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TOWARDS RECOVERY

Therapeutic approaches to improve the treatment of alcohol use disorder

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The best evidence-based treatments for alcohol dependence are currently those developed within multidisciplinary programmes based on a cognitive-behavioural approach, which include psychological, sociological, and medical dimensions. However, recovery is not always achieved. The percentage of individuals who abandon these programs and relapse is high throughout the whole process and an adequate state of wellbeing is not always found. This paper outlines some of the complements or techniques that could be incorporated into the most common treatments to enhance behavioural change while also considering long-term outcomes. Thus, the text highlights the importance of considering recovery as the culmination of the process of change towards improved health, wellbeing, and a self-directed life purpose, rather than just abstinence.

Keywords: **alcohol use disorder**, **cognitive-behavioural therapy**, **motivation**, **inhibitory control**, **recovery**.

INTRODUCTION

Addiction management requires a biopsychosocial approach, aimed at the well-being of the patient which also takes into account their individual, social, and biological characteristics. These models consider the recovery of alcohol-dependent individuals not only as the attainment of abstinence, but also as the culmination of a process of voluntarily sustained lifestyle change, leading to improvements in health, well-being, and self-direction of life purpose.

The complexity of this approach is derived from variability in the factors affecting the development of an addiction, which differ between individuals, such as their life experiences, neurobiological characteristics, and coping capacity. The fact that each person's ability to resolve these aspects is different results in the high heterogeneity we find in daily clinical practice in terms of alcohol use disorder symptomatology, treatments, and levels of efficacy. Thus, there are multiple therapeutic approaches whose goals are set in relation to individual demand and variability but which often include interventions from pharmacological, cognitive-behavioural, or psychosocial approaches. The goals of these treatments often include providing dependent individuals with sufficient cognitive and behavioural skills to modify their problematic behaviours and reduce their risk of relapse, so that these changes become sustainable over time, either by maintaining abstinence or by reducing harm. However, the results

«Addiction management requires a biopsychosocial approach, aimed at the well-being of the patient»

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obtained to date, although verified, are still relatively heterogeneous (Carroll & Kiluk, 2017). Pharmacological treatments or psychosocial approaches to alcohol abuse are widespread, however, this text will focus specifically on some of the issues relevant to the psychological approach to these disorders.

PSYCHOTHERAPIES FOR BEHAVIOURAL CHANGE

According to classical behavioural theories, a person starts using in the search for the positive reinforcement the substance provides; however, when dependence begins, the use is maintained through negative reinforcement (relief from discomfort), despite its harmful consequences. This substance-behaviour relationship is mediated by cognitive, emotional, allostatic, and social processes, which interact and modify the person's behaviour. Moreover, the influence of each particular aspect changes throughout the course of dependence. Thus, depending on which process is more extensively altered, therapeutic intervention will focus more on one aspect or the other and so, certain techniques will be preferred (Campbell et al., 2018). For example, in the initial stages of the detoxification process, pharmacological intervention is used to address withdrawal, while attentional or behavioural techniques focusing on behaviour modification are used to deal with craving. When there is an emotional imbalance, emotional recognition and regulation can also be useful techniques.

Undoubtedly, the therapeutic process starts when there is a clear intention to change. This intention arises as a consequence of recognising the negative consequences of drug use and attempting to change the associated habits. To help the patient in this process, psychotherapeutic interventions seek to promote changes and achievements in different areas of a person's life, thereby increasing motivation, improving coping skills, providing reinforcement alternatives, or promoting social support. For a comprehensive and detailed review of psychological interventions, see Cortés et al. (2018), which also provides information on the degree of evidence for each of the techniques and components reviewed.

Interventions based on changing motivation

The best known and most effective therapeutic programmes for alcohol dependence are those incorporating components from motivational interviewing, cognitive-behavioural techniques (such as coping or social skills training), or emotional regulation. These are often combined with some sessions specifically aimed at relapse prevention. Motivation-for-change programmes, based on Prochaska and Diclemente's (1986) transtheoretical model, promote intentional behavioural change. These authors proposed that, when contemplating behavioural change, an individual may go through a series of phases (stages of change): precontemplation, contemplation, preparation, action, and maintenance. The evolution of change is not linear and so the individual may go through the same phase several times during the process before being able to sustain significant change in a stable way. Thus, the individual actively moves through the phases and the

David Goehring

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therapist mixes different techniques to facilitate the desired change processes. These processes refer to the various activities of the individual as they move from one stage to another. For example, awareness raising, environmental and personal reappraisal (realising how unhealthy behaviours affect oneself and others), self-liberation (believing in one's ability to change and committing to change), stimulus control or contingency management (reward or punishment to increase or decrease particular behaviours), and seeking supportive relationships. Moreover, the change each person requires can cover different levels or «layers of depth», including symptomatic/situational (pattern of consumption and micro- and macro-environmental factors), maladaptive cognitions (expectations, beliefs, and evaluations, etc.), current interpersonal conflicts (hostility and assertiveness, etc.), systemic/family conflicts (support networks and legal problems, etc.), and intrapersonal conflicts (self-esteem and personality, etc.). Considering this, the therapist uses different techniques that act at the level of required change in order to facilitate the person's process of change and to progress along the motivational stages.

Throughout this process, relapse is considered to be another stage or a regression to a previous stage as the consequence of poor management of the problems that may arise once abstinence has been established. Experiencing negative conditions (emotions, interpersonal conflicts, and negative physical and physiological states) is the most frequent cause of relapse. In order to prevent this problem, the therapist and patient must try to identify which situations, thoughts, and affective states precede a potential episode and develop adaptive coping techniques such as assertiveness or social skills training. All of this involves training the person to identify and control the risk factors that may otherwise precipitate their drug use.

«The therapeutic process starts when there is a clear intention to change. This intention arises as a consequence of recognising the negative consequences of drug use»

The required change processes are not the same throughout the treatment. While awareness building or environmental reassessment are appropriate throughout the intervention, contingency management and stimulus control are useful during the action and maintenance stages. Consequently, therapeutic tools should be employed selectively; for example, psychoeducation would be appropriate for enhancing the awareness of a problem, stimulus control, or promoting social release, while assertiveness training may help enhance contingency management or counterconditioning and could be useful in relapse prevention.

Although the effectiveness of the interventions proposed in the previous paragraphs is well-documented, they do not guarantee therapeutic success and many patients experience a relapse during the first year. In fact, McQueen and his collaborators found that brief cognitive-behavioural interventions carried out in hospital (three or four sessions aimed at modifying beliefs or constructs associated with the problem as well as related loops) were moderately effective around six months into the treatment, but their effect disappeared after one year (McQueen et al., 2011). In contrast, motivational interventions (based on motivational interviewing) showed low short-term but significant long-term effectiveness (Smedslund et al., 2011). Beyond methodological reasons, therapeutic failure may be attributable to several factors such as the difficulty in self-regulating one's emotions (fundamental in craving management), managing different sources of stress that can act as powerful triggers or potential risky situations, or individual inability to exert inhibitory control over consumption in these situations.

