



ALICE RAP WA3: WP9

Deliverable 9.1: The determinants of a reduction in or cessation of harmful substance use and gambling.

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ABSTRACT

This report focuses on the determinants of reductions in or cessation of harmful use of substances and gambling, where harm may be a direct result of a behaviour or a consequence of societal reactions to that behaviour. We present findings on the determinants of harmful substance use and gambling from across 11 disciplines within five clusters: social and cultural factors, personal factors, patterns of usage and drug knowledge, cellular and molecular factors, and multidisciplinary models. Determinants identified are wide ranging and include availability, economic conditions, gender, personality traits, neurological changes, media campaigns, social identity and social networks. These determinants operate at three different levels (the innate, individual and societal) with some overlap between determinants at different levels and all three levels important for understanding the range of determinants of reductions in or cessation of harmful substance use and gambling across Europe. A key challenge related to this specific work was the scarcity of research in many disciplines relating to our focus on reductions in harmful use without formal treatment. In many of the disciplines involved in this work, research has traditionally focused on treatment populations and the impact of treatment on harmful use as addiction. The latter was particularly problematic as our broad definition of harm moved beyond addiction as *the* negative endpoint. Thus, future research should broaden the focus of the field to better understand both recovery without treatment and recovery from different forms of harm. Overall, our work has identified five implications for policy, for example around advertising controls and limits on the availability and accessibility of substances and gambling, and four for practitioners, for example the importance of emotional and technical support to reduce use, that reflect the understanding that we have developed from our expert-led discussions on reductions in harmful use.

1. INTRODUCTION

The science of addiction emerges from diverse fields of study in both the biomedical and social sciences, resulting in significant advances in our understanding of substance use and gambling disorders, what predicts them and the outcomes they may lead to. However, our understanding is fractured and knowledge from across the scientific disciplines is too rarely brought together. As a result, research evidence in this field is rather like the tale of “The elephant and the blind men”; each man touches and describes one part of the animal, but none can describe the whole beast. Even when analysing the same underlying questions, scientific disciplines often vary in their research foci, methods, data and outcomes. Overcoming these obstacles would permit more multidisciplinary approaches to science, in which data from a range of disciplines could be more effectively synthesised. By allowing us to see the ‘whole beast’, such approaches can enhance our understanding of current evidence, highlight new solutions to problems and signpost productive avenues for future, possibly cross-disciplinary, research.

A prime target for multidisciplinary study in substance use and gambling disorders is the identification and analysis of factors associated with the process of engaging in substance use and gambling. In different ways and to different degrees, scientific disciplines have sought to understand the characteristics of individuals and the contexts of engagement which are



associated with particular behaviours or outcomes. Identifying these behavioural determinants or risk factors can lead to better targeting and design of preventative and clinical interventions and public policy at all societal levels. It can also provide a more nuanced understanding of how and why individuals and societies engage with and respond to substance use and gambling in particular ways. Our work explores specific behavioural concepts (such as risky use and harmful use) to develop an understanding of how substance use and gambling behaviours emerge, escalate, extinguish, diminish or fluctuate over time, and thus where interventions can be targeted. This broad, behavioural concepts approach allows us to move away from a narrow focus on substance use disorders per se and onto a public health oriented view of the development of risky behaviour, harmful behaviour, and 'recovery' and related pathways.

1.1 Scope and Purpose

This is the final in a series of three reports describing the findings of a multidisciplinary study to identify the determinants of different stages of substance use and gambling behaviour using evidence from a range of scientific disciplines. The preceding two reports focused on the determinants of risky substance use and gambling (Work Package 7), and the determinants of harmful substance use and gambling (Work Package 8). These broad terms cover the clinical diagnoses within 'substance-related disorders' (including, among others, 'substance abuse' and 'dependence') and 'pathological gambling', according to DSM IV (American Psychiatric Association, 2000), but also other harmful consequences of substance use and gambling that do not meet DSM criteria (e.g. harm to others). Since 2013, the new corresponding terms in DSM-5 (American Psychiatric Association, 2013) are 'substance-related disorders' (again a group of diagnoses, including 'substance use disorders') and 'non-substance-use disorders' (a sole diagnosis related to gambling).

This report focuses on identifying determinants of a reduction in harmful substance use or harmful gambling defined as:

“Determinants of a material reduction of harmful behaviour of a social, mental or physical nature which are experienced by the user, other individuals or society at large, which is related to substance use or gambling”.

The aim of this report is to compile and integrate existing evidence on the determinants of reductions in harmful substance use or harmful gambling from seven disciplines: anthropology, economics, genetics, neurobiology, psychology, public policy and sociology. Additionally, we have received input from historians and experts in marketing, youth studies and comparative European studies through disciplinary reviews and/or discussions. The substances covered by our work are alcohol, tobacco and illicit drugs and so we perceive our findings to be of relevance for understanding the developmental processes of all psychotropic substances. We also include work on the determinants of gambling, both to identify the factors associated with developing a 'non-substance use disorder' that differ from the development of substance use disorders, and to identify commonalities of substance use disorders and non-substance use disorders. A set of determinants are drawn from each discipline and these are single factors, either individual-specific or environmental, which result in reductions in harmful substance use or gambling. Models or theories describing the interactions of multiple determinants and how these interactions lead to reductions in



harmful behaviour are also identified. These contribute to our efforts to synthesise evidence from different fields as such models and theories often draw on evidence from multiple disciplines.

This research report outlines the state of the current evidence from each discipline, highlights complimentary and contrasting data and discusses the implications of this body of evidence for both policy makers and researchers. A companion report (D9.2) presents multidisciplinary models illustrating the determinants of reductions in harmful substance use and gambling. In conjunction with the other two synthesis reports in this series, it is hoped that the synthesis of current scientific knowledge on different forms of engagement with psychotropic substances and gambling will afford policy makers new insights to assist them in the planning of strategies to tackle problematic engagement with such substances and behaviours across Europe. Further, by taking a multidisciplinary approach, gaps in current evidence or missing links between disciplines may be more easily identified, providing a focus for future research and funding. Finally, it is hoped that this report begins to better integrate the different disciplines dealing with addiction studies and provides a model of how these diverse sciences can come together to foster multidisciplinary research that translates into policy responses to improve societal well-being.

The remainder of this introductory chapter provides an overview of two areas that frame this research. First, we provide a brief description of the different scientific methods adopted by biomedical and social science disciplines to highlight a key challenge in multidisciplinary research such as this. Second, we give an overview of the different forms that a reduction in harmful substance use or harmful gambling may take within the definition that we have adopted in this research.

1.2 The challenge of integrating evidence from different scientific methods

Scientific disciplines take a number of different approaches towards understanding the world. These include positivism, realism, interpretivism, objectivism and constructivism. Each has a different perspective on what can be considered valid sources of evidence and a set of principles about the way in which the object of study (e.g. society) functions to which new evidence can be applied. The most common approach to understanding the different underlying approaches of disciplines is to make the somewhat crude distinction between the positivist natural sciences and constructivist social sciences.

The natural sciences, including physics, biology, chemistry as well as a large number of scientific concepts within psychology (as a 'behavioural science'), fit more comfortably within this distinction as their approaches are overwhelmingly positivist. The key feature of positivism is an emphasis on the use of repeated observation and quantitative measurement as a means to explain the underlying reasons for certain behaviours. This approach, which essentially proposes that the world can be understood through objective and rational quantification and categorisation, lies at the core of what became known as 'the scientific method'. To identify determinants of a particular outcome, statistical tests are typically used to measure how closely associated determinants and an outcome are, how accounting for additional factors may alter this relationship and whether other potential explanations for this association can be ruled out. To enable this, both the determinant and the outcome must be amenable to objective measurement or categorisation and considerable effort is often



invested in constructing suitable tools which can reliably measure complex concepts such as personality, well-being and addiction. The positivist approach has been criticised for, amongst other things, reducing a hugely complex social world to numbers and categories and for adopting an approach which prioritises reductive measurement and analysis by distant scientists over the detailed observations of individuals with close personal experience of the phenomena in question.

In contrast, social science has tended towards a more constructivist approach whereby objective measurement is not ignored but is de-prioritised, partly due to the perceived difficulty of objectively measuring or classifying important concepts for understanding society such as power relations, political philosophy or youth culture. Instead, concepts are often subjectively defined through detailed description. Particular attention is paid to how different constructions of the meaning and purpose of a concept may emerge when viewed in the context of interrelations between individuals and different levels of society, such as families, subcultures, institutions and nation states, and the practices, values and beliefs which are embedded within each of these social units. Constructivist approaches have been particularly criticised for treating subjective opinion or anecdote as robust evidence and for providing deep understanding that lacks validity beyond the case in point.

A comparison of the criticisms of positivism and constructivism highlights that, at the heart of the distinction between these two approaches is a debate as to whether there is an objective reality which can be understood with sufficient scientific effort or whether, to some extent, the world should be understood subjectively as humans and societies act on the basis of viewing the world through their own lens. The crudity of the positivist vs. constructivist distinction is worth noting, as although it highlights important differences between scientific disciplines, it is particularly caricatured for social science. Some social sciences, such as psychology and economics, have strong positivist slants and many of those working in other disciplines, such as sociology and anthropology, do not reject objective measurement per se, but simply try to provide further evidence to interact with it. Nor are positivism and constructivism the only approaches used across the scientific disciplines; however, they provide a useful dichotomy for demonstrating key divergences in scientific methods.

The underlying approaches which inform scientific disciplines are not solely philosophical points. As described above, they contribute to decisions about the kind of data that is regarded as acceptable evidence and where scientific effort is focused. As such, different disciplines have developed starkly different methods of conducting research. For example, the repeated experimentation and sophisticated well-defined measurement tools of natural science contrast sharply with the text-based description and recorded speech reflections collected in many sociological and anthropological studies. Similarly, the carefully quantified statistical relationships between determinant and outcome identified by positivist science sit uncomfortably with the richly contextualised relations between individuals, societal structures and cultural norms including the processes of cause and effect which are theorised using constructivist data. These divergences present important challenges for this project. Although, determinants of harmful behaviour drawn from positivist research are often straightforward to list and statistical analyses allow them to be arranged into evidence-based models, the broad concepts discussed in constructivist research and their varying meanings and complex interconnections make them less easy to succinctly summarise or to arrange into easily accessible models in informative ways. On the other hand, though research in a strongly



positivist paradigm will often establish clear evidence on causal relationships within the particular frame of the study, the relevance and applicability of the findings in a complex world, including such phenomena as human consciousness, social influences and other feedback loops, is often not clear. The meaning for treatment or policy approaches of laboratory findings can easily be over-interpreted, and we try to distinguish here between speculations about what findings might mean and actual tests of relationships “in vivo” and over time. Part of our work represents an attempt to develop working practices and research methods which can address these challenges.

1.3 Reductions in harmful substance use and gambling

The harms associated with harmful substance use and harmful gambling take many forms, including negative consequences for physical and mental health as well as financial, legal and social costs for the individual and those around them. Within our work we have defined harmful substance use and gambling as:

“Substance use or gambling which has caused material harms of social, mental or physical nature which are experienced by the user, other individuals or society at large, where cause mean outcomes which would not have occurred without the substance use or gambling”.

Leading on from this work here we are focused upon reductions of such harmful behaviour, which, just as the harms resulting from substance use and gambling can take many forms, equally the reduction of harm from substance use or gambling may arise through a variety of changes. Our working definition of such a reduction in harmful substance use and harmful gambling is:

“Determinants of material reductions of harmful behaviour of social, mental or physical nature which are experienced by the use, other individuals or society at large, which is related to substance use or gambling”

The most intuitive reduction in harmful substance use or harmful gambling may stem from a reduction in the individual’s levels of use. To reduce one’s use or abstain completely should limit further health harms, diminish financial costs associated with drug use or gambling, and facilitate the individual, with time, to return to a more normative role within society.

Beyond the harm derived directly from substance use or gambling, changes in an individual’s behaviour may result in a reduction in harm to those around them or wider society. For example, if a man with alcohol use problems stops beating his wife when drunk (e.g. having attended counselling for anger management), yet continues to drink at the same level, despite the individual harm remaining constant, the harm to his immediate family has decreased. Equally, changes in the social, physical or political environment may change the context of use in such a way that behaviour becomes less harmful without a direct change in drinking. For example, the de-penalisation of cannabis may not change an individual’s level of use, but may reduce the harm associated with the behaviour as use is no longer criminalised.

Individuals with diagnosed substance or non-substance use problems may be directed to treatment, either clinical or psychotherapeutic, and the relative merits and outcomes of such treatments have been widely analysed (1-5). However, the majority of individuals who engage in harmful behaviours do not access conventional treatment, and instead reduce or cease



their use either by themselves or with the help of those within their immediate social circles. Such 'natural recovery' has remained largely unexamined, yet it is estimated that 75% of alcohol dependents (6) and 54-69% of smokers (7) who do recover, do so without professional help. Given this apparent success of natural recovery methods for reducing harmful substance use, it is important that we understand and are able to maximise the use of informal mechanisms to help harmful users to reduce harm to themselves and others. Consequently, within this report we focus upon reductions in harm that occur without clinical or psychotherapeutic intervention. This approach poses methodological challenges given that, by definition, natural recovery operates outside of traditional treatment settings and therefore it is significantly harder to study for many of the disciplines included in the current research. Thus, in disciplines where literature surrounding natural recovery is limited, we present the available expert review of literature regarding determinants that prevent cessation or promote relapse of harmful substance use or harmful gambling, rather than determinants of the reduction in harmful substance use or harmful gambling.

Within this work we have examined reductions in harmful use of substances including alcohol, tobacco and illicit drugs and also reductions in harmful gambling. Until recently, gambling was considered separately to psychoactive substance use because of the absence of an ingested pharmacologically active substance, which was assumed to negate the potential for physical adaptations, cravings and compulsion to continue (8). However, recent research has highlighted commonalities between each of these harmful behaviours, with all exhibiting common behavioural patterns and exerting strong effects upon reward system neurocircuitry. Behaviours displayed by harmful users of both substances and gambling include tolerance and withdrawal effects, the prioritisation of immediate gratification followed by delayed deleterious effects, compromising social, occupational or recreational activities in order to persist with their behaviour, financial and relationship problems and high rates of relapse (9). Indeed, the American Psychiatric Association recently classified gambling as a 'non-substance use disorder' (10). Thus, the inclusion of harmful gambling within our research reflects relatively recent changes in scientific and political interest in gambling as an addictive behaviour with at least partially similar determinants to substance use disorders.

The term 'reduction of harmful use or harmful gambling' should not be confused with the concept of 'harm reduction', which is a small part of the reduction in harmful use. The concept of 'harm reduction' was developed around 1990 to reduce the negative consequences of regular use of illegal substances using measures including substitution therapy, needle exchange programmes and safer sex campaigns. Instead, our term covers a very broad range of harm reductions, from abstinence to reduction in specific harmful contexts (e.g. driving), from physical to mental and economic harm, and from individual to societal harm.

2. METHODS

2.1 Research method and process

This report is based on a synthesis of evidence on the determinants of a reduction in harmful substance use and gambling from disciplines across the biomedical and social sciences. The research team is made up of leading addiction scientists from each discipline in addition to the project management team and science writers responsible for evidence synthesis.



The report was completed through three overlapping processes. First, each expert produced a review of the relevant evidence from their discipline; second, the evidence within these reviews was integrated into a synthesis report by the science writers and, third, consensus meetings were held to discuss evidence from each discipline and development of the synthesis report. The descriptions of the research process below outline how and when this process took place.

2.1.1 Timings of process

An initial meeting of the project partners in May 2011 defined the work schedule for this research project; including a preliminary timeline for meetings, the outcomes for dissemination and the proposed format and content of the discipline reviews.

At a consensus meeting in April 2013, discipline experts agreed the definition for a reduction in harmful behaviour related to substance use and gambling. Experts then worked independently or in collaboration with epistemologically-similar disciplines to review relevant literature and draft expert papers by December 2013. Using each of these reviews, a draft of this synthesis report was produced by two science writers outlining key concepts, theories and determinants identified by the different disciplines. This draft report was circulated to the research team in April 2014 prior to a second consensus meeting in May 2014. Following this consensus meeting the science writers responded to feedback from the discipline experts to produce this final version of the report in June 2014.

2.1.2 Structure of reviews

Each disciplinary review presents an expert overview of the state of the art within that discipline. Substances or behaviours covered by the reviews include alcohol, amphetamines, cannabis, cocaine, ecstasy, gambling, hallucinogenic substances, opioids, synthetic drugs, and tobacco. Reviews were narrative and between 7000 and 10,000 words. Each review contained evidence on both theory and determinants of reductions in harmful substance use or gambling relevant to that discipline.

