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Short Commentary

# Genetic Framing of the Opiate/Opioid Epidemic in Native Americans: Is Reward Deficiency the Culprit?

**Gold MS[1,3], Badgaiyan RD[2] and Blum K[2,3,4]***

[1]Department of Psychiatry, Washington University, USA

[2]Department of Psychiatry, Wright University, Boonshoft School of Medicine, USA

[3]Department of Psychiatry and Behavioral Sciences, Keck School of Medicine, University of Southern California, USA

[4]Department of Psychiatry, University of Florida, USA

***Corresponding author:** Kenneth Blum, Department of Psychiatry, University of Florida, Box 100183, Gainesville, FL, 32610-0183, USA

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**Abstract**

With interest we read the American Society of Addiction Medicine (ASAM) newsletter concerning how the Native Americans have been hit hard by the opioid epidemic. In fact, it is no surprise that American tribal leaders from northern New Mexico- an area of the United States devastated by heroin and opioid substance use disorder (addiction)- met with the U.S. Justice Department over ways to combat opioid abuse amid high overdose deaths among Native Americans. One missing piece that may not be obvious or addressed is the potential genetic and epigenetic antecedents that are well researched in this very high risk population. Certainly, we are not dismissing a number of important cultural practices, like the spiritual use of marijuana. However, we are pointing out a number of important genetic association studies that reflect a very high inheritable frequency. Accordingly, the dopamine D2 receptor *Taq A1* allele's prevalence rate is 85% in the Native American population (Cheyenne). Carriers of the dopamine D2 receptor *Taq A1* allele have a reduced number (>30-40%) of dopamine D2 receptors loading on the addiction risk for alcohol and heroin. Other gene polymorphisms in this population, including the GABAB1 and OPRM1 are examples of additional genetic antecedents that could promote vulnerability to heroin. These genetic polymorphisms are magnified by the epigenetic parental effects of marijuana (THC) on F1 (first filial) generations having an enhanced sensitivity for heroin. We encourage targeted genetic based research in this community to assist in identifying those at risk and possible intervention with Pro-dopamine regulation as an epigenetic modality having possible therapeutic benefits.

**Keywords:** Native Americans; Opioid epidemic; Alcohol; Heroin; Marijuana; Dopamine; GABA; Opiate receptors gene polymorphisms; Epigenetics

## Short Commentary

A press release from Albuquerque, New Mexico was featured in American Society of Addiction Medicine's (ASAM's) newsletter has caught the attention of many concerned clinicians and neuroscientists. The concern is related to the high rates of heroin and opioid substance use disorder (addiction) in American Indian population of northern New Mexico. In fact, American tribal leaders from northern New Mexico- met with the U.S. Justice Department over ways to combat opioid abuse amid high overdose deaths among Native Americans [1]. New Mexico's drug overdose death rate was the second highest in the nation in 2014. The latest numbers released in October, 2016, by the New Mexico Department of Health, Rio Arriba County, had the highest drug overdose death rate in the state with 81.4 deaths per 100,000 residents last year. The following statistical facts paint the devastation faced by the Native American community across the United States: the number of overdose deaths from prescription painkillers has soared, claiming the lives of 165,000 people in the U.S. since 2000; a National Institute on Drug Abuse (NIDA) survey found that American Indian students' annual heroin and OxyContin use was about two to three times higher than the national averages from 2009 to 2012. While naloxone is becoming widely available to prevent fatality, understanding the possible root cause, especially in this vulnerable population seems, important at this critical time.

Without negating social and environmental impact, we submit that certain reward (e.g. dopaminergic etc.) genetic polymorphisms may provide an insightful scientific framework to help explain this observed and factual dilemma in the Native American population. One polymorphism in question relates to the initial finding of strong association between the Dopamine D2 Receptor *Taq A1* allele [chromosome 11] and alcoholism [2] and other addictions including heroin [3]. Tissue binding studies show that carriers of the Dopamine D2 Receptor *Taq A1* allele independent of any drug abuse had a 30-40% reduced number of D2 receptors [4] leading to a "dopamine deficiency". Subsequent to this work, Barr & Kidd [1993] assessed the distribution of the Dopamine D2 Receptor *Taq A1* allele as a function of ethnicity. They found a widespread distribution whereby Yemenite Jews carried the A1 allele in about 6% of the studied population (lowest measured) and Native Americans carried the A1 allele in about 85% of the studied population (highest measured). Understanding that carrying this polymorphism alone represents a very high risk for Substance Use Disorder, including alcohol and heroin abuse, suggests an extreme vulnerability in the Native American population.

We have seen this to be true for alcoholism whereby the rate of alcoholism in Native Americans is much higher than the rest of the population. In fact, and one in 10 Native American deaths are alcohol-related. This rate is three times the average for the broader





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population. Moreover, in 2002, Native Americans and Alaskan Natives were at a much higher risk than other minority populations for heavy drinking, binge drinking, and alcohol dependence. A study carried out from 2002 to 2005 reported that 10.7 percent of all Native American and Alaskan Native groups suffered from alcohol use disorder, whereas 7.6 percent of other ethnic groups reported the same disorder [5]. In addition, there is evidence for genetic linkage to alcohol dependence on chromosomes 4 and 11 from an autosome-wide scan in an American Indian population. Specifically, evidence is seen with D11S1984 (nominal P = 0.00007, lod approximately equal to 3.1) on chromosome 11p, in close proximity to the DRD4 dopamine receptor, Tyrosine Hydroxylase (TH) and even DRD2 genes. Additionally, evidence is seen with D4S3242 (nominal P = 0.0002, lod approximately equal to 2.8) on chromosome 4p, near the beta1 GABA receptor gene [6]. It is important to note that GABAB1 polymorphism has been linked to alcohol dependence [7].

Furthermore, in American Indians it was observed that there was a more intense response on one or more of the following items: buzzed, clumsy, dizzy, drunk, effects, high, nausea, sleepy, talkative, terrible, and/or uncomfortable after imbibing 2-3 drinks was significantly associated with having at least one minor allele for at least one of 7 SNPs ($p<0.01$) in the OPRM1 receptor gene [8]. Taken together these facts provide significant genetic evidence that polymorphisms in a number of important reward related genes (i.e., DRD2, GABAB1, OPRM1) could lead to a higher risk for both opioid/opiate and alcohol dependence in the Native American population.

It is well known that 5.6 percent of Native American youth aged 12 to 14 had used cannabis in the past month, compared to the national average of two percent; and between the ages of 15 and 17, 22.2 percent had used it compared to the national average of 11.6 percent. Adult consumption of Marijuana as a cultural representation of a higher power also represents a high abusable risk. Considering epigenetic evidence for increased heroin sensitivity is derived from a number of studies involving the one of active ingredients of marijuana, Tetrahydrocannabinol [THC]. One such study revealed that parental THC exposure in F1 generation leads to compulsive heroin-seeking and altered mRNA expression of cannabinoid, dopamine, and glutamatergic receptor genes in the striatum, a key component of the neuronal circuitry mediating compulsive behaviors and reward sensitivity [9].

## Summary

Based on these and many other studies it is our contention that the increased rate of opiate/opioid abuse and devastating overdose is not surprising when you account for potential genetic and epigenetic effects in this high risk population. We encourage targeted genetic based research in this community to assist in identifying those at risk (reward gene polymorphisms) and possible intervention with Pro-dopamine regulation as an epigenetic modality having possible therapeutic benefits.

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