Emotional regulation in alcohol dependence

Emotions play a particularly important role, both in establishing dependence and in the recovery process. Individuals attain and become accustomed to a positive affective state associated with the consumption of the substance as they continue to use it. This gives rise to an opposing affective reaction which seeks to achieve emotional balance. The search for balance raises the emotional activation threshold and so everyday experiences cease to generate positive emotions; thus, only drug use can improve the person's emotional status. Evidence that such emotional maladjustment may be related to relapse can be obtained by measuring a person's startle reflex. The startle reflex is a reflexive muscle contraction of the facial muscles, triggered by a sudden intense stimulus. It is influenced by factors such as emotional state, attention, or mental activity, but is beyond voluntary control. Therefore, an affective modulation of the

startle reflex can be used to assess the emotional valence of stimuli, i.e., whether the stimuli are considered by the individual as pleasant (positive valence) or unpleasant (aversive or negative valence).

The startle reflex will be greater with aversive stimuli and weaker when presented with pleasurable stimuli. It has been shown that consumption-related stimuli provoke an attenuated startle reflex, meaning that they have a very high positive valence, even after abstinence. So much so that these stimuli have been used as to predict relapse because having a very attenuated startle reflex in relation to alcohol before treatment is significantly related to the possibility of relapse after 12 weeks of intervention. That is, alcohol-dependent patients continue to assign an exceedingly high reinforcing value to alcohol, even after abstinence, which suggests that the appetitive valence system alteration remains even three months later (Jurado-Barba et al., 2015). Along the same lines, the affective modulation of the baseline startle reflex to alcohol can predict a dependent drinking pattern up to four years later. Moreover, people who were dependent afterwards seemed to show attenuated startle reflex levels at all valences, implying low psychophysiological reactivity, even to aversive stimuli, and thus providing evidence for emotional modulation difficulties (Jurado-Barba et al., 2017).

Thus, this type of result shows that emotional regulation training should be implemented in treatment to help patients to identify emotional states, respond adaptively to them, prevent relapse, and rebuild their reward systems.

Inhibitory control in alcohol dependence

Based on neuroscience models, several studies have proposed that neuromodulatory mechanisms are at the root of dependent behaviour and cause the brain's reward system to become sensitised, thereby facilitating substance-approaching behaviour in the absence of adequate frontal inhibitory control. Thus, these mechanisms give rise to compulsive behaviour which, far from eliciting positive emotions, generate a negative emotional state. Dual models explain that this apparently irrational approaching behaviour can be stopped by setting up a goal-driven reflexive system, as long as the inhibitory capacity is preserved. Consequently, several researchers have proposed addressing some of the following implicit mechanisms regulating the reflexive/reactive balance during treatment: 1) attentional bias towards the

Sozavisimost

Several therapeutic techniques have proved effective in treating patients with alcohol use disorder. These include cognitive-behavioural techniques such as coping or social skills training, as well as emotional regulation, so that the person can adaptively respond to emotional states that might lead them to a relapse.

Rudamese

Participating in care programmes based on mutual help, community reinforcement, and collaboration with the healthcare system can be a path to recovery for individuals with alcohol use disorder. According to Rubio et al. (2018), the relapse rate for the participants in the Ayúdate-Ayúdanos programme created by FACOMA ranged from 29 to 38%, while for those who do not participate in the programme it was 60–70%.

substance; 2) formation of behavioural patterns associated with it; and 3) substance-triggered action tendencies. Work on these three cognitive mechanisms could equip patients with strategies to consolidate the changes made throughout the therapeutic process, thereby enabling them to use techniques acquired during therapy to help control the direction of their attentional resources. For example, through stimulus control (paying attention to other types of stimuli) or by avoiding risky situations (not entering bars). However, it could also help to generate an alternative behavioural pattern that can be activated in response to alcohol-related stimuli, for example, by engaging in an activity chosen specifically for the individual, such as going to a particular place.

Joshua Hoehne

Recovery is understood as a complex process requiring actions to reinforce four relevant areas of an individual's life: their health (abstinence and the ability to make decisions that support physical and emotional well-being), home (a stable and safe place to live), purpose in life (meaningful daily activities), and community involvement (social networks and supportive relationships).

Regarding the modification of action tendencies, Wiers et al. developed a training programme called the «alcohol approach/avoidance task» (A-AAT) to enhance the regulative capacity of the reflexive system. A-AAT involves generating avoidance tendencies in response to stimuli related to alcohol use (Wiers et al., 2011). Applying this therapeutic complement, they found that patients treated using this system reported fewer relapses and displayed neurofunctional changes one year later. They showed reduced activation of the amygdala and the medial prefrontal cortex, which decreased mesolimbic activity associated with craving. Therefore, these authors concluded that A-AAT increased the effects of the therapy. Furthermore, these functional changes correlated significantly with a reduction in behavioural substance-approaching tendencies (Wiers et al., 2015), which was interpreted as an improvement in the control of automatic behaviours.

«Emotions play a particularly important role both in establishing dependence and in the recovery process»

Furthermore, the effect of A-AAT could be enhanced when it was performed during activation of the consumption-related mnemic imprint. In other words, by activating the memory of consumption (and of all that it implies including the behavioural pattern, desire, etc.) and then inducing an avoidance behaviour, the behavioural pattern provoked by alcohol was counter-conditioned. Building on this, Martínez-Maldonado et al. (2020) exposed a group of alcohol-dependent patients to A-AAT training in the context of updating their mnemic imprint of alcohol consumption. To achieve this, after eight months of abstinence, patients received the A-AAT training after watching a neutral video or an alcohol-related video. After the intervention, only patients who had watched the alcohol video before the training showed post-treatment changes in their approach/avoidance tendency and pattern of alpha brain oscillations (8–12 Hz waves are related to cortical activation, alertness, and active inhibition mechanisms), which may be evidence of brain activity reorganisation. This suggests that avoidance training alone may not be sufficient to restore brain activity levels. Such training

may need to be conducted in a context of updating consumption-related memories. Thus, exposure techniques connected to alternative-response planning could be particularly useful in strengthening inhibitory control. However, exposure techniques in the context of this pathology are not usually implemented because of the risks involved. To resolve this problem, virtual reality has been used to facilitate the implementation of exposure techniques – with response prevention, in safe environments, and with a level of activation and realism that can enhance the results and further generalise learned strategies – all with promising results.