2.1.3 Literature search and study selection

Discipline experts examined the literature in their field using the definition agreed during the consensus meeting in April 2013 (p.8). Appropriate research databases were used for each discipline, with some disciplines also dedicating substantial efforts to library searches as is relevant to their field. Direct consultation between experts from different disciplines aided the identification of relevant literature. No limits were imposed on the design or methodologies of studies included in reviews and, consequently, the studies are as diverse as the sciences represented and span historical analyses, ethnographies and other qualitative approaches and quantitative methods including laboratory-based, clinical and epidemiological approaches. This inclusive approach was crucial as each discipline has different research traditions and so systematic review methods would not have been appropriate.



2.1.4 Evidence synthesis and structure of the reviews

Each discipline review was examined by the science writers to identify the determinants that contribute to reductions in harmful substance use and gambling. Determinants that were identified by multiple disciplines were examined further to understand whether combining information between the two or more discipline reviews would provide further insight into the role of this determinant. As this process developed, disciplinary boundaries were blurred and, consequently, results are not presented by discipline but are instead clustered into themes:

Cluster 1: Social and cultural factors

Cluster 2: Personal factors

Cluster 3: Patterns of usage and drug knowledge

Cluster 4: Cellular and molecular factors

We also present here multidisciplinary models of reductions in harmful substance use or gambling where larger theories which span numerous levels of analysis incorporate many determinants in an attempt to further understanding of how such factors affecting the transition to a reduction in harmful substance use or gambling may interact.

The determinants of a reduction in harmful substance use or gambling are drawn together in Table 1 (Section 3.6, p.30). The determinants discussed further within the text of this report are those around which the disciplinary experts had focused in their disciplinary reports, and those which were mentioned by multiple disciplines.



3. RESULTS

This section presents a synthesis of the discipline reviews. Although many informative examples come from studies on the reduction of alcohol-related harms, many of the determinants can be seen as applicable across the different substances and also for gambling behaviours. This report has been written with a generalist target audience in mind, and we have deliberately attempted to use accessible language, avoiding subject-specific terminology where possible.

3.1 Social and Cultural Factors

At the societal level a range of factors may influence the reduction of harmful substance use, namely: networks, events and periods in time (such as economic changes) and different forms of regulation. The dynamics captured within this theme primarily represent the research findings from the disciplines of anthropology, sociology and economics.

3.1.1 Social identity and social networks

An individual's self-perception as a substance user or gambler and how they are perceived or stigmatised within society may lead to a reduction in harm. Additionally, the social networks within which people operate may serve to perpetuate or reduce their harmful behaviour.

Substance use or gambling often connects to certain social identities. Groups of users may share ideas, values and beliefs which can combine to constitute a subculture (11-17). Users may or may not wish to associate with these social identities and this may influence their success in the reduction of harmful use. For example, some long haul truck drivers in Australia report using amphetamines to combat tiredness, but also to fit with their reported self-image as rough truckers (18). Similarly, Biernacki's study of heroin users who recovered without treatment demonstrates the difficulty that users have in creating an alternative social identity and the obstacles this can present in terms of reducing their harmful use. Part of the problem for drug users, heavy drinkers and gamblers is that their behaviour is often stigmatised by society, which may lead to social exclusion (17, 19).

Stigma is a mark of shame or discredit, and the co-occurrence of its components – labelling, stereotyping, separation, status loss, and discrimination – further indicate that for stigmatization to occur, power must be exercised (20). Drug use implies shame, suspicion and blame, i.e. the stigmatization and discrimination of users. Socially, addiction emerges as an object of inquiry and concern when its associated behaviours become incompatible with the demands and expectations of modern life (21). From a psychological perspective, this concern would take the form of the emergence of a collective “shadow”, which is incompatible with the current morality (22). Patterns of heavy use may be reinforced in reaction to stigmatisation, as heavy users cluster together in a social world or subculture, a process known as “secondary deviance” (23-26). Societal reactions against the addictive behaviour may thus have the effect of perpetuating or even magnifying it.

Part of the role of NGOs such as Alcoholics Anonymous, Narcotics Anonymous, Gamblers Anonymous and other 12-step fellowships, which are based on the disease model, has been to stress the de-stigmatization of drug use. Reducing stigma and creating more opportunities for



people in recovery may enhance motivation for and sustain change by offering a chance at a satisfying life that “competes” with drug use and addiction (27).

In contrast to secondary deviance and the perpetuation of harmful use, the recognition of one’s identity as fitting a problematic substance user or gambler role, and the desire not to be associated with such a social identity, may provide the necessary impetus for an individual to change. Interviews with problem gamblers demonstrate that the realisation that one’s behaviour fits that of a gambler, perhaps triggered by an event or the reflection of family and friends, could promote a reduction in harmful gambling to escape this undesirable image (28). How potential identification with a derogated identity plays out may vary by substance and context, for example one study has found gender differences in such processes (29).

The social networks within which a user operates can influence whether or not they reduce their harmful substance use or harmful gambling behaviours. Studies of methamphetamine users in the US and middle-aged heroin addicts in Glasgow who were trying to cease drug use show that 1) returning to a neighbourhood in which drugs were used and 2) contact with social circles of drug users, are important factors in relapse (30, 31). For example, informants felt that they had nothing in common with their old friends other than drug use and that they experienced peer pressure to continue with their previous harmful behaviours to fit in (31).

Modifying social networks through making new friends and acquaintances and breaking old ties can have a positive impact on reducing harmful substance use and gambling. This may occur without any conscious intention on behalf of the individual, through a change in partner, or adoption of new friends through a shared interest or role (e.g. parenthood), who do not use drugs. Equally, it may be a deliberate choice, such as conversion to a religion which forbids the behaviour. For example, in present day Latin America joining the Pentecostal church is a common way for men to remove themselves from the social expectations of drinking and the financial drain this can have on family resources (32). A study of the ways in which Alcoholics Anonymous is effective in reducing alcohol consumption also demonstrated the potential benefits of changing social networks for reducing harmful drinking (33). Such findings around the utility of modifying social networks for reducing harmful use suggest that an individual may experience difficulties in reducing harmful substance use or harmful gambling without a simultaneous change in their social circles to remove the opportunities and pressures to continue harmful behaviours.

Thus, the desire to fulfil social norms or roles and changes in the individual’s social context of use can both drive reductions in the harmful use of substances or gambling as:

1. Evidence suggests that where harmful users are able to modify their environment of use to one in which non-harmful use is normal, they are more likely to enact successful behaviour change than individuals who cannot modify their environment of use, if that environment of use promotes harmful substance use or gambling.
2. The desire to maintain or acquire a specific social identity or social network may encourage a reduction in harmful use, if the user can identify their current self-image as corresponding to that of a harmful user and wishes to change. However, stigmatisation and the exclusion of those behaving in a deviant manner can have the inadvertent effect of consolidating harmful behaviour.



3.1.2 Economic and cultural changes

Economic factors are associated with a number of changes in substance use and gambling patterns. For example, in the area of alcohol consumption, socio-economic and demographic factors have been identified as more important determinants of change in consumption than preventive control policy measures (34). During periods of economic depression the affordability of psychoactive substances and gambling becomes limited. This effectively increases the relative price of these goods, and research has shown that increasing prices have been linked to increasing the incidents of smoking cessation (35, 36). However, this is not true across all societal groups, with indications that young smokers (15-24 years of age) are not price responsive in this manner, possibly due to the stronger, proximal influence of factors such as peer pressure (37). Furthermore, Madden's study of Irish female smokers, showed that only the lowest educated women quit smoking with price increases, demonstrating heterogeneity in response to affordability (38). (Further information regarding price as a determinant in the reduction of harmful use can be seen in Section 3.1.5, p.17). An additional link, beyond affordability, between economic cycles and outcomes is the factor of unemployment. During periods of economic depression unemployment levels increase, reducing the affordability of addictive behaviours and potentially reducing the harmful use of substances and gambling. However, unemployment is also linked to the perpetuation of such behaviours, as individuals have more free time to engage in these habits (39). (Further information relating to unemployment and the reduction of harmful substance use can be seen in Section 3.2.2, p.21). It is evident that the relationship between harmful substance use and economic factors is complex.

Economic development is also linked with changes in harmful behaviour patterns. For example, according to the AMPHORA-WP3 study, alcohol consumption in Italy, France and Spain, has been falling substantially since at least the 1970's and a number of economic, as well as socio-demographic factors like increased ageing and income, have been identified as contributing to this change. Urbanisation was also an important factor in reducing drinking levels, as traditionally urban dwellers drank less than rural people. Additionally, changes in women's status, with consequent changes in family rituals such as family members eating together, and different fashions and cultural preferences, such as the de-evaluation of wine as a peasant's drink, supported this reduction in drinking levels (34, 40, 41). The same economic and socio-demographic factors were shown to have an impact on increasing trends of total alcohol consumption in the Northern and Eastern countries of the AMPHORA-WP3 study.

Changes in living circumstances generated through industrialisation, such as urbanisation, have led to certain sub-populations becoming isolated from society. Such groups can feel dislocated as a result of the loss of social integration and the increased individualism and competition many feel living within a different culture, separate from their own community. This has impacted on harmful behaviours, such as alcohol use, which may increase as a coping mechanism amongst some groups. Re-establishing traditions and ties at a community level within populations of Canadian Indians has been shown to reduce such harmful behaviours, as social connections and customs are reinstated (42).

Over time perceptions of normal and harmful use may change. With increased awareness of the associated health harms and treatments available, individuals may be more alert to their own harmful use and seek help regarding their behaviour or cease use at an earlier stage. Conversely, if societal norms show patterns of increased usage, individuals may not show such



awareness of the consequences of their behaviours and may even increase their use in line with such norms (43-45).

3.1.3 Social movements

Throughout history different social movements have been linked with reductions in harmful behaviour. In particular, the reduction of harmful alcohol use is associated with the temperance movement of the early 19th century. With the first wave of temperance in Ireland between 1839 and 1841, 1.8 million people committed to abstaining from alcohol, with the result that crime temporarily fell to 1/16th of previous levels (46). At about the same time, alcohol consumption fell by 50% in the U.S. in the first great wave of popular temperance there (47). As the movement matured, motivating factors for this reduction in alcohol use included 'experience lectures', charismatic reformed drunks who lectured on their life experience and change to temperance (48). Temperance impulses and movements subsequently occurred in waves within the US, during the later 19th and early 20th centuries. Other major social movements, such as the labour movement and the women's movement in the late 19th and early 20th centuries, often overlapped with waves of the temperance movement and helped to drive down drinking levels in a number of northern and western European societies (49, 50). The shift in popular sentiment in the course of temperance movements often resulted in regulatory legislation reinforcing the shift. The modern experience, with the involvement of both cultural and legislative change in big changes in drinking driving and in cigarette smoking, supports the idea that the combination of social movements and regulatory controls can have long-lasting effects in reducing harmful use or behaviour (51).

A different kind of social movement which has been important in the reduction of harmful substance use and gambling is the rise of mutual-help groups. The best-known of these is Alcoholics Anonymous (AA) and other "12-Step Groups" such as Gamblers Anonymous and Narcotics Anonymous (52, 53). However, there is a wide variety of such groups across societies, some dating from the time of the classic temperance movements and others developed as an adaptation of groups like AA (54). A major element in the effectiveness of such groups in reducing or eliminating harmful behaviour is that they encourage and are often the vehicle for changes in social networks (33); through the group members make new friends who are supportive of their changed behaviour.

Additionally, such groups often include a spiritual or religious element. Whilst biopsychosocial is a familiar term in addiction programming, attention has been devoted to understanding how spiritual health can influence addiction behaviour (55). Alexander (2008) considered that while the traditional four pillars of treatment, prevention, law enforcement, and harm reduction could not be expected to bring addiction under control in the present free-market society, some form of philosophy or spirituality may be valuable for reducing drug use (42). Practices derived from contemplative religions, such as mindfulness, meditation and prayer can offer some respite and motivation for recovery (56). The importance of the 12-step movement and programmes, as well as of mindfulness-based interventions and conversion, are different journeys out of addiction that are based on search for life meaning and self-fulfilment, and can involve the individual opening up to a higher power (57).



3.1.4 Market regulation and formal social control

Societies and their governments play a role both in encouraging heavy use and its continuation, and in discouraging it. In recent decades, many governments have become dependent for revenue on the “voluntary taxation”, as it is sometimes termed, of gambling revenues, whether through state lotteries, through state fees or taxes on gambling machines and other forms of gambling. Similarly, taxes on psychoactive substances such as alcohol, tobacco and opium have been a major source of revenue for governments. They have been described as the “glue of empires”, in that the European expansion and empire-building of the period from about 1500 to 1950 depended to a considerable extent on sales of psychoactive substances to produce imperial revenue and often to extort or reward labour by subject populations (58). In the current world of free-market ideology, the promotion of legal psychoactive substances has been primarily left to private interests, often with only limited state regulation. These “market interests”, with or without state support, thus become a sustaining force for the consumption of heavy and problematic users.

In contrast, we also see examples how governments act to limit harm from heavy use or addictive behaviour. Such limits have taken two main forms: regulation of the market, most often enforced with licenses or other regulatory controls on those selling or providing the product, and social control of the consumer and of particular consumer behaviours, often enforced through criminal law. We have mixed evidence for the effectiveness of criminal controls. Where many of those affected are respectable and middle-aged, as in the case of drink-driving, deterrence through criminal law is relatively effective. On the other hand, for more marginalised populations or where the behaviour may be an alternative to rationality, as with illicit drug use or public drunkenness, criminalising the behaviour may have little effect on its incidence.

Evidence around regulatory controls on sellers suggests that they are relatively effective. Potential loss of a license to serve alcohol provides a strong economic motivation to the seller, counterbalancing the incentives of profits from flouting regulations. However, as a result, sellers have strong vested interests in influencing the state to weaken the market controls, and have often been effective in this. The advantage of “disinterested management”, without lobbying to weaken the controls, is a major reason why some states have chosen to operate a government monopoly which freezes private enterprise out of at least part of the alcohol market (59). Such a government monopoly, operated in the public health interest, thus tends to reduce levels of problematic use in a population (60).

A special form of regulatory control in the field of psychoactive substances is the prescription system, where doctors (and sometimes other health professionals) are licensed by the state to be gatekeepers on access to use of psychoactive substances for medical purposes, with another profession – pharmacists – licensed to manage and supervise the actual supply of the substance (61). The record of the effectiveness of prescription systems in controlling heavy or problematic use is mixed; often the result of restricting prescriptions of a particular substance has been that doctors switch to prescribing another and often more problematic one (62).

Prohibition of a substance or behaviour has been a common societal response to addictive behaviours over the last two centuries, first occurring in industrial societies for alcohol and gambling. Such prohibitions can involve market controls, but the international drug prohibition system currently in force requires that the system be supported by criminal laws



applicable to users. Historically, prohibitions have been shown to generate the greatest reduction in use when first adopted as over time the market is able to adapt by establishing illicit manufacturing and distribution chains. The development of a successful black market involving thousands of bootlegging operations and speakeasy clubs in the USA, which pushed the consumption of alcohol underground, resulted in the repelling of prohibition in USA in 1933, just 13 years after it was introduced (63). However, alcohol prohibition did impact on harm reduction, with rates of liver cirrhosis initially falling to one third of pre-prohibition levels, increasing to two thirds of the baseline level by the end of period (47). The opium prohibition in China, when the Maoist government came to power, was similarly effective and combined with cultural policies, which presented opium as a habit forced on the Chinese by the British, Japanese and other foreigners almost eliminated the non-medical use of opium (64). However, prohibition of opiates is considerably less effective in present-day China. The global prohibition on illicit drugs has proved largely ineffective, demonstrating that the success of prohibitions may depend upon a society's consensus against the prohibited behaviour (65).

In contrast, the gambling prohibition in English-speaking countries in the first half of the 20th century was effective in maintaining low levels of problem gambling in comparison to post-liberalisation of gambling legislation which has generated an increase in harmful gambling in the UK, US and Australia in recent decades (66). Indeed, even a partial prohibition through regulatory controls has been seen to be effective in reducing harmful use, in present-day circumstances of heavy marketing when the behaviour is legal; in Western Australia electronic gambling machines are banned except in one casino, and total expenditure per adult in this state is half of that in New South Wales, which has the highest number of electronic gambling machines (67). This is also true for the prohibition of online gambling in EU member states (Ludwig et al., 2012).

