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Molecular Genetics in Strategies for Opioid Addiction Management

Adel Turki Mubarak Alanazi[1], Bashaer Rajyan Maiuf Alqathama[2], Abdullah Rajyan Maiuf Alqathama[3], Saja Jazza Mosbel Alanazi[4], Naif Turki Naji AlAli[5], Amani Ahmed Mustafa AlAli[6]

1. Medical Laboratory specialist, Forensic Evidence Department in Public Security, Forensic Laboratories, Tabuk city, Saudi Arabia
2. Pharmacist, Maternity and Children Hospital, Makkah, Saudi Arabia
3. Pharmacist, Forensic Evidence Department in Public Security, Forensic Laboratories, Tabuk city, Saudi Arabia
4. Medical laboratory specialist, Ministry of Health, King Khaled Hospital, Tabuk City, Saudi Arabia
5. Medical Laboratory Specialist, King Salman Armed Forces Hospital in North Western Region, Tabuk City, Saudi Arabia
6. Nursing Specialist, Al Rawdah Primary Health Care Center, Tabuk city, Saudi Arabia

ABSTRACT

The enduring crisis of drug abuse has shaped societal dynamics across history, notably through events such as the Opium Wars and the recent opioid epidemic in the United States, which has led to over 50,000 overdose deaths annually and substantial economic burdens exceeding $500 billion per year. This study aims to illuminate contemporary strategies for treating opioid use disorder (OUD) amidst a backdrop of inadequate treatment access for the over 2.6 million diagnosed individuals. We assess current pharmacotherapies which include full agonists like methadone, partial agonists like buprenorphine, and antagonist treatments like naltrexone, noting their efficacy and limitations in long-term addiction management. Furthermore, we explore the roles of pharmacogenetic testing and epigenetic modifications in optimizing treatment for OUD, highlighting individual genetic susceptibilities that influence addiction behaviors. Our findings underscore the critical need for a multifaceted approach to OUD treatment, incorporating emerging strategies that bridge scientific research with clinical application to effectively address the complexities of addiction. We advocate for enhanced clinician training, reduced stigma around medications, and innovative treatment modalities as essential components in combating the current opioid crisis and preventing future epidemics.

KEYWORDS: molecular genetics, addiction, opioid, epigenetics, genetic susceptibility.

1. Introduction

The challenge of drug abuse has frequently marked significant epochs in human history. A century and three-quarters ago, with the release of the inaugural issue of what would later be known as the American Journal of Psychiatry, the Opium Wars

overshadowed life across Asia. Initially brought into China for medicinal use, opium quickly shifted to recreational consumption and widespread addiction, causing devastation throughout various societal levels. As Chinese emperors sought to curb this epidemic, Western powers engaged in conflicts to boost opium imports and taxes. Another heroin crisis emerged, particularly impacting urban areas in the United States during the 1970s, with American veterans of the Vietnam War being a major driving force behind the establishment of the Drug Enforcement Administration (DEA) in 1973 [1]. Today, a new wave of opioid addiction has affected every demographic group in the U.S., creating a significant healthcare and societal burden of epidemic scale, with economic repercussions exceeding $500 billion annually.

The opioid crisis affecting the nation has largely arisen from a skewed and inaccurate perception of addiction vulnerability, exacerbated by a significant over-prescription of opioid painkillers, which annually surpassed the clinical requirements of the entire adult population in the USA [2]. This widespread availability of strong opioids across various socioeconomic groups has driven many toward heroin; about 80% of new heroin users initially misused prescription opioid analgesics. Additionally, the illegal and more affordable alternatives to prescription drugs, such as fentanyl, gained traction as federal regulations limited access to legal prescriptions. The repercussions have been alarming, with over 50,000 overdose fatalities each year [3], a figure projected to persist without significant intervention. The overwhelming impact of the opioid crisis has resulted in severe medical challenges, illustrated by an astounding 3000% increase in healthcare services required for patients dealing with opioid misuse and dependence. This is reflected in the rise from approximately 217,000 patients receiving medical care in 2007 to nearly 7 million by 2014 [4].

