



Indivior: pioneering research and development in the treatment of addictions

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Drug addiction is a chronic, relapsing disorder that is characterized by the compulsion to seek and take a particular drug, by loss of control in limiting intake of the drug, and by the emergence of a negative emotional state (such as dysphoria, anxiety or irritability) when access to the drug is withdrawn.

The disorder is believed to trigger progressive changes to molecular and cellular mechanisms in specific neural networks. For example, neurological changes in the mesolimbic dopamine system may alter the way it modulates learning of the motivational significance of drug-related stimuli. This dysfunction may contribute to enhanced processing of drug-associated cues, leading to drug craving, compulsive drug use, and relapse to drug-seeking behavior. In addition, functional alterations in brain regions such as the amygdala, the anterior cingulate cortex, the dorsolateral prefrontal cortex, and the orbitofrontal cortex (which are involved in attention, emotional processing, goal-directed behavior, associative learning, decision making, and response suppression) will ultimately compromise cognitive regulatory processes, so the individual fails to inhibit self-defeating urges or desires.

The complexity of these neuroadaptations means that the therapeutic management of substance-use disorders (SUDs) poses a major challenge for research and drug development. Despite the societal burden of drug addiction and related psychiatric problems, there are still no effective drug strategies that promote long-lasting drug abstinence and recovery while ensuring satisfactory patient compliance.

It is estimated that globally, in 2012,

between 162 million and 324 million people (between 3.5% and 7.0% of the world's population aged 15–64) had used an illicit drug, such as cannabis, opioids, cocaine and psychostimulants, at least once in the previous year¹. Opioids (which include heroin and prescription opioids used for non-medical purposes) are the biggest source of global drug-related deaths, which totaled between 95,000 and 226,000 in 2012¹. In the United States, the National Survey on Drug Use and Health 2013 revealed that an estimated 21.6 million persons aged 12 or older (8.2%) were diagnosed with substance dependence or abuse in the previous year², based on criteria specified in the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition*. Of these, 2.6 million were classified with dependence or abuse of alcohol and illicit drugs; 4.3 million had dependence or abuse of illicit drugs but not alcohol; and 14.7 million had dependence or abuse of alcohol but not illicit drugs. The illicit drugs with the greatest dependence or abuse were marijuana (4.2 million), opioid pain relievers (1.9 million), cocaine (855,000) and heroin (517,000)². Slightly more than half (52.2%, an estimated 137 million) of Americans aged 12 or older reported being current drinkers of alcohol in the 2013 survey. Nearly one-quarter (22.9%, about 60.1 million people) had been binge alcohol users in the past 30 days. Heavy drinking was also reported by 6.3% of the population aged 12 or older, which is 16.5 million people².

Indivior's vision and mission

Indivior aims to ensure that all patients around the world can have unrestricted access to high-quality treatment for

the chronic relapsing conditions and co-morbidities of addiction. It is a speciality pharmaceutical business that was originally developed and managed as a separate division of Reckitt & Colman and, since 1999, Reckitt Benckiser. Indivior has a long history of supporting the addiction-treatment community — it discovered buprenorphine in 1966, and has been involved in manufacturing and supplying it to patients since 1996 as a treatment for addiction.

In the United States, a significant breakthrough in the treatment of opioid-use disorder occurred with the introduction of methadone in the 1960s. However, the federal narcotic (methadone) treatment regulations in 1972 and the Narcotic Addict Treatment Act (NATA) of 1974 limited methadone maintenance treatment to the context of the Opioid Treatment Program (OTP) (methadone clinic) setting. This established a closed distribution system for methadone such that to receive methadone treatment, patients were required to attend an OTP. Efforts to bring opioid-dependence treatment to the mainstream of medical care began to take shape again in the 1990s. In July 1990, Charles R. Schuster, then director of the US National Institute on Drug Abuse (NIDA), convened a NIDA technical review meeting on the status of buprenorphine as a potential treatment for opioid dependence. NIDA grantees and researchers from the NIDA Addiction Research Center presented data from clinical pharmacology studies and clinical trials involving the use of buprenorphine for detoxification or maintenance therapy. Perhaps the most compelling data were in a preliminary report that was later published in the *Journal of the American Medical Association*³.

In April 1994, NIDA and Reckitt & Colman signed a cooperative research and development agreement (CRADA) entitled “*Development of Buprenorphine Products for the Treatment of Opioid Dependence*”. The goal of the CRADA was “to cooperatively design and perform the necessary research and cooperatively analyze the data generated to develop and attempt to gain FDA approval of two buprenorphine products for the treatment of opioid dependence”. The first product, buprenorphine, was administered ‘on premises’ in clinics registered pursuant to the requirements of the federal NATA. A second development product, buprenorphine

combined with naloxone, was used as a ‘take home’ medication. The presence of naloxone minimized the likelihood of illicit use by opioid-dependent persons. The CRADA was extended four times to complete the requirements for the new drug application (NDA) and to perform a ‘best practices’ study, and finally ended in October 2003.