3.1.5 Regulation of the market and of availability

Regulatory control of substance use and gambling has been attempted via many routes, in order to reduce harmful substance use and harmful gambling.

Pricing regulations

Increasing the price of substances, such as alcohol and cigarettes, through increased taxation, reduces affordability and has been repeatedly associated with increased quit attempts amongst users. For alcohol, studies from the US show that increased taxation is associated with a reduction in the incidence of liver cirrhosis (68) and general mortality (69). Moreover, increases in beer tax were linked to a decrease in suicide, particularly amongst younger adults, and increased pricing of alcohol has been linked to reductions in violence, including rape, robbery, assault, domestic violence and child abuse (70, 71) and a reduced rate of sexually transmitted infections (72). A systematic review of the effect of pricing on alcohol consumption concluded that those who drink at the most harmful levels, and particularly dependent drinkers (73), tend to favour cheaper alcohol products, and that the taxation of alcohol is particularly effective in reducing the harm from young drinkers and heavy drinkers (74). In line with these results, offering reduced strength alcohol with lower levels of taxation



targets the pricing policy more towards those drinkers who drink in a harmful manner, whilst individuals who drink in a safer fashion are less affected (75). For tobacco, similar trends have been observed, with the majority of evidence showing that increasing taxation and prices influences those who smoke towards quitting (35, 36, 76, 77). Studies show that this impact of price on smoking cessation is greater than on the initiation of smoking (35, 36, 76-78), though there is heterogeneity in studies, particularly amongst young users, who engage with smoking in part due to the risk and forbidden nature of underage smoking (78) and poor users, where living in hardship acts as a deterrent to quitting (35). Despite the good evidence surrounding the effect of pricing on both alcohol and tobacco, weaker evidence exists for its effect on the cessation of illicit drug use, with a lack of price responsiveness reported (79), though the number of studies surrounding the topic are limited. Overall, evidence suggests that the price regulation is effective in reducing harmful substance use.

Availability regulations

The regulation of substance and gambling availability has also been linked to reductions in harmful use (61, 67, 70, 81-85). For example, in a systematic review of the influence of community level availability of alcohol on heavy drinking, Bryden et al. found an increased likelihood of heavy drinking related to higher off-trade (shops) and on-trade (bars and restaurants) outlet density within a community (86). Similarly a meta-analysis of studies conducted in Australia and New Zealand demonstrated the prevalence of problem gambling increased with increasing density of electronic gambling machines, and that the introduction of each additional machine resulted in an average increase of 0.8 problem gamblers within an area (82). Thus, the restriction of availability through the regulation of outlet density can reduce harmful substance use or gambling (87).

Accessibility regulations

An alternative regulatory strategy to limit harmful use is to control accessibility. This has been successful for tobacco, with the introduction of smoke-free legislation in public spaces across Europe increasing the number of smokers who both attempt and are successful in quit attempts (88, 89). Similarly, bans on public drinking are associated with reduced fighting, vandalism and underage drinking (90). Thomas et al. (2011) suggest that conditions of use for gambling facilities such as low entrance fees, ease of use and door-to-door transport services provided for heavy gamblers increase their accessibility and thus prevent successful cessation of harmful gambling.

Advertising regulations

Restrictions on advertising alcohol and tobacco products have been successful in reducing harmful use (81, 91) through limiting the use of adverts that users perceived to be detrimental to quit attempts (92, 93). Studies measuring the impact of plain compared with branded cigarette packaging show that plain packaging has a deterrent effect on smoking, triggering thoughts of quitting in users, and strengthening users' resolve to quit (94). Given that problem gamblers cite advertisements as one of the most common triggers to gamble (95, 96), it could be suggested that restrictions on gambling advertising may result in a similar reduction in



harmful use. However, the recent AMPHORA European study showed that the impact of advertising restrictions on alcoholic beverages may differ between countries (34).

Rationing goods

The rationing of substances has been demonstrated to be effective in reducing harmful levels of use. For example, the end of alcohol rationing in Sweden under the Bratt system in 1955 saw a large increase in liver cirrhosis amongst the population (97). Additionally, alcohol rationing in Poland during a political crisis resulted in reduced binge drinking episodes, a reduction in hospital admissions for alcohol induced psychosis (60%) and liver disease (25%), and a 15% reduction in deaths from injuries (98). Finally, during both the First and Second World Wars, disruption of supplies and rationing of alcohol resulted in a decrease in the incidence of liver cirrhosis in many countries (99). Additionally, restrictions on drinking imposed by military institutions on young adult males during the two World Wars may have played a role in the observed reduction in harm during these periods (100). We observe a rapid impact of alcohol rationing on rates of conditions such as liver disease because of the large proportion of the population who are on the cusp of liver failure, and who therefore benefit from the change in availability of alcohol because their consumption decreases, facilitating some liver recovery. On reflection therefore, rationing may work well as a control measure, particularly targeting the heavy and harmful users within society. Indeed rationing is in existence in many countries for certain substances, such as prescription medications. However, in the current political climate of acceptance and indeed promotion of the market economy in legal addictive goods, rationing regimes for psychoactive substances are not widely accepted or promoted.

3.1.6 Formal social control

Criminalisation, and increased penalties

The international drug prohibition regime has had very limited success in eliminating illicit markets, despite heroic efforts (101). Criminological findings concerning drinking driving as well as other crimes, is that the likelihood of being caught, and the quickness of punishment, has some deterrent effect but that severity of punishment has little effect, and indeed raising the stakes may have a perverse effect by provoking a more vigorous defence (102). While many governments moved away from punishments and controls directed at the individual drinker found drunk in public in the 1960s and 1970s, on grounds both of civil liberties and of ineffectiveness, in recent years there has been a drift back towards individualised controls, including through criminal conviction and probation restrictions. At present we lack effectiveness evidence to support the claim that such approaches are effective in doing more than just moving drinking around (103).

Depenalisation

Depenalisation of illicit substances works to reduce the harm associated with substance use, not by restricting availability, but through removing criminal sanctions associated with use and the consequent criminalisation of the user. Despite the expectations of some, this reduction in



the criminal sanctions associated with substance use is not associated with an increased use in the general population, as studies with cannabis have shown (104). The Netherlands has more liberal cannabis laws compared with other European countries, and comparative studies have shown that this has not resulted in an increased level of harmful use among the Dutch population, although levels of any use within the population are higher (105). Although the level of use may remain the same amongst those individuals who engage in cannabis use, depenalisation reduces the harm associated with use through involvement in the criminal justice system.

3.2 Personal Factors

Individuals' living circumstances, including their family environment and changes within it, and their own psychological disposition, from cognitive biases to mental disorders, may all influence an individual's ability to stop or reduce harmful substance use or gambling. These determinants are described here in the broad categories of 'emotional and psychological determinants' and 'life circumstances'. These determinants originate from disciplines of psychology, economics and neurobiology.

3.2.1 Emotional and Cognitive Determinants

From behavioural and mental disorders to personality traits and implicit biases, a large range of psychological processes have been shown to influence the ability to reduce harmful substance use and gambling, either through promoting a reduction in or maintenance of harmful behaviours.

Harmful substance use or harmful gambling commonly exist in the presence of another mental disorder, such as mood disorders (106-109). Mood disorders, like depression and bipolar disorder, have been shown to co-occur in a number of substance users across all substances, with the influence of major depressive disorder and alcohol and cannabis use disorders being shown to be bi-directional and to play a role in maintaining the individual's substance use disorder (110-115). Indeed, in those gambling at harmful levels a life-time mood disorder was predictive of a delay in the achievement of abstinence (116). Anxiety disorder showed a similar high level of co-occurrence in those with substance use disorders or disordered gambling (109, 114), with the absence of current post-traumatic stress disorder (PTSD) associated with a remission from problematic gambling in a subset of Hispanic and American Indian veterans (109).

Absence of a comorbid mental disorder (e.g. PTSD) is associated with a remission from harmful substance use or harmful gambling (109) and an increased number of mental disorders is negatively associated with recovery (108). In individuals who recover without treatment from both substance use and gambling disorders, a modification to one substance or non-substance use disorder has shown to be positive for remission of the other (117). For example, gamblers who recovered without treatment reported fewer lifetime mental disorders than untreated active gamblers with comparable gambling histories (118). These findings suggest that treating comorbid mental disorders may enable individuals to reduce their harmful use of psychoactive substances/gambling.

Many personality traits, such as negative emotionality, are associated with perpetuating the



harmful use of substances or gambling, or promoting relapse once an individual has initially refrained from use. However, despite a general consensus that negative emotionality is associated with the promotion of harmful behaviours (119, 120), the experience of such emotions, (e.g. stress, panic, depression and guilt), are often cited by individuals as a motivator to reduce harmful behaviours such as problematic gambling (117, 121).

Impulsivity has also been associated with harmful substance use and harmful gambling (119, 120). Impulsivity encompasses traits such as increased novelty seeking and delay discounting. These give rise to thought patterns where the individual responds rapidly and without forethought to an environmental situation, or is unable to inhibit a response once they have started, and can result in misinformed or inappropriate actions (122). Studies repeatedly show that individuals who suffer with an alcohol or other substance use disorder demonstrate higher levels of impulsivity and are also more likely to exhibit an externalising disorder than those who do not have a substance use disorder (123-126). Thus, we conclude that innately lower levels of impulsivity or a reduction in an individual's impulsivity over time may promote their successful reduction in harmful substance use or gambling.

Finally, cue reactivity is the unconscious association of cues within the environment, for example an image, noise, smell etc. with a particular behaviour (such as a cigarette lighter with the activity of smoking). Cue reactivity occurs through rapid habit-based thought patterns, which give rise to increased responses of the reward system of the brain and feelings of cravings within the individual (127), resulting in an automatic motivation to particular behavioural outcomes. This aligns with neuroeconomic theory where an individual with a greater addiction is more likely to be sensitive to advertisements for such products (128). Consequently, alcohol advertisements and point of sale displays for tobacco can hinder cessation attempts and encourage relapse in users (93, 129-131), highlighting the potential importance of controls on the marketing and promotion of addictive products to facilitate reductions in harmful use.

3.2.2 Life circumstances

An individual's life circumstances may influence changes in substance use or gambling behaviour, for example where changing life circumstances prohibit continuation of existing habits (e.g. moving to a different neighbourhood) or conflict with personal or family responsibilities. Key determinants include gender, marital status, health and employment status.

Gender has been shown to be important in natural recovery from harmful substance use and gambling, with men less likely to achieve remission from alcohol, nicotine, cannabis or cocaine dependence in a representative cross-sectional study of 43,093 US Americans (107). However, women have been shown to be less likely to enter substance abuse treatment than men (132). This may be due to the design of the majority of treatment programmes which are targeted at men and do not take into account women's specific needs such as childcare assistance, pregnancy, parenting, domestic violence, sexual trauma and victimisation (132, 133). In contrast to recovery from substance use disorders, a study of problem gamblers showed that the proportion of men that recover without treatment (92%) was substantially higher than women (56%) (134), suggesting that the relationship between gender and recovery without treatment may vary by behaviour.



Interviews with problem gamblers suggest that an individual's marital status may play an important role in natural recovery from harmful gambling, for example being married promotes cessation of harmful behaviours for reasons including 1) the controlling effect of a partner and 2) the partner not sharing an interest gambling. Conversely, participants who were single, divorced or widowed described fewer constraints on their behaviour, money and time, facilitating the continuation of harmful behaviour (28).

Wider family relationships have also been cited as important for the reduction of harmful behaviour, with family members acting as both a direct challenge to an individual's behaviour and as a lens through which they were able to appraise their own behaviour (28, 118, 135-137). For example, following the realisation that significant relationships were at risk given a continuation of harmful behaviour, many problem gamblers reassessed their behaviour and were able to view themselves in a new light (28). Furthermore, many family members actively supported those with gambling problems to stop or control their gambling, by taking control of the individual's finances so they were unable to gamble, or accompanying them when they went out to stop them from gambling (28). Naturally recovered gamblers were less likely to have a family member with a problem than untreated active gamblers with comparable gambling histories (118), suggesting that gambling may be normalised within that family environment or that they lack the necessary support to tackle their dependence. Alternatively, this may reflect the absence of an innate factor in those who recover naturally compared with other harmful gamblers.

The age at which an individual initially engages with substance use or gambling may play a role in their subsequent cessation of such behaviours. Individuals with a later onset of harmful substance use (≥ 14 years) were found to be more likely to successfully make the transition from user to non-user, particularly following increases in drug prices (76, 138, 139). However, it has been recently identified that an early age of first drunkenness, and not an early age of first drink is the main risk factor for various problems behaviours in adolescence (140). Thus, we need to better understand the impact of the distinction between early onset of use and early age of first intoxication experience, to better target interventions.

The experience of substance or gambling-related negative health outcomes may motivate change among individuals with a substance use or gambling disorder. The work of Dawson et al., examining drinking patterns for different age groups over two waves of NESARC, demonstrated that the chance of transitioning from regular drinking to cessation increased with age from 4.9% in those aged 18-20 to 12.9% in those aged 75 years and older. In the same study, reasons for cessation changed in each age group, with the younger age group stating pregnancy or parenthood, an alcohol, nicotine or drug use disorder, or liver disease, whereas cessation of drinking in the older age group was associated with having an education, higher income, ethnicity, presence of a mood disorder and cardiovascular disease. Hence, factors relating to the cessation of harmful use vary over the life course (141).

Compared with unemployment, employment is protective against relapse into harmful alcohol and opiate use (39, 142-144). This may be a result of reduced free-time of individuals in employment, which restricts their ability to engage in substance use. Alternatively, it may be that employment removes them (at least part of the time) from social networks which may negatively influence their behaviour. Additionally, employment is associated with increased responsibilities, which are often not compatible with harmful substance use. In contrast to evidence around alcohol and opiate use, the evidence for the impact of employment status on



the reduction of harmful tobacco use is inconclusive. Findings suggest that unemployment may reduce cessation and promote relapse, although this relationship is inconsistent within the literature (39).

3.3 Patterns of usage and drug knowledge

Beyond cessation of or reduction in an individual's level of substance use or gambling, associated harms may be reduced through increasing awareness of the possible harms arising from substance use and gambling, enabling users to adapt their behaviour to avoid potential harms. Knowledge can be developed in a number of ways, including public health campaigns and self-help books (e.g. classical examples of a journey out where the personal individuation process had a major role are the autobiographical reports of Bill Wilson (57) and Christina Grof (145). The context of use may also be modified (such as by increasing the availability of needle exchanges), to remove or reduce the impact of harms generated by the social context of use.

Harm reduction strategies for substance use include needle exchanges, street level nursing, drop-in centres and hostels for the homeless. These strategies reduce the harm associated with substance use by reducing the incidence of associated illnesses (such as the transition of blood-borne viruses), pains and other harms related to substance use; for example, by providing clean equipment for drug injection. Needle exchange programmes are associated with a reduction in needle sharing and injection frequency amongst needle exchange programme participants (146), reductions in the incidence of HIV, hepatitis B and C infections (147-152), decreased needle sharing among HIV-negative and HIV-positive individuals (152-154), decreases in syringe reuse (155) and increased rates of entry into drug treatment programmes (156-158). One study demonstrated that in 29 US cities with needle exchange programmes the incidence of HIV infection decreased by 5.8% annually, whilst in 51 cities without such programmes the incidence increased by 5.9% annually (159). Similarly, reductions in the harms associated with substance use were noted in Coyle's (1998) study on community based outreach centres, with positive outcomes in relation to cessation of injecting, reduced injection frequency, reduced use of needles and syringes, reduction or cessation of crack cocaine use, needle disinfection and increased condom use/reduced unprotected sex (160).

Due to the success of such policies an increase in treatment services and lower treatment thresholds are being recommended (70, 161). This has both increased the number of individuals undergoing treatment for harmful substance use may have raised awareness of the harms associated with substance use and dependence (28).

Despite the tendency to see those with harmful substance use problems as passive agents influenced by drugs, several studies show rather how users are active agents within their own lives, actively managing and improving their own health within the context of continued substance use (162-167). Drumm et al's (2005) observations of drug users in Miami showed that they make conscious efforts to improve their nutrition, engage in physical activity, address medical concerns, regulate substance use and reduce sexual risk, whilst still engaging in active drug use. Through measures to improve their health the drug users are attempting to offset the negative effects of their substance use, in order to reduce the overall health harm experienced as a result of their substance use. Further to this, studies show that users



consider the harms and benefits of substance use when deciding if and how to take drugs. For example, not taking drugs whilst alone as a safety precaution so that people would be around to help in case something should happen (165, 167).