LONG-TERM RECOVERY

The recovery process is particularly complex and ensuring its success requires understanding recovery as the attainment of wellbeing, beyond symptoms, i.e., a solutions-oriented approach, rather than a pathology-focused one. On this note, different definitions of this concept have been put forward by various organisations. Despite their subtle differences, they all agree that recovery is a process of voluntary (self-directed) change through which (physical and psychological) health, quality of life, and participation in society are maximised, leading to an improvement in the overall wellbeing of the individual (Kelly & Hoeppner, 2015).

Thus, although the new definitions include abstinence, this concept is not equated with recovery, which is a much more complex process requiring continuation in therapeutic programmes – almost from the beginning – and the involvement of other actors such as patient associations. To this end, four relevant areas should be reinforced: individual health (abstinence and the ability to make decisions that support physical and emotional well-being), home (a stable and safe place to live), purpose in life (meaningful daily activities), and community involvement (social networks and supportive relationships) (National Academies of Sciences, Engineering and Medicine, 2016). The Ayúdate-Ayúdanos (translated as "Help Yourself–Help Us") programme was created with this goal in mind (FACOMA, 2016). It involves a continued care agenda based on mutual help, with community reinforcement in collaboration with the health-care system or the hospital environment. In this structure, patients undergo treatment for an average of six to seven years, using techniques tailored to their individual current situation, but with the ultimate goal of recovering

Sabine van Erp

For the process of recovery from alcohol use disorder to be successful we must understand recovery as the attainment of wellbeing, beyond mere abstinence.

«Recovery is a process of voluntary change through which health, quality of life, and participation in society are maximised»

in the sense described above. For the first two years, treatment takes place in the hospital setting, but from the outset patients are encouraged to engage with the programme where they receive support for themselves and their families. The programme promotes adopting a healthy lifestyle, which in turn fosters personal growth, recovery of values, and reinstatement of personal needs.

In more advanced stages of the therapeutic process, or during long-term stages after the beginning of abstinence, the use of techniques from positive psychology makes it possible to actively access a new life project. In the long term, this allows people to rebuild their self-images, self-esteem, accept both positive and negative emotions, and consequently achieve the physical and psychological wellbeing inherent to recovery.

The results of this approach show that, after two years of co-treatment, the number of cumulative months of abstinence is higher, the dropout rate decreases, anxiety levels are lower, and patients have

an increased sense of purpose in life. In fact, the relapse rate for the peer support group ranged from 29 to 38 %, while for those who did not participate in the programme it was 60–70 % (Rubio et al., 2018).

CONCLUSIONS

An integrative treatment approach seems essential to achieve recovery or maintain abstinence in the long term. This involves sequencing and mixing techniques so that the characteristics of each stage can combine traditional management with the promotion of inhibitory control, emotional regulation, and the generation of new reinforcements. Techniques from positive psychology are used, which make it possible for values to grow, facilitating reconstruction of the individual and bringing them closer to the well-being that recovery entails. This biopsychosocial approach was able to promote long-term changes not only in behaviour and its associated cognitions, but also in the underlying neural mechanisms, thereby strengthening individual recovery.

REFERENCES

Campbell, E. J., Lawrence, A. J., & Perry, C. J. (2018). New steps for treating alcohol use disorder. *Psychopharmacology, 235*(6), 1759–1773. https://doi.org/10.1007/s00213-018-4887-7

Carroll, K. M., & Kiluk, B. D. (2017). Cognitive behavioral interventions for alcohol and drug use disorders: Through the stage model and back again. *Psychology of Addictive Behaviors, 31*(8), 847–861. https://doi.org/10.1037/adb0000311

Cortés, M. T., Fernández, S., García, B., Martínez, V., & Sierra, R. (2018). Intervenciones psicológicas basadas en la evidencia en trastornos adictivos. In C. Pereiro & J. J. Fernández (Eds.), *Guía de adicciones para especialistas en formación* (pp. 389–399). Socidrogalcohol.

FACOMA. (2016). Ayúdate-Ayúdanos. https://facoma.org/

Jurado-Barba, R., Duque, A., López-Trabada, J. R., Martínez-Gras, I., García-Gutiérrez, M. S., Navarrete, F., López-Muñoz, F., Jiménez-Airrero, M. A., Ávila, C., Manzanares, J., & Rubio, G. (2017). The modulation of the startle reflex as predictor of alcohol use disorders in a sample of heavy drinkers: A 4-year follow-up study. *Alcohol Clinical and Experimental Research, 41*(6), 1212–1219. https://doi.org/10.1111/acer.13399

Jurado-Barba, R., Rubio Valladolid, G., Martínez-Gras, I., Alvarez-Alonso, M. J., Ponce Alfaro, G., Fernández, A., Moratti, S., Heinz, A., & Jimenez-Arriero, M. A. (2015). Changes on the modulation of the startle reflex in alcohol-dependent patients after 12 weeks of a cognitive-behavioral intervention. *European Addiction Research, 21*(4), 195–203. https://doi.org/10.1159/000371723

Kelly, J. F., & Hoeppner, B. B. (2015). A biaxial formulation of the recovery construct. *Addiction Research & Theory, 23*(1), 5–9. https://doi.org/10.3109/16066359.2014.930132

Martínez-Maldonado, A., Jurado-Barba, R., Sion, A., Domínguez-Centeno, I., Castillo-Parra, G., Prieto-Montalvo, J., & Rubio, G. (2020). Brain functional connectivity after cognitive-bias modification and behavioral changes in abstinent alcohol-use disorder patients. *International Journal of Psychophysiology, 154*, 46–58. https://doi.org/10.1016/j.ijpsycho.2019.10.004

McQueen, J., Howe, T. E., Allan, L., Mains, D., & Hardy, V. (2011). Brief interventions for heavy alcohol users admitted to general hospital wards. *Cochrane Database of Systematic Reviews, 8*, CD005191. https://doi.org/10.1002/14651858.CD005191.pub3

National Academies of Sciences, Engineering and Medicine. (2016). *Measuring recovery from substance use or mental disorders: Workshop Summary*. The National Academies Press. https://doi.org/10.17226/23589

Prochaska, J. O., & Diclemente, C. C. (1986). Toward a comprehensive model of change. In W. R. Miller, & N. Heather (Eds.), *Treating addictive behaviors: Processes of change* (pp. 3–27). Plenum Press. https://doi.org/10.1007/978-1-4613-2191-0_1

Rubio, G., Marín, M., Arias, F., López-Trabada, J. R., Iribarren, M., Alfonso, S., Prieto, R., Blanco, A., Urosa, B., Montes, V., Jurado, R., Jiménez-Arriero, M., Á., & de Fonseca, F. R. (2018). Inclusion of alcoholic associations into a public treatment programme for alcoholism improves outcomes during the treatment and continuing care period: A 6-year experience. *Alcohol and Alcoholism, 53*(1), 78–88. https://doi.org/10.1093/alcalc/agx078