In October 2000, the Children’s Health Act was enacted into law, and title XXXV provided a “Waiver authority for physicians who dispense or prescribe certain narcotic drugs for maintenance treatment or detoxification treatment of opioid-dependent patients”. This part of the law is also known as the Drug Addiction Treatment Act of 2000 (DATA 2000). Under the provisions of DATA 2000, qualifying physicians can obtain a waiver from the special registration requirements in the NATA of 1974, and its enabling regulations, to treat opioid dependence with schedule III, IV and V opioid medications that have been specifically approved by the US Food and Drug Administration (FDA) for that indication. It allows them to prescribe and dispense these medications in treatment settings other than licensed OTPs, including in office-based settings.

In October 2002, the FDA approved two sublingual (‘under the tongue’) tablet formulations of buprenorphine as opioid-dependence treatment medications: buprenorphine alone (Subutex®) and a combination tablet containing buprenorphine plus naloxone in a 4:1 ratio (Suboxone®). Suboxone® relies on the fact that naloxone is more effective by injection than by the sublingual route. If the combination is taken sublingually, as directed, the small amount of naloxone that is systemically available does not interfere with the desired effects of buprenorphine. However, if the combination form is dissolved and injected by an individual who is physically dependent on full agonist opioids, the increased bioavailability of naloxone by this route will precipitate an opioid withdrawal syndrome. Both Subutex® and Suboxone® tablets, and more recently Suboxone® sublingual film, are schedule III opioids under the US Controlled Substance Act of 1970 and are therefore eligible for use to treat opioid addiction under DATA 2000.

Outside the United States, Indivior currently markets Subutex® sublingual tablet CIII (containing 0.4 mg, 2.0 mg or 8.0 mg buprenorphine) as well as a Suboxone®

sublingual tablet. Suboxone® sublingual film (CIII), initially launched in the United States in 2010 and currently marketed in the United States, Australia and Malaysia, was developed with the intention of producing similar safety and efficacy to the Suboxone® tablet, using MonoSol Rx proprietary PharmFilm® technology to deliver a fast-dissolving sublingual film in unit-of-use child-resistant packaging.

Indivior’s research & development

Progress in science and technology constantly opens new vistas, and Indivior is working to provide better treatments and methodologies that improve the measurement of clinical efficacy and safety. Novel drug options are based on a greater understanding of pathophysiology through a variety of molecular approaches, aided by advances in pharmaceutical science, and are targeted at patients whose conditions are understood at a mechanistic level through objectively assessed biological effects. Given Indivior’s focus on putting the patient first, the company’s research and development (R&D) mission targets patients’ unmet needs, aiming for stable drug delivery, decreased frequency of dosing, increased treatment adherence and retention, decreased diversion and misuse of drugs, better management of overdose, and treatments for the co-morbidities of addiction. Matrix teams allow Indivior’s R&D strategies to be translated into integrated plans that influence the development stages, commercialization and product life cycle.

Product development at Indivior occurs in four clusters of projects that have specific aims: expanding access to treatment for opioid-use disorder; providing access to rescue medications (for opioid overdose and cocaine intoxication); addressing unmet medical needs in the treatment of alcohol-use disorder; and treating the psychiatric co-morbidities of addiction. We will explore each of these in turn.

Expanding access to treatment for opioid-use disorder

Indivior is developing a new buprenorphine sustained-release formulation using the Atrigel® delivery system, which consists of a polymeric solution of a biodegradable poly-(DL-lactide-co-glycolide) co-polymer dissolved in *N*-methyl pyrrolidone (NMP), a water-miscible biocompatible solvent⁴.

After subcutaneous injection, NMP interacts with body fluids, which replace the NMP as it diffuses out of the polymer matrix. This precipitates the polymer, trapping the drug inside and forming an amorphous solid implant *in situ*. The implant releases buprenorphine over a one-month period by diffusion as the polymer biodegrades. This product is currently in a phase III randomized, double-blind, placebo-controlled, multicenter trial (NCT02357901) to assess the efficacy, safety and tolerability of multiple subcutaneous injections of the formulation over 24 weeks in treatment-seeking subjects with opioid-use disorder.