It has been suggested that through engaging in substance use or gambling individuals learn to control their own behaviour, via an ongoing process of learning from experience, regarding the specific effects, side-effects, risks and benefits of different drugs (11, 166, 168). By developing policies which accept that such harmful behaviours exist within our environment and working to limit harm, we propagate this understanding amongst users and may generate the development of protective practices (Grund 1993). However, information and education campaigns have had mixed success in bringing about self-change in relation to harmful substance use and gambling behaviours. For smoking, hard hitting media campaigns and bold warnings on tobacco packaging have shown to be successful in increasing smokers' unaided quitting (169). Similarly, mass media campaigns to reduce drinking and driving have been successful in reducing the harm associated with alcohol use, resulting in an estimated reduction of 13% in alcohol-related crashes (170). However, relatively little research has been carried out into the effects of education on illicit drug use. This may be partially explained by the integration of education relating to one substance or another into wider programmes that are evaluated in their entirety. Where evaluations do exist, the impact of education on drug-related outcomes is largely insignificant (104).

Finally, an indicator of the potential for natural recovery from alcohol, illicit drug and gambling use is an individual's severity of use. Those with less severe use, such as alcohol abuse rather than dependence (171) or fewer symptoms in DSM-V (Diagnostic and Statistical Manual of Mental Disorders) (139), show a greater reduction in harmful use over time than those with more severe usage patterns (117, 172). This may highlight the importance of intervention at an early stage in a user's career to prevent the development of more severe patterns of use, which are harder to resolve without formal treatment.

3.4 Cellular and Molecular Factors

An individual's genetic profile or neurobiological characteristics may affect their reduction in harmful substance use or harmful gambling, through influencing their thoughts, emotions and metabolic processes. The determinants discussed within this section under the themes of 'changes in neurocircuitry' and 'changes in neurotransmitters' are derived from the disciplines of neurobiology and genetics and include evidence from both human studies and, where human evidence is absent, preclinical studies of animal models. Whilst there are many reports characterising differences in brain structure and function in addicts compared with healthy controls and how these may be related to behaviour, less is known about resilience. Thus, when we discuss resilience, it is generally in relation to *not* developing abuse rather than recovering or maintaining abstinence.

3.4.1 Changes within neurocircuitry

Much harmful drug use and harmful gambling arises through dysfunction in neurobiological mechanisms, particularly those governing inhibitory control and reward processing, which are known to operate differently within the brains of addicts (173, 174). The two key areas of the



brain involved in reward and cognitive control are the ventral striatum (reward) and prefrontal cortex (cognitive control), thus a successful reduction in harmful behaviour at the cellular and molecular level likely involves a rebalance between these two centres. Consequently research has focused on these brain centres in trying to understand reductions in harmful behaviours (175-178). For this review we concentrate on those studies.

In one of few longitudinal prospective studies in this field, Beck et al. 2012 reported that 1) brain activation in the ventral tegmental area (VTA) and subthalamic nucleus to salient alcohol cues was greater in abstainers compared with those who subsequently relapsed, and 2) abstainers had enhanced functional connectivity between the midbrain and the amygdala and between the midbrain and the orbitofrontal cortex (OFC). Finding an increased activation in such key areas is noteworthy given that greater activity reported in cross-sectional studies of addicts compared with healthy controls has generally assumed to be associated with negative outcomes in relation to cessation. Thus, greater activation has been reported to be associated with substance use relapse, e.g. for alcohol (179, 180), cocaine, (181) and nicotine (182). Regions where this is reported include the striatum, insula and putamen, which are all implicated in habitual or compulsive drug seeking. The individuals who subsequently relapsed showed increased levels of atrophy in the regions of the brain responsible for error monitoring and behavioural control, the bilateral orbitofrontal cortex and in the right medial prefrontal and anterior cingulate cortex (183).

Increased activity in the neurocircuitry of successfully abstinent addicts was also noted in a study examining cocaine addicts. Here fMRI studies show greater engagement of the subcortical and ventral prefrontal networks during motivational processing correlated with abstinence (184). Further, a study examining cocaine addicts in the first six months of abstinence found that increased responses within the VTA of the midbrain and the thalamus were associated with reduced drug seeking. These changes were hypothesised to be related to the normalisation of the dopaminergic pathways of the brain's neurocircuitry following abstention from cocaine (185).

Given the key role played by cues in relapse/recovery, assessing cue reactivity in the brain has been commonly studied in addicts. In a meta-analysis of studies in alcoholism, cue-elicited activation of the ventral striatum was most frequently studied, with correlations with behavioural measures and reduction by treatment described (186). However activation in non-mesolimbic areas was also consistently seen in parietal and temporal regions, including posterior cingulate, precuneus and superior temporal gyrus. A meta-analysis of fMRI studies of salient smoking cues in tobacco smokers reported greater activation in the extended visual system (lingual gyrus, fusiform gyrus, and cuneus), occipital, inferior temporal and posterior parietal lobes, in the insula, cingulate gyrus and prefrontal cortex (ACC, DLPFC) (187). Whilst such meta-analyses suggest altered brain activation and cue-reactivity in recovering addicts and abstainers, few have explicitly looked at relapse per se.

Improvement in the inhibitory control systems in abstinent addicts has been demonstrated, with, for example, former cocaine addicts showing similar inhibitory control to non-users as quickly as one month following cessation of use (174). An increase over time in inhibitory control was noted in former heroin addicts using the Iowa Gambling Task as a form of assessment, with those who were recently abstinent (<30 days) showing reduced inhibitory control compared to those with longer periods of abstinence (>3-24 months), and no difference between former addicts and controls noted beyond 24 months of cessation (188).



These findings suggest that the brain's neurocircuitry can recover from the effects of harmful substance use. Increased inhibitory control has been associated with increased activation of the neurocircuitry underlying cognitive control in both cocaine addicts and former smokers, where longer abstinence was associated with increased activity within the prefrontal cortex (189, 190). Abstinent addicts can demonstrate increased activity within these brain areas compared to both addicts and drug-naïve individuals, thus it has been hypothesised that this 'supernormal' level of activity within abstinent users may indicate that the recovery from addiction is a distinct process rather than a reversion to the pre-addicted state of the individual (191).

The development of increased cognitive control seen in abstinent addicts can be disrupted under the influence of stress. For example, former heroin addicts were not able to perform as well as drug naïve controls at the Iowa Gambling Task following the Trier Social Stress Test (188). This highlights the importance of stress avoidance during recovery and states whilst inhibitory control may improve with abstinence, it may not be as robust as in a non-addict and stress may derail their recovery due to vulnerability in inhibitory control.

Whilst previously it was thought that 'extinction', a process where all drug reinforcing stimuli are removed the environment, must occur to disassociate cues from drugs and prevent relapse, it has now become clear that new learning is important in the development of inhibitory control and new cue-associations (192-194). Indeed, studies using the pre-clinical models of cocaine addicted rodents introduced the threat of or actual punishment alongside cocaine seeking and observed cessation in all but 20% of the population, supporting learning by negative feedback. It was assumed that the remaining 20% of the animals that persisted in drug seeking behaviours were likely to have experienced longer periods of consumption (195), and suggests that the time period over which harmful use is sustained may determine how resistant an individual is to new learning and negative feedback on substance use. Given that worldwide, punishment is the predominant approach to drug addiction, these studies may be important in reflecting the effectiveness of such methods. Furthermore, despite our learning around the potential of negative reinforcement, the current clinical focus is on positive reinforcement, for example contingency management. However, 1) the applicability of such animal studies to human conditions is currently questionable, and 2) these studies were largely concerned with stimulant use and as such the findings may not be generalizable to all addictive or harmful substances or behaviours.

3.4.2 Changes within neurotransmitters

At the molecular level, five large scale twin studies, analysing the variation between the habits of identical twins to determine relative heritability and environmental contributions to specific behaviours, have demonstrated a link between smoking persistence and an individuals' genetic profile. These studies showed that 50-70% of the total variance in smoking persistence could be attributed to the individuals' genetic profile (196-201). Furthermore, the proportion of the genetic influence on nicotine withdrawal symptoms was estimated by one study to be between 26-41% dependent upon the symptom (202), and at a total of 31% in another (201). This reflects the idea that despite an individuals' possible underlying genetics which may prevent their disengagement from harmful substance use or harmful gambling, there is a large element of personal and societal influence in such behaviours.



There is overwhelming evidence on the role of dopamine in the neurological and behavioural changes observed during the development of compulsive stimulant taking, with transition of dopaminergic neurons from the ventral to the dorsal striatum (195). Yet information regarding the possible reversal or flexibility of these adaptations is lacking. Reduction in dopamine receptor (DRD2) availability under chronic cocaine use has been noted in studies of non-human primates, and following cessation of cocaine use, receptor availability was seen to increase. However, this was not the case for all animals, particularly following longer periods of exposure, and in the animals whose DRD2/3 availability did not recover a reduced response to food was observed prior to any cocaine exposure, suggestive of a pre-existing dysregulated reward circuit (203, 204). These results demonstrate that although many can return to normal function following harmful stimulant use, some individuals may be pre-disposed to drug use through the dysregulation of neurotransmitters. Indeed, it is acknowledged in stimulant users and alcoholics that a hypodopaminergic state is a vulnerability factor for continued use and relapse (205-208). Further, carriers of different variants of the dopamine receptors may suffer more severe withdrawal symptoms, with variants of both *DRD3* and *DRD5* having been associated with increased withdrawal severity, and thus a reduced likelihood of a reduction in harmful alcohol use (209, 210). Additionally a specific variant of the *DRD4* gene variable number tandem repeat has been associated with increased craving sensations for alcohol, tobacco and heroin upon cessation, again increasing the likelihood of relapse in the harmful use of such substances (211).

Glutamate is the brain's main excitatory neurotransmitter, and neuroadaptation of synaptic glutamatergic transmission from the medial prefrontal cortex to the nucleus accumbens has been proposed as a final common pathway for drug seeking behaviour. The glutamatergic inputs from the amygdala, hippocampus, and prefrontal cortex to the nucleus accumbens play a key role by integrating environmental stimuli with memories of related experiences that can shape behaviour, and thus such processes may determine whether an individual can cease or reduce their harmful addictive behaviours. Imaging work in abstinent addicts has shown increased glutamate levels compared with controls, and this increased glutamate correlated with increased impulsivity (212). Similarly, increased glutamate has been noted in the brains of detoxified alcoholics (212-214). In early alcohol withdrawal, glutamate levels increase dramatically within the brain, possible accounting for the neurotoxicity of withdrawal including consequences such as seizures, blackouts, amnesia and neuronal death (215-217). Such severe withdrawal effects are a common driver for many to continue with their harmful drinking behaviour (218).

Opiate receptors are present in many of the brain regions involved in addictive processes and play key roles in abuse, not only of opioids, but also for other addictive drugs or behaviours (219). The opioid system modulates reward, signalled through the μ -opioid receptor, and has been shown more recently to play a role in motor impulsivity (219-221). Within the opioid system, evidence for changes in the balance of neurotransmitters following cessation of harmful substance use in humans include an increase in the availability of the μ -opioid receptor following abstinence from heroin, cocaine and alcohol (206, 222-225). This observed increase in μ -opioid receptors was associated with increased craving in both alcohol and cocaine addicts (206, 224, 225).

Despite an increased understanding of the biological characteristics of both addiction and abstinence, determinants of the cessation of harmful use are often not clearly understood at



the cellular and molecular level. This highlights the need for further longitudinal analyses of individuals' neurobiology and genetic profiles during the process of addiction and abstinence to allow determinants to be identified and the adaptations appreciated.

3.5 Multidisciplinary models of reductions in harmful substance use or gambling

The previous sections have introduced a range of individual determinants from across a range of scientific disciplines. Section 3.5 outlines multidisciplinary models of harmful substance use that draw together determinants from a number of disciplines to develop an understanding of how the factors affecting the transition to a reduction in harmful substance use or gambling may interact.

3.5.1 Developmental processes

The process of 'maturing out' of harmful substance use or harmful gambling is often cited as a means of natural recovery, and the method by which the majority of individuals cease such harmful behaviours (226, 227). The incidence of harmful behaviours (such as substance use and gambling) increases during late adolescence, often peaking in the mid-twenties, and then declines with increasing age. This decline in harmful behaviour during the twenties and early thirties has been characterised as a process of maturing out, and is believed to develop as a result of psychological maturation and the adoption of adult roles and responsibilities.

In many European countries the period of young adulthood, during which an individual may move away from the parental home but has not yet established their own family, is discernable by much experimentation (228-230). Moffit developed a theory of adolescent limited behaviour that described the shared expectations within a society regarding appropriate adolescent and young adult behaviour (231). Moffit posits that at a certain age adults should reduce their levels of experimentation in line with social norms governing their behaviour at a given age in a certain context. Whilst this theory may find support in some cultures, evidence does not support the existence of such cultural norms in all countries, for example, no variation between the ages of 20 and 65 is apparent in Germany (232).

Within the concept of maturing out, the transition to adulthood includes the ending of formal education, the beginning of employment, financial independence from parents, the establishment of new living arrangements (alone or cohabiting), getting married and starting a family (233). Such maturational life events are often stated as reasons for the reduction in an individual's harmful behaviour (234), and may occur as a result of increasing levels of responsibility that prompt the user to assess and modify their own behaviour (28). In addition to supporting reduced use, maturing out may support continued abstinence or low-risk use, with a study of problem gamblers identifying that such life events were responsible maintaining an individual's recovery once achieved through providing new responsibilities and interests with which they could occupy the time they had previously given over to substance use or gambling (28, 117).

Anderson's (2009b) study, regarding the realisation and acceptance of problem gambling behaviours in gambling individuals, identifies increased self-perception as a reason for change, facilitating the limitation of behaviour without formal intervention because of a desire to be perceived differently. Reductions in harmful gambling have also been associated with reduced



recklessness and changes to gambling patterns characterised by willpower, setting limits and only spending within means (28). The examination of changes in personality traits associated with maturation has identified the reduction in extraversion, impulsivity and neuroticism and the rise in conscientiousness as related to the decrease in alcohol use between the ages of 21 and 35, even after accounting for the influence of life events, such as marriage or parenthood. The effects of these changes in personality traits upon the change in alcohol use was mediated by changes in the individuals' motives to drink, specifically a reduction in their desire to drink as a coping strategy to regulate negative affect (235-237).

At the neurobiological level, maturing out may be viewed as the closing of the temporal gap in the development of the brain's circuitry. The brain continues to develop throughout adolescence; however the timing of development of the different neurological systems is not uniform. At the beginning of adolescence the striatal circuits develop; these are important in detecting and learning about novel and rewarding cues within the environment (238). Also, the mechanisms for social evaluation, through interactions between the striatum and the medial prefrontal cortex, develop during the early teenage years (238, 239). However, the development of the prefrontal cortex, known to be important for cognitive control does not occur until much later in the mid-twenties, leaving a neurological imbalance during adolescence which is associated with a heightened sensitivity to reward through the activity of the striatum, and a preoccupation with peer influence and appraisal due to still-maturing social and emotional systems. This misalignment in the development of the neurological circuits manifests as risk-taking with potentially concomitant heavy substance use (238). However, with the development of the prefrontal cortex the individual acquires the necessary capacity for self-control, which limits the individual's desire to engage in such harmful substance use or harmful gambling as they are more able to make a balanced assessment of the positive and negative consequences of these activities (238, 239). Thus, maturing out of harmful behaviours such as substance use and gambling may be associated with the natural development of brain neurocircuitry.

Maturing out, as a form of natural recovery from heavy substance use or gambling, is widely used within Western societies to explain why rates of harmful use of substances and gambling decline sharply during early-mid adulthood. The multidisciplinary nature of evidence to support the concept of maturing out supports the promotion of the concept as a truly multidisciplinary model for the reduction in or cessation of harmful substance use and harmful gambling.



4. DISCUSSION

In reframing addiction, or in the most recent terms of DSM 5 – ‘substance use disorders’ and ‘non-substance use disorders’ such as gambling – ALICE-RAP aims to expand policy debates beyond a reductionist approach focusing solely on mental disorders and instead facilitate discussion of broader aspects of psychotropic substance use and gambling. These clinically defined substance and non-substance use disorders do not develop overnight, but can be characterized as a developmental process with critical thresholds from low risk to risky and subsequent harmful use. These processes are highly individual with regards duration, pattern and problem severity. A better understanding of individual and social risk and protective factors that modulate these developments is needed to improve public policy, prevention and early intervention. The primary aim of this report was to examine current evidence on the determinants of reductions in harmful substance use and harmful gambling, collating evidence from across several disciplines. In this work we have focused on factors and processes related to recovery without formal support (e.g. professional treatment), as recovery without treatment is a widely under-researched area, yet important both for future strategies to tackle substance and non-substance use disorders within a larger share of our populations and to limit future public health expenditure.

