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Molecular genetics and new medication strategies for opioid addiction

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Abstract

The opioid epidemic is at the epicenter of the drug crisis with an unimaginable number of overdose deaths and exorbitant associated medical costs that have crippled many communities throughout the socioeconomic spectrum in the US. Classic medications for the treatment of opioid use disorders predominantly target the opioid system and thus unfortunately have been underutilized in part due to their own abuse potential and heavy regulatory burden for patients and clinicians. Opioid antagonists are now evolving in use not only to prevent acute overdoses but as extended use treatment options. Strategies that target specific genetic and epigenetic factors and novel non-opioid medications hold promise as future therapeutic interventions of opioid abuse. Success in increasing the treatment options in the clinical toolbox will hopefully help break the historical pattern of recurring opioid epidemics.

Introduction

The scourge of drug abuse has often defined key periods of human history. 175 years ago, when the first issue of what would become the American Journal of Psychiatry appeared, the Opium Wars dominated life in Asia (1, 2). Opium, which initially been imported into China for medicinal purposes, had quickly transitioned to recreational use and addiction that penetrated into much of the region devastating all levels of society. As the Chinese emperors attempted to halt the epidemic, Western nations fought the Chinese to increase opium imports and taxes Another heroin epidemic, this time particularly affecting urban cities in the United States in the 1970s and American veterans of the Vietnam war served as the major impetus for the creation of the Drug Enforcement Administration (DEA) in 1973 (3). Today, the scourge of a new wave of opioid addiction has transcended every sociodemographic community in the U.S. leading to severe healthcare and societal burden of epidemic proportions with an economic cost of over $500 billion per year (4).

The opioid tsunami that has gripped the country stemmed in large part from a distorted and biased understanding of addiction vulnerability, fueled by a fervent over-prescription of opioid analgesics which yearly exceeded the clinical needs of the entire adult population in

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the USA. The broad exposure to potent opioids, across the socioeconomic spectrum, led many individuals to heroin (approximately 80% of new heroin users started out misusing opioid prescription analgesics)(5–7), or the illegal and cheaper version of prescription medications such as fentanyl whose popularity and illegal sales increased after federal regulations reduced access to legal prescriptions. The consequences have been shocking with over 50,000 overdose deaths yearly (8, 9), a number expected to continue in coming years if drastic interventions are not taken. The devastating impact of the opioid epidemic has had profound medical consequences with an approximate 3000% rise in medical services needed for patients with opioid misuse and dependence as evident with an increase of ~217,000 patients provided medical care in 2007 to approximately 7 million in 2014 (10).

Despite the significant need for therapeutic interventions to meet the urgent demands of the opioid crisis, most of the over 2.6 million people diagnosed with an opioid use disorder (OUD) receive minimal treatment for their addiction. The most common pharmacotherapies for OUDs are opioid substitution medications that paradoxically bear marked stigma and tight governmental regulations due to their abuse liability and potential diversion to the black market. Additionally, these medications require very close clinical monitoring that altogether incur a significant healthcare burden. Thus, together with the scarcity of clinicians trained in the recognition and treatment of substance use disorders, the ability of the current treatment system has been limited to service the enormous proportions of people needed to be treated in the current epidemic. We submit that a multi-pronged strategy including a broad repertoire of treatment options based on science-driven approaches are critical to meet not only the current epidemic, but also to prevent future outbreaks. We summarize below current opioid therapeutic strategies and explore some of the diverse and unique approaches being developed to expand the clinical toolbox for treating OUD.

Current Strategies of Opioid treatments

Addiction is a chronic brain disorder that requires long term treatment. Disturbingly, commercials touting an expensive addiction "cure" after 30 days in a spa-like residential program receiving group therapy reflect an abysmal lack of knowledge of the abundant clinical research literature. Such abstinence only residential treatment programs, despite the promise of a "cure," have very high relapse rates shortly after "graduation" or discharge. Medication assisted treatment (MAT) has the best long term results and for opioid use disorder; there are currently several different medication options.