Suboxone® was originally delivered sublingually to avoid the metabolism of buprenorphine in the gastrointestinal tract and liver. Indivior is now developing buprenorphine hemiadipate, an ester of buprenorphine and adipic acid, as a pro-drug to improve the oral bioavailability of buprenorphine for the treatment of opioid-use disorder. This new oral capsule also provides a naloxone-free formulation that acts as a physical barrier to deter users from attempting to extract the drug, by filling a gel-like formulation into a hard gelatine capsule and by adding excipients such as guar gum (a viscosity enhancer) and hydroxypropyl methylcellulose (a gelling and swelling agent).

Providing access to rescue medications

Opioid overdose was the second leading cause of accidental death in the United States in 2013, claiming 16,235 lives from overdose of opioid pain relievers and 8,257 lives from heroin overdose⁵. The standard medical protocol for treating opioid overdose is to administer naloxone, an injectable opioid-receptor antagonist that rapidly and effectively reverses the effects of natural and synthetic opioids, including propoxyphene, methadone and certain mixed agonist-antagonist analgesics such as nalbuphine, pentazocine, butorphanol and cyclazocine. Despite the proven clinical efficacy of naloxone, the injectable format limits the drug's availability where and when it is needed most — on the front line at the time of overdose. Indivior is currently developing a novel formulation of naloxone for nasal administration with a data and regulatory package to support the filing of an NDA in 2015.

Indivior's guiding principles

Indivior fosters a culture based on the four principles of entrepreneurship, teamwork, commitment and achievement. Additionally, all disciplines are encouraged to embrace the core values of communication, mutual respect and excellence to succeed in the above stated mission. Indivior also lives by a set of guiding principles. These principles assist Indivior in the conduct of its daily business and are represented below:



Focus on patient needs to drive decisions

Indivior believes that as long as its employees remain true to the patients and what is best for them, decisions will come easily and remain pure in intent.



Seek the wisdom of the team

Success in the Indivior business model requires local knowledge of the challenges and issues in order to implement the right solutions.



Believe that people's actions are well intended

Indivior's corporate culture is conducive to people doing their best work based on an inherent trust.



Care enough to coach

By learning from each other, Indivior is able to grow its core competencies and gain economies of scale where 1+1 can equal 3.



See it, own it, make it happen

In addition to instilling a patient-focused culture, Indivior's employees are driven by a 'roll up the sleeves' attitude.



Demonstrate honesty and integrity at all times

Honesty and integrity in all personal and professional dealings are an essential element of Indivior's corporate ethos.

Cocaine abuse and dependence continue to be a major health problem globally². A high proportion of cocaine users suffer medical and psychiatric consequences associated with its use. The latest data from the Drug Abuse Warning Network (DAWN)⁶ show that 505,224 users presented to US emergency departments in 2011. Cocaine-related visits to emergency departments can be associated with a variety of complaints and conditions, including chest pain, cardiac arrhythmia, myocardial ischemia, systolic hypertension, exacerbation of asthma, agitation and seizures^{7,8}. Indivior is currently developing a cocaine esterase formulation that catalyzes the hydrolysis of cocaine to the inactive metabolites ecgonine methyl ester and benzoic acid. This action mimics

endogenous, natural butyrylcholinesterase, but has approximately 1,000-fold greater activity⁹. The formulation is derived from characterized cells isolated from *Rhodococcus* bacteria. It has the potential to transform the management of cocaine intoxication in emergency departments, including faster resolution of symptoms and shorter visits to emergency departments, fewer hospitalizations, possibly fewer deaths, and a reduced cost to the medical care system. A recent phase IIa trial (NCT01846481)^{10,11} demonstrated that the cocaine esterase formulation rapidly hydrolyzed plasma cocaine and decreased cocaine-induced physiological effects, supporting its use for the treatment of cocaine intoxication.

Addressing unmet needs in the treatment of alcohol-use disorder

Alcohol-use disorder is a chronic disease with a multifactorial etiology that is characterized by excessive drinking, alcohol craving, loss of control of alcohol intake, tolerance and physical dependence with a risk of potentially life-threatening alcohol withdrawal syndrome if alcohol consumption suddenly stops. Chronic alcohol consumption affects nearly all neurotransmitter or neuromodulator systems, either directly or indirectly, with long-term adaptive changes in gamma-aminobutyric acid (GABA) receptors, glutamate receptors, central noradrenaline activity, and downregulation of the dopaminergic system¹². Several decades of research have focused on the way alcohol enhances inhibitory GABA-mediated transmission, mainly by potentiation of the GABA_A receptor function, and possibly through an indirect increase in GABA release.