The commentary in this report goes beyond the rigid structure and inclusion criteria of a systematic review to interpret a disparate range of evidence that has rarely been brought together. Despite the variation between disciplines in the volume and quality of evidence, it has been possible to identify a range of determinants of reductions in harmful addictive behaviour. The determinants drawn out from the different disciplines included within the synthesis are diverse, but there are also some areas of overlap suggesting a scientific convergence on some of the key determinants of reductions in harmful substance use and gambling. Such areas of overlap are summarised in the following section.

4.1 Key findings

The standard approach to reduce harmful substance use and gambling is a range of different types of treatment, either outpatient or inpatient, short- or long-term, with pharmaceuticals, psychotherapy, social support measures or combinations, by professionals, semi-professionals (self-help groups) or both. These interventions are well documented and show positive effects. However, this segment of professional public or private care reaches only a small minority of the affected population: from nearly unmeasurably small (tobacco) to about 10% (alcohol), with the single exception of about 50% for heroin-users. It would be extremely expensive to expand the service system to capture a significantly larger share of patients. In addition, not all subjects outside the system need intensive professional treatment. We know that up to 80% (80) of substance users reduce their harmful behaviour completely or partially over time. Own motivation, support from significant others, information and support-manuals in books and from the internet might facilitate or complicate these forms of recovery without formal treatment. Societies are well advised to develop a better understanding of these factors and processes in order to facilitate and support individuals to change their behaviour and at the same time avoid extremely high treatment costs.

As we have highlighted throughout this report, research evidence on the factors and processes that support individuals to change harmful behaviours is scarce – the area is astonishingly



under researched. Individuals who do go through self-change from substance use or gambling may do so to avoid the stigma of associated with formal treatment programmes, with natural recovery an inherently more hidden process. The relatively private nature of natural recovery means that access to individuals undergoing recovery in this manner is more difficult and so they are a more challenging population to access for research. The dearth of research on the determinants of successful self-change is a contrast to analyses related to professional treatment where characteristics of successful and unsuccessful patients are well known and are taken into consideration to improve programmes and outcomes. Given the low level of evidence it is difficult to summarize common determinants beyond scientific disciplines for natural recoveries. However, what we do know is summarised here.

Many of the determinants that have been identified as influential in the reduction of harmful behaviours in non-treatment populations lie at the social environmental level. A key determinant is regulation, for example, controlling the availability and price of alcohol can promote a reduction in harm through making heavy use inconvenient and unaffordable. It is important to note that while the promotion of cessation or a reduction in substance use and gambling should reduce harm to both the user and others, additional harm reduction strategies such as educating users in safer practices and improving levels of drug-related knowledge can also promote safer use, and as such may provide easier targets to reduce the harm associated with addictive behaviours. Furthermore, changes in the level of risk within environments of use, without changing an individuals' use *per se*, may also indeed promote a reduction in harm, both through enabling users to incorporate use into their daily lives and potentially altering the social context and stigmatisation of use (240, 241).

Whilst we identified a lack of evidence across most disciplines, it was particularly acute in research at the molecular and cellular level, where there is a knowledge gap concerning the biological mechanisms at play in the reduction of harmful behaviours through natural recovery. Where evidence is available within the molecular sciences this predominantly refers to treatment populations or pre-clinical models (which do not reflect the complex nature of human addiction where repeated quit attempts may take place and harm reduction may arise through alternative routes to that of simple behaviour cessation). Indeed, findings from the biological disciplines are largely concerned with the physiological state of either addicted individuals or those who are abstinent, and do not examine changes occurring in the lead up to and during reduction in use or cessation, making the identification of determinants of such processes at this level very difficult. Longitudinal studies are required to address this absence of knowledge at the biological level. Further research is also required to understand how we can contextualise studies (and related findings) conducted at the cellular and molecular level in a broader social and environmental context, given the importance of social environmental factors for the development of and reduction in harmful substance use and gambling.

In our work we have identified little interdisciplinary work in this field; consequently there is limited overlap between the data from different disciplines. Indeed, the lack of a social context for many of the biological experiments we examined, such as those using preclinical animal studies, prevent the findings being integrated here, as there are no direct links between the molecular data and individual personality traits or actions. The inferences offered by such studies, for example around a gene impacting neurotransmitter levels that are linked to a specific personality trait implicated as increasing the likelihood of cessation of addictive behaviours, are currently in the elemental stages and require further research to confirm

relationships and allow the integration of findings into a human context.

It is expected that different determinants will affect different users in different ways and at different times, and as such the determinants listed here may act in concert as both proximal and distal factors for different users, resulting in clusters of determinants being important in different sub-populations. Further delineating the exact nature of such determinant interactions for sub-populations will give additional information on how to best target measures to reduce harmful use. To enable such strategies, further multidisciplinary research is required to fill gaps in knowledge that we have identified here, and thus improve understanding of the determinants of a reduction in or cessation of harmful use. In our expert group some of the members found it useful to frame the interaction of the determinants in a similar manner to the bioecological model posed by Bronfenbrenner (242), as displayed in Figure 1 below. The group perceived policy to exert the greatest influence at the environment level and those closest to it, and that to affect changes through policy is increasingly difficult as you move towards the individual and cellular/molecular level (the centre of the model in Figure 1). As we have a better understanding of, and perceive that it is easier for policy to impact at, the environmental levels, we suggest that should be the primary focus of efforts to reduce harmful substance use and gambling.

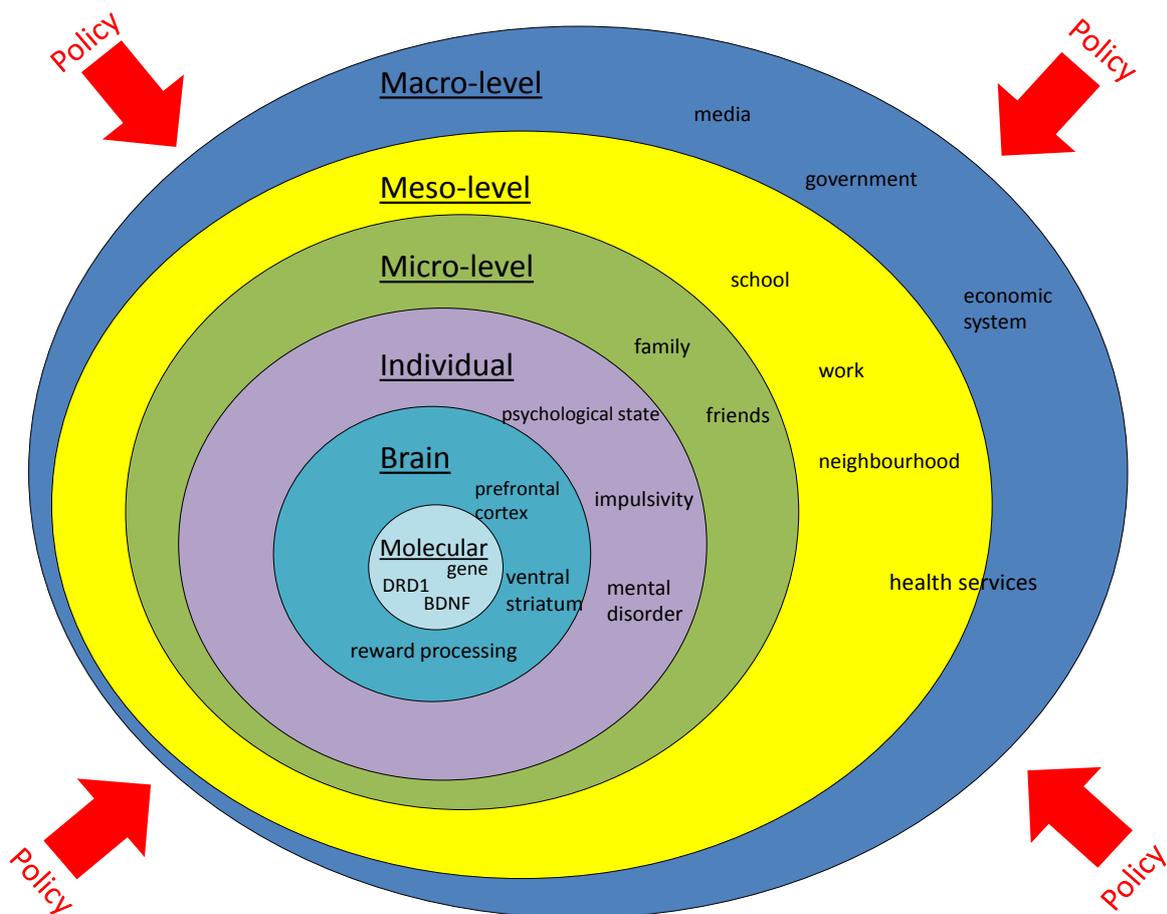


Figure 1: Determinants of addiction. Adapted from Bronfenbrenner’s bioecological theory of development (242).



Finally, it is clear that research supports that economic and social environmental factors play a major role in the initiation of self-change, for example economic crises, increased prices, reduced availability and accessibility. Economic changes are probably a pre-condition in a “four factor model” which needs to be supported by individual changes (negative health signals), individual consciousness of negative emotional or economic social reactions (partner, work, significant others), and individual preparedness and/or social support for behaviour changes to reduce harm. All four potential “ingredients” of effective self-change to reduce harm can be supported by societal measures and significant others. To better understand details of these determinants and processes, further research is needed, e.g. on the relevance of the factors involved and on interactions between determinants.

4.2 Limitations

We have identified three limitations of our approach. We present each limitation in turn now.

The first limitation of our approach is the panel of experts involved. Although we included a wide breadth of disciplines in the addiction field, there are numerous others that are not included. For example, whilst members of our group are medical professionals and therefore we have given some consideration to health as a determinant, given the huge breadth of addiction research from the medical field it was not possible to include this plethora of evidence here. Furthermore, as we have progressed through the project, experts within the group have reflected on how other disciplines, such as criminology or evolutionary biology, might have contributed to our work. However, it is crucial to acknowledge the already large scope of this project, both in terms of disciplines involved and stages of the development of addiction researched, and, given the challenges of ensuring shared understanding and language each time a new discipline enters a collaboration such as ours, involving more disciplines would likely, in practice, have hindered progress. We highlight this limitation to acknowledge that the choice of disciplines in any project such as this will influence the focus of the work. In short, more might equal slightly different rather than better.

Secondly, we identified determinants of addiction using expert reviews and though we have attempted to provide a representative overview of the knowledge base from each discipline, it is possible that certain concepts have been overlooked within our work. However, this limitation is inherent in any project of this kind, and only by means of increasing the number of multidisciplinary projects within this field to allow comparative studies will a full reflection of the field be developed.

Finally, within this report we have discussed the determinants of a reduction in harm from the use of both licit and illicit substances and gambling. However, for brevity we have exemplified many of the determinants using alcohol. Despite many similarities in the determinants of each of the different addictive behaviours, the lack of research surrounding certain substances, in addition to the plethora of different types of gambling opportunities available, mean that a nuanced understanding of the determinants of each behaviour is not possible here.

4.3 Implications for research, policy and practice

A detailed list of implications from this report on reductions will be outlined in the companion report (D9.2 models, transition probabilities and recommendations for research, policy and



practice). Here we outline some first implications from our findings in this report.

4.3.1 Implications for research

The implications for research from this work include an urgent need for further research across all disciplines to better understanding the determinants of a reduction in harmful substance use and gambling. Relatively little research literature was identified during the development of this report, and this extended to all disciplines and involved both licit and illicit substances and gambling. Moreover, further research is required into the process of natural recovery, which was the focus of this report, as the majority of research to date has concentrated on the development of addiction and formal treatment of heavy users. As the majority of users undergo self-change without the aid of formal treatment regimens, and this is likely to be a more cost-effective strategy, we suggest that improving understanding of the determinants of self-change processes, both cessation of use and alternative routes to harm reduction, is imperative to the promotion of a reduction in harmful substance use and gambling.

Highlighted within this report is the need for an increased number of longitudinal studies, particularly within the biological field, to enable the determinants of transitions between harmful use and less harmful use to be accurately identified. At present, research is focused on cross-sectional analyses or case studies that do not allow for a complete and accurate picture to be assembled of the factors influencing change over time. Similarly, the reliance on preclinical models to infer predictors of human activity offers limited scope for developing our understanding and so we need more studies to examine genetic determinants in human subjects so that we are better able to contextualise findings.

Few multidisciplinary studies were found on the reduction in harmful substance use and harmful gambling. We suggest future multidisciplinary work in the addiction field would facilitate the development of a more nuanced understanding of addiction that incorporates evidence from across the biomedical and social sciences. Such research would also help us to better understand the interplay between the different determinants identified, enabling a more targeted and individual approach to reducing the harm associated with substance use and gambling, and to promote the recovery of harmful users without formal treatment interventions. Moreover, future multidisciplinary work in this area would facilitate the contextualisation of research results across the different scientific disciplines. Only by working in this multidisciplinary manner will the research findings of different disciplines be best utilised to tackle the multi-faceted problem of addiction.

Finally, the “four factor model” outlined above (p.34) is a heuristic concept of broad themes that are perceived to play a relevant role in stimulating, processing and maintaining effective self-change to reduce substance use and gambling related harm. Social conditions, individual preparedness, self-efficacy and cognitive control, as well as a supportive social environment, are seen as relevant factors, but many details are unknown: Which determinants stimulate the onset of change processes? Are all determinants equally relevant? Do individual differences matter? How can we best support effective change? These are key questions for further research.



4.3.2 Implications for policy

We have identified five implications for policy from our synthesis of evidence on the determinants of a reduction in harmful substance use and gambling. Research funding should be directed to the following three important areas for the development of understanding:

1. Self-change of harmful substance and non-substance use behaviour, to maximise the potential of self-change in harmful behaviours and reduce the burden on healthcare and drug treatment services.
2. Longitudinal studies in the biological field that both strive to contextualise biological research within a human context and that allow the predictors of transitions between stages in the development of harmful substance and non-substance use disorders to be identified.
3. Multidisciplinary research that encourages diverse disciplines to work together to develop a more nuanced, contextualised understanding of self-change.

Further policy implications beyond research funding include:

4. We have a more detailed understanding of factors affecting reductions in harm at the social environmental level and policy is also relatively easily able to focus at this level, so we could target here for maximum impact. Evidence suggests that targets such as advertising controls and limits on the availability and accessibility of substances and gambling would be successful in reducing harmful use.
5. Harm reduction is an important part of decreasing the harm experienced from substance and non-substance use disorders. Many countries have already taken steps to reduce the harm from some substance use behaviours, such as drug injection, and further harm reduction strategies should be pursued to generate additional returns.

4.3.3 Implications for practice

For practitioners, we support the use of the “four factor model” outlined above to stimulate and support self-change to reduce harm. Each of the individual and social components within the model can be addressed. For example, we can:

- Influence people to feel the need to change through shaping social conditions, improving health education on early risk factors, and educating and motivating significant others (e.g., family or friends) to discuss harmful substance use and gambling early.
- Support individuals to improve their self-efficacy through training and the help of significant others.
- Improve cognitive control through simple training tasks in self-help manuals. Severe deficits in this area, such as impaired cognitive control or high impulsivity, might be risk factors impeding effective self-change and signal the need for professional treatment.
- Provide emotional and technical support for both changes in behaviour and



maintenance of change, for example through family, friends and work colleagues. These groups might be educated and motivated by public activities to improve awareness of substance and non-substance use disorders.

4.4 Conclusions

In recent decades, research in the field of a reduction in harmful substance use and gambling has focused on 1) developing and testing effective professional treatments and 2) motivating more subjects to enter treatment, as utilization rates are currently low. However, a significant increase in treatment system use would be extremely expensive and unsustainable given current service provision and budgets. Therefore, we need an alternative approach to a reduction in harmful substance use and gambling.

From epidemiological studies, we know that a large proportion of subjects who use substances or gamble in a harmful way do engage more or less effectively in self-change processes to reduce harm. These “natural recoveries” are widely under-researched and as such are neglected within public health approaches. This report represents the first time that researchers from a wide variety of scientific disciplines and approaches have collaborated interdisciplinarily to collect and critically examine the determinants of these self-change processes, and then derive first implications for research, policy and practice.



