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DIAGNOSIS OF ADDICTIONS

*Marc Auriacombe, Fuschia Serre, Cécile Denis,
and Méлина Fatséas*

What is addiction? Core and constellation: a clarification challenge

Both substances and behaviors can be considered to be forms of addictions, understood as an abnormal long-lasting pattern of use or practice that is reinforcing and may be repeated to excess, to the point that it endangers the individual. This excess of use or practice is typically visible to an observer, but, equally, users themselves may also report it as disturbing. The dangerous consequences may sometimes spread from the individual to his environment, making addiction an individual characteristic (a disease or disorder), with environmental and social consequences (public health impact, political and societal implications).

Although excess is a common characteristic of addictions, its definition is difficult. Excess may be defined by use over a pre-determined threshold that may be defined by quantity or frequency. Excess may also be defined by any quantity/frequency as long as it has negative consequences, acute or chronic. Nevertheless, substances that are commonly taken to excess have been shown to directly activate the brain reward system, which is involved in the reinforcement of behaviors and the production of memories (Volkow *et al.* 2016). Similarly, behaviors that are practiced to excess have been shown to activate most of the same reward pathways activated by substances (Noori *et al.* 2016). The pharmacological mechanisms by which each class of substances activates the reward pathways are different, but a common outcome is the production of pleasure (an experience that motivates repetition). This is also reported for behaviors that can be practiced to excess. Although the pleasure produced by most of the substances is more intense and reliable than that produced by behaviors, inter-individual variability is important to recognize. Gambling and gaming, physical exercise, sex, and use of the Internet are all examples of behaviors for which the activation of the reward system has been documented and for which there are reports of a pleasurable effect. It is an open question whether excessive food consumption is more like a substance addiction or a behavioral addiction (Gearhardt *et al.* in this volume).

Loss of control over substance use or practice is considered to be the core of addiction, which must be differentiated from the surrounding constellation of preexisting risk factors and consequences, whether toxicological, physical or environmental. Once settled all these characteristics coexist making distinguishing them difficult (Figure 11.1). Loss of control is typically expressed through observer or subject reports of excessive use or behavior. This is a major dilemma for addiction modeling and research as excessive use or behavior is not easy to define.

A core ... and a constellation

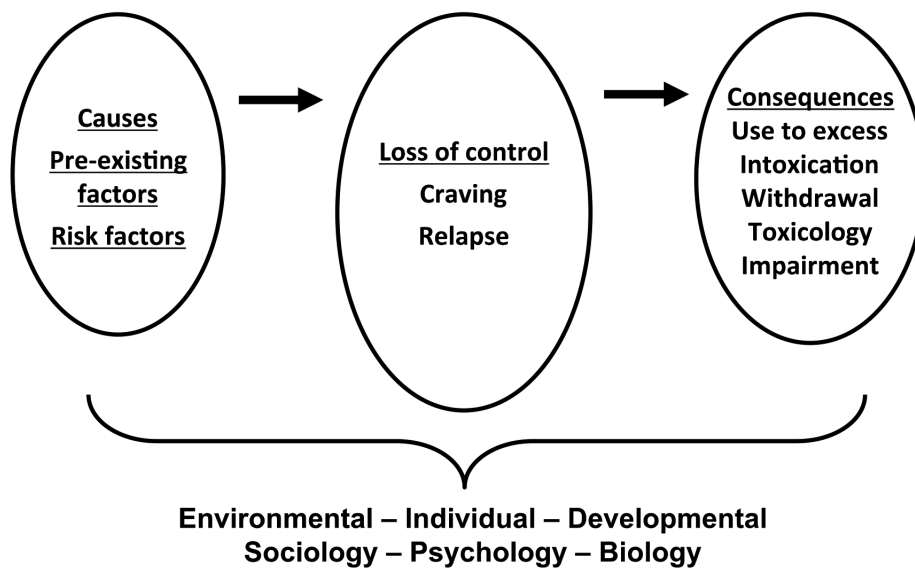


Figure 11.1 A model for addiction diagnosis criteria.

