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Chemical and Behavioral Addictions

New Perspectives and Challenges

Kris Baetens, Falk Kiefer, Arnt Schellekens, and Geert Dom

Introduction

Substance use and substance use disorders (SUD) are highly prevalent and represent a significant burden for affected individuals and their families, as well as extremely high costs for society [1,2]. In 2016, substance use caused 2.1 million deaths in the WHO European Region, 48.6 million years lost living (YLL), and 57.9 million disability adjusted life years (DALYs) lost, representing 22.4%, 29.0%, and 20.4% of all deaths, YLL, and DALYs, respectively. The substance-attributable burden of disease was higher in men and in Eastern European countries. Of importance, changes in the number of deaths, YLL, and DALYs lost between 2010 and 2016 were almost uniformly downward, with the largest proportional changes observed for men. Exposure to tobacco, alcohol, and illicit drugs also decreased uniformly [1].

In recent years, the Section on Addictive Behaviors of the European Psychiatric Association (EPA) has touched upon many domains of current relevance in the field. In this chapter we highlight some topics of current and future importance for the development of this fast-growing field. Within the scope of a book chapter, it is impossible to give a comprehensive overview of all the research domains and developments in addiction research. Hence, we opted to highlight a limited selection, and our choice is mainly guided by those touched upon within the Section's activities.

Challenges in the Field

The Challenge of Epidemiologic Drug Trends in Europe

Typical for SUD, the prevalence rates depend (in part) on the availability of substances of abuse. Trends in this can change rapidly, particularly in the case of novel psychoactive substances. The wide variety of substances of abuse, with their different chemical, physical, and behavioral patterns, often create a challenge in terms of the clinical presentation of patients in emergency settings and treatment facilities.

On the side of the "legal" substances, alcohol and nicotine remain the main (in most countries legally available) substances of abuse. Alcohol is directly responsible for 5.3% of deaths and 5.1% of the burden of disease and injury globally [3]. Specifically, in both Western and Eastern European regions, population-level alcohol consumption remains very high, with subsequent detrimental consequences.

Drug use in Europe encompasses a wide range of substances. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) provides yearly data on trends and

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developments in the European Drug Report (www.emcdda.europa.eu/system/files/publica tions/13838/TDAT21001ENN.pdf). Despite interdiction efforts, all routine indicators suggest that at the beginning of 2020 the European drug market was characterized by the widespread availability of a diverse range of drugs of increasingly high purity or potency.

Cannabis is the most used drug (lifetime use in Europe: 27% of adults); the prevalence of use is about five times that of other substances. Importantly, cannabis use is an area of growing complexity, which is only likely to increase in the future. Partly because of developments outside of the European Union, more forms of cannabis are appearing and new ways of consuming are emerging. Within Europe, we also see increasing concerns about the availability of high-potency products on the one hand, and how to respond to low tetrahydrocannabiol (THC) products on the other. Synthetic cannabinoids, and the health risks they pose, further complicate this picture.

While the use of heroin and other opioids remains relatively rare, these continue to be the drugs most associated with the more harmful forms of use, including injecting and overdose mortality. Indeed, opioids were found in 76% of all fatal overdoses in Europe in 2020. The extent of stimulant use and the most common types vary across European countries, and evidence is growing of a potential increase. Lifetime adult use can be estimated to be 3% for amphetamines, 4.8% for cocaine, and 3.6% for MDMA. The number of high-risk heroin/ opioid users is estimated to be 0.36% (1 million users). There is growing concern around the misuse of benzodiazepines and the appearance of new benzodiazepines on the psychoactive substances market. At the end of 2020, the EMCDDA was monitoring around 830 new psychoactive substances, 46 of which were first reported in Europe in 2020. Synthetic cannabinoids and cathinones accounted for almost 60% of the number of seizures reported in 2019 in the EU Member States, with arylcyclohexylamines (largely ketamine) accounting for a further 10%. Synthetic cannabimimetics (CS) contained in so-called spice products are full agonist with a very high affinity for the CB1/CB2 receptors. In contrast, THC, the main psychoactive ingredient in natural cannabis, is a partial receptor agonist and its activity is moderated by other substances within the cannabis plant (e.g., cannabidiol [CBD] and cannabivarin [CBDV]). In addition, it is increasingly becoming clear that CS also interact with noncannabinoid receptor systems, such as serotonin, glutamate and acetylcholine [4]. Intoxication with spice-like products is associated with atypical and potentially serious symptoms, including hallucinations, agitation, cardiological (dysrhythmias, infarction), and neurological (seizures, stroke) effects [5]. Synthetic cathinones include more than 180 different molecules that show structural similarities with amphetamines, mostly being inhibitors of serotonin (SERT), dopamine (DAT), and noradrenaline (NET) transporters. A popular example is 3-Methylmethcathinone (3-MMC or metaphedrone) which is frequently used in the context of "chemsex" activities and, if injected, gives rise to fast development of addictive behavior. Importantly, 3-MMC is associated with hepatotoxicity and deaths [6].