Smedslund, G., Berg, R. C., Hammerstrøm, K. T., Steiro, A., Leiknes, K. A., Dahl, H. M., & Karlsen, K. (2011). Motivational interviewing for substance abuse. *Cochrane Database of Systematic Reviews*, 5, CD008063. https://doi.org/10.1002/14651858.cd008063.pub2

Wiers, C. E., Stelzel, C., Gladwin, T. E., Park, S. Q., Pawelczack, S., Gawron, C. K., Stuke, H., Heinz, A., Wiers, R. W., Rinck, M., Lindenmeyer, J., Walter, H., & Bermpohl, F. (2015). Effects of cognitive bias modification training on neural alcohol cue reactivity in alcohol dependence. *The American Journal of Psychiatry, 172*(4), 335–343. https://doi.org/10.1176/appi.ajp.2014.13111495

Wiers, R. W., Eberl, C., Rinck, M., Becker, E. S., & Lindenmeyer, J. (2011). Retraining automatic action tendencies changes alcoholic patients' approach bias for alcohol and improves treatment outcome. *Psychological Science, 22*(4), 490–497. https://doi.org/10.1177/0956797611400615

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Xisco Mensua. «Addictions» series, 2020. Watercolour, 23.5 × 31 cm.

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MEDICATIONS AGAINST DRUGS

Development of medications to prevent and treat substance use disorders

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Substance use disorder (SUD) is a significant public health concern. Unfortunately, there are few safe and effective medications to treat SUD and efficacy is suboptimal. There are important financial and scientific obstacles to develop new compounds, but recent advances in the discovery of new brain receptors and neurocircuits are offering opportunities to develop new pharmacotherapies. A systematic scientific approach to develop medications is required to demonstrate their safety and efficacy, bring it to market, and prescribe it to patients. The purpose of this manuscript is to provide a general overview of the challenges and opportunities in medications development for SUD, describe the phased approach of this development, the medications approved, and those that appear most promising.

Keywords: **medications development**, **substance use disorders**, **treatment**, **clinical trials**.

INTRODUCTION

Medications development to prevent and treat illicit substance use disorder (SUD) is a high public health priority that requires scientific and financial collaborations among academic investigators, government agencies, and pharmaceutical industry. According to the National Survey of Drug Use and Health of the United States (NSDUH) of 2019, there were approximately 8.3 million individuals with SUD but only 1.5 million were treated with a medication approved by the Food and Drug Administration (FDA) for the disorder (SAMHSA, 2019). Thus, most patients with SUD do not receive a medication to treat it. This is, in part, because of a lack of access to pharmacological treatment, but mainly due to the dearth of medications approved for their disorder and their limited efficacy. This treatment gap needs to be urgently addressed with more pharmacotherapies that are safe, effective, and available to patients with SUDs (Rasmussen et al., 2019).

Despite the critical need, there is only a handful of biotechnology or pharmaceutical companies interested in developing medication for SUD. This is due in part to the misconception that there is low return on the investment and the challenges posed by the target patient population, due to their multiple medical and psychiatric comorbidities, unpredictable motivation to stay in treatment, and poor treatment outcomes. However, the current market of medications approved for opioid use disorders exceeds $1.2 billion per year and multiple strategies to incentivize the pharmaceutical industry to get into the SUD field have been proposed, including vouchers and lengthening the duration of drug patents, but they have not been implemented and

«Most patients with substance use disorder do not receive a medication to treat it»

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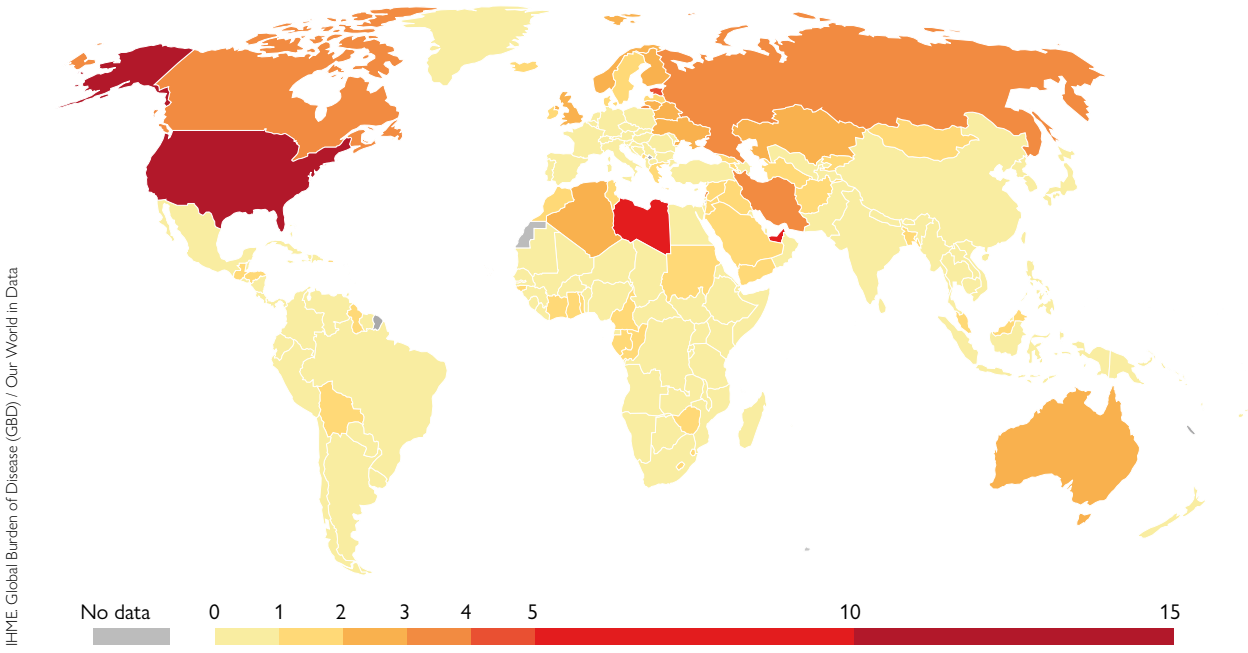


Map showing the world-wide death rates from opioid overdoses for 2017, measured as the number of deaths per 100,000 individuals. With 13.34 death per 100,000 people, the United States lead the raking above countries such as Libya (7.27) and the United Arab Emirates (5.4).

more companies are abandoning the development of psychotherapeutics for brain disorders, including SUD (Skolnick & Volkow, 2012).

CHALLENGES AND OPPORTUNITIES

The development of SUD medications requires significant financial and scientific support. The average time from the discovery of a new compound to obtain approval from the regulatory agencies, for example the FDA, is about 14 years, if everything goes well. The approximate cost of a successful medication development from discovery to approval is about $2.4 billion. On the other hand, investing in developing safe and effective medications to treat SUDs can save millions of dollars in loss of productivity and, more importantly, many lives. Therefore, increasing the treatment options for SUD patients is clearly cost-effective as well as profitable.