5. REFERENCE LIST

- (1) Simkin DR, Grenoble S. Pharmacotherapies for Adolescent Substance Use Disorders. *Child and Adolescent Psychiatric Clinics of North America* 2010; 19(3):591-608.
- (2) Dutra L, Stathopoulou G, Basden SL, Leyro TM, Powers MB, Otto MW. A meta-analytic review of psychosocial interventions for substance use disorders. *Am J Psychiatry* 2008; 165(2):179-187.
- (3) van den Brink W. Evidence-based pharmacological treatment of substance use disorders and pathological gambling. *Curr Drug Abuse Rev* 2012; 5(1):3-31.
- (4) Cousijn J, Goudriaan AE, Wiers RW. Reaching out towards cannabis: approach-bias in heavy cannabis users predicts changes in cannabis use. *Addiction* 2011; 106(9):1667-1674.
- (5) Wiers RW, Gladwin TE, Rinck M. Should we train alcohol-dependent patients to avoid alcohol? *Front Psychiatry* 2013; 4:33.
- (6) Dawson DA, Grant BF, Stinson FS, Chou PS. Estimating the effect of help-seeking on achieving recovery from alcohol dependence. *Addiction* 2006; 101(6):824-834.
- (7) Smith AL, Chapman S, Dunlop SM. What do we know about unassisted smoking cessation in Australia? A systematic review, 2005-2012. *Tobacco Control* 2013.
- (8) American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition: DSM-IV-TR. American Psychiatric Association; 2000.
- (9) Jazaeri SA, Habil MH. Reviewing two types of addiction - pathological gambling and substance use. *Indian J Psychol Med* 2012; 34(1):5-11.
- (10) American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: Dsm-5. Amer Psychiatric Pub Incorporated; 2013.
- (11) Becker HS. Outsiders: Studies in the Sociology of Deviance. Free Press; 1963.
- (12) Biernacki P. Pathways from Heroin Addiction: Recovery Without Treatment. Temple University Press; 1986.
- (13) Decorte T. Drug users perceptions of controlled and uncontrolled use. *International Journal of Drug Policy* 2001; 12(4):297-320.
- (14) Gourley M. A Subcultural Study of Recreational Ecstasy Use. *Journal of Sociology* 2004; 40(1):59-73.
- (15) Jarvinen M, Ravn S. From recreational to regular drug use: qualitative interviews with young clubbers. *Sociology of Health & Illness* 2011; 33(4):554-569.
- (16) Measham F, Newcombe R, Parker H. The normalization of recreational drug use amongst young people in north-west England. *Br J Sociol* 1994; 45(2):287-312.
- (17) Zinberg NE. Drug, Set, And Setting: The Basis for Controlled Intoxicant Use. Yale University Press; 1986.
- (18) Davey J, Richards N, Freeman J. Fatigue and Beyond: Patterns of and Motivations for Illicit Drug Use Among Long-Haul Truck Drivers. *Traffic Injury Prevention* 2007; 8(3):253-259.
- (19) Room R. Stigma, social inequality and alcohol and drug use. *Drug Alcohol Rev* 2005; 24(2):143-155.



- (20) Link BG, Phelan JC. Conceptualizing Stigma. *Annu Rev Sociol* 2001; 27(1):363-385.
- (21) Raikhel E, Garriot W. Tracing new paths in the anthropology of addiction. In: Raikhel E, Garriot W, editors. *Addiction Trajectories*. Duke University Press; 2013. 1-35.
- (22) Zoja L, Romano ME. *Drugs, addiction, & initiation: the modern search for ritual*. Sigo Press; 1989.
- (23) Moore LL. disability and illicit drug use: an application of labeling theory. *Deviant Behavior* 2001; 22(1):1-21.
- (24) Bourgois P. *In Search of Respect: Selling Crack in El Barrio*. Cambridge University Press; 2003.
- (25) Pearson G. Drugs and deprivation. *J R Soc Health* 1996; 116(2):113-116.
- (26) Waterston A. *Street Addicts in the Political Economy*. Temple University Press; 1997.
- (27) Laudet AB. The Road to Recovery: Where Are We Going and How Do We Get There? Empirically Driven Conclusions and Future Directions for Service Development and Research. *Subst Use Misuse* 2008; 43(12-13):2001-2020.
- (28) Anderson S, Dobbie F, Reith G. Recovery from problem gambling: a qualitative study. Final Report. 2009. Scottish Centre for Social Research.
- (29) Ray MC, Downs WR. An Empirical Test of Labeling Theory Using Longitudinal Data. *Journal of Research in Crime and Delinquency* 1986; 23(2):169-194.
- (30) Boshears P, Boeri M, Harbry L. Addiction and sociality: Perspectives from methamphetamine users in suburban USA. *Addict Res Theory* 2011; 19(4):289-301.
- (31) Mullen K, Hammersley R. Attempted cessation of heroin use among men approaching mid-life. *Drugs Edu Prev Pol* 2006; 13(1):77-92.
- (32) Eber C. Take my water: liberation through prohibition in San Pedro Chenalh, Chiapas, Mexico. *Social Science & Medicine* 2001; 53(2):251-262.
- (33) Kaskutas LA, Bond J, Humphreys K. Social networks as mediators of the effect of Alcoholics Anonymous. *Addiction* 2002; 97(7):891-900.
- (34) Allamani A, Voller F, Baccini M, Massini G, Pepe P. Europe. An analysis of changes in the consumption of alcoholic beverages: the interaction between consumption, related harms, contextual factors and alcoholic beverage control policies. *Substance Use and Misuse* 2014.
- (35) Chaloupka FJ, Straif K, Leon ME. Effectiveness of tax and price policies in tobacco control. *Tobacco Control* 2011; 20(3):235-238.
- (36) Wilson LM, Avila TE, Chander G, Hutton HE, Odelola OA, Elf JL et al. Impact of tobacco control interventions on smoking initiation, cessation, and prevalence: a systematic review. *J Environ Public Health* 2012; 2012:961724.
- (37) Liu F. Cutting through the smoke: separating the effect of price on smoking initiation, relapse and cessation. *Applied Economics* 2009; 42(23):2921-2939.
- (38) Madden D. *Smoke and Strong Whiskey: Factors Influencing Female Smoking and Drinking in Ireland*. Dublin, Ireland: University College Dublin, Centre for Economic Research; 2007.
- (39) Henkel D. Unemployment and Substance Use: A Review of the Literature (1990-2010). *Current Drug Abuse Reviews* 2011; 4:4-27.
- (40) Allamani A, Prini F. Why the decrease in consumption of alcoholic beverages in Italy between



- the 1970s and the 2000s? Shedding light on an Italian mystery. *Contemp Drug Probl* 2007; 34[2]:187-198.
- (41) Tusini S. The decrease in alcohol consumption in Italy: sociological interpretations. *Contemp Drug Probl* 2007; 34[2]:253-286.
- (42) Alexander B. *The Globalisation of Addiction: A Study in Poverty of the Spirit*. Oxford: Oxford University Press; 2008.
- (43) Blomqvist J. Perceptions of addiction and recovery in Sweden: The influence of respondent characteristics. *Addict Res Theory* 2012; 20(5):435-446.
- (44) Nordlund S. Popular norms, alcohol policy and drinking behaviour. In: Anderson P, Braddick F, Reynolds J, Gual A, editors. *Alcohol Policy in Europe: Evidence from AMPHORA*. 2011. 24-31.
- (45) Lederman S. *Alcool, Alcoolisme, Alcoolisation Données Scientifiques de Caractère Physiologique, Economique et Social*. Paris: Presses Universitaires de France, Institut National d'Etudes Démographiques; 1956.
- (46) Room R. Preventing Youthful Substance Use and Harm: Between Effectiveness and Political Wishfulness. *Subst Use Misuse* 2012; 47(8-9):936-943.
- (47) Gerstein D. Alcohol use and consequences. Moore M, Gerstein D, editors. *Alcohol and Public Policy: Beyond the shadow of prohibition*. 182-224. 1981. Washington D.C., National Academy Press.
- (48) Crowley JW. *Drunkard's Progress: Narratives of Addiction, Despair, and Recovery*. Johns Hopkins University Press; 1999.
- (49) Barrows S, Room R. Introduction. In: Barrows S, Room R, editors. *Drinking Behaviour and Belief Systems in Modern History*. Berkeley: University of California Press; 1991. 1-23.
- (50) Levine HG. Temperance Cultures: Alcohol as Problem in Nordic and English-speaking Cultures. In: Lender M, Edwards G, editors. *The Nature of Alcohol and Drug Related Problems*. Oxford, England: Oxford University Press; 1992. 16-36.
- (51) Room R. Alcohol and harm reduction, then and now. *Critical Public Health* 14, 329-344. 2004.
- (52) Eisenbach-Stangl I, Rosenqvist P. Diversity in Unity: Studies of Alcoholics Anonymous in Eight Societies. Helsinki, Finland: Nordic Council for Alcohol and Drug Research (NAD); 1998.
- (53) Makela K, Alcoholics A, World Health Organization. Regional Office for Europe. Alcoholics Anonymous as a Mutual-help Movement: A Study in Eight Societies. University of Wisconsin Press; 1996.
- (54) Room R. Mutual help movements for alcohol problems in an international perspective. *Addiction Research* 1998; 6:131-145.
- (55) Miller WR. Addiction and Spirituality. *Subst Use Misuse* 2013; 48(12):1258-1259.
- (56) DiClemente CC. Paths Through Addiction and Recovery: The Impact of Spirituality and Religion. *Subst Use Misuse* 2013; 48(12):1260-1261.
- (57) Alcoholics Anonymous World Services i, Alcoholics A. "Pass it On": The Story of Bill Wilson and how the A.A. Message Reached the World. Alcoholics Anonymous World Services; 1984.
- (58) Courtwright D. *Forces of Habit: Drugs and the Making of the Modern World*. Harvard University Press; 2002.



- (59) Room R. Alcohol monopolies as instruments for alcohol control policies. In: Osterburg E, editor. International seminar on alcohol retail monopolies. Helsinki: National Research and Development Centre for Welfare and Health Themes 5/2000; 2000. 7-16.
- (60) Her M, Giesbrecht N, Room R, Rehm J. Privatizing alcohol sales and alcohol consumption: evidence and implications. *Addiction* 1999; 94(8):1125-1139.
- (61) Babor T. Drug Policy and the Public Good. OUP Oxford; 2010.
- (62) Babor T. Prescription regimes and nother measures to control misuse of psychopharmaceuticals. In: Barbor T, editor. *Drug Policy and the Public Good*. OUP Oxford; 2010. 179-203.
- (63) Okrent D. Last Call: *The Rise and Fall of Prohibition*. Scribner; 2010.
- (64) Yongming Z. Nationalism, identity and state building: the anti-drug crusade in the People's Republic 1949-1952. Brook T, Wakabayashi BT, editors. *Opium Regimes: China, Britain and Japan, 1839-1952*. 380-403. 2000. Berkeley, University of California Press.
- (65) Room R, Reuter P. How well do international drug conventions protect public health? *Lancet* 2012; 379(9810):84-91.
- (66) Dixon D. *From Prohibition to Regulation: Bookmaking, Anti-Gambling, and the Law*. Clarendon Press; 1991.
- (67) Productivity Commission. Report No.50 Melbourne. Gambling. 2010. Commonwealth of Australia, Productivity Commission.
- (68) Ponicki WR, Gruenewald PJ. The impact of alcohol taxation on liver cirrhosis mortality. *J Stud Alcohol* 2006; 67(6):934-938.
- (69) Maldonado-Molina MM, Wagenaar AC. Effects of Alcohol Taxes on Alcohol-Related Mortality in Florida: Time-Series Analyses From 1969 to 2004. *Alcohol Clin Exp Res* 2010; 34(11):1915-1921.
- (70) Babor T. *Alcohol: No Ordinary Commodity : Research and Public Policy*. Oxford University Press, Incorporated; 2003.
- (71) Sen B. The Relationship between Beer Taxes, Other Alcohol Policies, and Child Homicide Deaths. *Topics in Economic Analysis and Policy* 2006; 6[1].
- (72) Markowitz S. Alcohol, Drugs and Violent Crime. *International Review of Law and Economics* 2005; 25(1):20-44.
- (73) Foster JH, Ferguson CS. Home Drinking in the UK: Trends and Causes. *Alcohol and Alcoholism* 2012.
- (74) Booth A, Meier P, Stockwell T, Sutton A, Wilkinsons A, Wong R et al. *Independent Review of the Effects of Alcohol Pricing and Promotion*. Review 1: The effec of pricing and taxation on alcohol consumption. Review 2: The effect of promotion on alcohol consumption. 2008. University of Sheffield.
- (75) Sharma A, Vandenberg B, Hollingsworth B. Minimum Pricing of Alcohol versus Volumetric Taxation: Which Policy Will Reduce Heavy Consumption without Adversely Affecting Light and Moderate Consumers? *PLoS One* 2014; 9(1):e80936.
- (76) Pacula R. *Examining the Impact of Marijuana Legalization on Harms Associated with Marijuana Use*. 2010. Santa Monica, CA, RAND Corporation.
- (77) Richardson K, ASH., Great B. Smoking, Low Income and Health Inequalities: Thematic



- Discussion Document. ASH; 2001.
- (78) DeCicca P, Kenkel D, Liu F. *Who pays cigarette taxes? The impact of consumer price research*. 2010. Cornell University, Dept. of Policy Analysis and Management.
 - (79) van Ours JC, Williams J. Cannabis prices and dynamics of cannabis use. *J Health Econ* 2007; 26(3):578-596.
 - (80) Perkonigg A, Rumpf H, Wittchen H. Remission from substance dependence without formal help among adolescents and young adults. *Sucht* 2009; 55(2):86-97.
 - (81) Levy DT, Chaloupka F, Gitchell J. The effects of tobacco control policies on smoking rates: a tobacco control scorecard. *J Public Health Manag Pract* 2004; 10(4):338-353.
 - (82) Storer J, Abbott M, Stubbs J. Access or adaptation? A metaanalysis of surveys of problem gambling prevalence in Australia and New Zealand with respect to concentration of electronic gaming machines. *International Gambling Studies* 2009; 9[3]:225-244.
 - (83) Breen H, Gainsbury S. Aboriginal gambling and problem gambling: A review. *International Journal of Mental Health and Addiction* 2013; 11[1]:75-96.
 - (84) Bryden A, Roberts B, McKee M, Petticrew M. A systematic review of the influence on alcohol use of community level availability and marketing of alcohol. *Health & Place* 2012; 18(2):349-357.
 - (85) Thomas A, Bates G, Moore S, Kyrios M, Meredyth D, Jessop G. Gambling and the Multidimensionality of Accessibility: More Than Just Proximity to Venues. *Int J Ment Health Addiction* 2011; 9(1):88-101.
 - (86) Popova S, Giesbrecht N, Bekmuradov D, Patra J. Hours and Days of Sale and Density of Alcohol Outlets: Impacts on Alcohol Consumption and Damage: A Systematic Review. *Alcohol and Alcoholism* 2009; 44(5):500-516.
 - (87) Anderson P, Chisholm D, Fuhr DC. Effectiveness and cost-effectiveness of policies and programmes to reduce the harm caused by alcohol. *The Lancet* 2009; 373(9682):2234-2246.
 - (88) Caroline MF, Stanton AG. Effect of smoke-free workplaces on smoking behaviour: systematic review. *BMJ* 2002; 325.
 - (89) Mackay DF, Haw S, Pell JP. Impact of Scottish Smoke-Free Legislation on Smoking Quit Attempts and Prevalence. *PloS One* 2011; 6[11].
 - (90) Gliksman L, Douglas RR, Rylett M, Narbonne-Fortin C. Reducing Problems Through Municipal Alcohol Policies: the Canadian experiment in Ontario. *Drugs Edu Prev Pol* 1995; 2(2):105-118.
 - (91) Smith LA, Foxcroft DR. The effect of alcohol advertising, marketing and portrayal on drinking behaviour in young people: systematic review of prospective cohort studies. *BMC Public Health* 2009; 9:51.
 - (92) Tapert SF, Schweinsburg AD, Drummond SPA, Paulus MP, Brown SA, Yang TT et al. Functional MRI of inhibitory processing in abstinent adolescent marijuana users. *Psychopharmacology* 194(2):173-183.
 - (93) Wolberg JM, Hovland R, Hopson RE. Cognitive restricting as a relapse prevention strategy: teaching alcoholics to talk back to beer ads. *Alcoholism Treatment Quart* 1999; 17[4], 29-51.
 - (94) Moodie C, Stead M, Bauld L, McNeill A, Angus K, Hinds K et al. Plain tobacco packaging: A systematic review. 2012.