The full **agonist** approach is represented by methadone. This treatment was developed in the 1960s when it was discovered that opioid-addicted patients could be maintained on a single daily dose of methadone with reduction in craving and drug-seeking behavior. Over 50 years of data have demonstrated that correctly treated patients on methadone plus counseling are able to function well in school or employment and maintain a good quality life. Tolerance develops to all opioid agonists and methadone is no exception. But tolerance does not continue to increase so methadone can be prescribed at the same dose for many years. Problems, however, do arise when the medication is stopped since detoxification can be difficult and take many months.

The **partial agonist** approach is represented by buprenorphine. This medication has high affinity for the mu opioid receptor (MOR), but has an upper limit or "ceiling" on maximal opioid effects. It blocks craving and drug-seeking similar to methadone, but its limited ceiling effect means that patients with a very high pharmacological level of opioid dependence may not be able to be transferred directly to buprenorphine. In the United States, a combination medication is generally used consisting of buprenorphine and Naloxone (Suboxone). If the combination is injected, instead of ingested by the normal oral/sublingual route, naloxone reduces the pleasurable effects of MOR stimulation and thus discourages abuse.

A recent treatment innovation is the development of several extended release injectable formulations. One that provides slow release of buprenorphine for 30 days is expected to be marketed beginning in 2018. Others lasting as long as 6 months are currently under FDA review.

The **antagonist approach** is represented by naltrexone. The oral version was approved by the FDA in 1985. It occupies opioid receptors and prevents agonist drugs such as heroin or methadone from binding to the receptors and as a pure antagonist does not produce euphoria or reward. The oral version requires daily or three times weekly administration but patients can relapse simply by stopping the medication for 48 hours. Thus, the oral form of naltrexone had very limited success. More recently, an extended release version of naltrexone has become available. This version prevents relapse to opioid addiction for 30 days. Many patients find it convenient to return monthly for an injection rather than to take a daily medication. In a 2016 clinical trial in volunteer patients in the probation system, those randomly assigned to 6 months on extended release naltrexone had significantly more drug-negative urines and a lower relapse rate than patients given usual treatments in the community (11). Antagonist treatments are currently not as yet widely accepted. It is considered challenging to integrate them into the normal opioid agonist treatment regimens because detoxification of the patients is required before an antagonist can be administered. The fact that initial detoxification normally occurs in residential treatment does an important clinical window in which antagonist treatment can be initiated before individuals leave the protected environment.

Overall, looking back over the course of the opioid epidemic has highlighted several challenges with conventional opioid medications that need to be considered in trying to change the trajectory of this crisis. First, very few physicians were trained in the biology of addiction and the use of opioid medications. As such, existing opioid treatments are still not optimally used in treating pain. Second, there continues to be a bias toward opioid agonists for initial treatment. While this is an important option particularly for OUD individuals maintained for years on these agonists, newly afflicted individuals are rarely given the opportunity to be treated with the extended release antagonists that are effective and devoid of the addictive properties associated with opioid agonists. Moreover, limited non-opioid strategies exist.

LOOKING FORWARD TO DIFFERENT APPROACHES

A number of new therapeutic strategies are currently being explored that might help to expand current ways of thinking to eventually accelerate the development of effective interventions.