From the scientific point of view, SUD is a chronic clinical condition characterized by the compulsive use of a drug, despite the physical, psychological, and social negative consequences of its use. The initiation and progression of drug use is associated with biological, social, and psychological risk factors. Chronic drug use has been associated with brain changes that may explain the changes in life priorities and clinical manifestations such as drug withdrawal syndrome and craving, which perpetuate the drug use.

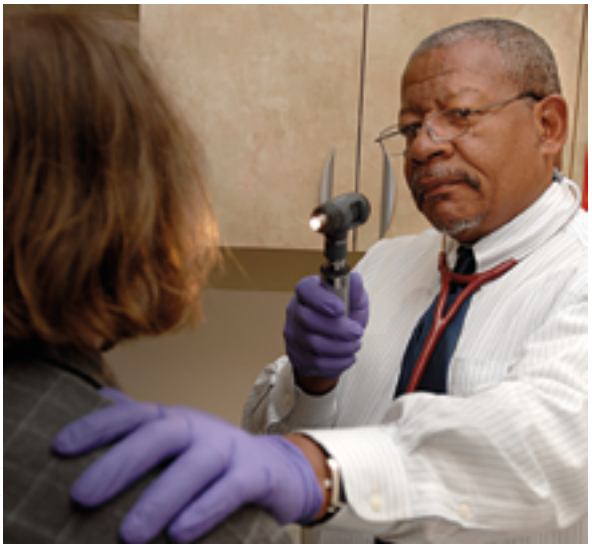
Scientific advances in understanding the effects of acute and chronic use of drugs on the brain and its neurotransmitters and neurocircuits are offering unprecedented opportunities to discover new pharmacological targets and the development of new medications to treat SUDs. Furthermore, advances in understanding the genetic and epigenetic basis of SUD have opened new opportunities to learn about pharmacogenetics of the individual effects of drugs of abuse as well as the safety and efficacy of medications that are allowing more individualized pharmacological approaches.

Advances in immunology are also making possible the development of biologics such as vaccines, monoclonal antibodies, and enzymes, which can alter the pharmacokinetic profile of drugs and be used for the treatment of SUDs as well as prevention of drug overdoses. Anti-drug vaccines produce an immunological response characterized by the production of antibodies against the specific drug of abuse. Monoclonal antibodies produced in the laboratory bind to the drug of abuse and create a large antigen-antibody which does not cross the blood-vein barrier and thus prevents the access of the drug to the brain. The ultimate effect of vaccines and monoclonal antibodies is to produce a pharmacokinetic antagonism and protect the central nervous system from the effects of the drug of abuse and its neurobehavioral consequences. Engineered enzymes

that are being developed to treat SUD have the property of significantly accelerating the catabolism of the drug of abuse at a pace that is much faster than the natural enzymes. That way, when the drug of abuse enters the blood system, the engineered enzyme will break down the drug in plasma before it is able to enter the brain and, thus, prevent the neurobehavioral effects of the drug, including the brain reward mechanisms responsible for the compulsive use (Montoya, 2016).

MEDICATION DEVELOPMENT PHASES

In order to have new medications approved by regulatory agencies and reach patients, new compounds must go through a rigorous process of scientific and unbiased evaluation, which includes comprehensive pre-clinical and clinical research. For SUD, this process has some unique aspects, given that the disorder is associated with the compulsory intake of an illegal substance, which may interact pharmacologically with the study medication. Besides, there is also the risk that the study medication may have addictive properties and increase the risk of adding another addiction to the patient.



NIDA (NIH)

Clinical research for new medications to treat substance use disorder entails the risk that the study medication may have addictive properties which could add another addiction to the patient. Usually, Phase I of clinical research counts on the collaboration of volunteers who are not seeking treatment. On the image, a clinician of the National Institute of Drug Abuse examines an ambulatory patient going through a research treatment.

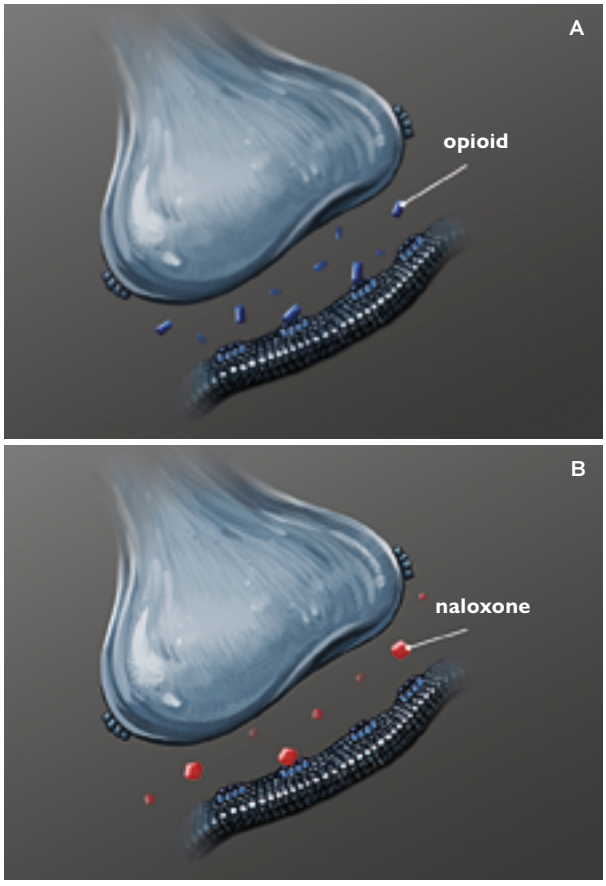
Preclinical phase

In the preclinical research phase, the compound is tested in animals to determine its potential safety to be administered to humans and its preliminary efficacy in the pertinent animal models of SUD. Animal studies are critical in this development process. For SUD, it is necessary to evaluate the abuse liability of new compounds and determine the risk of developing addiction. A compound that demonstrates abuse liability in animals is unlikely to be approved to be tested in humans for further development. Drug discrimination, conditioned place preference, and drug self-administration paradigms help to determine if animals can recognize or prefer the medication over food or other reinforcers. Animal studies are also important to determine potential toxicological effects and adverse interactions with other drugs of abuse or other medications. One of the concerns about animal models of SUD is the heterogeneity of SUDs and the predictability of such models to the human condition. However, they are widely used, and investigators need to continue using them until they can be validated with medications that have demonstrated efficacy (Banks et al., 2019).

