



Indivior Inc.
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Fighting apathy and lack of awareness in the struggle against substance use disorder

Taking a patient-centered approach, Indivior is developing innovative treatments for addiction to opioids, alcohol, and stimulants, as well as accompanying illnesses such as schizophrenia.

Drug addiction is a chronically relapsing disorder characterized by long-lasting changes in the brain. Dysfunction in the neural circuits that control cognitive regulatory processes leads to the compulsion to seek and take the drug, the loss of control in limiting intake, and the emergence of a negative emotional state when access to the drug is withdrawn. Substance use disorder is a global health crisis that has reached epidemic proportions. Despite the availability of medications, many individuals who struggle with addiction do not get the help they need owing to social stigma, lack of awareness of or access to treatment, or comorbid illnesses that contribute to high rates of nonadherence and relapse.

Indivior is a global specialty pharmaceutical company with a mission to discover and develop innovative medications that help transform patients' lives through its industry-leading understanding of addiction and the chronic conditions and co-occurring disorders of addiction.

"The inherent complexity and multidimensional nature of relapse requires pioneering scientific solutions," said Indivior's CSO Christian Heidbreder. "Indivior's R&D [research and development] is dedicated to the development of innovative therapeutics that support patients on their pathway to recovery."

Overcoming opioid use disorder

In the United States alone, opioid use disorder costs more than half a trillion dollars and contributes to nearly 50,000 deaths attributed to drug overdose.

Despite the availability of medications to treat opioid use disorder, only a minority of patients have ever received treatment. Even for those receiving treatment, the high rate of nonadherence to daily medications has been associated with increased odds of relapse and higher total health-care costs compared with adherent patients.

Indivior has a long history of supporting the addiction treatment community through education on the importance of continuity of care and through the manufacture and supply of buprenorphine, a μ -opioid receptor partial agonist and κ -opioid receptor antagonist. The Indivior Group launched the first buprenorphine-based medication for the treatment of opioid dependence in 1996. The company's medications are available in more than 40 countries and include buprenorphine sublingual tablets (SUBUTEX), buprenorphine and naloxone sublingual tablets (SUBOXONE), buprenorphine and naloxone sublingual film (SUBOXONE film), and the first US Food and Drug Administration (FDA)-approved once-monthly injectable buprenorphine formulation (SUBLOCADE) (Fig. 1).

SUBLOCADE represents an evidence-based shift in the treatment of opioid use disorder. Clinical trials have suggested that this treatment results in brain μ -opioid receptor occupancy of 70% to 80% over the entire one-month period, blocking the subjective drug-liking effects of illicit opioids and helping to control withdrawal symptoms and craving. Taken together, these properties reduce illicit opioid use with no compensatory non-opioid illicit drug use (Fig. 2).

The FDA approval of SUBLOCADE last year was only the first step of a long commitment to better understand how to address the unmet needs of patients suffering from opioid use disorder. Indivior recently established a partnership with Virginia Commonwealth University, Inova Fairfax Hospital and Virginia Tech Carilion Research Institute to study the effects of SUBLOCADE in the emergency room environment to prevent repeated opioid overdoses and potentially change standards of care.

"Another example of our focus on patients also involves the implementation of real-world studies to understand the true determinants of recovery in patients initiating treatment with SUBLOCADE," Heidbreder said.

All-encompassing approach

Beyond the development of treatments for opioid use disorder, Indivior is pioneering therapies to address the unmet needs of patients addicted to alcohol and stimulants. To that end, the company is developing innovative approaches that target γ -aminobutyric acid type B (GABA_B), orexin-1, and dopamine (DA) D₃ receptors.

Long-term exposure to drugs of abuse causes adaptive changes in several neurotransmitter systems, including GABA receptor signaling. Exposure to psychostimulants depresses the normal function of GABA_B receptor signaling in the mesolimbic dopaminergic system, which plays a role in the positive reinforcing properties of several drugs of abuse and may also contribute to the negative

