficient transparency and inadequate rules of the game in place to ensure level playing fields for discussions across all actors. There is no simple solution for moving forward. However, three opportunities present themselves.

Well-being
First, societal well-being, as captured, for example, by OECD (Figure 2) provides a frame for improved governance. Well-being has various dimensions, including quality of life (health, education and skills, social connections, civic engagement, and personal security), material conditions (income, employment and housing) and sustainability over time. Drugs and drug-related harms are affected by and affect all of these dimensions. Well-being analyses find that, whilst some drug policies may reduce health harms, they often come at the expense of adverse side effects including criminalization, social stigma and social exclusion, all of which also independently exacerbate health harms. A well-being frame calls for whole-of-society approaches that avoid criminalization due to drug use.

Figure 2 OECD societal well-being frame. Source: OECD (2015).

Whole-of-government and whole-of-society approaches
Drug governance strategies need to be comprehensive, addressing legal and illegal substances. Strategies should manage drugs as a whole, with a focus on well-being, and the impact of harm addressed independently of the
drug. Approaches should be anticipative rather than reactionary, with regulation embedded within international coordination. The structures to support the strategy should be based on coordinated networked governance, with complex organizational structures and stakeholder involvement. Silos need to be broken inside of government, bringing together health, social welfare, justice, well-being and international treaties. Regional and local public policies can create policy communities and networks for responses, within an overall common strategy. The creation of new organizational structures to manage new drugs should be avoided.

When managing the private sector, the leading role in determining the strategy of public drug policy should be in public sector hands to enhance societal well-being. An evolved co-production system needs to include means of avoiding co-option by both industry and non-governmental organizations dependent on public budgets. Transparency, and checks and balances should be ensured as the drivers to increase evidence-based impact, benefitting public health and well-being in decision-making. The relation with stakeholders should establish the rules of the game regarding which phase of the policy cycle and which typologies of stakeholders can provide a contribution for the public good, simultaneously to their own interests.

Drug governance, in particular, needs to address marketing, which includes all the actions undertaken by producers of drugs to persuade consumers to buy and consume more, including creating and facilitating opportunities, eliciting and shaping social cognitions, and activating and using automatic responses through distribution, pricing, product design, as well as advertising. There are existing models of how to control marketing effectively for public health, the most notable being the Framework Convention on Tobacco Control, an international treaty whose articles include controls on the advertising, display, packaging and design of tobacco products.

**Accountability**

Structural drivers of harm from drug use include biological attributes and functions, population size and structure, and levels of wealth and income disparities within jurisdictions (Figure 3). Core drivers refer to the processes, mechanisms, and characteristics that influence harm, sometimes through the structural drivers, and sometimes not. Core drivers of harm include: drug potency and drug exposure levels, the technological developments that might influence these, and social influences and attitudes, including social stigma and social exclusion. Included in the policy drivers group are measures that reduce drug exposure, actions that promote research and development to reduce drug potency, measures that maximize co-benefits and minimize adverse side-effects of policies and actions, incentives for healthy individual behaviour, and legislation aimed at managing markets, such as the definition and enforcement of rules of engagement of the private sector. Policies and measures affect the core drivers of harm. The structural and core drivers may, in turn, influence policies and measures.
Placed at the centre of the drivers is the Health Footprint, the accounting system for identifying the determinants of drug-related harm and the management tool to evaluate opportunities by the public and private sectors and civil society to reduce harm. Modelled on the carbon footprint, the health footprint can be defined as a measure of the total amount of drug-attributable disability adjusted life years (DALYs) of a specific population, sector or action of interest, defined by specific spatial (e.g., jurisdiction) and temporal (e.g., year) boundaries. The Health Footprint can measure the impact of a range of structural and core drivers of impaired health and the policies and measures that impact upon them. The Health Footprint, thus, accounts for who and what causes the harm done by drugs. Drug-related health footprints could become standard components of annual reporting by relevant public and private sector bodies.

References


3. EFSA Opinion of the Scientific Committee on a request from EFSA related to a harmonised approach for risk assessment of substances which are both genotoxic and carcinogenic. EFSA J. 2005, 282:1-31.