«There is only a handful of biotechnology or pharmaceutical companies interested in developing medication for substance use disorder»

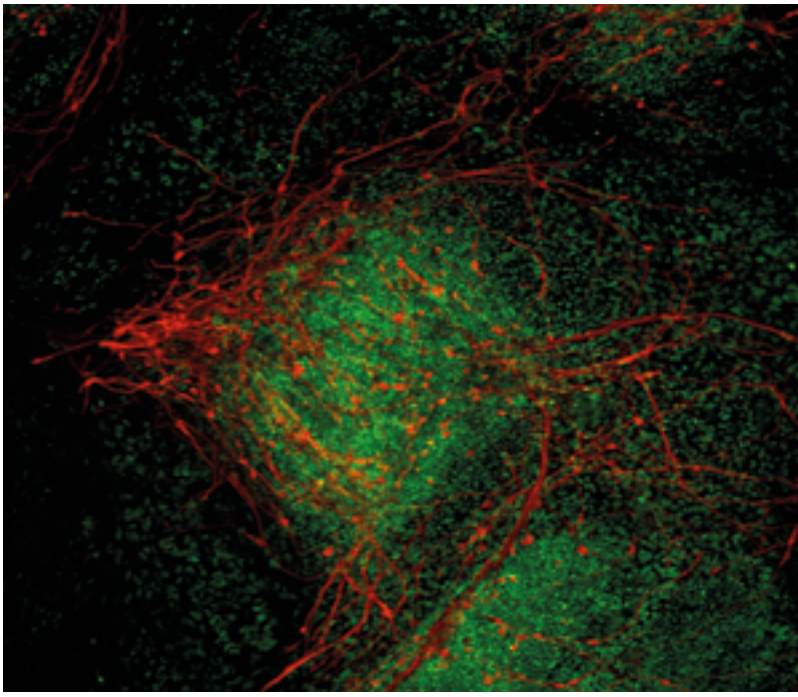
Clinical phase

The clinical research phase is divided in four phases. They are described by the FDA as Phase I to Phase IV. Phase I studies are also called «first-in-human» studies because the goal is to determine the medical safety of administering the new compound to humans. They usually include a relatively small number of study participants who may or may not have a history of drug use and who are financially reimbursed to be exposed to the potential risks of the new medication. This type of study may be followed by a second Phase I study, usually called «Phase Ib», to determine the pharmacological interactions of the new medication and drugs of abuse. This type of study is particularly relevant when it is suspected that the study medication may increase the risk or exacerbate the effects of drugs of abuse. An important component in the Phase I studies is the evaluation of the abuse liability of the new medication. These studies are conducted in human research volunteers who have experience with the effects of the other drugs in the same pharmacological class. For ethical reasons, these studies are conducted in individuals who are not seeking treatment, given that they will be



NIDA (NIH)

Opioid receptors (seen in bright blue in images A and B) are found on nerve cells around the body and have several effects when activated by opioid substances, such as feeling of comfort and sleepiness. As an opioid antagonist, naloxone sits on opioid receptors (image B), blocks them, and knocks other opioids off. Naloxone was approved in 1971 for the treatment of opioid overdose, and new products have been recently approved, such as an intranasal formulation approved by the FDA in 2015.



Currently there are no FDA-approved medications to treat patients with cannabis, cocaine, or methamphetamine use disorder. Above these lines, neuroimaging of cocaine effects on the brain, from a study which may serve to identify new pharmacological targets.

exposed to drugs which may have abuse potential. The standard measures include subjective ratings of drug effects including drug «liking», euphoria, somnolence, and other cognitive and behavioral effects (Epstein et al., 2006).

Phase II clinical trials are often called «proof-of-concept» studies because the purpose is to determine the preliminary efficacy of the medication in patients who are seeking treatment. These studies are usually conducted in outpatient settings and with samples that can range from 50 to 100 study participants. In consequence, it is critical to select endpoints or outcome measures that represent a clinically meaningful improvement of the SUD that is being evaluated. The outcome measure is going to depend on the specific SUD of the patient. Toxicology tests in urine and other human fluids allow to somewhat objectively assess the frequency and intensity of drug use and the severity of the SUD. However, clinically, a drug test result is not an indicator of the whole functioning of the individual. Therefore, other outcome measures have been developed and validated with the goal of obtaining a more comprehensive idea of the clinical situation of the patient. They include, for example, the Clinical Global Impression (CGI), or the Addiction Severity Index (ASI) (Kiluk et al., 2016; Kleykamp et al., 2019; Loflin et al., 2020; Montoya et al., 1995).

Phase III clinical trials are the gold standard to establish the safety and efficacy of a compound. They are usually conducted in large sample of patients who are expected to resemble the «real world» patients with the disorder. Their aim is to confirm the efficacy demonstrated in the Phase II trials and serve as basis to support the specific treatment indication of the medication. Therefore, the proper selection of the study endpoints and statistical approach in the previous phase are essential because study results are presented to regulatory agencies with the goal of obtaining approval to market the product (Yu et al., 2008).

Phase IV studies are usually referred as post-marketing surveillance and usually carried out by the sponsor pharmaceutical company. The purpose is to

NIDA

identify rare adverse effects of the medication that were not discovered in the previous phases. This phase also includes studies in populations that were included in the studies in the previous phases.

MEDICATIONS APPROVED AND UNDER DEVELOPMENT

Currently, there are some medications for SUDs that have gone through this rigorous evaluation and approval process. For opioid use disorder, methadone was approved by the FDA in 1972 and it is widely used in most of countries. Buprenorphine alone and in combination with naloxone were approved in 2002 and has quickly gain acceptance among prescribers because of its unique pharmacological property of being an opioid partial agonist. More recently, in 2016, a six-month implant and, in 2017, a long-acting injectable formulation of buprenorphine were approved.

For relapse prevention of opioid use disorder, oral naltrexone (an opioid antagonist) has been approved since 1984 but adherence to the prescription of this medication is very poor. To overcome this barrier, a long-acting (monthly) formulation of naltrexone was approved in 2010. Its acceptance by clinicians and patients has been low because patients must be detoxified and not using opioids for at least two weeks before the first injection, to prevent precipitating an opioid withdrawal (Coffa & Snyder, 2019).

«Anti-drug vaccines produce an immunological response characterized by the production of antibodies against the specific drug of abuse»

According to the NSDUH, in 2019 in the U.S., there were 746,866 patients in treatment with buprenorphine, 637,157 with methadone, and 77,872 with naltrexone (SAMHSA, 2019). Other medications that are part of the armamentarium of treatments but no included in the NSDUH are naloxone and lofexidine. Naloxone was approved in 1971 for the treatment of opioid overdose and more recently, given the opioid use epidemic in the U.S., an intranasal formulation was developed and was approved by the FDA in 2015. This formulation has saved the life of many people who have overdosed with opioids. However, the overdose epidemic in the United States persists and in 2018 there were almost 50,000 opioid overdose deaths, with nearly 35,000 of them due to fentanyl or other synthetic opioids besides methadone (Kreek et al., 2019). Lofexidine is an anti-hypertension medication that was approved by the FDA in 2018 to treat the symptoms of opioid withdrawal in opioid-dependent patients who discontinue the use of opioids. This medication can help patients who want to be detoxified from opioids and possibly transition to relapse prevention with naltrexone (Yu et al., 2008).