Note: Core criteria of addiction and surrounding constellation of signs and symptoms consequential to addiction need to be better assessed and controlled. The challenge is to tease apart core criteria of addiction from preexisting risk factors or individual causal characteristics as well as the consequences of addiction per se. When assessing individuals with addiction, expression of core and constellation symptoms may be mixed at any given time. Statistically, all these signs and symptoms aggregate together (Auriacombe *et al.*, 2016b, Fatséas *et al.*, 2015b, Serre *et al.*, 2015).

If defined as use over a pre-determined threshold, how do we determine the threshold? And if defined as use with consequences, how do we differentiate loss of control of use or behavior from any use in a toxic range? The dilemma is that any use, excessive or not, has consequences that are independent of the how and the why of use (i.e., independent of addiction). Be that as it may, excessive use or behavior nonetheless has short-, medium- and long-term toxicological consequences for the brain and many body parts, as well as social consequences, both direct and indirect (brain-induced social impairment). If excessive use is common in addiction, it is not enough by itself to characterize addiction, as excessive use may simply reflect a voluntary pattern of use or behavior among individuals without addiction. Most models of addiction, animal and human, have failed to introduce an appropriate distinction between addiction and its consequences. In other words, addiction is not sufficiently defined by use or behavior with consequences. Moreover, the diagnostic criteria that are driven by population-based epidemiological studies cannot make the needed distinction between causes and consequences, because these necessarily aggregate statistically.

Another important characteristic, and potential controversy, surrounding the question of what is addiction, is that it is a fairly stable condition: it persists beyond detoxification and substance/behavior abstinence. This is expressed in the repeated relapses and intense cravings that may occur when individuals with addictions attempt to control excessive use through abstinence. This craving, defined as a repeated unwanted intrusive psychological state that is characterized by an intense and compulsive desire to use a substance or to engage in hedonic

behaviors, might be the core of addiction (see the section that begins on page 137 of this chapter). Contrary to withdrawal and tolerance that reverse rapidly, craving persists years after substance or behavior discontinuation and is highly predictive of relapse. From this perspective, addiction may be considered as a chronic disease, and may benefit from long-term approaches to treatment, in line with other areas of health (McLellan *et al.* 2000).

What are the diagnostic criteria?

The *Diagnostic and Statistical Manual of Mental Disorders* (DSM) and the *International Statistical Classification of Diseases and Related Health Problems* (ICD) have approached mental disorders as largely discrete entities that are characterized by distinctive signs, symptoms, and natural histories. Addiction diagnosis was included in the DSM and the Mental Disorders section of ICD at its implementation. Since the mid-1980s the DSM and ICD have brought considerable diagnostic reliability (Kraemer 2014). Properly assessed using the DSM (which in this respect is in advance of the ICD (Hasin *et al.* 2013)), addictions have high inter-rater reliabilities (Lobbestael *et al.* 2011), and are internally coherent and valid statistically (Kraemer *et al.* 2012; Nelson *et al.* 1999). However, no reliable biological markers have emerged yet from this approach, to the disappointment of many who consider important the progress of knowledge in neurosciences in general and very specifically in the addiction area (Kwako *et al.* 2016; Noori *et al.* 2016; Volkow *et al.* 2016). Some have considered this a flaw in the DSM and ICD process, which relies too much on epidemiology and statistics in its approach and does not take sufficiently into account biological knowledge in neurosciences, genetics and imaging. In response, in 2009, the Research Domain Criteria (RDoC) initiative was launched by the NIMH. Its objective was to ground mental disorders in biology by going from knowledge of neurocircuitry activity up to meaningful clinical entities (Lilienfeld and Treadway 2016). The DSM/ICD and RDoC approaches have been considered to be opposed to one another. The DSM/ICD is considered too categorical, making too many distinctions among mental disorders; and the RDoC too dimensional in its perspective, leading to confusion between biological continuity and behavioral and emotional expressions. However, to date, the RDoC approach has yet to make good on its promises. Further, categorical and dimensional perspectives do not need to be opposed, indeed both aspects are needed to characterize disorders from the perspective of interventions, whether these are in the form of prevention or treatment (Kraemer 2015), as some degree of dimensionality is needed for outcome monitoring. Recently, Kwako and colleagues have suggested a neuroscience-based framework for diagnosis of addictive disorders (Kwako *et al.* 2016). Nonetheless, at this time, the DSM approach is the most prevalent state-of-the-art diagnostic system for the addictions.