Although these novel psychoactive substances (NPS) are not (yet) widely used, they can cause dangerous forms of abuse and present with atypical clinical symptoms of difficult detection, diagnosis, and treatment. Indeed, most routine laboratories are often not yet equipped to detect these substances, thereby adding to the risk of misdiagnoses and nondetection.

Finally, overall patterns of drug use are becoming more complex, with many people using more drugs (polysubstance users). This is creating various health concerns due to the use of more novel substances and the interaction of the effects when multiple substances are used in combination.

Overall, the drug scene is changing rapidly as regards the availability of substances and the development of new substances.

Behavioral Addictions: A New Challenge

Increasingly, behavioral addictions (i.e., gambling and internet gaming) are being recognized as an important public health problem, entailing significant suffering for affected individuals and their families [7]. The worldwide prevalence of problematic gaming, as defined by standard addiction criteria, is about 1–2% [8]. The introduction of behavioral addiction within the chapters on addiction of DSM-5 and ICD-11 has been gradual and is supported by the growing awareness that similar neurobiological characteristics underlie both chemical and nonchemical addictions [9,10]. In DSM-IV and earlier versions, "pathological gambling" was included in the section of Impulse-Control Disorders Not Elsewhere Classified [11]. From the DSM-5, gambling disorder (GD) is included in the section on addictive behaviors. Both DSM-5 ("Disorders in the Use of Substances") and ICD-11 include sections providing key definitions of both chemical and nonchemical (behavioral) addictions and related conditions. Internet gaming disorder (IGD) was considered as a potential mental disorder for the DSM-5, but the task force decided to list it only as a condition for further study. The DSM-5 criteria were consistent with substance use and addictive disorders, including reference to loss of control, tolerance, and withdrawal. Gaming disorder is now included in the ICD-11 among "disorders due to addictive behaviors" [12].

Public Health Challenges: Is Europe Following the US Opioid Epidemic?

In the slipstream of the (still ongoing) opioid epidemic in the United States, concerns have been raised as to whether this same trend is apparent in Europe. In a recent study on the evolution of prescription opioid use (PO) in 19 European countries in the period 2010–18, findings were relatively reassuring [13,14]. The authors concluded that, apart from the British Isles and especially Scotland, there is no indication of an opioid crisis comparable to that in the United States in the 19 European countries included in the study. This finding is in line with the EMCDDA data showing no clear increase in opioid-related overdose death, and findings of earlier surveys [15]. However, the situation in some countries, such as the United Kingdom, remains precarious, with very high rates of high-risk opioid use, opioid-related hospitalizations, and opioid-related deaths. Of importance, there is a substantial growth in Europe of the number of chronic (noncancer) pain patients. Although these populations differ substantially from substance-abusing populations, this trend needs careful monitoring for evolutions in PO use and possible misuse [16,17].

Conceptual Challenges

Within the field of addiction psychiatry, like many fields in psychiatry, conceptual challenges and discussions concerning both the validity of the disease models and the traditional outcome variables are a topic of debate [18].

