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GLOBAL OPIOID EPIDEMIC: DOOMED TO FAIL WITHOUT GENETICALLY BASED PRECISION ADDICTION MEDICINE (PAM™): LESSONS LEARNED FROM AMERICA

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CONFLICT OF INTEREST

Kenneth Blum, PhD owns stock in RDSS LLC, Synaptamine, INC, Igene LLC, Geneus Health, LLC, and RestoreGen, LLC. Synaptamine is the exclusive distributor worldwide of patents related to Reward Deficiency Syndrome (RDS). Dr. Blum is the Chief Scientific Advisor for Dominion Diagnostics. Blum, Modestino, Steinberg, Neary, Gondre-Lewis, Barh, Badgaiyan, Siwicki, and Hauser are on the Scientific Advisory Board of Geneus Health, LLC. There are no other competing interests to declare.

FINANCIAL DISCLOSURE

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Abstract

It is a reality that globally opioid deaths have soared for men and women of all social, economic status and age from heroin and fentanyl overdoses. Specifically, in the United States, deaths from narcotic overdoses have reached alarming metrics since 2010. In fact, the Fentanyl rise is driven by drug dealers who sell it as heroin or who use it to lace cocaine or to make illegal counterfeit prescription opioids. The President's Commission on the crisis has linked the death toll as equivalent to "September 11th every three weeks." In fact, The U.S. Centre for Disease Control (CDC) released data showing that opioid-related overdoses were up 15% in the first three quarters of 2016 compared to 2015. Various governmental organizations including NIDA, are actively seeking solutions. However, we argue that unless the scientific community embraces genetic addiction risk coupled with potential precision or personalized medicine to induce "dopamine homeostasis" it will fail. We now have evidence that a ten-gene and eleven single nucleotide polymorphism (SNP) panel predicts Addiction Severity Index (ASI) for both alcohol and drugs of abuse (e.g., Opioids). In a large multi-addiction centre study involving seven diverse treatment programs, the genetic addiction risk score (GARS™) was shown to have a predictive relationship with ASI–MV derived alcohol (≥ seven alleles), and other drugs (≥ 4 alleles) severity risk scores. In a number of neuroimaging studies, we also display that in both animal (bench) and abstinent Chinese severe heroin-dependent patients (bedside), BOLD dopamine activation across the brain reward circuitry revealed increases in resting state functional connectivity as well volume connectivity. It is also known that published nutrigenomic (coupling gene polymorphisms with altered KB220z) studies reveal improved clinical outcomes related to obesity.

Keywords

addiction; dependence; Genetic Addiction Risk Score™; heroin; opioid epidemic

INTRODUCTION

Drug, alcohol and other addiction rehabilitation in the United States was a $35 billion business in 2015. There are over 14,500 treatment facilities and growing. A total of 2.5 million patients received treatment, but much more need it and many facilities are at capacity. Additionally, insurance coverage for rehabilitation is limited. As a result, most of the bill is paid by government/state agencies or out of pocket by the patients. High-end establishments have emerged for the higher income population, and new nooks are developing in areas such as: problem gamblers, sex addiction, nicotine addiction and Internet addiction. Facilities are also diversifying into treating people with anxiety disorders, eating disorders, and posttraumatic stress.

Addiction concerns

Often, the greatest fear for a parent is that their children might become addicted to drugs and/or alcohol. According to a survey by Parent.co, which included 1500 participants, fear

of drug and alcohol addiction vastly outweighed concerns about terrorism, economic collapse, crime, and war. Most Americans have first-hand experience with someone struggling with addictions.

- 44% of Americans know someone with a history of painkiller addiction, CNBC reports.
- 20% claimed it was one of their family members.
- 24.6 million Americans abused drugs.
- This is equivalent to 9.4% of the U.S. population (up from 8.3% in 2002).
- Essentially, this is equivalent to the population of Texas.

Nationwide American trends

Annual surveys conducted by the Substance Abuse and Mental Health Services Administration (SAMHSA) reveal that drug abuse is increasing in America. The participants in the National Survey on Drug Use and Health, those who are 12 years and older, provided critical commentary on the use and abuse of various substances. This included information for different periods, such as weekly, monthly, and even lifetime use of alcohol and drugs.