Current state of the art: a focus on the recent edition of the DSM-5 diagnostic criteria

Diagnosis of addiction is based on a set of criteria established by an international and multidisciplinary team of experts who consider the latest advances in research and clinical knowledge (American Psychiatric Association 2013). The DSM-5 has lumped substance-use disorders and gambling disorder into one new diagnostic category based on the many commonalities they share; and has made suggestions for a possible internet gaming disorder to be studied for inclusion in future revisions (Hasin *et al.* 2013; Petry *et al.* 2014a; Petry *et al.* 2014b; Denis *et al.* 2012a). A new eating behavior has been characterized that very much overlaps with addictions, “Binge Eating Disorder”, although it has been placed in the Eating Disorders chapter and not, in

contrast with Gambling, in the Substance-related and Addictive Disorders chapter. This opens the door for food addiction and other non-substance addictions to be included as disorders in future editions of the DSM.

Features of the DSM diagnostic criteria: core and constellation

The essential feature of the DSM Substance Use Disorder is a cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues using despite significant substance-related problems. The diagnosis of a Substance Use Disorder can be applied to any reinforcing substance that may be used to excess. For certain substances, some criteria are less salient, and in a few instances may not apply. These set of criteria have also been thought to apply to reinforcing behaviors such as food, sex, gambling and gaming. As noted above, in DSM-5, of these only gambling is treated as an addictive-type disorder, retained from earlier editions with a modified set of criteria.

Overall, the diagnosis of a Substance Use Disorder is based on a pathological pattern of behaviors related to use of the substance. Criteria can be considered to fit within four groupings that correspond to impaired control, social impairment, risky use, and pharmacological adaptation. We argue that the first grouping describes the core of addiction, while the other three groupings are a constellation of pre-existing risk factors and consequences.

Core criteria of addiction

IMPAIRED CONTROL OVER SUBSTANCE USE (CRITERIA 1-4)

The individual may take the substance in larger amounts or over a longer period than was originally intended (Criterion 1). The individual may express a persistent desire to cut down or regulate substance use and may report multiple unsuccessful efforts to decrease or discontinue use (Criterion 2). The individual may spend a great deal of time obtaining the substance, using the substance, or recovering from its effects (Criterion 3). In some instances of more severe Substance Use Disorders, virtually all of the person's daily activities revolve around the substance. Craving (Criterion 4) is manifested by an intense desire or urge for use which may occur at any time.

Pre-existing risk factors and consequences

SOCIAL IMPAIRMENT (CRITERIA 5-7)

Recurrent substance use may result in a failure to fulfill major role obligations at work, school, or home (Criterion 5). The individual may continue substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (Criterion 6). Important social, occupational, or recreational activities may be given up or reduced because of substance use (Criterion 7). The individual may withdraw from family activities and hobbies in order to use the substance.

RISKY USE OF THE SUBSTANCE (CRITERIA 8-9)

This may take the form of recurrent substance use in situations in which it is physically hazardous (Criterion 8). The individual may continue substance use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or

exacerbated by the substance (Criterion 9). The key issue in evaluating this criterion is not the existence of the problem, but rather the individual's failure to abstain from using the substance despite knowledge or evidence of the difficulty it is causing.

PHARMACOLOGICAL ADAPTATION (CRITERIA 10-11)