Genetic Strategies in opioid treatment – Pharmacogenomics

Individual differences in relation to genetics play an important role in OUD vulnerability. It is estimated based on twin studies that approximately 50% of the variation in opioid addiction is attributed to genetic factors (12, 13). While genetics is not deterministic for developing a substance use disorder, especially if the person is never exposed to the agent, knowledge regarding genetic vulnerability can help provide important insights regarding the underlying neurobiology of the disorder, reveal novel biological target for potential therapeutic development, and potentially optimize personalized medication therapy. The *OPRM1* gene on chromosome 6 that encodes the mu opioid receptor (MOR) has logically been a high-priority candidate for studies investigating disease risk and pharmacogenomic factors of opioid use. The locus of the *OPRM1* gene that has received most attention is the common missense single-nucleotide polymorphism (SNP) A118G rs1799971, a nonsynonymous point mutation that changes the amino acid sequence of the protein (14). The *OPRM1* variants have been demonstrated to have functional relevance in relation to *in vitro* MOR binding and signaling (15–17), *in vivo* MOR binding (18, 19), MOR signaling in human postmortem specimens (20–22) and opioid neuropeptide gene expression levels in the human brain relevant to addiction (23). Most of the findings suggest reduced MOR in A118G subjects. Other *OPRM1* variants have also been investigated in relation to heroin addiction (24–27) and the functional relationship to MOR signaling and downstream transcriptional regulation (21).

Multiple studies have addressed the relationship of the rs1799971 polymorphisms to heroin/opioid abuse (15, 23, 28–30). Not surprisingly the *OPRM1* results from the candidate gene studies to date have been equivocal due in part to low sample sizes, differences in race and ethnicity or potential phenotype/environmental variables among other factors. Meta-analysis studies that attempt to increase the statistical power by combining the results from multiple investigations have also been inconclusive regarding OUD (31, 32) but suggest a contribution to addiction liability shared across different addictive substances (33). There is also research implicating the rs1799971 allele in naltrexone response in the treatment of alcohol use disorder (34, 35). Based particularly on the multifaceted nature of addiction it is evident that a single gene is an extremely limited strategy to demonstrate conclusive genetic contributions. Indeed, a large comprehensive replication study demonstrated that the rs1799971 SNP was only associated with heroin addiction in the presence of another SNP (rs3778150), which had been identified as a disease-associated expression quantitative trait loci (eQTL) that influenced *OPRM1* expression in the human prefrontal cortex (26). These finding may explain some of the discrepant literature regarding the association between the rs1799971 genotype and heroin/opioid addiction and also highlights the importance of haplotype strategies for complex disorders like addiction, where the combination of alleles

that are inherited together has stronger statistical power in associating a genetic link with the phenotype.

An important question for guiding future clinical care is whether documented functional differences of *OPRM1* variants could be leveraged to improve the pharmacological response in patients undergoing opioid treatment (e.g., methadone) and to prevent adverse effects including addiction vulnerability in healthy individuals being prescribed opioid analgesics. Determining the effective individual dose for methadone is often clinically challenging since under-dosing can lead to craving and relapse and high doses can induce euphoria and sedation as well as other side effects. Implementing an agnostic genome-wide association study (GWAS) approach Gelernter and colleagues (36) recently identified one statistically significant region in the genome that was associated with higher daily methadone dosing in opioid-dependent African-Americans (but not European-Americans) patients. Interestingly, the region was on chromosome 6 with the lead SNP rs73568641 localized in the *OPRM1* gene. The authors replicated the finding showing the SNP associated with increased morphine dose requirement for pain relief in an independent sample of African-American surgical patients. Significant research remains to be conducted to determine whether the rs73568641 SNP has a causal relationship to the expression or function of the MOR. Nevertheless, the findings are a critical step forward suggesting that *OPRM1* genetics could be potentially useful clinically in determining appropriate opioid medication dose. Recent meta-analysis (37) and other studies (38, 39) also suggest that the A118G rs1799971 allele variant can influence opioid pain management with individuals carrying the A118G rs1799971 allele requiring higher opioid doses than A118A subjects. The fact that the *OPRM1* might hold promise as a genetic predictor of opioid medication dose in the setting of addiction treatment and in analgesia could be potentially helpful in identifying non-dependent individuals who might be at potential addiction risk when being treated with opioid prescription medications. Large-scale investigations still, however, are needed before individual *OPRM1* genetics can be incorporated into the clinical formula in the future for setting optimal opioid treatment dosage in OUD and pain management.