Disease Model and Diagnosis

The core problems that characterize SUD are summarized in 11 symptom criteria on which the diagnosis is based in the DSM-5 and follow the same pattern across substances (and

nonchemical addictions): impaired control, social impairment, risky use, craving, and dependence. In addition, a severity continuity is defined within the DSM-5 differentiating between light, moderate, and severe in view of the number of symptoms that apply in each individual case. Though an improvement compared with earlier DSM versions, there are plenty of criticisms. One of the major issues is the broadness of the concept, defining even individuals with few symptoms as having a disorder in substance use, while other people with the same diagnosis have severe clinical symptoms, suggesting that different underlying psychopathological processes could exist. As such, the categorization in the ICD-11 between abuse and dependency might be closer to the clinical and pathogenic reality.

Defining Treatment Response

Despite evidence-based treatments, there remains a lack of consensus regarding the optimal measure to define treatment efficacy in addictions [19]. Definitions of outcome measures, such as abstinence and relapse, differ widely between studies [20]. Given the chronic relapsing character of many addictive processes, defining treatment efficacy solely on the achievement of a sustained period of abstinence may be overly restrictive. Within this context, measures of reduction in alcohol consumption have been recently accepted as valid outcome measures for alcohol use disorder (AUD) treatment [21]. Currently, there is no such acceptable reduction-based equivalent for other drugs of abuse, in part due to the lack of standard units for measuring dosing. Given that cannabis use is both highly prevalent and, in a growing number of countries, now legalized, the development of a standard unit cannabis (joint) is imperative, not only in view of studies on treatment outcome and reduction as a possible outcome, but also in view of developing public health measures and advices [22,23]. Overall, many challenges remain concerning the conceptualization of addiction as a disorder and the exploration of optimal outcome measures.

Legal Challenges: Legalization of Cannabis

A specific feature of the addiction field is that different types of drugs are continuously available and introduced to the market. As such, changes in legislation may have considerable impact on subsequent substance use problems with the population. In the last decade there have been significant changes in policies toward cannabis use. Currently, cannabis is widely used worldwide. There has been increasing legalization of cannabis and cannabis-derived products, and a commensurate increase in novel ways of consumption (i.e., edibles, pills, and vaping) [24–27]. Together with these novel routes of using, and new legislations, products with varying amounts of THC and CBD have become available on a large scale. Overall, these changes in both legislation and use patterns intensify the public perception of cannabis as safe, non-addictive, and increasingly socially acceptable. This contrasts with the accumulating evidence that long-term use of cannabis products with very high THC concentrations does impact life-quality, comorbid psychopathology (e.g., depression or psychosis), and neural and cognitive processes [28]. Of importance, recent US studies show that the use of highly potent cannabis products is more likely in states with recreational cannabis laws versus those without cannabis legislation, suggesting a clear effect of legal regulations on cannabis use patterns. Given these societal changes, understanding the effects of cannabis on the brain (and on psychopathologic processes), and how these alternate methods of use or different cannabinoids may affect the brain, is an important challenge for the field of addiction research [24].

Challenges Associated with the COVID-19 Pandemic

The COVID-19 pandemic has hit hard on individuals with SUD from many perspectives. First, on a prevalence level, accumulating data throughout the different waves indicate an increase in alcohol and illicit drug use within many (but not all) groups in the general population. Next, it is becoming increasingly evident that individuals with SUD are more likely to get infected with COVID-19 and, subsequently, to have a more detrimental course of the infection. Of importance, data suggest that fully vaccinated SUD individuals are at higher risk for breakthrough COVID-19 infection, and this is largely due to their higher prevalence of comorbidities and adverse socioeconomic determinants of health [29]. In addition, during lockdown facilities for restriction treatment, specifically for the most marginalized and vulnerable SUD patients, lacked continuity [30].

Important challenges remain to provide continuity of care during pandemic periods. In this respect, telehealth is increasingly documenting its efficacy in addiction treatment, and implementation of these modalities is steadily spreading [31].

