



## Commentary

## Epigenetic pharmacotherapy for substance use disorder

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## ABSTRACT

Identifying novel therapeutics for the treatment of substance use disorder (SUD) is an area of intensive investigation. Prior strategies that have attempted to modify one or a few neurotransmitter receptors have had limited success, and currently there are no FDA-approved medications for the treatment of cocaine, methamphetamine, and marijuana use disorders. Because drugs of abuse are known to alter the expression of numerous genes in reward-related brain regions, epigenetic-based therapies have emerged as intriguing targets for therapeutic innovation. Here, I evaluate potential therapeutic approaches and challenges in targeting epigenetic factors for the treatment of SUD and highlight examples of promising strategies and future directions.

## 1. Emerging support for epigenetic pharmacotherapies in SUD

Initially coined by Conrad Waddington in 1942, contemporary use of the term epigenetics generally refers to the broad spectrum of molecular mechanisms that regulate chromatin dynamics and gene expression, independent of changes in DNA sequence (For reviews on epigenetics see Refs. [1–5]). Biochemically, DNA methylation and histone modifications (e.g., acetylation, methylation and phosphorylation) are the primary epigenetic mechanisms that have been investigated. However, hundreds of additional modifications to DNA, histones, and RNAs, with yet to be determined functions, have been recently identified [6–8]. Acting as a guide or anchor for chromatin remodeling complexes, long non-coding RNAs are also considered to be part of the epigenetic repertoire by facilitating gene- and cell type-specific activity of ubiquitous histone and DNA-modifying proteins [9,10]. In the central nervous system, recent evidence indicates that modifications to DNA and histones play an essential role in the development and maintenance of neuronal networks, learning and memories processes, and behavioral output in response to environmental stimuli [11]. In some cases, epigenetic alterations are also associated with enduring, pathophysiological changes in neural function and disease susceptibility [12].

In multifactorial, polygenic disorders such as SUD, epigenetics is a particularly intriguing area of research. Indeed, repeated exposure to drugs of abuse alters the expression of hundreds of genes in reward-related brain regions, triggering maladaptive changes at the molecular, cellular, and circuit levels that promote drug-seeking and -taking behaviors [13–15]. Concomitant deviations in histone- and DNA-modifying enzyme activity and gene-specific epigenetic modifications are also observed following drug use. For example, in preclinical studies,

cocaine [16–22], methamphetamine [23,24], amphetamine [25], nicotine [26,27], 3,4-methylenedioxy-methamphetamine (MDMA) [28], opiates [29,30], ethanol [31,32], cannabis [33,34], and inhalants [35] alter DNA and/or histone modification in the nucleus accumbens, a key brain region involved in reward processing. Similar to pre-clinical studies, variations in epigenetic modifications, non-coding RNAs, and histone-modifying enzymes have also been observed in post-mortem brain samples from human drug abusers [14,36–38].

In animal models for SUD, pharmacological manipulation of some epigenetic-related proteins is sufficient to ameliorate drug-induced behavioral, transcriptional, and physiological changes [39]. For example, non-selective histone deacetylase (HDAC) inhibitors trichostatin A and phenylbutyrate dose-dependently reduced cocaine self-administration [40], and the HDAC3-selective inhibitor, RGFP-966, enhanced extinction of cocaine conditioned place preference (CPP) [41], an animal model that measures contextual reward processing. Sirtinol, a class III histone deacetylase (sirtuin) inhibitor, reduced cocaine conditioned place preference, whereas the sirtuin agonist, resveratrol, had the opposite effect [42]. Following repeated cocaine administration, histone acetylation reader protein, BRD4, is elevated in the nucleus accumbens and recruited to promoter regions of addiction-related genes, and pharmacological inhibition of BRD4 attenuated transcriptional and behavioral responses to cocaine and heroin [37,43]. Additionally, pharmacological manipulation of other DNA- and histone-modifying enzymes such as, DNMT [44–53], KDM6b [54], G9a [20], and PRMT1 [55] alter behavioral responses to drugs of abuse (Table 1). Outside of small molecule inhibitors, viral-mediated manipulation of DNA- and/or histone-modifying genes has also been found to alter drug-seeking behaviors [56–61]. Thus, with the potential to reverse or normalize the

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**Table 1**  
Effects of epigenetic pharmacotherapies on drug-seeking behaviors.