Despite the urgent need for therapeutic interventions to address the opioid crisis, a majority of the over 2.6 million individuals diagnosed with an opioid use disorder (OUD) receive limited treatment for their addiction. The primary pharmacotherapies for OUDs are opioid substitution medications, which ironically face significant stigma and stringent governmental regulations due to their potential for abuse and risk of diversion to the illicit market [5]. Furthermore, these treatments necessitate intensive clinical monitoring, contributing to a substantial healthcare burden. Consequently, coupled with a shortage of clinicians qualified to recognize and treat substance use disorders, the current treatment system has struggled to adequately address the vast number of individuals requiring care during this epidemic. We propose that a multi-faceted strategy, incorporating a wide array of treatment options grounded in scientific principles, is essential not only to tackle the present crisis but also to avert future outbreaks [6].

Objectives:

We aimed in this study to:

1. Identify the current Strategies of Opioid treatments

2. Assess the role of pharmacogenetic testing in optimizing medication prescriptions for individuals with opioid use disorder.

3. Examine epigenetic modifications linked to opioid exposure and how they influence addiction behaviors.

4. evaluate the genetic susceptibility on addiction

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 [7].

The full agonist approach:

The full agonist method is exemplified by methadone. This form of treatment emerged in the 1960s after it became evident that individuals with opioid addiction could be stabilized on a single daily dose of methadone, which resulted in a decrease in cravings and drug-seeking behavior. Extensive data collected over more than 50 years has shown that patients on methadone, when combined with counseling, can perform effectively in educational or professional settings and enjoy a high quality of life. Although tolerance develops to all opioid agonists, including methadone, this tolerance does not continually escalate, allowing for the medication to be administered at a consistent dose over many years. Nonetheless, challenges can occur when the medication is discontinued, as detoxification may prove to be challenging and could take several months [8].

The partial agonist approach:

The partial agonist strategy is exemplified by buprenorphine, a medication that exhibits a strong affinity for the mu opioid receptor (MOR). However, it possesses an inherent limit or "ceiling" on its maximum opioid effects. Similar to methadone, it effectively mitigates cravings and drug-seeking behaviors; yet, due to its capped effect, patients with severe opioid dependence may not be suitable candidates for a direct transition to buprenorphine. In the United States, a commonly prescribed combination therapy includes buprenorphine and Naloxone, known as Suboxone. When this combination is administered via injection rather than through the typical oral or sublingual routes, naloxone serves to diminish the rewarding effects associated with MOR activation, thereby deterring potential misuse [9].

A recent advancement in treatment involves the introduction of various extended-release injectable formulations. One formulation, which is designed to provide a gradual release of buprenorphine over 30 days, is anticipated to be available for marketing starting in 2018. Meanwhile, other formulations that can last up to six months are currently undergoing evaluation by the FDA.

The antagonist approach:

The antagonist approach is exemplified by naltrexone, which received FDA approval

for its oral form in 1985. Naltrexone binds to opioid receptors, blocking agonist drugs like heroin or methadone from attaching to these receptors. As a pure antagonist, it does not induce euphoria or create a sense of reward. The oral formulation necessitates daily administration or usage three times a week; however, patients may experience relapse merely by halting the medication for 48 hours. Consequently, the oral version of naltrexone has seen very limited effectiveness. Recently, an extended-release formulation of naltrexone has been introduced [10]. This modified version helps prevent relapse to opioid addiction for 30 days. Many patients prefer the convenience of a monthly injection over daily medication. In a 2016 clinical trial involving volunteer patients on probation, those assigned to six months of extended-release naltrexone demonstrated significantly more drug-negative urine tests and lower relapse rates compared to those receiving standard community treatments [11]. Despite these benefits, antagonist treatments are not yet widely embraced. Integrating them into standard opioid agonist treatment protocols presents challenges, as detoxification must occur prior to the administration of an antagonist. The initial detoxification usually takes place in residential treatment, creating a crucial clinical opportunity to initiate antagonist therapy before individuals leave the supportive environment.