It is also important to reemphasize that it is unlikely that only the *OPRM1* gene will be able to inform and improve clinically relevant treatment based on genetics. Functional genetic variations of other genes such as those involved with liver metabolic enzyme activity were recently reported to associate with the steady-state plasma concentration of methadone enantiomers, which provide a measure of methadone metabolism and are used clinically as an index of treatment response and efficacy of methadone therapy (40, 41). If replicated, such strategies will help individualize treatment to achieve dose optimization for OUD patients to reduce and avert the onset of withdrawal symptoms as well as to optimize opioid pain management for non-dependent subjects.

Alternative Splicing to Guide Targeted Opioid Medications

DNA sequence variations and the mechanism of their regulation of gene expression and disease phenotype are complex and not well understood, but multiple processes have begun to be explored as potential targets for medication development. Alternative splicing of genes is an efficient means of generating variation in protein function and thus has been of

growing interest in attempts to personalize and optimize pharmacological therapies. Splicing determine which of a gene's exons that code for its amino acid product, i.e., the mu opioid receptor, are used or not used to synthesize the final receptor. As a result, there can be multiple subtypes of the mu receptor, based on differences in splicing. Not surprising, the development of novel medications based on molecular genetics has also involved consideration of the multiple isoforms of the MOR. An array of MOR variants are produced by alternative pre-mRNA splicing of the single-copy of the *OPRM1* gene (42, 43). The extensive alternative splicing of *OPRM1* creates at least three structurally distinct classes of splice variants that are conserved from rodent to human thus improving the possibility for preclinical scientific studies to better inform human investigations. Animal studies have shown, for example, that the different truncated variants at the C-termini generated from 3′ alternative splicing of the *OPRM1* gene do not substantially affect morphine analgesia, but differentially alter morphine-induced tolerance, physical dependence and reward behavior (44). Additionally, whereas normal analgesia is maintained for morphine and methadone analgesia in variants within exon 11 of the *OPRM1* gene, the analgesic actions of heroin and fentanyl are markedly decreased (45). Thus, developing opioid analgesics that lack the side effects of traditional opioids may be possible by targeting truncated splice variants of the MOR (46, 47). Altogether, research efforts to dissociate the desirable analgesic properties of opioids from undesirable side effects of addiction appear possible. Targeting specific regions of the MOR could be an effective therapeutic strategy to reduce the abuse and addiction liability of opioids while maintaining analgesic properties.

The recent selective molecular targeting of the MOR through biased agonism, though not a genetic approach, is also a significant advance in being able to selectivity target specific downstream signal transduction pathways in the same G-protein coupled receptor (GPCR) for medication development (48–50). In contrast to the classic categorization of ligands as full, partial or inverse agonists or antagonists, biased agonism leverages the capability of GPCRs to stabilize receptor conformation to regulate different signaling pathways. As such agonists have been designed to deliver different physiologic outcomes by biasing a selective downstream signal transduction pathway (such as G-protein signaling, beta-arrestin recruitment and receptor internalization) mediated by the same receptor. This strategy significantly expands the repertoire for drug discovery for ligands targeting MOR signaling to potentially have analgesic properties (such as those recruiting beta-arrestin proteins) while avoiding tolerance or other opioid adverse effects (linked to G-protein signaling) (51, 52). Clearly, the fact that individual variation exist for genes aligned to distinct GPCR pathways indicates that genetic factors might also dictate which individuals might respond to certain biased agonists.

Epigenetics inform opioid treatment—In addition to genetics, susceptibility to opioid addiction is known to be strongly influenced by environmental factors. As such epigenetics —biological mechanisms that mediate genetic control of gene expression without a change in DNA sequence—could be of significant importance for understanding individual vulnerability to addiction and response to treatment. The epigenetic mechanisms that turn on and off genes to set the state of gene expression patterns and thus cellular function include methylation of DNA and modifications (e.g., methylation, acetylation, phosphorylation) of