Tolerance (Criterion 10) is signalled by requiring a markedly increased dose of the substance to achieve the desired effect or a markedly reduced effect when the usual dose is consumed. Tolerance must be distinguished from individual variability in the initial sensitivity to the effects of particular substances. Withdrawal (Criterion 11) is a syndrome that occurs when blood or tissue concentrations of a substance decline in an individual who had maintained prolonged heavy use of the substance. After developing withdrawal symptoms, the individual is likely to consume the substance to relieve the symptoms if they have the opportunity. Withdrawal symptoms vary greatly across the classes of substances. Neither tolerance nor withdrawal is necessary for a diagnosis of a Substance Use Disorder. Furthermore, symptoms of tolerance and withdrawal occurring during appropriate medical treatment with prescribed medications (e.g., opioid analgesics, sedatives, stimulants, etc.) are specifically not counted when diagnosing a Substance Use Disorder. The appearance of normal, expected pharmacological tolerance and withdrawal during the course of medical treatment has been known to lead to an erroneous diagnosis of "addiction" even when these were the only symptoms present. Persons whose only symptoms are those that occur as a result of medical treatment (i.e., tolerance and withdrawal as part of medical care) do not qualify for the diagnosis of a Substance Use Disorder.

Diagnostic criteria change overtime. Example of changes introduced by the DSM-5

Changes in the concept of addiction have led to the evolution of its definition and its diagnostic criteria, as reflected by the successive and revised editions of the DSM since its first publication in 1952. The last edition was published in May 2013, nearly 20 years after the previous edition, the DSM-IV, published in 1994.

A major change of the last edition was the introduction of a dimensional approach: individuals exhibit a more or less severe addiction depending on number of criteria met. This dimensional perspective is a change from the previous purely categorical approach, and the DSM-5 diagnosis of Substance Use Disorder combines the DSM-IV criteria for substance abuse and for substance dependence. Indeed, item response theory (IRT) analysis conducted in many studies, of more than 200,000 subjects in total, revealed the uni-dimensionality of all DSM-IV criteria for abuse and dependence, except for one, namely, legal problems (Hasin *et al.* 2013).

In addition to the introduction of a dimensional perspective, the revision process between DSM-IV and 5 also considered whether some criteria could be dropped. The legal problems criterion was removed, based on its low prevalence and its low discrimination power in IRT analysis. This criterion was also dependent on the legislation, and therefore introduced variability of diagnosis by country.

Gambling disorder, previously integrated as pathological gambling in the DSM-IV section of Impulse-Control Disorders, is now joined to substance use disorders in the DSM-5 diagnostic category of Substance-Related and Addictive Disorders. This evolution reflects the frequent comorbidity between gambling disorder and substance use disorders (Grant and Chamberlain 2015), and their many behavioral and biological similarities (Petry *et al.* 2014a; Bosc *et al.* 2012; Rennert *et al.* 2014). The criterion "illegal acts" was removed for the same reasons that legal

problems were removed from substance use disorders; and the diagnostic threshold was reduced from five to four or more criteria to improve classification accuracy. The possibility of using criteria for substance use disorders to assess gambling was shown to be feasible and reliable with the DSM-IV dependence criteria (Denis *et al.* 2012a). Future work should explore if gambling disorder might be assessed using the same criteria as those used for Substance Use Disorders in DSM-5, which include a specific focus on craving.

This is indeed a major revision between DSM-IV and 5, namely, the addition of a new criterion: craving. It should be acknowledged that this criterion was implicated by the dependence criteria in ICD-10, although the word “craving” itself is not used (World Health Organization 1993). Although this new criterion does not seem to provide any additional information statistically, the IRT analysis revealed that it fits well with the other criteria and does not perturb their factor loadings, severity and discrimination. Support for adding craving comes from human research studies (Auriacombe *et al.* 2016b; Hasin *et al.* 2013; Sayette 2016; Serre *et al.* 2015).

The core of addiction: is craving the link between behavior, brain and environment?

Craving is often cited as intrinsically linked to relapse, making it an interesting and useful criterion for research and clinical purposes (Auriacombe *et al.* 2016b; Sayette 2016). However, how to define craving represents a challenge for patients, clinicians and researchers. In the addiction field, standard definitions of craving refer to an irrepressible and intense urge to use a substance or to perform a rewarding behavior. The distinction between craving and urge is then based on intensity. However, craving is often described by individuals as an unwanted experience – an unwanted urge to use. Many definitions of craving do not make explicit this involuntary aspect. More than the intensity of the urge, it is also that it occurs at an inappropriate moment (time/place) that contributes to the associated distress (Auriacombe *et al.* 2016b). This is an ego-dystonic experience, which causes distress and discomfort for those who experience it. A further challenge to defining craving is that when experiencing an unwanted craving, individuals may lack verbal means to adequately describe and communicate their distress. As a result, although clinicians and researchers have been interested in craving for a long time (Childress *et al.* 1986; O’Brien *et al.* 1998), it has not been fully investigated because of the difficulty of pinpointing the experience within clinical and research contexts. A final challenge is to distinguish craving from the acute phenomenon of withdrawal, both in its clinical expression and in the underlying pathophysiological mechanisms. For many years, craving has been listed among symptoms of withdrawal, even though it can occur long after withdrawal symptoms have abated.