Updates from Preclinical and Clinical Research

Neuroimmune Mechanisms and Microbiome

Early work using animal models highlighted the effects of drug exposure on mesolimbic dopamine transmission originating from the ventral tegmental area (VTA) and terminating in the corticolimbic structures (i.e., nucleus accumbens [NA]) [32]. More recent studies point to the role of other molecular pathways and cellular circuitries involved in the cycle of addiction [33]. Immune mechanisms have recently come into the picture in this context. Glial cells within the central nervous system and immune cells within the periphery are capable of modulating brain plasticity and behavior through complex interactions that may underlie substance abuse and relapse vulnerability [34,35]. Together, microglia and astrocytes orchestrate modulatory control over synaptic plasticity through immunomodulatory factors, such as cytokines. Cytokines have been shown to have a role in learning, memory, and synaptic plasticity [36]. Overall, a growing consensus indicates that inflammation is of importance in cognitive impairment following substance consumption and, as such, might provide alternative therapeutic avenues; a considerable increase in research efforts in this domain is urgently required [37]. This is in line with findings in other domains of psychiatry and evokes the question of whether these results help to differentiate between disorders or whether they suggest a common underlying pathogenic dimension making individuals vulnerable to developing multiple comorbidities [38].

Cognitive Neuroscience

Research into the cognitive drivers underlying addictive behaviors is growing exponentially and might provide new treatment targets and interventions. The dual process models that have been proposed to explain addictive behaviors suggest that the difficulty of controlling substance use behavior can be explained in part by an interplay of relatively automatic and controlled processes [39]. People with SUD, including those related to alcohol, stimulants, and opioids, have cognitive deficits of moderate magnitude and longevity. Meta-analytic research suggests that several cognitive processes are significantly impaired in users of different drugs, including selective attention and related attentional biases (automatic),

responses to drug-related stimuli, episodic memory, executive functions (working memory, inhibition, and shifting), and reward-based decision-making [40,41]. However, although these findings are consistent in differentiating SUD populations from healthy control groups, many questions and challenges remain. First, it needs to be explored whether these deficits vary and differentiate between different (clinical) types of SUD or whether they constitute a general vulnerability (or consequence) underlying all types of addictive behaviors and/or other psychiatric disorders that are often comorbid with SUD. In line with this, the question remains whether these deficits are associated with the severity of the substance use itself or with the substance-related problems [42]. Second, challenging work lies ahead in exploring the possibilities of "deep cognitive phenotyping" as a tool for better and more personalized treatment. Indeed, cognitive remediation treatment is high on the research agenda, but findings remain inconsistent [40]. Two broad cognitive domains are the main focus of research on cognitive remediation (and pharmacological) interventions: attentional bias processes and regulatory (executive) control. For the latter, different types of cognitive training/mediation interventions have been developed. A recent meta-analysis concluded that cognitive remediation, and specifically goal management training, may be an effective treatment for addressing impulsive choice in addiction. However, at this point the preliminary evidence does not support the use of computerized cognitive training or pharmacological enhancers to boost impulse control in addiction [43].

Among the interventions focused on changing attentional bias processes, cognitive bias modification (CBM) has been the most studied. Attentional bias represents a category of relatively automatic processes, namely heightened attentional capture of substance-relevant cues and/or increased difficulty in disengaging attention from these cues. Both components are suggested to contribute to increased salience of substance-related cues, thereby enhancing craving and subsequent risk for continued substance use and relapse [44]. Based upon these ideas, (computerized) CBM programs have been developed aimed at retraining these biases and reducing relapse rates. These programs have been offered both as stand-alone interventions and as add-ons to usual therapy. Although the original studies, mainly as add-on therapy in alcohol-dependent inpatients, showed promising results, later studies are inconsistent overall, with both positive and negative findings for long-term effectivity on substance use [44–47]. In addition, online formats of CBM might not be as effective, and neuromodulation does not seem to strengthen the training effect [48]. Clearly, future studies need to explore the underlying dynamics and working mechanisms of this paradigm – for example, delineating the role of engagement and disengagement bias in the persistence of addiction, and the role of a treatment goal in the effectiveness of attentional bias modification (ABM) interventions [39]. In addition, besides the need for a larger body of evidence, research would benefit from a stronger adherence to the current methodological standards in randomized controlled trial design and the systematic investigation of shared protocols of CBM [45]. Moreover, some flaws in the current trials, which impact the efficacy of the CBM treatment, might need to be reconsidered. One potential factor here concerns the methodology of typical CBM training procedures, usually involving the presentation of only two static stimuli. As such, these trainings lack the complexity of real-life substance use circumstances filled with multiple, different stimuli. More complex, multiple stimuli procedures within the CBM procedures might need to be developed. Next, the number of training sessions needs to be considered (and standardized), whereby, in view of a sustainable effect, more sessions are probably needed than are currently offered.