Drug of abuse	Epigenetic inhibitor	Target(s)	Route of delivery	Behavioral effect	Reference(s)
Cocaine	TSA	HDACs	Systemic	↓ SA	[40]
	Phenylbutyrate	HDACs	Systemic	↓ SA	[40]
	Garcinol	HATs	Systemic	↓ Reinstatement of SA	[113]
	RGFP-966	HDAC3	Systemic	↑ Extinction of SA	[68]
	RGFP-966	HDAC3	Systemic	↑ Extinction of CPP	[41]
	RG108	DNMTs	Intra-NAc	↓ Incubation of craving	[44]
	TSA	HDACs	Intra-NAcS	↑ SA	[114]
	JQ1	BETs	Systemic and intra-NAc	↓ Acquisition of CPP	[43]
	SKLB-639	PRMT1	Systemic	↓ Acquisition of CPP	[55]
	GSK-J4	KDM6B	Systemic	↓ Reinstatement of CPP	[54]
	Methionine	DNA methylation	Systemic	↓ Acquisition of CPP	[52]
	BIX01294	GLP/G9a	Intra-NAc	↑ Acquisition of CPP	[20]
	Sirtinol	Sirtuins	Intra-NAc	↓ Acquisition of CPP	[42]
	Nicotine	Phenylbutyrate	HDACs	Systemic	↓ Acquisition of CPP
NaB		HDACs	Systemic	↓ Reinstatement of SA	[116]
Morphine	NaB	HDACs	Systemic	↑ Extinction of CPP	[117]
	NaB	HDACs	Systemic	↑ Acquisition Of CPP	[118]
Heroin	JQ1	BETs	Intra-DS	↓ SA	[37]
	NaB	HDACs	Systemic	↑ Reinstatement of SA	[119]
Ethanol	NaB and MS-275	HDACs	Systemic	↓ SA	[120]
	RG108	DNMTs	Intra-mPFC	↓ SA	[48]
	5-Aza-dc	DNMTs	Intra-mPFC	↓ SA	[53]

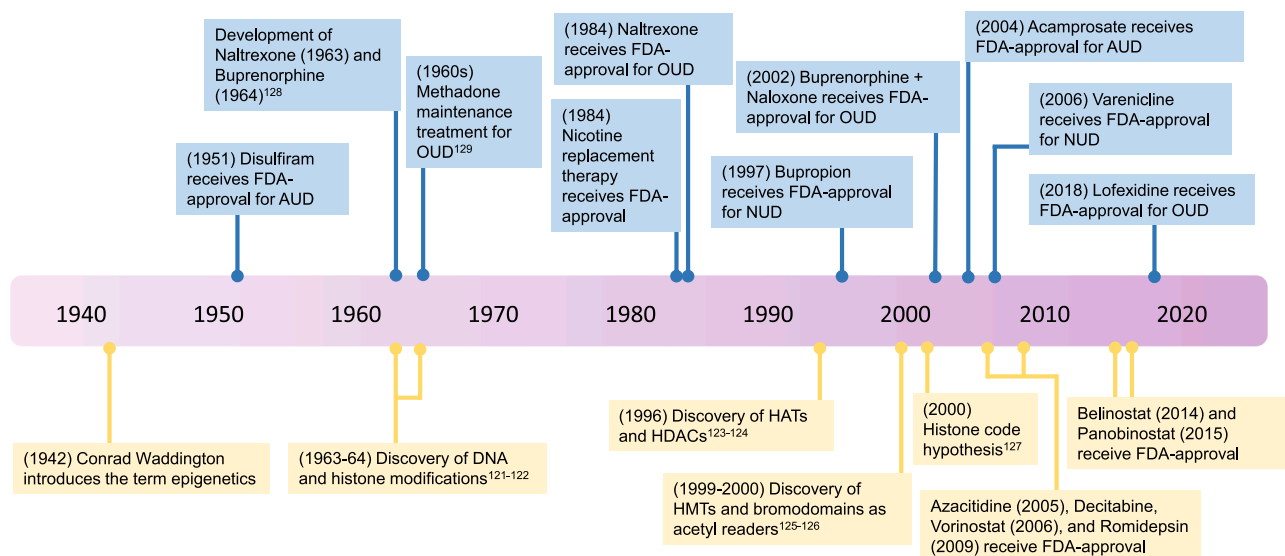
5-Aza-dc, 5-aza-2'-deoxycytidine; BETs, bromodomain and extra terminal domain; CPP, conditioned place preference; DNMTs, DNA methyltransferases; DS, dorsal striatum; GLP, G9a-like protein; HATs, histone acetyltransferases; KDM6B, lysine demethylase 6B; mPFC, medial prefrontal cortex; NaB, sodium butyrate; PRMT1, protein arginine methyltransferase 1; NAc, nucleus accumbens; NAcS, nucleus accumbens shell; SA, self-administration; TSA, Trichostatin A.