The World Health Organization (WHO) emphasized in 1954 that the term “craving” was confusing and had the disadvantage of implying negative connotations in popular English usage (World Health Organization 1955). This is not a problem for other languages in which the term “craving” does not exist. As a consequence, the use of the word “craving” introduces a need for clarification and thus can serve to contribute to a better understanding of what is meant, requiring us to characterize craving as a unique experience of individuals with addiction, thereby facilitating individuals’ report of this experience. Unfortunately, WHO suggested avoiding the term “craving.” The term “pathological desire” was recommended instead for describing “symbolic craving” as opposed to a form of “physical craving” more related to withdrawal. This contributed to many misunderstandings about craving vis-à-vis withdrawal. On a conceptual level, the term “craving,” is sometimes defined as a subjective desire to feel the effects of the substance, and is differentiated from the term “urge,” which is characterized as a consequence of craving, and represents the intention to use (Marlatt 1987).

The lack of consensus and clarity on the definition of “craving” led to the development of a multitude of very heterogeneous measurement tools (Rosenberg 2009; Sayette *et al.* 2000). Many studies use a visual analogue scale, allowing a simple and rapid measurement of the intensity of craving. Other studies use multi-item tools to examine different dimensions of craving (Flannery *et al.* 1999). Difficulty in defining and measuring craving can be explained by the complexity of the phenomenon and its multidimensional aspect (Shadel *et al.* 2001). A recent meta-analysis (Noori *et al.* 2016) has suggested that cue-mediated craving involves mechanisms that are not exclusive for addictive disorders but rather resemble the intersection of information pathways for processing reward, emotional responses, non-declarative memory and obsessive-compulsive behavior. According to the theoretical models chosen, the concept of craving can integrate cognitive, affective, motivational or physiological components. Thus, tools have been developed to better capture some of these aspects.

From a prognostic perspective, craving could be the ideal candidate to predict relapse (Miller *et al.* 1996; Fatséas *et al.* 2011; Tiffany and Wray 2012). It is of great importance, both for research and clinical purposes, to discover a measurable criterion to identify risk of relapse. Craving is often reported as a conscious precipitating factor for relapse by individuals with addiction. Although it is generally accepted that craving is a core symptom of addiction, controversy still exists concerning its role in substance use and relapse. Many theoretical models of addiction place craving as the major motivational substrate of substance use and relapse during abstinence attempts (Baker *et al.* 1986; Ludwig *et al.* 1974; Marlatt and Gordon 1980; Robinson and Berridge 1993; Wise 1988), but some others suggest that craving is not necessarily involved in substance use (Baker *et al.* 2004; Tiffany 1990). Two recent systematic literature reviews have tried to distinguish the predictive value of craving in relapse, treatment outcomes, and substance use in general (Serre *et al.* 2015; Wray *et al.* 2013). The first review was restricted to tobacco studies and concluded that, although craving was frequently associated with relapse, this association was not systematic (Wray *et al.* 2013). The association between craving and relapse seemed to be highly dependent on the time of measurement of craving (post-quit craving more predictive than pre-quit craving) and the context in which craving was measured (cue-induced craving in the laboratory is weakly associated with relapse). The second review was restricted to studies evaluating the relationship between craving and substance use in ecological conditions of daily life, through the EMA (Ecological Momentary Assessment) method (Serre *et al.* 2015). This method uses smartphones to collect real-time data, several times a day, in the natural environment of study participants (Stone and Shiffman 1994). The EMA offers the possibility to study prospective links between events, integrating the influence of environmental factors. This systematic review collected studies concerning all substances, and concluded that craving was associated with substance use and relapse in 92% of studies. This finding was most pronounced when craving occurred shortly (minutes or hours) before substance use. In a recent study conducted in the context of daily life using the EMA method, the role of environmental stimuli in the induction of craving and relapse was examined among patients treated for addiction to a variety of substances (Fatséas *et al.* 2015b). The results of this study showed that the intensity of craving was a powerful predictor of substance use in the following hours. Furthermore, exposure to factors previously associated with use, and specific to each individual, were potent inducers of craving followed by relapse, within hours of exposure to these person-specific stimuli. These person-specific factors, such as places, contexts, and emotions are very specific to each individual, linked to personal history and provide stronger inducers of craving than more universal substance-specific cues.