- (95) Binde P. Exploring the Impact of Gambling Advertising: An Interview Study of Problem Gamblers. *Int J Ment Health Addiction* 2009; 7(4):541-554.
- (96) Planzer S, Wardle H. The Comparative Effectiveness of Regulatory Approaches and The Impact of Advertising on Propensity for Problem Gambling. 2011.
- (97) Norstrom T. The Abolition of the Swedish Alcohol Rationing System: effects on consumption distribution and cirrhosis mortality. *British Journal of Addiction* 1987; 82(6):633-641.
- (98) Moskalewicz J, Sawiatkiewicz G. Alcohol consumption and its consequences in Poland in the light of official statistics. In: Leifman H, Edgren Henrichsen N, editors. Statistics on alcohol, drugs and crime in the Baltic sea region. Helsinki: Nordic Council for Alcohol and Drug Research; 2000. 143-161.
- (99) Terris M. Epidemiology of cirrhosis of the liver: national mortality data. *Am J Public Health Nations Health* 1967; 57(12):2076-2088.
- (100) Fillmore KM, Roizen R, Farrell M, Kerr W, Lemmens P. Wartime Paris, cirrhosis mortality, and the ceteris paribus assumption. *J Stud Alcohol* 2002; 63(4):436-446.
- (101) Babor T. Supply Control. In: Babor T, editor. Drug Policy and the Public Good. Oxford, England: Oxford University Press; 2010. 139-162.
- (102) Babor T. Criminalization and decriminalization of drug use or possession. In: Babor T, editor. Drug Policy and the Public Good. Oxford, England: Oxford University Press; 2010. 163-178.
- (103) Room R. Individualized control of drinkers: Back to the future? *Contemp Drug Probl* 2012; 39(2):311-343.
- (104) Hunt N, Ashton M, Lenton S, Mitcheson L, Nelles B, Timson G. A review of the evidence-base for harm reduction approaches to drug use. 2003. London, Forward Thinking on Drugs.
- (105) MacCoun R, Reuter P. Evaluating alternative cannabis regimes. *The British Journal of Psychiatry* 2001; 178(2):123-128.
- (106) Lev-Ran S, Imtiaz S, Rehm J, Le FB. Exploring the association between lifetime prevalence of mental illness and transition from substance use to substance use disorders: results from the National Epidemiologic Survey of Alcohol and Related Conditions (NESARC). *Am J Addict* 2013; 22(2):93-98.
- (107) Lopez-Quintero C, Hasin DS, de Los Cobos JP, Pines A, Wang S, Grant BF et al. Probability and predictors of remission from life-time nicotine, alcohol, cannabis or cocaine dependence: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Addiction* 2011; 106(3):657-669.
- (108) Swendsen J, Conway KP, Degenhardt L, Glantz M, Jin R, Merikangas KR et al. Mental disorders as risk factors for substance use, abuse and dependence: results from the 10-year follow-up of the National Comorbidity Survey. *Addiction* 2010; 105(6):1117-1128.
- (109) Westermeyer J, Canive J, Thuras P, Kim SW, Crosby R, Thompson J et al. Remission from pathological gambling among Hispanics and Native Americans. *Community Ment Health J* 2006; 42(6):537-553.
- (110) Florez-Salamanca L, Secades-Villa R, Budney AJ, Garcia-Rodriguez O, Wang S, Blanco C. Probability and predictors of cannabis use disorders relapse: results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *Drug Alcohol Depend* 2013; 132(1-2):127-133.



- (111) Hoch E, Noack R, Henker J, Pixa A, Hofler M, Behrendt S et al. Efficacy of a targeted cognitive-behavioral treatment program for cannabis use disorders (CANDIS). *Eur Neuropsychopharmacol* 2012; 22(4):267-280.
- (112) Khan SS, Secades-Villa R, Okuda M, Wang S, Perez-Fuentes G, Kerridge BT et al. Gender differences in cannabis use disorders: results from the National Epidemiologic Survey of Alcohol and Related Conditions. *Drug Alcohol Depend* 2013; 130(1-3):101-108.
- (113) Pacek LR, Martins SS, Crum RM. The bidirectional relationships between alcohol, cannabis, co-occurring alcohol and cannabis use disorders with major depressive disorder: results from a national sample. *J Affect Disord* 2013; 148(2-3):188-195.
- (114) Magidson JF, Wang S, Lejuez CW, Iza M, Blanco C. Prospective study of substance-induced and independent major depressive disorder among individuals with substance use disorders in a nationally representative sample. *Depress Anxiety* 2013; 30(6):538-545.
- (115) de GR, Bijl RV, ten HM, Beekman AT, Vollebergh WA. Pathways to comorbidity: the transition of pure mood, anxiety and substance use disorders into comorbid conditions in a longitudinal population-based study. *J Affect Disord* 2004; 82(3):461-467.
- (116) Hodgins DC, Peden N, Cassidy E. The association between comorbidity and outcome in pathological gambling: a prospective follow-up of recent quitters. *J Gambl Stud* 2005; 21(3):255-271.
- (117) Hodgins DC, el-Guebaly N. Natural and treatment-assisted recovery from gambling problems: a comparison of resolved and active gamblers. *Addiction* 2000; 95(5):777-789.
- (118) Toneatto T, Cunningham J, Hodgins D, Adams M, Turner N, Koski-Jannes A. Recovery from problem gambling without formal treatment. *Addict Res Theory* 2008; 16(2):111-120.
- (119) Hasin D, Fenton MC, Skodol A, Krueger R, Keyes K, Geier T et al. Personality disorders and the 3-year course of alcohol, drug, and nicotine use disorders. *Arch Gen Psychiatry* 2011; 68(11):1158-1167.
- (120) Hicks BM, Durbin CE, Blonigen DM, Iacono WG, McGue M. Relationship between personality change and the onset and course of alcohol dependence in young adulthood. *Addiction* 2012; 107(3):540-548.
- (121) Hodgins D, Wynne H, Makarchuk K. Pathways to Recovery from Gambling Problems: Follow-Up from a General Population Survey. *J Gambl Stud* 1999; 15(2):93-104.
- (122) Enticott PG, Ogloff JRP. Elucidation of impulsivity. *Australian Psychologist* 2006; 41(1):3-14.
- (123) Littlefield AK, Sher KJ, Steinley D. Developmental trajectories of impulsivity and their association with alcohol use and related outcomes during emerging and young adulthood I. *Alcohol Clin Exp Res* 2010; 34(8):1409-1416.
- (124) McKellar J, Ilgen M, Moos BS, Moos R. Predictors of changes in alcohol-related self-efficacy over 16 years. *J Subst Abuse Treat* 2008; 35(2):148-155.
- (125) Solowij N, Jones KA, Rozman ME, Davis SM, Ciarrochi J, Heaven PC et al. Reflection impulsivity in adolescent cannabis users: a comparison with alcohol-using and non-substance-using adolescents. *Psychopharmacology (Berl)* 2012; 219(2):575-586.
- (126) von DL, Bassani DG, Fuchs SC, Szobot CM, Pechansky F. Impulsivity, age of first alcohol use and substance use disorders among male adolescents: a population based case-control study. *Addiction* 2008; 103(7):1198-1205.



- (127) Loewenstein G, O'Donoghue T. The Heat of the Moment: Modeling Interactions Between Affect and Deliberation. 2007.
- (128) Saffer H. New approaches to alcohol marketing research. *Addiction* 2011; 106(3):473-474.
- (129) Filbey FM, Claus E, Audette AR, Niculescu M, Banich MT, Tanabe J et al. Exposure to the Taste of Alcohol Elicits Activation of the Mesocorticolimbic Neurocircuitry. *Neuropsychopharmacology* 2007; 33(6):1391-1401.
- (130) Carter BL, Lam CY, Robinson JD, Paris MM, Waters AJ, Wetter DW et al. Generalized craving, self-report of arousal, and cue reactivity after brief abstinence. *Nicotine & Tobacco Research* 2009; 11(7):823-826.
- (131) Kahn S, Gallinat J. Common biology of craving across legal and illegal drugs: a quantitative meta-analysis of cue-reactivity brain response. *European Journal of Neuroscience* 2011; 33(7):1318-1326.
- (132) Greenfield SF, Brooks AJ, Gordon SM, Green CA, Kropp F, McHugh RK et al. Substance abuse treatment entry, retention, and outcome in women: a review of the literature. *Drug Alcohol Depend* 2007; 86(1):1-21.
- (133) Volpicelli JR, Markman I, Monterosso J, Filing J, O'Brien CP. Psychosocially enhanced treatment for cocaine-dependent mothers: evidence of efficacy. *J Subst Abuse Treat* 2000; 18(1):41-49.
- (134) Slutske WS, Blaszczynski A, Martin NG. Sex differences in the rates of recovery, treatment-seeking, and natural recovery in pathological gambling: results from an Australian community-based twin survey. *Twin Res Hum Genet* 2009; 12(5):425-432.
- (135) Copello A, Orford J, Hodgson R, Tober G. *Social Behaviour and Network Therapy for Alcohol Problems*. Taylor & Francis; 2009.
- (136) Joosten J, Knibbe RA, Derickx M, Selin KH, Holmila M. Criticism of drinking as informal social control: a study in 18 countries. *Contemp Drug Probl* 2009; 36(1-2):85-109.
- (137) Room R. Patterns of family responses to alcohol and tobacco problems. *Drug Alcohol Rev* 1996; 15(2):171-181.
- (138) Bretteville-Jensen AL. To Legalize or Not To Legalize? Economic Approaches to the Decriminalization of Drugs. *Subst Use Misuse* 2006; 41(4):555-565.
- (139) Compton WM, Dawson DA, Conway KP, Brodsky M, Grant BF. Transitions in illicit drug use status over 3 years: a prospective analysis of a general population sample. *Am J Psychiatry* 2013; 170(6):660-670.
- (140) Kuntsche E, Rossow I, Simons-Morton B, Bogt TT, Kokkevi A, Godeau E. Not Early Drinking but Early Drunkenness Is a Risk Factor for Problem Behaviors Among Adolescents from 38 European and North American Countries. *Alcohol Clin Exp Res* 2013; 37(2):308-314.
- (141) Dawson DA, Goldstein RB, Grant BF. Prospective correlates of drinking cessation: variation across the life-course. *Addiction* 2013; 108(4):712-722.
- (142) Bretteville-Jensen AL. Illegal drug use and the economic recession - what can we learn from the existing research? *Int J Drug Policy* 2011; 22(5):353-359.
- (143) Adamson SJ, Sellman JD, Frampton CM. Patient predictors of alcohol treatment outcome: a systematic review. *J Subst Abuse Treat* 2009; 36(1):75-86.
- (144) Brewer DD, Catalano RF, Haggerty K, Gainey RR, Fleming CB. A meta-analysis of predictors of



- continued drug use during and after treatment for opiate addiction. *Addiction* 1998; 93(1):73-92.
- (145) Grof C. *The Thirst for Wholeness: Attachment, Addiction, and the Spiritual Path*. HarperCollins; 1994.
- (146) Buning EC, Coutinho RA, van Brussel GH, van Santen GW, van Zadelhoff AW. Preventing AIDS in drug addicts in Amsterdam. *Lancet* 1986; 1(8495):1435.
- (147) Normand J, Vlahov D, Moses LE, Programs PNEB, Medicine I, Medicine NRCI. *Preventing HIV Transmission: The Role of Sterile Needles and Bleach*. National Academies Press; 1995.
- (148) van Ameijden EJ, Coutinho RA. Maximum impact of HIV prevention measures targeted at injecting drug users. *AIDS* 1998; 12(6):625-633.
- (149) Lurie P, Reingold AL. *The public health impact of needle exchange programs in the United States and abroad. Summary, conclusions and recommendations*. 1993. Centre for AIDS Prevention Studies.
- (150) Des Jarlais DC, Hagan H, Friedman SR, Friedmann P, Goldberg D, Frischer M et al. Maintaining low HIV seroprevalence in populations of injecting drug users. *JAMA* 1995; 274(15):1226-1231.
- (151) Hagan H, Jarlais DC, Friedman SR, Purchase D, Alter MJ. Reduced risk of hepatitis B and hepatitis C among injection drug users in the Tacoma syringe exchange program. *Am J Public Health* 1995; 85(11):1531-1537.
- (152) Vlahov D, Junge B, Brookmeyer R, Cohn S, Riley E, Armenian H et al. Reductions in high-risk drug use behaviors among participants in the Baltimore needle exchange program. *J Acquir Immune Defic Syndr Hum Retrovirol* 1997; 16(5):400-406.
- (153) Bluthenthal RN, Kral AH, Gee L, Erringer EA, Edlin BR. The effect of syringe exchange use on high-risk injection drug users: a cohort study. *AIDS* 2000; 14(5):605-611.
- (154) Vertefeuille J, Marx M, Tun W, Huettner S, Strathdee S, Vlahov D. Decline in Self-Reported High-Risk Injection-Related Behaviors Among HIV-Seropositive Participants in the Baltimore Needle Exchange Program. *AIDS Behav* 2000; 4(4):381-388.
- (155) Heimer R, Khoshnood K, Bigg D, Guydish J, Junge B. Syringe use and reuse: effects of syringe exchange programs in four cities. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998; 18 Suppl 1:S37-S44.
- (156) Heimer R. Can Syringe Exchange Serve as a Conduit to Substance Abuse Treatment? *Journal of Substance Abuse Treatment* 1998; 15(3):183-191.
- (157) Brooner R, Kidorf M, King V, Beilenson P, Svikis D, Vlahov D. Drug abuse treatment success among needle exchange participants. *Public Health Rep* 1998; 113 Suppl 1:129-139.
- (158) Strathdee S, Celentano D, Shah N, Lyles C, Stambolis V, Macalino G et al. Needle-exchange attendance and health care utilization promote entry into detoxification. *J Urban Health* 1999; 76(4):448-460.
- (159) Hurley SF, Jolley DJ, Kaldor JM. Effectiveness of needle-exchange programmes for prevention of HIV infection. *The Lancet* 1997; 349(9068):1797-1800.
- (160) Coyle SL, Needle RH, Normand J. Outreach-Based HIV Prevention for Injecting Drug Users: A Review of Published Outcome Data. *Public Health Reports (1974-)* 1998; 113:19-30.
- (161) Anderson P, Moller L, Galea G. *Alcohol in the European Union. Consumption, harm and policy*



- approaches*. 2012. Regional Office for Europe, Copenhagen, World Health Organisation.
- (162) Clarke RV, Cornish DB. Modeling offenders' decisions: A framework for research and policy. Tony M, Morris N, editors. *Crime and justice: an annual review of research*. 147-185. 1985. Chicago, The University of Chicago Press.
- (163) Drumm RD, McBride D, Metsch L, Neufeld M, Sawatsky A. I'm a Health Nut! Street Drug Users' Accounts of Self-Care Strategies. *Journal of Drug Issues* 2005; 35(3):607-629.
- (164) Preble E, Casey JJ. Taking care of business- the heroin users life on the street. *International Journal of Addictions*; 1969 4[1], 3-24.
- (165) Sorensen JK. *Substance Use, Rituals and Risk Management: Danish Rock Festivals*. Department of Sociology, University of Copenhagen; 2009.
- (166) Shukla RK, Kelley MS. Investigating How Decisions to Use Marijuana Change Over Time. *Subst Use Misuse* 2007; 42(9):1401-1425.
- (167) Plant MA, Plant M. *Risk-takers: Alcohol, Drugs, Sex, and Youth*. Tavistock/Routledge; 1992.
- (168) Grund JPC. *Drug Use as a Social Ritual: Functionality, Symbolism and Determinants of Self-regulation*. Instituut voor Verslavingsonderzoek (IVO), Erasmus Universiteit Rotterdam; 1993.
- (169) Wakefield MA, Durkin S, Spittal MJ, Siahpush M, Scollo M, Simpson JA et al. Impact of Tobacco Control Policies and Mass Media Campaigns on Monthly Adult Smoking Prevalence. *Am J Public Health* 2008; 98(8):1443-1450.
- (170) Elder RW, Shults RA, Sleet DA, Nichols JL, Thompson RS, Rajab W. Effectiveness of mass media campaigns for reducing drinking and driving and alcohol-involved crashes: A systematic review. *American Journal of Preventive Medicine* 2004; 27(1):57-65.
- (171) De Bruijn CAR, van den Brink WIM, de Graff RON, Vollebergh WAM. Alcohol abuse and dependence criteria as predictors as a chronic course of alcohol use disorders in the general population. *Alcohol and Alcoholism* 2005; 40(5):441-446.
- (172) Klingemann H, Sobell MB, Sobell LC. Continuities and changes in self-change research. *Addiction* 2010; 105(9):1510-1518.
- (173) Dackis CA, O'Brien CP. Cocaine dependence: a disease of the brain's reward centers. *Journal of Substance Abuse Treatment* 2001; 21(3):111-117.
- (174) Morie KP, Garavan H, Bell RP, De Sanctis P, Krakowski MI, Foxe JJ. Intact inhibitory control processes in abstinent drug abusers (II): A high-density electrical mapping study in former cocaine and heroin addicts. *Neuropharmacology* 2013;(0).
- (175) Bechara A. Decision making, impulse control and loss of willpower to resist drugs: a neurocognitive perspective. *Nat Neurosci* 2005; 8(11):1458-1463.
- (176) Goldstein RZ, Volkow ND. Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. *Nat Rev Neurosci* 2011; 12(11):652-669.
- (177) Koob GF, Volkow ND. Neurocircuitry of addiction. *Neuropsychopharmacology* 2010; 35(1):217-238.
- (178) Verdejo-Garcia A, Bechara A. A somatic marker theory of addiction. *Neuropharmacology* 2009; 56 Suppl 1:48-62.
- (179) Braus DF, Wrase J, Grusser S, Hermann D, Ruf M, Flor H et al. Alcohol-associated stimuli activate the ventral striatum in abstinent alcoholics. *J Neural Transm* 2001; 108(7):887-894.