Epigenetics and individual differences in vulnerability to addiction and related phenotypes:

“Epigenetics” is now used with both classical and recently-revised definitions. Classical defintions of “epigenetic” emphasize influences of variations that are not encoded in primary DNA sequence but nevertheless inherited “… a change in the state of expression of a gene that does not involve a mutation, but that is nevertheless inherited in the absence of the signal (or event) that initiated the change” [12]. However, more recent definitions of “epigenetic” emphasize gene regulatory mechanisms that do not alter primary DNA sequence while paying less attention to documenting heritability.

In this review, the focus is primarily on heritable epigenetic factors. One notable instance of a classical heritable epigenetic influence is imprinting, which transmits information from parents to offspring through mechanisms such as DNA methylation or histone acetylation. These processes preserve the primary DNA sequence while significantly modifying the function of certain genes. For instance, DNA methylation occurring at CpG sites within gene promoter regions can greatly impact gene transcription. The process of methylation during the development of maternal oocytes (or paternal sperm) is critical, and this can lead to observable patterns of gender-specific inheritance that highlight this particular subset of heritable epigenetic influence [13]. However, the quality of existing family datasets related to addiction is relatively low, which limits their usefulness in making strong inferences about parent-of-origin effects. To date, we are unaware of any segregation data supporting substantial parent-of-origin effects on substance dependence. Although it is clear that nonheritable “epigenetic” factors play significant roles in the biology of addiction, there is currently no convincing evidence of strong effects from overall heritable “epigenetic” influences as traditionally defined. Nonetheless, we must remain vigilant for such influences as we explore the impacts of variants in specific genes [14].

Genetic Susceptibility on Addiction:

The genetic underpinnings of substance use disorders are frequently studied. Classic genetic approaches such as twin, family and adoption studies show that there are significant genetic influences on drug addiction. Heritability is the proportion of observed differences on a phenotypic trait among individuals of a population that are due to genetic differences, and the heritability of addiction has been estimated at 0.4–0.6 [15]. In recent years, huge advances in computer technology have made molecular genetic approaches possible. Linkage studies, genetic association studies, and genome-wide association studies can identify and locate associated genes. There have now been a number of studies on addiction behaviors using molecular approaches [16]. Classical genetic approaches have shown that addiction is heritable; molecular genetic approaches suggest that specific addiction-related behaviors are associated with specific genes.

Classic Genetic Research and Molecular Genetic Research on Addiction:

Genetic epidemiology is an ever-evolving and rapidly growing field of research that offers important insights into the complexities of substance use disorders [17]. By integrating findings from both classical genetic research and more contemporary molecular genetic studies, researchers can uncover critical information regarding the genetic underpinnings of various addiction-related disorders. This section aims to review the most recent genetic research concerning disorders associated with substances such as tobacco, alcohol, and opiates. Additionally, the following section will delve into the potential genetic connections between opioid addiction and particular behavioral patterns. In their comprehensive review, Kreek et al. proposed a three-domain model to understand the interplay between genetics, diverse environmental influences, and drug-induced effects in the context of addiction [18]. Historical investigations into the genetic aspects of addiction can be traced back to 1960, when Kaij et al. conducted pioneering research on alcoholism in twins. This foundational study laid the groundwork for later research. In 1966, Partanen et al. followed up with a comparable twin study, which examined the correlations between cognitive factors such as intelligence and personality traits in relation to alcohol consumption. These early investigations were significant as they suggested a heritable component to specific addictions, indicating that genetics play a critical role in the predisposition to substance use disorders [19]. Further reinforcing the genetic link to alcohol abuse, Cloninger et al. conducted an adoption study that demonstrated a notable resemblance in alcohol-related behaviors among adopted individuals and their biological relatives, as opposed to their adoptive families. The findings from this research provided a classical method for distinguishing the impacts of genetic factors from environmental influences [20]. In another significant study conducted in 1988, Merikangas et al. reported that relatives of individuals suffering from drug disorders were eight times more likely to experience similar issues themselves, particularly for those addicted to the same substance, highlighting the familial aggregation of such disorders [21]. In an influential twin study, Tsuang posited that both genetic predispositions and environmental factors significantly contribute to an individual's risk for drug abuse. Tsuang's research further revealed that commonly abused substances—namely, opiates, marijuana, sedatives, psychedelics, and stimulants—exhibited an overall genetic variance estimated