These discoveries have led to drugs that target the GABA system, such as baclofen. The pharmacological properties of baclofen have led to studies of its potential benefit in treating alcohol-use disorder. The FDA originally approved baclofen in 1977 for use in spasticity associated with neurologic conditions, such as multiple sclerosis and spinal-cord lesions. Baclofen is an agonist at the B subunit of the GABA receptor. GABA_B receptors are highly expressed in the limbic system, suggesting a major role in regulating emotional behavior. Numerous case reports, case series and open-label trials have demonstrated that baclofen prolongs the time to first drink, reduces the number of drinking days, and helps to maintain abstinence¹³. The evidence also suggests that baclofen can be used safely by patients who also have cirrhosis of the liver, a disease that is not uncommon in alcohol-dependent patients¹³. Also unique is the observational evidence gathered in France over the past few years in which patients with alcohol dependence resistant to the usual treatments were treated with escalating doses of baclofen and no upper dose limit. Based on these data, in March 2014 the French regulatory agency — Agence Nationale de Sécurité du Médicament et des Produits de Santé — granted a temporary recommendation for baclofen to be used to treat alcoholism after other treatments have failed.

Nonetheless, baclofen has several pharmacokinetic limitations, including a narrow window of absorption in the upper small intestine and rapid clearance from the blood. The short half-life of baclofen in the plasma following oral administration partly explains why the drug must be administered three or four times per day to maintain therapeutic levels, resulting in fluctuating circulating plasma drug levels. Avoiding repeated peaks and troughs during the day while maintaining a greater average blood baclofen concentration may minimize any side effects. In order to overcome the clinical deficiencies of baclofen, Indivior is currently developing arbaclofen placarbil, a novel transported prodrug of R-baclofen that is designed to be absorbed throughout the intestine both by the active nutrient transporter monocarboxylate transporter-1 (MCT-1) and by passive diffusion¹⁴. After oral administration, arbaclofen placarbil is efficiently converted to R-baclofen by non-specific carboxylesterases, primarily human carboxylesterase-2 (hCE-2) in gastrointestinal tissues. Unlike baclofen, arbaclofen placarbil is well absorbed from the large intestine, allowing the drug to be successfully formulated in a sustained-release formulation that may allow for less frequent dosing and reduced fluctuations in the plasma. This innovative delivery may lead to better clinical efficacy and tolerability, increased subject convenience and compliance from less frequent dosing (just twice a day rather than three or four times), and an improved safety profile. A detailed clinical development plan is currently being drafted to assess the clinical efficacy and safety of arbaclofen placarbil for the treatment of alcohol-use disorder.

Exploring the psychiatric co-morbidities of addictions

Epidemiological and clinical studies¹⁵ have shown that psychiatric disorders, including borderline and antisocial personality disorders, bipolar disorders, psychosis, depression and anxiety, are highly co-morbid with SUDs. Two or more disorders present at the same time are known as co-occurring (or sometimes 'dual') disorders. Co-occurring disorders can increase the severity of addiction and complicate the recovery; it can be helpful to use a multidisciplinary and holistic approach to the treatment of patients suffering from SUDs. Schizophrenia, for

example, is a chronic disorder characterized by a life-long pattern of acute psychotic episodes superimposed on chronically poor psychosocial adjustment. The symptoms can be grouped into four domains: positive, such as delusions, hallucinations and disorganized speech and behavior; negative, including social withdrawal, avolition (a lack of goal-oriented activity) and 'blunted' affect (a lack of emotional response); cognitive, such as impaired sustained attention, executive function and working memory; and affective, such as anxiety, depression, hostility, aggression and increased risk of suicide. These occur in different combinations and to different degrees in each patient. Given the extensive heterogeneity of symptoms among individual patients, schizophrenia can be considered a clinical syndrome rather than a single disease entity.

Indivior is developing a sustained-release formulation of the antipsychotic drug risperidone using the Atrigel® delivery system for the subcutaneous administration of risperidone at monthly intervals for the long-term treatment of schizophrenia¹⁶⁻¹⁸. A phase III randomized, double-blind, placebo-controlled, multicenter trial (NCT02109562) to assess its efficacy, safety and tolerability in subjects with acute schizophrenia is currently underway.

Concluding remarks

The treatment of addiction aims to reduce drug use by decreasing cravings and addressing any withdrawal symptoms and co-occurring disorders through pharmacological and behavioral therapy, as well as psychosocial support to eventually end illicit drug-taking behavior. There are many barriers that stop patients accessing the support they need, however, from societal prejudices to an absence of trained professionals and a lack of information about treatment options. Indivior is committed to working with patient groups, prescribers and governments to better understand and overcome these barriers, and to contribute to a comprehensive multidisciplinary approach. This will include pharmacological and psychosocial interventions that can result in the reduction and ultimate cessation of drug use by the patient, preventing future harms associated with the abuse of drugs, and improving the quality of life and well-being of patients with SUDs.

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