extensive transcriptional dysregulation and maladaptive behaviors caused by repeated drug use, epigenetic pharmacotherapy is a promising area of drug discovery for SUD.

## 2. Epigenetic therapeutic innovation and potential treatments for SUD

Despite the thousands of lives lost during the current opioid epidemic and the high rates of cocaine-linked deaths in African American and Hispanic populations over the past 3 decades [62], a dearth of new

and effective clinical treatments for SUD remains. In fact, almost all current FDA-approved pharmacological treatments for SUD and other psychiatric disorders are based on neurotransmitter receptor agonist/antagonist that were identified over 40 years ago [63] (Fig. 1). It is clear, however, that SUD is more complex than changes in neurotransmission, and new multifaceted treatment options are urgently needed. Although preclinical studies have revealed a plethora of potential therapeutic targets [39,64,65], few pharmaceutical companies have shown interest in pursuing novel treatments for SUD [66]. This is particularly troubling considering that some companies contributed to



**Fig. 1.** Timeline of milestones in SUD treatments and epigenetics. (Top) Relatively few FDA-approved treatments for SUD are currently available, and most treatments target neurotransmitter receptors. There are no FDA-approved medications for cocaine, methamphetamine, and cannabis use disorders. (Bottom) The majority of histone and DNA-modifying proteins were identified in the last few decades. Multiple epigenetic-based therapies have received FDA-approval in recent years for the treatment of cancer, but there are currently no FDA-approved, epigenetic-related treatments for SUD. FDA, Food and Drug Administration; HATs, histone acetyltransferases; HDACs, histone deacetylases; HMTs, histone methyltransferases; NUD, nicotine use disorder; OUD, opioid use disorder. (See above-mentioned references for further information.)

and profited from the current opioid epidemic.

While many pharmaceutical companies have abandoned their psychiatry and neuroscience research programs, drug discovery and development in the field of epigenetics has recently flourished. Illustrating the recent surge of interest, over 200 epigenetic-related clinical trials are currently recruiting patients, compared to only 12 recruiting studies from 2000 to 2010 (clinicaltrials.gov). Seven epigenetic-related drugs have been FDA-approved for various types of cancers (Azacitidine, Decitabine, Vorinostat, Romidepsin, Panobinostat, and Belinostat) and epilepsy/bipolar disorder (valproic acid), and over 200,000 compounds targeting histone- and DNA-modifying enzymes are published on ChEMBL, a chemical database of bioactive molecules [67]. Though the vast majority epigenetic-based treatments are aimed at treating cancer, many of the same enzymes are dysregulated in the brain following chronic drug use. Several pre-clinical studies have found that epigenetic inhibitors, with similar mechanisms as FDA-approved epigenetic drugs, reduce drug-seeking behaviors [40,53], indicating that related therapies could be tested in patients with SUD.