One of the major challenges negatively impacting the field of cognitive research in addiction is the lack of easy implementable cognitive test batteries capturing cognitive domains relevant to addictive processes and that can be widely accepted as standard in future studies [41]. Addressing this lack might allow better comparisons between studies and include larger and more differentiated patient samples. One recent attempt is the development of a unified online test battery for cognitive impulsivity showing promise in validation with real-world behaviors [49]. This is in line with other developments highlighting the importance of developing and accepting standard protocols (e.g., neuromodulation and functional imaging designs), allowing for more and better comparison between studies worldwide [50,51].

Relevance to Clinical and Research Practice

Comorbidity

For SUD, as for many psychiatric disorders, comorbidity, specifically for the most severe patients, is the rule rather than the exception. Underlying, shared vulnerabilities might be one of the primary drivers for this comorbidity. Among others, shared genetic influences are prominent. Exemplary are the findings of a recent study showing that alcohol, nicotine, and cannabis dependence are significantly genetically correlated with several other mental disorders, including attention deficit hyperactivity disorder (ADHD), schizophrenia, and major depression [52]. Future studies are needed to unravel the complex mechanisms underlying the comorbidity between SUD and other mental disorders.

From a clinical viewpoint, evidence-based interventions need to be developed to improve treatment outcome for people with comorbid disorders. Indeed, these patients are characterized by poor outcomes on different domains (clinical, suicide, justice, medical, and social) and current interventions and care organization are often inadequate. One promising intervention is contingency management (CM), in which positive reinforcers (vouchers, money) are given to patients to provide incentives to maintain abstinence and/or to adhere to treatment programs. In addition to treatment as usual, CM has proven to be a very effective treatment in terms of both maintaining abstinence and treatment adherence in patients with SUD. In a recent review and metanalysis, CM was associated with medium effect sizes for abstinence ($d = 0.58$) and treatment adherence ($d = 0.62$) [53]. Although most studies on CM focused on SUD-only populations, the efficacy of CM in dual-disorder patients (i.e., substance use and severe [other] mental illness) has recently been documented. Albeit currently for a small number of studies, a first meta-analysis showed a minor but significant effect on maintaining abstinence in patients with psychosis and SUD [54].

Neuromodulation in Addiction Treatment

Recent decades have seen a burst of research into non-invasive brain stimulation (NIBS) techniques as an addiction treatment, especially since Food and Drug Administration (FDA) approval in 2008 of transcranial magnetic stimulation (TMS) for the treatment of major depressive disorder [55]. NIBS encompasses both TMS and transcranial electric stimulation (tES), with transcranial direct current stimulation (tDCS) being the most studied form of tES. TMS and tDCS effects both presumably rely primarily on long-term potentiation and depression [56,57]. Interest in NIBS as an addiction intervention has been

spurred on by demonstrations of its impact on executive processes supposedly crucial in addiction [58–60]. Ultimately, NIBS offers perspective on the development of low-cost, brain-circuit-specific treatments without serious side effects [61–64]. Taken together, recent reviews outline the potential role of NIBS in the treatment of addictions in general [65–74,51], alcohol dependency [75,76], tobacco cessation [77–79], cocaine, (met)amphetamines [80], and opioids use [81]. Interest has extended into behavioral addictions, such as pathological gambling [82,83] and food craving [84,85].