histones, around which DNA is bound that together constitutes chromatin. Epigenetics has emerged as an important biological driver of addiction pathology (53–56). Most epigenetic studies to date relevant to OUD have focused on DNA methylation. A number of investigations have reproducibly observed that chronic exposure to opioids (chronic opioid-treated pain patients, active heroin abusers or former heroin users undergoing methadone maintenance) induce epigenetic changes in peripheral marks (lymphocyte and blood) including increased methylation of the *OPRM1* gene (57–59) (60, 61). The hypermethylation of DNA located in the *OPRM1* promoter appears to block the binding of transcription activators such as Sp1 which ultimately leads to silencing of the *OPRM1* (62). Reduced MOR expression that has been detected in various brain regions of heroin abusers (21, 63, 64) might relate to their increased opioid requirement. Consistently, pain relief in cancer patients has been shown to correlate with methylation of the *OPRM1* promoter with high-dose opioid use associated with *OPRM1* hypermethylation (57). These and other studies suggest that DNA methylation in peripheral blood samples, and thus a potential proxy for CNS MOR function, could provide a biomarker for *OPRM1* function that could aide in determining opioid dosage. It is, however, important to emphasize the cell-specific nature of epigenetic mechanisms where clear DNA methylation differences have recently been revealed in different neurons and glia in the prefrontal cortex of heroin abusers (65), so it is unclear what specific CNS function alterations of peripheral *OPRM1* methylation would predict. Additionally, while the *OPRM1* is a rationale target for research in guiding future clinical care, the gene list needs to be expanded based on gathering genome-wide unbiased data from large scaled clinical studies to more efficiently direct pharmacoepigenetic approaches.

A critical aspect of epigenetics that makes it an intriguing strategic therapeutic target is that the modifications are reversible. Moreover, multiple families of proteins are involved in adding (writers), recognizing (readers) or removing (erasers) epigenetic marks (66, 67). This plethora of proteins provides a diverse system to tweak the tone of gene expression and thus cellular functions and phenotypes relevant to addiction. The importance of epigenetic to OUD was highlighted in a recent postmortem interrogation of the striatum of human heroin abusers (53). Epigenetic disturbances were observed to correlate with alterations of genes relevant to glutamatergic function and synaptic plasticity, impairments of which are well acknowledged as a hallmark of addiction pathology (68, 69). Interestingly, enhanced histone acetylation levels (and specifically acetylation of histone H3 protein, lysine 27) in the striatum of abusers correlated significantly with the years of heroin use. It is well known that acetylated-lysine residues on chromatin are specifically recognized and 'read' by the BET (bromodomains and extra-terminal) subfamily of proteins. BET inhibitors have become a popular strategy developed as anti-cancer medications that could provide novel agents to repurpose as potential treatments for OUD. A small molecular BET inhibitor, JQ-1, reduced heroin self-administration and heroin-seeking behavior in a rodent model thus setting the stage for BET inhibitors to be investigated in clinical trials in subjects with OUD. The wide range of epigenetic molecules being developed for many clinical symptoms and diseases opens a treasure trove of compounds that could be examined in relation to epigenetic pathlogies in addiction.