Decreasing drug intake and craving, alleviating withdrawal symptoms, and preventing relapse are the primary treatment goals for patients with SUD. In preclinical studies, the HDAC3-selective inhibitor, RGFP-966, enhanced memory processes involved in extinction of cocaine-seeking behavior and attenuated relapse-like behavior for cocaine [41,68]. Based on these results, HDAC3-selective inhibitors might be useful as a co-therapy to facilitate cognitive-behavioral treatments aimed at reducing drug consumption and relapse in SUD patients. Increased drug craving during abstinence is mediated by numerous molecular neuroadaptations that drive drug-seeking behaviors [69,70]. The BET inhibitor, JQ1, has been shown to decrease the expression of multiple genes and/or proteins (e.g., *Bdnf*, *GluA1*) [43,71,72] that are elevated during abstinence. Therefore, with the potential to reverse multiple drug-induced molecular factors that drive craving and relapse, BET inhibitors may promote abstinence in SUD patients. Persistent drug use to alleviate withdrawal symptoms is another aspect that contributes to the cycle of addiction. The HDAC inhibitor suberoylanilide hydroxamic acid (SAHA) has been shown to reduce alcohol withdrawal-induced hyperalgesia in rodents [73], and perhaps similar epigenetic treatments may be an effective way to mitigate withdrawal symptoms in SUD patients. To facilitate clinical studies, the recent development of PET ligands for multiple histone-modifying proteins [74] could also be used to measure target engagement and brain biomarkers in SUD patients. Thus, epigenetic-based therapies for SUD and other psychiatric disorders may help fill a void where traditional medications have failed or have had limited success.

### 3. Epigenetic biomarkers for SUD

In patients with SUD, epigenetic differences are potentially detectable in easily accessible tissues such as blood, saliva, and cerebral spinal fluid [75]. Thus far, most studies have compared DNA methylation of specific genes or levels of non-coding RNAs in blood samples of control vs. SUD patients [76–79]. Some epigenetic changes have been correlated with drug history and/or propensity to relapse [80], an indication that the epigenome may offer a new source of biomarkers to identify patient subpopulations and treatment opportunities for personalized medicine. Given that the vast majority of drugs entering clinical trials for neuropsychiatric diseases do not produce marketable compounds [81], adding epigenetic biomarkers to clinical studies may diminish drug failure rates. Blood-derived epigenetic biomarkers, however, do have limitations, as epigenetic modifications are known to vary widely across tissues [82]. To overcome this challenge, PET ligands are now being utilized to measure histone-modifying proteins in the human brain. Radioligands for HDACs and bromodomain and extra terminal domain (BET) inhibitors have been developed and tested in animals and/or humans [74,83,84]. Age- and disease-related changes in HDAC activity are presently being studied in Alzheimer's patients [85] and

similar strategies are likely to be employed in future SUD studies. Therefore, the integration of epigenetic biomarkers with existing diagnostic tools (e.g., physiologic measurements and genetic variables) will conceivably improve therapeutic decision making and successful clinical outcomes in SUD patients.