Despite generally favorable results, many outstanding issues limit practical implementation of NIBS. Both TMS and tDCS require choosing from a near infinite number of possible parameter combinations: stimulation target, intensity, site(s) and frequency, number of sessions, coil/electrode type, and so on. Given the lack of systematic investigation of these parameters, there is currently no established best practice [65,51,86]. While direct comparison of all meaningful combinations is unfeasible, even fundamental issues, such as the adequate number of stimulation sessions, remain largely unexplored. Most studies to date have employed few (often single) stimulation sessions, while effective protocols often require 20–30 sessions [76,86], and multiple sessions seem to be associated with stronger effects [87]. Available studies have mainly focused on stimulation of the dorsolateral prefrontal cortex (dlPFC), particularly in the left hemisphere, following protocols for depression [67]. However, an emerging trend indicates that excitation of the right dlPFC may be associated with better outcomes [65,66,70,76]. Only a few studies have targeted regions other than the dlPFC, namely to influence reward mechanisms rather than executive functions, through medial prefrontal structures [88]. Stimulation parameters aside, there is a shortage of research employing objective outcome measures (as opposed to, e.g., subjective craving), and several reviews have stressed the utility of neuroimaging measures (fMRI/ EEG) [51,65,88,89]. First, insight in alterations of neural processes could help in the evaluation of protocol parameters independently from long-term clinical outcome measures, which are notoriously difficult to acquire. Furthermore, these measures could provide invaluable (state and trait) biomarkers predicting treatment response [51,68], given the high interindividual variability [90]. For example, baseline-event-related potentials have been shown to predict tDCS impact on behavioral measures [91]. There is increasing attention to the influence of stimulation context [92,93,67]; given that NIBS likely exerts its effects through modulation of plasticity, neural activity around or during stimulation could be of paramount importance. Indeed, exposure to smoking cues during TMS stimulation has been found to enhance treatment response in terms of cigarette consumption [94]. On the other hand, a series of studies combining tDCS with CBM training involving substance cues has shown weak or null effects [95–98]. Another important and largely ignored contextual factor is the patients' pharmacological regimen [99], which could exert both synergistic and blocking effects (e.g., diazepam during alcohol detox may reduce LTP-like plasticity) [67]. The influence of polysubstance abuse and comorbid psychiatric disorders presents a thorny but essential issue, given the large comorbidity rates in the addiction population [65]. Some favorable results in this vein have already been reported, for example in schizophrenia patients with tobacco addiction [100]. Finally, there are a number of technical topics of actual interest: improvement of sham (placebo) procedures [101,102]; development of TMS coils allowing deeper tissue penetration [67]; enhancement of tDCS focality by increasing the number of electrodes [103]; investigation of other forms of tES, such as transcranial alternate current stimulation (tACS) [104]; and

development of remotely supervised-at-home tDCS protocols, opening the door for larger scale studies and higher potential clinical utility [105–107].

Public Health Interventions

Substance use and associated disorders are, more than other mental disorders, in interaction with societal developments and cultures. Thus, public health approaches (e.g., limitation of availability and regulations) have been used for decades. Since the early days of the prohibition period, the focus has been on limiting access to addictive substances. These ideas have been at the heart of the so-called war on drugs in the United States and many other countries, often being not useful to reducing drug consumptions. However, even today, in many countries drug use continues to be penalized, even though punishment does not ameliorate SUDs or related problems. Imprisonment, whether for drug or other offenses, leads to much a higher risk of drug overdose upon release. More than half of those in prison have an untreated SUD, and illicit drug and medication use typically increases significantly following imprisonment. For untreated opioid use disorder, relapse to drug use can be fatal due to the loss of opioid tolerance that may have occurred while the person was incarcerated [108].

In 2017, the 193 members of the United Nations General Assembly Special Session on Drugs unanimously voted to recognize the need to approach SUDs as public health issues rather than punishing them as criminal offenses [109]. Public-health-based alternatives to criminalization range from drug courts and other diversion programs to policies decriminalizing drug possession.

In addition to policy research, proactive research is needed to address the racial disparities related to drug use and addiction. From the opioid crisis, we have learned that large research initiatives can be mounted engaging multiple stakeholders – including the justice system (courts, prisons, jails) and the health care system – to cooperate toward the common purpose of reducing this devastating health problem [108].

Personalized Treatment

Although evidence-based treatments do exist for SUD, outcomes are variable across individuals and many individuals experience multiple, unsuccessful treatment attempts. A more personalized approach (i.e., precision medicine) may help to identify individuals at particular risk of relapse, and to improve treatment outcome by better matching of treatments to specific patient characteristics or needs. Although much work still needs to be done and the practical implications for the field are limited, some findings are worth mentioning.