To respond to the public health need of having more medications available to treat SUDs, in 1989, the U.S. Congress mandated the creation of the Medications Development Program at the National Institute on Drug Abuse (NIDA) with the goal of rapidly and efficiently respond to the drug use crisis by supporting and funding the development of medications for SUDs. Since its inception, the program has evaluated hundreds of medications and only a few have reached the finishing line of obtaining FDA approval. The program has been credited for supporting the development of naltrexone, levo-alpha-acetylmethadol (LAAM), buprenorphine alone and in combination with naloxone, buprenorphine implant, and lofexidine (Johnson & Vocci, 1993; Vocci & Ling, 2005).

After more than 30 years of research, there are no FDA-approved medications to treat patients with cannabis, cocaine or methamphetamine use disorder. This is particularly unfortunate because the use disorder and overdose deaths with these drugs have dramatically increased in recent years. It has been reported that between 2010 and 2018, the overdose deaths for cocaine and methamphetamine have more than quadrupled reaching a total of 14,666 and 12,676, respectively. Currently, there are about 4.5 million individuals with a cannabis SUD, 1 million with methamphetamine, another 1 million with cocaine use disorder (SAMHSA, 2019). Therefore, an approved medication for any of these disorders will be an important public health contribution and a unique market opportunity for a pharmaceutical company committed to this field.

For stimulant use disorders (cocaine and methamphetamine) after many years of research and large amounts of time and funds invested, there is no successful pharmacotherapy approved by regulatory agencies. Multiple approaches, targets, medications, and biologics have been tried. The most common pharmacological target has been the dopaminergic system, with disappointing results. Other systems such as the noradrenergic, serotonergic, glutamatergic,

GABAergic, etc., have been targeted and the results have also been disappointing. More recently, biologics such as vaccines, monoclonal antibodies, and engineered enzymes have been tested, with similar results. Unfortunately, currently there are no medications in Phase III clinical trials for these disorders and we may be years away from having any pharmacological treatment approved. This is an area where more collaboration among industry, academics, and government agencies is urgently needed (Montoya, 2012; Montoya & McCann, 2010; Ronsley et al., 2020).

For cannabis use disorders, there is controversy about the need of treatments given the generalized public perception of low risk of cannabis use. However, as it has been reported in the NSDUH of 2019, almost 5 million individuals in the U.S. met criteria and 827,000 people were treated for this disorder. Moreover, enough research has been carried out to confirm that the chronic use of cannabis can produce serious physical and psychological consequences, including cannabis withdrawal syndrome. Therefore, there is a clear need to develop medications to treat the disorder. Several medications have been investigated, some of them targeting the whole disorder and others some specific aspects, for example, sleep disturbances, withdrawal syndrome, reduction reinforcing effects, and relapse prevention. Most tested medications can be two groups: 1) those that have their effect on the cannabinoid system (e.g., cannabinoid agonists, partial agonists, agonists, etc.) and 2) those that have their effect on other neurotransmitter systems (e.g., serotoninergic, GABAergic, noradrenergic, etc.). Unfortunately, the efforts to find a safe and effective medication for cannabis use disorder have not been successful. However, NIDA in partnership with academic and industry investigators continue the search for safe and effective pharmacological interventions for this disorder (Montoya & Weiss, 2018; SAMHSA, 2019; Vandrey & Haney, 2009).

Given the current opioid use epidemic in the United States, efforts have significantly increased to support the development of safer and more effective medication for opioid use disorder. This effort has been channeled through the Helping to End Addiction Long-term (HEAL) initiative of the National Institutes of Health (NIH). Currently more than 40 new compounds and medications are being evaluated under this program. They include small molecules and biologics to prevent or treat opioid use disorder and overdose. The goal is to enhance the armamentarium of options for clinicians to treat these conditions (Collins et al., 2018).

U.S. Food and Drug Administration

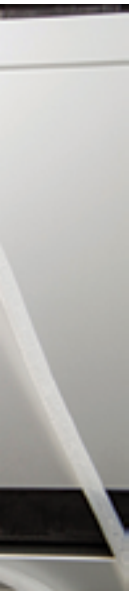
The development of substance use disorder medications requires significant financial and scientific support. The average time from the discovery of a new compound to obtain approval from the regulatory agencies, such as the Food and Drug Administration of the United States, is about fourteen years, if everything goes smoothly. On the image, an FDA researcher at work.

«The development of medications to treat substance use disorder is a challenging and expensive process that often does not result in regulatory approval»

CONCLUSIONS

The development of medications to prevent or treat SUD and drug overdose is a challenging and expensive process that often does not result in regulatory approval. A new compound may fail because of medical safety concerns or lack of efficacy. In addition to the usual medical safety risks, compounds for SUD may fail because of potential abuse liability and iatrogenically inducing a new drug addiction, as well as adverse interactions with drugs of abuse (e.g., increase of respiratory depression of opioids or cardiovascular toxicity of stimulants).

Multiple efforts by academic, industry and government investigators have resulted in the regulatory approval of pharmacotherapies for opioid use disorder and overdose. However, there is room to improve their safety and efficacy. Initiatives by the U.S. government, like the NIH HEAL Initiative and NIDA's Medications Development Program, in partnership with academic and industry investigators, are boosting the research and development of medications for SUD. The expectation



is that in few years more medications will be approved, which will enhance the therapeutic arsenal to significantly reduce the public health burden of SUDs and improve the quality of life of those suffering it.

On a final note, the COVID-19 pandemic has had devastating consequences on SUD and the progress of its medication's development research (Volkow, 2020). The temporary shut-down of animal research laboratories has significantly delayed the pre-clinical testing of new compounds and for clinical research the situation has been worse. Many institutional review boards ordered stopping recruitment of new study participants in clinical trials and those that were recruited before the pandemic were only allowed to remain in the studies for clinical care with minimal collection of data. In addition, some of the study methods, laboratory tests, and assays had to be adapted to accommodate the COVID-19 priorities. Moreover, the FDA had to prioritize all COVID-19 related regulatory submissions, and approvals for non-COVID-19 related medications are significantly delayed. Therefore, the progress in medications development for SUD that had been made before the pandemic slowed down and it is likely that the availability of new medications for patients will delayed. After the pandemic is over or we learn to live with the virus, the hope is that medications development will be accelerated and research can recuperate some of the time that was lost, and safe and effective medications to treat SUD will be available in the near future.