### 4. Future directions and limitations of epigenetic-based therapies for SUD

With the staggering loss of life from the ongoing opioid crisis [86,87], there has never been a more important time to identify effective treatments for SUD. So why are there so few pharmacological treatments options? SUD and other psychiatric disorders have long been stigmatized and perhaps this is one reason why many pharmaceutical companies have not pursued new therapeutic avenues. Another reason may be related to the complexity of SUD. Indeed, chronic drug use evokes a torrent of maladaptive neuroadaptations—intricate changes that may be difficult to reverse using traditional, single neurotransmitter receptor-targeted therapies. With the ability to regulate multiple transcriptional networks altered by drugs of abuse, epigenetic pharmacotherapy has emerged as a new treatment tactic. However, some may contend that epigenetic-based treatments are too risky because of their pleiotropic activities and potential side-effects. While adverse side-effects are always a threat for new therapies, one could argue that epigenetic-based medication is a tractable approach based on several factors. First, multiple epigenetic drugs have been FDA-approved and many more have completed phase I and II clinical trials, indicating that these treatments can be tolerated in humans. Furthermore, the potential side effects may be reduced in SUD, as pre-clinical SUD experiments typically require much lower effective doses and treatment frequency compared to cancer studies [43,88]. Second, several safe and commonly-prescribed medications such as statins, anti-epileptics and others exhibit direct epigenetic effects in addition to their commonly understood mechanisms of action [89–91]. Third, humans are exposed to endogenous and exogenous epigenetic inhibitors on a daily basis. The foods that we eat contain health-promoting compounds that modify epigenetic enzyme activity (e.g. catechins, curcumin, lycopene, resveratrol) [92]. Additionally, our gut bacteria and liver produce molecules with epigenetic effects (e.g., beta hydroxybutyrate) that enter the CNS and promote brain health [93,94]. Though clearly more studies are needed to understand epigenetic-based treatment regimens for SUD (e.g., dose and duration), such medications are a potentially safe option.

In order for epigenetic pharmacotherapy to become a viable clinical option for SUD, further work needs to be done to verify the effectiveness of epigenetic inhibitors in advanced animal models that more accurately resemble specific aspects of compulsive drug seeking observed in human drug users. Thus far, the majority of studies have used the conditioned place preference procedure in male rodents to study the effects of epigenetic pharmacotherapies on drug-seeking behaviors. While this procedure is sufficient at measuring contextual reward processing, animals are only acutely exposed to drugs and the drugs are administered by the experimenter [95]. In self-administration procedures, the gold standard of SUD models, animals learn to press a lever (or nose poke) to receive a drug infusion [96]. Over the years, several variations of the self-administration procedure have been developed to model specific aspects of addiction, yet few studies have examined epigenetic mechanisms in these advanced models—a major impediment in epigenetic drug development for SUD (For more information on animal models of SUD, see [97–104]).

Testing epigenetic compounds that are FDA-approved or in phase II/III clinical trials and able to penetrate the blood brain barrier should be a priority, as these treatment options are more likely to be quickly approved for clinical testing in SUD patients. Likewise, natural or endogenous epigenetic inhibitors that are known to be relatively safe is another promising treatment route. Though epigenetic

pharmacotherapy is still in its infancy, isoform-specific epigenetic inhibitors are already being developed to address potential side-effects of first-generation, non-selective epigenetic compounds. Some of these isoform-specific HDAC inhibitors have been shown to reduce drug-seeking behaviors in animals [68] and may be considered for clinical testing. Though selective epigenetic inhibitors will likely reduce potential side effects, a major limiting factor in epigenetic pharmacotherapy for SUD is that many epigenetic targets are expressed in all cells and/or tissues. Moreover, some drug-induced epigenetic modifications are regulated in a cell type-specific manner within the brain [105]. New gene- and cell type-specific epigenetic techniques have been utilized in pre-clinical studies to address these issues [106,107]. Viral-mediated gene delivery, which has recently been utilized in humans (e.g., Clinicaltrial.gov identifier NCT00749957), could potentially be employed alone or in combination with other techniques (e.g., ultrasound) [108,109] to achieve brain region- and/or cell type-specific epigenetic manipulations in SUD patients. Additionally, certain non-coding RNAs are selectively expressed in the brain and in specific cell types within the brain [110,111] and may be targeted in patients using chemically modified, single-stranded oligonucleotides [112], though more research is needed in this area. Therefore, as advances in epigenetic pharmacotherapies and viral-mediated approaches unfold, the prospect of clinically effective treatments for multifactorial brain diseases, such as SUD, may be realized in the near future.

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## Declaration of Competing Interest

None.

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