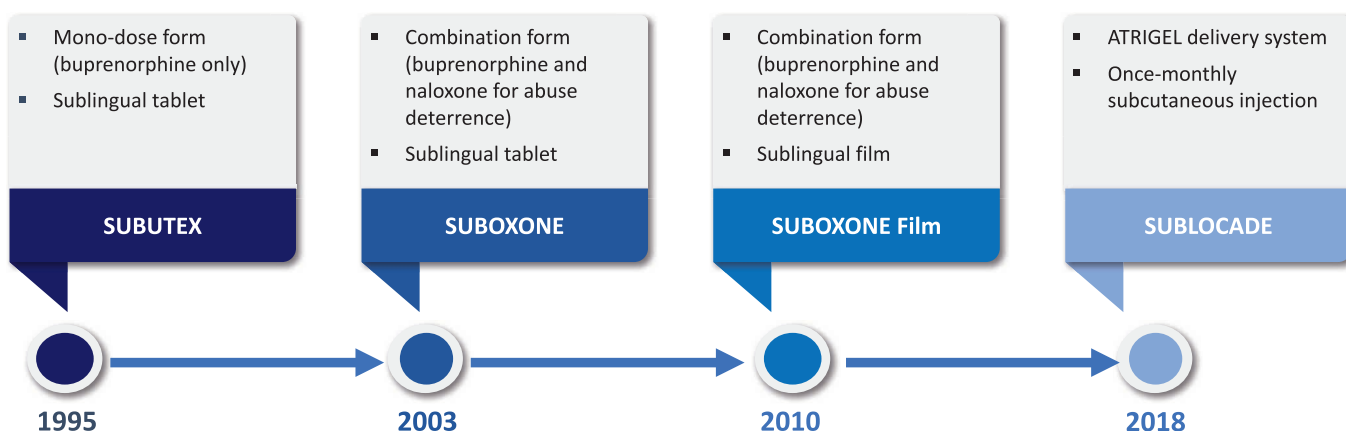


Fig. 1 | Four generations of buprenorphine treatments to fight opioid use disorder. SUBLOCADE represents the fourth generation of buprenorphine-based medications and is an evidence-based shift in the treatment of opioid use disorder. Clinical trials have suggested that this treatment results in a μ -opioid receptor occupancy in the brain of 70% to 80% over the entire 1-month period, blocking the subjective drug-liking effects of illicit opioids and helping to control withdrawal symptoms and craving. Taken together, these properties reduce illicit opioid use with no compensatory nonopioid illicit drug use.

reinforcing effects associated with their withdrawal. GABA_B agonists such as baclofen have been the target for the development of pharmacotherapies for alcohol and stimulant use disorders. Indivior is developing arbaclofen placarbil, a novel transported prodrug of (*R*)-baclofen, the more active of the two baclofen enantiomers, for the treatment of alcohol use disorder. In partnership with Addex Therapeutics, Indivior is also pursuing another strategy with their lead molecule ADX71441, which only enhances the activity of GABA_B receptors when and where needed physiologically. As a result, this lead compound is expected to offer superior selectivity and to be suitable for long-term treatment without tolerance.

A second molecular target that has been identified by Indivior as a priority pathway for the treatment of substance use disorders is the orexin receptor. Two identified orexin receptors (OX1 and OX2) seem to have distinct patterns of expression in the brain and differential functionality: the OX2 receptor is involved in the regulation of the sleep/wake cycle and energy homeostasis, whereas selective blockade of the OX1 receptor decreases drug seeking and prevents relapse or reinstatement of drug-seeking behavior during abstinence in animal models of addiction. Indivior has entered into a partnership with C4X Discovery to develop their lead molecule, C4X3256, a selective OX1 receptor antagonist.

Research has also pointed toward activation of the mesolimbic DA system as a common denominator in response to drugs of abuse. The restricted high-density localization of the DA D₃ receptor into key elements of the mesolimbic DA system, together with evidence of changes in the expression of the DA D₃ receptor following repeated exposure to drugs of abuse, suggested that selectively targeting the DA D₃ receptor may translate into a new treatment option for substance use disorder. This hypothesis is supported by a series of nonclinical studies demonstrating that selective DA D₃ receptor antagonists reduce drug-induced incentive motivation, attenuate the drug's rewarding efficacy, and reduce reinstatement of drug-seeking behavior triggered either by re-exposure to the drug itself, re-exposure to environmental cues that have been previously associated with drug-taking behavior, or stress. Indivior is currently developing a selective DA D₃ receptor antagonist, APV202701A, in partnership with Aptuit.

In addition, Indivior has built a new R&D Center of Excellence in Hull, United Kingdom, and has expanded its R&D facilities in Fort Collins, Colorado, to pioneer novel treatments for patients struggling with substance use disorders. "As Indivior's largest capital investment in R&D, we will leverage these new research centers to advance the science of addiction and make significant contributions to addiction medicine," Heidbreder said.

Addressing associated illnesses

Epidemiological and clinical studies have shown that substance use disorders are highly comorbid with psychiatric disorders, including anxiety, depression, bipolar disorder, attention-deficit hyperactivity disorder, borderline personality disorder, antisocial personality disorder, and schizophrenia. For example, a recent systematic review and meta-analysis revealed that the prevalence of any substance use disorder in treatment-seeking patients diagnosed with schizophrenia or first-episode psychosis was 42%.