Craving is also reported as an important symptom among individuals with gambling disorder, persisting months after gambling abstinence (Ladouceur *et al.* 2007) and a key determinant

of relapse in gambling disorder (Smith *et al.* 2015; Tavares *et al.* 2005). A recent study showed that craving ratings in participants with gambling disorder increased following gambling cues compared with non-gambling cues; that gambling cues in individuals with gambling disorder increased brain responses in reward-related circuitry; and that this response co-varied with craving intensity (Limbrick-Oldfield *et al.* 2017). Animal studies have suggested the addictive liability of sugar (Ahmed *et al.* 2013). Obese subjects with possible food addiction have been shown to report more severe food craving than their non-addicted counterparts (Davis *et al.* 2011; Meule and Kubler 2012; Fatséas *et al.* 2015a). Food craving has been suggested to contribute to unsuccessful attempts to reduce calorie intake, and early dropout from obesity treatment programs (Batra *et al.* 2013). A prospective link between the intensity of food craving and the decrease in dieting success and meeting other criteria for food addiction has been shown (Fatséas *et al.* 2015a; Meule *et al.* 2016).

These results support consideration of craving as a common and important criterion for all addictions. Hence, it is possible to hypothesize a simplified universal model for addiction, with craving as its specific marker (Figure 11.2).

From a treatment perspective, craving appears as a prime target for the treatment of addiction, both in psychotherapy and pharmacotherapy (Auriacombe *et al.* 2016a). Several medications aiming to reduce craving have been developed over the past 30 years (O'Brien 2005). These include naltrexone (O'Malley *et al.* 1992; Volpicelli *et al.* 1992) and acamprosate (Kranzler 2000; Mason 2001) for alcohol addiction, methadone and buprenorphine for opiate addiction (Fatséas *et al.* 2016; Auriacombe *et al.* 2003; Fareed *et al.* 2011) and nicotine patches for tobacco addiction (Shiffman and Ferguson 2008; Auriacombe *et al.* 2003). Many psychotherapeutic interventions target the management of craving. This is often done through identification of cues/triggers so as to avoid them and/or develop strategies to cope with them and thus reduce occurrences of craving. In case craving occurs a plan is anticipated to avoid use and relapse through distraction and/or getting external support or more cognitive-based interventions (Beck *et al.* 1993; Marlatt and Gordon 1985; Witkiewitz *et al.* 2013). Craving can also be useful as an indicator of treatment efficacy, and evolution of craving during treatment could be used by therapists as a marker of the impact of the implemented treatment, whether psychotherapy or pharmacotherapy (Tiffany *et al.* 2012).



Figure 11.2 A simplified universal model for addiction diagnosis, inclusive of substance and behavioral addictions.

Note: Based on human research documenting that the intensity of craving is a powerful predictor of substance use and behavior practices, it is possible to suggest a simplified model with craving as the specific mediator to use. Furthermore, exposure to factors previously associated with use, and specific to each individual, are potent inducers of craving in the hours following exposure to these stimuli. These person-specific factors, such as places, contexts, and emotions, are unique to each individual, linked to personal history, and are stronger inducers of craving than more generic cues (Auriacombe *et al.*, 2016b, Fatséas *et al.*, 2015b, Serre *et al.*, 2015).