Medical Cannabinoid — Cannabidiol—Recent attention has focused on so-called "medical marijuana" as a potential non-conventional strategy. While still in their infancy in gathering data, some epidemiological studies have recently emerged suggesting that in states with medical marijuana laws there has been a reduction in opioid-related deaths, opioid prescriptions and opioid-related car fatalities (70–74). Many reasons, even those unrelated to the pharmacology of cannabis on brain function relevant to opioid use, might account for the apparent associations. It is, however, clear that the broad usage of the term "medical marijuana" (often confused with conventional recreational marijuana) ignores the complex nature of the plant with hundreds of cannabinoids and other entourage chemicals essential to consider in the development of a clinically useful medication. What is known from a number of preclinical studies is that different cannabinoids can have adverse or beneficial effects on opioid sensitivity. For example, whereas THC, the psychoactive component of cannabis, can enhance the reward sensitivity to opioids (75–78), the exposure to cannabidiol (CBD), a non-rewarding cannabinoid, reduces the reward-facilitating effect of morphine (79) and reduces cue-induced heroin-seeking behavior even weeks following the last CBD exposure (80). CBD normalizes glutamatergic impairments induced by heroin self-administration (80). Such findings have set in motion many research studies evaluating not only opioids, but other drugs of abuse in relation to the potential impact of CBD. Moreover, results from pilot clinical studies have suggested replication of the animal findings with CBD reducing cue-induced craving, as well as anxiety, in heroin-abstinent subjects (81). Intriguingly, similar to the rodent model, CBD maintained a reduction of heroin craving even a week after its last administration. The protracted effects of CBD might be of particular benefit for a successful therapeutic strategy for OUD since it could maintain protective effects to reduce craving and thus relapse even if the individual missed a daily dose. Importantly, CBD lacks any rewarding effects (79, 82–85), has a wide safety margin (86–88) and thus would not require the restrictive governmental regulations associated with opioid agonist medications that have abuse potential and are diverted to the black market. However, CBD is still currently under the cannabis umbrella of a Schedule I drug. As additional clinical trials are conducted, the knowledge gained will hopefully help revise the federal regulations so that a full battery of research can be explored to determine the potential of CBD for OUD treatment. Similar to all other novel strategies, the future application of "medicinal Cannabidiol" for OUDs needs to determine what specific aspect of the complex clinical spectrum of the disorder (e.g., craving versus acute reward substitution) this approach would be most optimal to target.

Vaccines: Although not new, another "outside the box" approach that originally had been considered nearly 40 years ago involves the development of anti-drug vaccines. The first vaccine was designed to target opioids (89). Vaccines for the treatment of other drugs of abuse such as nicotine (90–92) and cocaine (93–96) have been tested to a greater extent in human subjects with mixed results seeming to depend on individual variability in antibody titer levels. The challenge of raising sufficiently high antibody titers has been recently addressed with a novel strategy to develop a more efficacious heroin conjugate vaccine in combination with specific carrier proteins and adjuvants (97, 98). This anti-heroin vaccine approach was recently evaluated in pre-clinical models (mice and non-human primates) and resulted in a significant 15-fold reduction of heroin operant responding for 8 months in non-

human primates (99). Future clinical studies will help to determine whether the promise of anti-heroin vaccines can indeed achieve their long promise.

CONCLUSION: Steps to move forward/roadmap forward

We cannot address the current opioid epidemic with old tools including declarations of an opioid 'war' and harsh judicial ramifications as previously employed over the past century. They failed in the past and exacerbated psychosocial pathologies that persists today. Instead, it is essential that education of prescribing physicians and the general public about the benefits and dangers of opioids are complemented with the rapid development and translation of novel strategies to expand the currently available medications. To meet an epidemic, a different mentality needs to be employed where specific paths are created at the level of the federal and state governments to mobilize the efforts of scientists and clinicians to advance care, prevention and ultimately treatments. Strategies should span the improvement of current opioid treatments by leveraging genetic and epigenetic factors as well as the development of new therapies such as medical cannabinoids and innovative medications that could specifically strengthen impaired synaptic plasticity in the management of OUD. These approaches might also be employed to reduce the transition to addiction in non-dependent patients administered prescription opioids for chronic pain.

What continues to be missing in the development of novel medications, especially in consideration of personalized medicine and the complex nature of addiction disorders, is structured phenotyping of patients on which to integrate genetic and epigenetic data. Such knowledge can provide a strong biological foundation on which to truly develop better targeted personalized medication strategies. Nevertheless, irrespective of developing the most effective innovative medication for OUD, supportive social services must go hand in hand with drug development. There will not be a miracle therapeutic strategy. The science-based future medication approaches discussed above and in other publications are interesting, but even the most promising will fail to be realized without fast-track transition of preclinical and early stage phase I clinical studies to full clinical trials and incorporating an "all hands on board" approach that even involves input from patients and families. There is much to be learned after 175 years on which to transform the medication clinical toolkit in coming years.

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