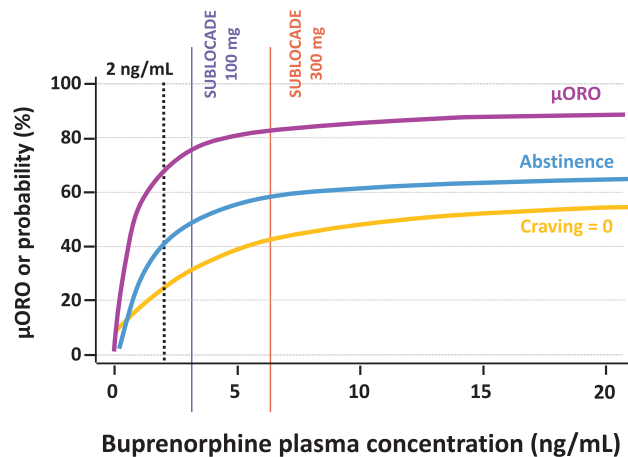


Fig. 2 | Exposure-response relationships between clinical endpoints and predicted whole brain

μ-opioid receptor occupancy (μORO). The threshold plasma concentration of buprenorphine needed to effectively block the subjective drug-liking effects of a full opioid agonist such as hydromorphone with 70% μORO was found to be 2 ng/mL. The overall probability of negative illicit opioid use (that is, abstinence) increased within the range of 70% to 90% μORO. The probability of zero craving also increased between 70% to 90% μORO. SUBLOCADE 300/100 mg data suggested that monthly 100 mg doses following two initial doses of 300 mg maintained mean average (C_{avg}) buprenorphine plasma concentrations of 3.14 ng/mL, which corresponded to 75% μORO. SUBLOCADE 300/300 mg data suggested that repeated monthly doses of SUBLOCADE 300 mg provided a buprenorphine plasma C_{avg} of 6.32 ng/mL, which corresponds to 83% μORO.

Long-acting injectable antipsychotics may facilitate improvements in medication compliance. Indivior recently received FDA approval for PERSERIS, the only once-monthly, long-acting injectable form of the antipsychotic drug risperidone for the treatment of schizophrenia in adults.

"Although the causality or directionality of the comorbidity is sometimes difficult to establish, it is important for us to look at patients with substance use disorders from a more holistic perspective and address any mental illnesses they may suffer from," Heidbreder said.

Patient-focused culture

Thoroughly characterizing the clinical efficacy and safety of new pharmacotherapies remains essential to drug development and the regulatory approval process. Equally important is the elucidation of patients' personal experiences with respect to their symptoms, their medication, and their quality of life. Indivior has invested a substantial amount of time and effort into the integration of patient-reported outcome measures as part of its clinical development plans.

For example, Indivior has launched the Remission from Chronic Opioid Use: Studying Environmental and Socioeconomic Factors on Recovery (also known as the RECOVER Study), which is collecting up to 24-month longitudinal data from patients suffering from opioid use disorder. The data collected encompass demographics, drug use, drug treatment, family relationships, quality of life, mental and physical health, health-care utilization, crime, housing, employment, and urine drug screening.

"We believe that these integrated clinical development programs actively engage patients and their communities and will progressively break down barriers and misconceptions about substance use disorders and their treatment," Heidbreder said. "Focusing on the importance of continuity of care, monitoring patient progress in the short, medium, and long-term, providing evidence-based training to

health-care providers, and understanding better the underlying causes of relapse are the hallmarks of our mission and vision in addiction medicine."

Catalyzing change

Since Indivior's inception, the company has actively partnered with health-care professionals, the public health community, policymakers, and payers to humanize people suffering from addiction and to treat addiction as a chronic, relapsing medical condition rather than a social disorder. Through collaborations with health-care and scientific communities, the company is advancing knowledge about the unmet needs of patients and the most effective ways to deliver the best available treatments.

Through close collaboration with regulators, physicians, and pharmacists, Indivior is helping to ensure treatment integrity by minimizing diversion, misuse and abuse of addiction medications, and activating risk-management programs to ensure patient safety.

"Through a grassroots effort, we've established global and community-based partnerships and engaged at all levels across the addiction treatment spectrum to promote alternative options, including office-based treatment. We've also worked diligently and strategically to identify and address the unmet needs of patients," Heidbreder said. "We're proud of our history but, more than that, we're excited about our future."

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