between 0.3 and 0.5. Among these substances, heroin was noted to possess the highest overall genetic variance at 0.54, along with a shared genetic variance of 0.2 with other substances. Interestingly, while many drugs demonstrated low variance concerning specific genetic influences, heroin stood out with a unique specific genetic variance of 0.4, suggesting that particular genetic factors may uniquely affect opioid abuse. In a landmark twin study focusing on substance use disorders, Kendler and colleagues found that lifetime use of substances such as cannabis, cocaine, hallucinogens, sedatives, stimulants, and opiates exhibited a range of additive genetic variance, or heritability, ranging from 0.3 to 0.5 [22]. These foundational studies—from twin studies to adoption studies and spanning across substances from alcohol to various other drugs—offer robust evidence supporting the significant role of genetics in the development of substance use disorders. Building upon these classical genetic investigations, recent molecular genetic studies have further examined heritability in a more nuanced manner.

2. Conclusion:

In conclusion, the opioid epidemic presents an urgent and complex public health crisis that requires a multi-faceted response encompassing medical, psychological, and societal interventions. Despite significant advancements in understanding the genetic and epigenetic underpinnings of addiction, as well as the implementation of various pharmacotherapeutic strategies, a substantial treatment gap persists for those affected by opioid use disorders. Current approaches, including full agonists, partial agonists, and antagonists, demonstrate varying levels of efficacy, highlighting the need for personalized and adaptive treatment plans tailored to individual patients. Furthermore, ongoing research into genetic susceptibility and epigenetic influences is essential to refine treatment options and inform prevention strategies. As we navigate this multifarious challenge, it is imperative to integrate science-driven methodologies with compassionate care to alleviate the profound toll of opioid addiction on individuals and society as a whole. Addressing these intertwined dimensions will be crucial in curbing the epidemic and preventing future outbreaks, ensuring that those in need receive comprehensive support and effective treatment.

References

Lovell J. The Opium War: Drugs, Dreams, and the Making of Modern China. The Overlook Press: 2015. [Google Scholar]

2. Fay P. The Opium War, 1840-1842: barbarians in the Celestial Empire in the early part of the nineteenth century and the war by which they forced her gates ajar. 2000 [Google Scholar]

The DEA Years: 1970-1975. https://www.dea.gov/about/history.shtml.

Advisers TCoE: The Underestimated Cost of the Opioid Crisis. 2017 [Google Scholar]

Muhuri P, Gfroerer J, Davies C. Associations of nonmedical pain reliever use and initiation of heroin use in the United States. CBHSQ Data Review. http://archive.samhsa.gov/data/2k13/DataReview/DR006/nonmedical-pain-reliever-use-2013.pdf2013.

Banerjee G, Edelman EJ, Barry DT, Becker WC, Cerda M, Crystal S, Gaither JR, Gordon AJ, Gordon KS, Kerns RD, Martins SS, Fiellin DA, Marshall BD. Non-medical use of prescription opioids is associated with heroin initiation among US veterans: a prospective cohort study. Addiction. 2016;111:2021–2031. [PMC free article] [PubMed] [Google