REFERENCES

Banks, M. L., Townsend, E. A., & Negus, S. S. (2019). Testing the 10 most wanted: A preclinical algorithm to screen candidate opioid use disorder medications. *Neuropsychopharmacology, 44*(6), 1011–1012. https://doi.org/10.1038/s41386-019-0336-5

Coffa, D., & Snyder, H. (2019). Opioid use disorder: Medical treatment options. *American Family Physician, 100*(7), 416–425.

Collins, F. S., Koroshetz, W. J., & Volkow, N. D. (2018). Helping to end addiction over the long-term: The research plan for the NIH HEAL Initiative. *JAMA, 320*(2), 129–130. https://doi.org/10.1001/jama.2018.8826

Epstein, D. H., Preston, K. L., & Jasinski, D. R. (2006). Abuse liability, behavioral pharmacology, and physical-dependence potential of opioids in humans and laboratory animals: Lessons from tramadol. *Biological Psychology, 73*(1), 90–99. https://doi.org/10.1016/j.biopsycho.2006.01.010

Johnson, D. N., & Vocci, F. J. (1993). Medications development at the National Institute on Drug Abuse: Focus on cocaine. *NIDA research monograph, 135*, 57–70.

Kiluk, B. D., Carroll, K. M., Duhig, A., Falk, D. E., Kampman, K., Lai, S., Litten, R. Z., McCann, D. J., Montoya, I. D., Preston, K. L., Skolnick, P., Weisner, C., Woody, G., Chandler, R., Detke, M. J., Dunn, K., Dworkin, R. H., Fertig, J., Gewandter, J., … Strain, E. C. (2016). Measures of outcome for stimulant trials: ACTTION recommendations and research agenda. *Drug and Alcohol Dependence, 158*, 1–7. https://doi.org/10.1016/j.drugalcdep.2015.11.004

Kleykamp, B. A., De Santis, M., Dworkin, R. H., Huhn, A. S., Kampman, K. M., Montoya, I. D., Preston, K. L., Ramey, T., Smith, S. M., Turk, D. C., Walsh, R., Weiss, R. D., & Strain, E. C. (2019). Craving and opioid use disorder: A scoping review. *Drug and Alcohol Dependence, 205*, 107639. https://doi.org/10.1016/j.drugalcdep.2019.107639

Kreek, M. J., Reed, B., & Butelman, E. R. (2019). Current status of opioid addiction treatment and related preclinical research. *Science Advances, 5*(10), eaax9140. https://doi.org/10.1126/sciadv.aax9140

Loflin, M. J. E., Kiluk, B. D., Huestis, M. A., Aklin, W. M., Budney, A. J., Carroll, K. M., D'Souza, D. C., Dworkin, R. H., Gray, K. M., Hasin, D. S., Lee, D. C., Le Foll, B., Levin, F. R., Lile, J. A., Mason, B. J., McRae-Clark, A. L., Montoya, I., Peters, E. N., Ramey, T., … Strain, E. C. (2020). The state of clinical outcome assessments for cannabis use disorder clinical trials: A review and research agenda. *Drug and Alcohol Dependence, 212*, 107993. https://doi.org/10.1016/j.drugalcdep.2020.107993

Montoya, I. D. (2012). Advances in the development of biologics to treat drug addictions and overdose. *Adicciones, 24*(2), 95–103. https://doi.org/10.20882/adicciones.101

Montoya, I. D. (Ed.). (2016). *Biologics to treat substance use disorders*. Springer International Publishing. https://doi.org/10.1007/978-3-319-23150-1

Montoya, I. D., Hess, J. M., Preston, K. L., & Gorelick, D. A. (1995). A model for pharmacological research-treatment of cocaine dependence. *Journal of Substance Abuse and Treatment, 12*(6), 415–421. https://doi.org/10.1016/0740-5472(95)02017-9

Montoya, I. D., & McCann, D. J. (2010). Drugs of abuse: Management of intoxication and antidotes. In A. Luch (Ed.), *Molecular, Clinical and Environmental Toxicology. Experientia Supplementum, vol 100* (pp. 519–541). Birkhäuser Basel. https://doi.org/10.1007/978-3-7643-8338-1_15

Montoya, I. D., & Weiss, S. (Eds.). (2018). *Cannabis use disorders*. Springer International Publishing. https://doi.org/10.1007/978-3-319-90365-1

Rasmussen, K., White D. A., & Acri, J. B. (2019). NIDA's medication development priorities in response to the Opioid Crisis: Ten most wanted. *Neuropsychopharmacology*, *44*(4), 657–659. doi: https://doi.org/10.1038/s41386-018-0292-5

Ronsley, C., Nolan, S., Knight, R., Hayashi, K., Klimas, J., Walley, A., Wood, E., & Fairbairn, N. (2020). Treatment of stimulant use disorder: A systematic review of reviews. *PLOS One, 15*(6), e0234809. https://doi.org/10.1371/journal.pone.0234809

SAMHSA. (2019). *Key substance use and mental health indicators in the United States: Results from the 2018 National Survey on Drug Use and Health* (HHS Publication No. PEP19-5068, NSDUH Series H-54). Center for Behavioral Health Statistics and Quality. Substance Abuse and Mental Health Services Administration. https://www.samhsa.gov/data

Skolnick, P., & Volkow, N. D. (2012). Addiction therapeutics: Obstacles and opportunities. *Biological Psychiatry, 72*(11), 890–891. https://doi.org/10.1016/j.biopsych.2012.08.004

Vandrey, R., & Haney, M. (2009). Pharmacotherapy for cannabis dependence: How close are we? *CNS Drugs, 23*(7), 543–553. https://doi.org/10.2165/00023210-200923070-00001

Vocci, F., & Ling, W. (2005). Medications development: Successes and challenges. *Pharmacology and Therapeutics, 108*(1), 94–108. https://doi.org/10.1016/j.pharmthera.2005.06.010

Volkow, N. D. (2020). Collision of the COVID-19 and addiction epidemics. *Annals of Internal Medicine, 173*(1), 61–62. https://doi.org/10.7326/m20-1212

Yu, E., Miotto, K., Akerele, E., Montgomery, A., Elkashef, A., Walsh, R., Montoya, I., Fischman, M. W., Collins, J., McSherry, F., Boardman, K., Davies, D. K., O'Brien, C. P., Ling, W., Kleber, H., & Herman, B. H. (2008). A Phase 3 placebo-controlled, double-blind, multi-site trial of the alpha-2-adrenergic agonist, lofexidine, for opioid withdrawal. *Drug and Alcohol Dependence, 97*(1-2), 158–168. https://doi.org/10.1016/j.drugalcdep.2008.04.002

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