- (180) Grusser S, Wrase J, Klein S, Hermann D, Smolka M, Ruf M et al. Cue-induced activation of the striatum and medial prefrontal cortex is associated with subsequent relapse in abstinent alcoholics. *Psychopharmacology* 2004; 175(3):296-302.
- (181) Prisciandaro JJ, Myrick H, Henderson S, McRae-Clark AL, Santa Ana EJ, Saladin ME et al. Impact of DCS-facilitated cue exposure therapy on brain activation to cocaine cues in cocaine dependence. *Drug and Alcohol Dependence* 2013; 132(12):195-201.
- (182) Janes AC, Pizzagalli DA, Richardt S, Frederick Bd, Chuzi S, Pachas G et al. Brain Reactivity to Smoking Cues Prior to Smoking Cessation Predicts Ability to Maintain Tobacco Abstinence. *Biological psychiatry* 2010; 67(8):722-729.
- (183) Beck A, Wustenberg T, Genauck A. Effect of brain structure, brain function, and brain connectivity on relapse in alcohol-dependent patients. *Archives of General Psychiatry* 2012; 69(8):842-852.
- (184) Worhunsky PD, Stevens MC, Carroll KM, Rounsaville BJ, Calhoun VD, Pearlson GD et al. Functional brain networks associated with cognitive control, cocaine dependence, and treatment outcome. *Psychol Addict Behav* 2013; 27(2):477-488.
- (185) Moeller FG, Hasan KM, Steinberg JL, Kramer LA, Dougherty DM, Santos RM et al. Reduced Anterior Corpus Callosum White Matter Integrity is Related to Increased Impulsivity and Reduced Discriminability in Cocaine-Dependent Subjects: Diffusion Tensor Imaging. *Neuropsychopharmacology* 2004; 30(3):610-617.
- (186) Schacht JP, Anton RF, Myrick H. Functional neuroimaging studies of alcohol cue reactivity: a quantitative meta-analysis and systematic review. *Addiction biology* 2013; 18(1):121-133.
- (187) Engelmann JM, Versace F, Robinson JD, Minnix JA, Lam CY, Cui Y et al. Neural substrates of smoking cue reactivity: a meta-analysis of fMRI studies. *Neuroimage* 2012; 60(1):252-262.
- (188) Zhang XL, Shi J, Zhao LY, Sun LL, Wang J, Wang GB et al. Effects of stress on decision-making deficits in formerly heroin-dependent patients after different durations of abstinence. *Am J Psychiatry* 2011; 168(6):610-616.
- (189) Connolly CG, Foxe JJ, Nierenberg J, Shpaner M, Garavan H. The neurobiology of cognitive control in successful cocaine abstinence. *Drug and Alcohol Dependence* 2012; 121(12):45-53.
- (190) Nestor L, McCabe E, Jones J, Clancy L, Garavan H. Differences in bottom-up and top-down neural activity in current and former cigarette smokers: Evidence for neural substrates which may promote nicotine abstinence through increased cognitive control. *NeuroImage* 2011; 56(4):2258-2275.
- (191) Garavan H, Weierstall K. The neurobiology of reward and cognitive control systems and their role in incentivizing health behavior. *Prev Med* 2012; 55 Suppl:S17-S23.
- (192) Prisciandaro JJ, Myrick H, Henderson S, McRae-Clark AL, Brady KT. Prospective associations between brain activation to cocaine and no-go cues and cocaine relapse. *Drug and Alcohol Dependence* 2013; 131(12):44-49.
- (193) Yoon JH, Newton TF, Haile CN, Bordnick PS, Fintzy RE, Culbertson C et al. Effects of D-cycloserine on cue-induced craving and cigarette smoking among concurrent cocaine- and nicotine-dependent volunteers. *Addictive behaviors* 2013; 38(2):1518-1526.
- (194) Watson BJ, Wilson S, Griffin L, Kalk NJ, Taylor LG, Munafo MR et al. A pilot study of the effectiveness of d-cycloserine during cue-exposure therapy in abstinent alcohol-dependent subjects. *Psychopharmacology* 2011; 216(1):121-129.



- (195) Everitt BJ, Robbins TW. Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nat Neurosci* 2005; 8(11):1481-1489.
- (196) Agrawal A, Lynskey MT. Are there genetic influences on addiction: evidence from family, adoption and twin studies. *Addiction* 2008; 103(7):1069-1081.
- (197) Heath AC. Persist or quit? Testing for a genetic contribution to smoking persistence. *Acta Genet Med Gemellol (Roma)* 1990; 39(4):447-458.
- (198) Heath AC, Martin NG. Genetic models for the natural history of smoking: evidence for a genetic influence on smoking persistence. *Addictive behaviors* 1993; 18(1):19-34.
- (199) Madden PA, Heath AC, Pedersen NL, Kaprio J, Koskenvuo MJ, Martin NG. The genetics of smoking persistence in men and women: a multicultural study. *Behav Genet* 1999; 29(6):423-431.
- (200) Madden PA, Pedersen NL, Kaprio J, Koskenvuo MJ, Martin NG. The epidemiology and genetics of smoking initiation and persistence: crosscultural comparisons of twin study results. *Twin Res* 2004; 7(1):82-97.
- (201) Xian H, Scherrer JF, Madden PA, Lyons MJ, Tsuang M, True WR et al. Latent class typology of nicotine withdrawal: genetic contributions and association with failed smoking cessation and psychiatric disorders. *Psychol Med* 2005; 35(3):409-419.
- (202) Pergadia ML, Heath AC, Martin NG, Madden PAF. Genetic analyses of DSM-IV nicotine withdrawal in adult twins. *Psychological Medicine* 2006; 36(07):963-972.
- (203) Nader MA, Morgan D, Gage HD, Nader SH, Calhoun TL, Buchheimer N et al. PET imaging of dopamine D2 receptors during chronic cocaine self-administration in monkeys. *Nat Neurosci* 2006; 9(8):1050-1056.
- (204) Gould R, Porrino L, Nader M. Nonhuman Primate Models of Addiction and PET Imaging: Dopamine System Dysregulation. In: Carter CS, Dalley JW, editors. *Brain Imaging in Behavioral Neuroscience*. 11 ed. Springer Berlin Heidelberg; 2012. 25-44.
- (205) Ersche KD, Turton AJ, Pradhan S, Bullmore ET, Robbins TW. Drug addiction endophenotypes: impulsive versus sensation-seeking personality traits. *Biological psychiatry* 2010; 68(8):770-773.
- (206) Heinz A, Siessmeier T, Wrase J, Buchholz HG, Grunder G, Kumakura Y et al. Correlation of alcohol craving with striatal dopamine synthesis capacity and D2/3 receptor availability: a combined [18F]DOPA and [18F]DMFP PET study in detoxified alcoholic patients. *Am J Psychiatry* 2005; 162(8):1515-1520.
- (207) Martinez D, Gil R, Slifstein M, Hwang DR, Huang Y, Perez A et al. Alcohol Dependence Is Associated with Blunted Dopamine Transmission in the Ventral Striatum. *Biological psychiatry* 2005; 58(10):779-786.
- (208) Martinez D, Slifstein M, Narendran R, Foltin RW, Broft A, Hwang DR et al. Dopamine D1 Receptors in Cocaine Dependence Measured with PET and the Choice to Self-Administer Cocaine. *Neuropsychopharmacology* 2009; 34(7):1774-1782.
- (209) Gorwood P, Le Strat Y, Ramoz N, Dubertret C, Moalic JM, Simonneau M. Genetics of dopamine receptors and drug addiction. *Human genetics* 2012; 131(6):803-822.
- (210) Schmidt LG, Sander T. Genetics of alcohol withdrawal. *European Psychiatry* 2000; 15(2):135-139.



- (211) Gorwood P. L'addiction génétique-à: l'alcool-dépendance et le gène récepteur dopaminergique D3. *Pathologie Biologie* 2001; 49(9):710-717.
- (212) Schmaal L, Veltman DJ, Nederveen A, van den Brink W, Goudriaan AE. N-acetylcysteine normalizes glutamate levels in cocaine-dependent patients: a randomized crossover magnetic resonance spectroscopy study. *Neuropsychopharmacology* 2012; 37(9):2143-2152.
- (213) Lee E, Jang DP, Kim JJ, An SK, Park S, Kim IY et al. Alteration of brain metabolites in young alcoholics without structural changes. *Neuroreport* 2007; 18(14):1511-1514.
- (214) Miese F, Kircheis G, Wittsack HJ, Wenserski F, Hemker J, Madder U et al. 1H-MR Spectroscopy, Magnetization Transfer, and Diffusion-Weighted Imaging in Alcoholic and Nonalcoholic Patients with Cirrhosis with Hepatic Encephalopathy. *American Journal of Neuroradiology* 2006; 27(5):1019-1026.
- (215) Heilig M, Egli M, Crabbe JC, Becker HC. Acute withdrawal, protracted abstinence and negative affect in alcoholism: are they linked? *Addiction biology* 2010; 15(2):169-184.
- (216) Fadda F, Rossetti ZL. Chronic ethanol consumption: from neuroadaptation to neurodegeneration. *Progress in Neurobiology* 1998; 56(4):385-431.
- (217) Breese G, Overstreet D, Knapp D. Conceptual framework for the etiology of alcoholism: a kindling/stress hypothesis. *Psychopharmacology* 2005; 178(4):367-380.
- (218) Tsai G, Coyle JT. The role of glutamatergic neurotransmission in the pathophysiology of alcoholism. *Annu Rev Med* 1998; 49:173-184.
- (219) Guo Y, Wang HL, Xiang XH, Zhao Y. The role of glutamate and its receptors in mesocorticolimbic dopaminergic regions in opioid addiction. *Neuroscience & Biobehavioral Reviews* 2009; 33(6):864-873.
- (220) Boettiger CA, Kelley EA, Mitchell JM, D'Esposito M, Fields HL. Now or Later? An fMRI study of the effects of endogenous opioid blockade on a decision-making network. *Pharmacology Biochemistry and Behavior* 2009; 93(3):291-299.
- (221) Olmstead MC, Ouagazzal AM, Kieffer BL. Mu and delta opioid receptors oppositely regulate motor impulsivity in the signaled nose poke task. *PLoS One* 2009; 4(2):e4410.
- (222) Ghitza UE, Preston KL, Epstein DH, Kuwabara H, Endres CJ, Bencherif B et al. Brain Mu-Opioid Receptor Binding Predicts Treatment Outcome in Cocaine-Abusing Outpatients. *Biological psychiatry* 2010; 68(8):697-703.
- (223) Williams TM, Daghlish MR, Lingford-Hughes A, Taylor LG, Hammers A, Brooks DJ et al. Brain opioid receptor binding in early abstinence from opioid dependence: positron emission tomography study. *Br J Psychiatry* 2007; 191:63-69.
- (224) Williams TM, Davies SJC, Taylor LG, Daghlish MRC, Hammers A, Brooks DJ et al. Brain opioid receptor binding in early abstinence from alcohol dependence and relationship to craving: An [11C]diprenorphine PET study. *European Neuropsychopharmacology* 2009; 19(10):740-748.
- (225) Zubieta JK, Gorelick DA, Stauffer R, Ravert HT, Dannals RF, Frost JJ. Increased mu opioid receptor binding detected by PET in cocaine-dependent men is associated with cocaine craving. *Nat Med* 1996; 2(11):1225-1229.
- (226) Winick C. Maturing out of narcotic addiction. *Bulletin on Narcotics* 1962; 14:1-7.
- (227) Heyman GM. Quitting Drugs: Quantitative and Qualitative Features. *Annu Rev Clin Psychol* 2013; 9(1):29-59.



- (228) Kerr WC, Greenfield TK, Bond J, Ye Y, Rehm J. Age, period, cohort modelling of alcohol volume and heavy drinking days in the US National Alcohol Surveys: divergence in younger and older adult trends. *Addiction* 2009; 104(1):27-37.
- (229) Meng Y, Holmes J, Hill-McManus D, Brennan A, Meier PS. Trend analysis and modelling of gender-specific age, period and birth cohort effects on alcohol abstinence and consumption level for drinkers in Great Britain using the General Lifestyle Survey 1984-2009. *Addiction* 2013.
- (230) Room R. Drinking and coming of age in a cross-cultural perspective. In: Bonnie RJ, O'Connor ME, editors. *Reducing underage drinking: A Collective Responsibility*. Washington D. C.: National Academy Press; 2004. 654-677.
- (231) Moffitt TE. Adolescence-limited and life-course-persistent antisocial behavior: a developmental taxonomy. *Psychol Rev* 1993; 100(4):674-701.
- (232) Pabst A, Kraus L, Piontek D, Muller S. Age, period, and cohort effects on time trends in alcohol consumption in the German adult population. *Sucht* 56, 349-359. 2010.
- (233) O'Malley PM. Maturing out of problematic alcohol use. *Alcohol Research and Health* 2005; 28(4):202-204.
- (234) Cunningham JA, Hodgins DC, Toneatto T. Natural history of gambling problems: Results from a general population survey. *Journal of Addiction Research and Practice* 2009; 55(2):98-103.
- (235) Littlefield AK, Sher KJ, Wood PK. Is "maturing out" of problematic alcohol involvement related to personality change? *J Abnorm Psychol* 2009; 118(2):360-374.
- (236) Littlefield AK, Sher KJ, Wood PK. A personality-based description of maturing out of alcohol problems: extension with a five-factor model and robustness to modeling challenges. *Addict Behav* 2010; 35(11):948-954.
- (237) Littlefield AK, Sher KJ, Wood PK. Do changes in drinking motives mediate the relation between personality change and "maturing out" of problem drinking? *J Abnorm Psychol* 2010; 119(1):93-105.
- (238) Casey BJ, Jones RM. Neurobiology of the Adolescent Brain and Behavior: Implications for Substance Use Disorders. *Journal of the American Academy of Child & Adolescent Psychiatry* 2010; 49(12):1189-1201.
- (239) Somerville LH, Jones RM, Ruberry EJ, Dyke JP, Glover G, Casey BJ. The Medial Prefrontal Cortex and the Emergence of Self-Conscious Emotion in Adolescence. *Psychological science* 2013; 24(8):1554-1562.
- (240) Rhodes T, Singer M, Bourgois P, Friedman SR, Strathdee SA. The social structural production of HIV risk among injecting drug users. *Social Science & Medicine* 2005; 61(5):1026-1044.
- (241) Rhodes T. Risk environments and drug harms: A social science for harm reduction approach. *International Journal of Drug Policy* 2009; 20(3):193-201.
- (242) Bronfenbrenner U, Morris PA. *The Bioecological Model of Human Development*. Handbook of Child Psychology. John Wiley & Sons, Inc.; 2007.