Scholar]
Compton WM, Jones CM, Baldwin GT. Relationship between Nonmedical Prescription-Opioid Use and Heroin Use. N Engl J Med. 2016;374:154–163. [PubMed] [Google Scholar]
Provisional Counts Of Drug Overdose Deaths, as of 8/6/2017. CDC •National Center for Health Statistics• National Vital Statistics System. 2017 [Google Scholar]
Ahmad F, Rossen L, Spencer M, Warner M, Sutton P. Provisional drug overdose death counts CDC/National Center for Health Statistics. 2018 [Google Scholar]
The Impact of the Opioid Crisis on the Healthcare System. A FAIR Health White Paper. FAIR Health; 2016. [Google Scholar]
McDonald RD, Tofighi B, Laska E, Goldfeld K, Bonilla W, Flannery M, Santana-Correa N, Johnson CW, Leibowitz N, Rotrosen J, Gourevitch MN, Lee JD. Extended-release naltrexone opioid treatment at jail reentry (XOR) Contemp Clin Trials. 2016;49:57–64. [PMC free article] [PubMed] [Google Scholar]
Ptashne M. On the use of the word 'epigenetic'. Curr Biol. 2007;17(7):R233–R236. [PubMed] [Google Scholar]
Tan EK. The role of common genetic risk variants in Parkinson disease. Clin Genet. 2007;72(5):387–393. [PubMed] [Google Scholar]
Kendler K.S., Jacobson K.C., Prescott C.A., Neale M.C. Specificity of genetic and environmental risk factors for use and abuse/dependence of cannabis, cocaine, hallucinogens, sedatives, stimulants, and opiates in male twins. Am. J. Psychiatry. 2003;160:687–695. doi: 10.1176/appi.ajp.160.4.687. [PubMed] [CrossRef] [Google Scholar]
Tsuang M.T., Lyons M.J., Meyer J.M., Doyle T., Eisen S.A., Goldberg J., True W., Lin N., Toomey R., Eaves L. Co-occurrence of abuse of different drugs in men: The role of drug-specific and shared vulnerabilities. Arch. Gen. Psychiatry. 1998;55:967–972. doi: 10.1001/archpsyc.55.11.967. [PubMed] [CrossRef] [Google Scholar]
Xie P., Kranzler H.R., Krauthammer M., Cosgrove K.P., Oslin D., Anton R.F., Farrer L.A., Picciotto M.R., Krystal J.H., Zhao H. Rare nonsynonymous variants in alpha-4 nicotinic acetylcholine receptor gene protect against nicotine dependence. Biol. Psychiatry. 2011;70:528–536. doi: 10.1016/j.biopsych.2011.04.017. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
Burton P.R., Tobin M.D., Hopper J.L. Key concepts in genetic epidemiology. Lancet. 2005;366:941–951. doi: 10.1016/S0140-6736(05)67322-9. [PubMed] [CrossRef] [Google Scholar]
Kreek M.J., Nielsen D.A., LaForge K.S. Genes associated with addiction: Alcoholism, opiate, and cocaine addiction. Neuromol. Med. 2004;5:85–108. doi: 10.1385/NMM:5:1:085. [PubMed] [CrossRef] [Google Scholar]
Kaij L., Rosenthal D. Alcoholism in twins. Studies on the etiology and sequels of abuse of alcohol. J. Nerv. Ment. Dis. 1961;133:272. doi: 10.1097/00005053-196109000-00019. [CrossRef] [Google Scholar]
Partanen J., Bruun K., Markkanen T. Inheritance of Drinking Behavior: A study on Intelligence, Personality, and Use of Alcohol of Adult Twins. Volume 14 Finnish Foundation for Alcohol Studies; Stockholm, Sweden: 1966. [Google Scholar]
Cloninger C.R., Bohman M., Sigvardsson S. Inheritance of alcohol abuse: Cross-fostering analysis of adopted men. Arch. Gen. Psychiatry. 1981;38:861–868. doi: 10.1001/archpsyc.1981.01780330019001. [PubMed] [CrossRef] [Google Scholar]
Merikangas K.R., Stolar M., Stevens D.E., Goulet J., Preisig M.A., Fenton B., Zhang H., O'Malley S.S., Rounsaville B.J. Familial transmission of substance use disorders. Arch. Gen. Psychiatry. 1998;55:973–979. doi: 10.1001/archpsyc.55.11.973. [PubMed] [CrossRef] [Google Scholar]