Prediction of Outcome and Relapse Risk

Despite a large degree of between-patient heterogeneity, individual differences in traditional, clinical variables (e.g., severity, gender) are not sufficient to predict or account for differences in outcomes [110,111,20]. More recently, scientific literature supports the idea that individual differences in brain function and structure are linked to differences in clinical outcomes. However, the wide variety of (mostly neuroimaging) studies has not consistently used strategies to minimize risks of overfitting (e.g., cross-validation), leading to inflated effect size estimates and reduced reproducibility in novel clinical samples [112].

Machine learning (cross-validated, predictive modeling) may be better suited for dealing with heterogeneous data. In the context of addiction treatment, the goal of predictive modeling is to estimate an individual's clinical outcome using data acquired at the start of treatment. Taken together, current studies show that by using brain-based variables, predictive modeling has comparable or higher accuracy compared to traditional clinical variables. However, all studies to date have relatively modest sample sizes, and only a limited number have included external validation [112]. Thus, in addition to the problems of implementation in clinical practice, brain-based predictive modeling of addictive outcomes remains a nascent area of investigation. Much more work is needed prior to clinical translation of existing models, including rigorous comparisons of imaging- versus nonimaging-based predictive models [112]. As such, developments in the field of addictions meet the same translational problems as have been highlighted for the broader field of psychiatric research [113].

Personalized Pharmacotherapy

In the last decade, important steps have been made in the direction of a more personalized treatment approach. Pharmacogenetic findings have mostly been documented for the treatment of nicotine dependence [114]. For other substances of abuse, pharmacogenetic studies remain difficult to interpret. There is a clear lack of replication of (the often very small) studies, and the (pathogenic) link between the polymorphism under investigation with SUD dimensions is often not clear. The most studied is the mu-opioid receptor (OPRM1). Indeed, there is a wide interindividual variability in response to the treatment of AUD with the opioid receptor antagonist naltrexone. To identify patients who may be most responsive to naltrexone treatment, studies have examined the moderating effect of rs1799971, a single nucleotide polymorphism (SNP) that encodes a nonsynonymous substitution (Asn40Asp) in the mu-opioid receptor gene OPRM1. However, although earlier studies showed promising results, a recent review and meta-analysis concluded that it remains unclear whether rs1799971, the OPRM1 Asn40Asp SNP, predicts naltrexone treatment response in individuals with AUD or heavy drinking [115]. More recent studies point to a possible role of epigenetic changes of the OPRM1 as a moderator of the therapeutic response on naltrexone in reducing alcohol consumption and craving [116].

Parallel to the pharmacogenetic studies, a recent line of studies show that naltrexone is highly effective in reducing alcohol use in patients with a clinical profile that can be described as high-reward/low-relief drinkers. Using a simple self-report questionnaire to identify these AUD patients, different studies replicated these positive findings and show important effect sizes on drinks per drinking day ($d = 2.05$) and percent heavy drinking days ($d = 1.75$) [117,118]. Importantly, high-reward drinking as a clinical phenotype is reflected by high cue-reactivity on alcohol triggers in fMRI paradigms. Cue-reactivity has also been shown to be a strong moderator of the effectivity of naltrexone, showing impressive NNT (1.8–3.2) for reduction/return to heavy drinking, specifically in patients with high cue-reactivity [119,120]. The reward-drinking phenotype and cue-reactivity can be considered as important (bio)markers helping clinical decision-making on the use of opioid antagonists (naltrexone, nalmefene) in the treatment of patients with AUD.

Future Perspectives

Many of the challenges ahead parallel those in other fields of psychiatry. Nevertheless, despite these challenges, the clinical and research field of addiction is growing rapidly. Future avenues to explore cover large domains, from public health measures (e.g., tackling the opioid crisis) to translating neuroscientific findings into clinically efficacious and implementable interventions. Of importance, there is the growing need to develop standardized and broadly accepted research paradigms. Indeed, to make significant progress the addiction field needs to build upon comparable data sets. This accounts most surely for a set of addiction-relevant cognitive test measures. In addition, standardized neuroimaging protocols (e.g., on cue-reactivity) might also allow the growing of a body of comparable data. Finally, standardized protocols for neurostimulation may support the same goal of accumulating large, comparable data sets, allowing for in-depth analyses into underlying working mechanisms, personalization of treatment, and optimization of the best application protocols. All this requires global collaboration between addiction researchers and clinicians worldwide. International scientific organizations can play an important facilitating role.

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