Broadening diagnosis to severity assessment and comprehensive treatment planning

Besides measuring the severity of addiction by counting the number of endorsed DSM-5 criteria (Hasin *et al.* 2013), a more comprehensive evaluation of the disorder and its consequences are needed for clinicians and therapists. Several tools have been developed for that purpose over the past 30 years. Among them, the most widely used instrument to assess the severity of addiction in different settings and among different populations is the Addiction Severity Index (ASI) (Cacciola *et al.* 2011; McLellan *et al.* 2006). Introduced in 1980, it has since been translated into many languages (McLellan *et al.* 1980). The ASI aims to assess impairments that commonly occur in individuals with addictions and to help clinicians design better comprehensive and integrated treatments (McLellan *et al.* 2006). Although the initial ASI focused on alcohol and drugs, it was modified (mASI) by adding specific items to systematically gather data on tobacco use, gambling, eating disorders and other putative non-substance addictions (Auriacombe *et al.* 2004). The ASI and mASI produce relevant, reliable and valid data for both clinical and research evaluation (Makela 2004; Denis *et al.* 2016; Denis *et al.* 2012b). For instance, higher ASI scores have been shown to be concordant with substance use disorder diagnoses and gambling disorder; they also reasonably approximate DSM dependence diagnosis (Denis *et al.* 2016; Rikoon *et al.* 2006). The ASI interview is not designed as a self-standing diagnostic tool, but for use with individuals who have been antecedently screened and determined to have an addictive disorder. The standardized properties of the mASI permit a comprehensive and systematic assessment of all addictions independently of individuals' perceived problems and treatment settings, hence facilitating better-personalized treatment planning. The mASI may be helpful for clinicians to design the best treatment plans for a patient; for policy makers to objectively understand the needs of patients in treatment; and for care centers, other institutions, and also researchers to measure progress and outcomes in addiction treatment. For research purposes, the use of a unique non-substance-specific instrument allows researchers to better address the similarities and differences between addictions by avoiding potential confusion due to a multiplication of tools. In addition, a multifactorial assessment tool allows research to control for the impact of co-addictive disorders on treatment progress and outcome of another addictive disorder.

Looking to the future. What to anticipate for DSM6+ and ICD12+?

The most important challenge for the future of addiction diagnosis is arguably to clarify whether craving is or is not a reliable marker of addiction. This would require a clear and agreed definition of craving, e.g. as an unwanted phenomenon, to better determine how it can be distinguished from related phenomena such as urges and desires. There is also a need to better distinguish addiction from co-occurring mental disorders, and the latter from addiction-induced pseudo-mental disorders. This is a significant challenge, as mental disorders and addictive disorders both produce similar symptoms, such as anxiety, depression and thought distortion. In the case of addiction, these are consequences of intoxication, withdrawal and craving, whereas they may also be the direct expression of a mental disorder. In this respect, the current set of criteria would benefit from being organized according to what is a core expression of addiction (loss of control and craving) *versus* what is consequential or pre-existing and/or more of a severity measure.

The lumping together by DSM-5 of some non-substance addictions with the usual substance addictions should be further explored, no doubt cautiously but also with some focus and determination. If this is valid, behavioral addictions should be based on the same set of criteria as

those used for substance use disorders. This has already started to occur with respect to gambling and food addiction (Denis *et al.* 2012a; Gearhardt *et al.* 2009), with some success.

For diagnoses that are noted in the DSM Appendix because of lack of evidence at the time of the DSM-5 publication (i.e., caffeine use disorder, gaming use disorder) further studies might provide sufficient evidence for eventually including these diagnoses in the Substance-related and Addictive Disorder chapter.

In addition to further study of craving, the identification of reliable biomarkers is a valuable goal to pursue, notwithstanding the many disappointments and controversies to date. Neuroimaging data have allowed for a better understanding of the dimensions of cue-reactivity, impulsivity, and cognitive control, associated with mediators and moderators of treatment outcomes in addictive disorders. However, biomarkers of treatment response have yet to be identified to date (Garrison and Potenza 2014). The combination of the neuroimaging and the findings of genetic and epigenetic studies might identify both reproducible and predictable biomarkers of addictive disorders (Volkow *et al.* 2015) that eventually could be integrated in future classification of addictive disorder.

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