According to the 2013 survey results:

- 23.5 million U.S. citizens are addicted to alcohol and drugs.
- Marijuana accounts for the majority of this increase as 19.8 million Americans disclosed to using it in 2013. This is an increase from 14.5 million in 2007.
- Marijuana, after alcohol, accounts for the increased rates of dependence (4.2 million in clinical trials for treatment of abuse)
- 1.9 million people fulfilled the criteria for dependence on painkillers and 855k met the criteria for cocaine.
- Methamphetamine use and abuse increased to 595k in 2013 (up from 353k in 2010).
- Cocaine, however, is currently trending downwards, from 2.4 million reported uses from 2002 to 2007, down to 1.4 million uses in 2013.

Emerging trends in opiate addiction

The nature of heroin addiction in the America has transformed over recent decades. Relocating from urban areas to the more suburban, from lower incomes to that of more affluent neighbourhoods, the portrait of a heroin addict progressed from poor, urban, black and male users and transformed to predominantly Caucasian addicts of whom half are females.

According to Dr. Theodore Cicero (Washington University in St Louis), first-time users of heroin tend to be in their mid-20s. In decades past, first-time users tended to be around age 16. Between 2007 and 2013, heroin use has increased dramatically, from 370,000 to 680,000 users [1].

Similar to illicit substance abuse, the patterns observed in the market for prescription painkillers like oxycodone addiction have skyrocketed in recent years. In the 1990s, there was an increase in the accessibility of prescription painkillers. This culminated in a crest of addiction, which surpassed the combined use of illicit substances (i.e., LSD, methamphetamines, ecstasy, and cocaine). In 2012, the mortality was 16 thousand deaths due to painkillers and thus, clinicians, regulatory agencies, government and other professionals have been working to counter the excessive use of prescription painkillers. For example, oxycodone is now being produced so that it cannot be easily crushed to allow for dissolving for injection or even snorting [2].

Foreign illicit drug markets are responding to the increased demand for heroin in the U.S. Mexico is the main supplier of heroin to the U.S., as it is cheaper than sources from Columbia or Asia. The legalization of marijuana in the U.S., has resulted in a significant decrease in demand from illegal foreign sources. This market was quickly replaced by opium and opium compounds from Mexico. Additionally, user preferences for brown heroin, which is more readily snorted and smoked, surpassing the use of injectable drugs which are more widely used and potentially less fatal, is well known on the street [3]. However, the Opiate/opioid epidemic is a world-wide problem, with European, Middle Eastern and Asian countries reporting significant uptick in overdoses and overdose deaths. The reasons for this is not easily explained.

Addiction and overdose

In 2016, the NY Times noted that the U.S. had seen significantly increased overdoses leading to death, from heroin and prescription medications. Overdose mortality rates are comparable to those caused by HIV in the 1980s- 1990s. Unlike HIV mortality, overdose-related deaths are not localized to just cities but everywhere. Specific regions and states have been experiencing the impact of opiate overdoses more acutely than others. Based on information from the Centre for Disease Control (CDC) [4], the Southwest regional U.S. and Appalachia (specifically in West Virginia) tend to be the most affected. In the Appalachia region, overdose mortality is primarily due to prescription painkillers often prescribed to blue-collar workers, initially to treat chronic pain resulting from job-related injuries. Due to laws put in place to prevent abuse of such prescription medications, many have turned to illicit substances like heroin for relief. Subsequently, this has led to addiction.

With inadequate resources available to provide services and addiction-related treatment, the increases overdose mortality has soared. State by state discrepancies in access to treatment and expenditures for such treatment also is becoming more apparent. For example, in New Hampshire (N.H.), an overdose of opiates, mostly connected to fentanyl, caused 326 deaths in 2014 [5]. N.H. allocated less funding per capita than all other states (excluding Texas) in providing the desperately needed treatment services. In New Mexico, heroin overdose deaths has persisted since the 1990s, where it is often considered akin to a hereditary disease. According to Jennifer Weiss-Burke, the executive director of the non-profit organization, Healing Addiction in Our Community, heroin addiction is seemingly passed down through generations.

Furthermore, Ms. Weiss-Burke has noticed that the younger generations are often more difficult to treat. In fact, some are unwilling to get sober. These individuals vacillate between treatment centers and jail. This chronic situation is due to staying within the same environment, surrounded by the very same people. Almost more trouble is the rise of fentanyl abuse, for which a greater amount of Naloxone is necessary to resuscitate overdose victims versus that of a heroin overdose. Naloxone is also used to reverse other opioid drug overdoses, and it is not specific to fentanyl [6].

Combating prescription medications and illicit heroin use in the US

In March 2016, President Obama enunciated a multifaceted plan to enhance resources and treatment facilities and provided greater access to naloxone. The Obama administration appealed for $1.1 billion in the hopes of funding new measures aimed at reducing continued opioid overdose mortality. President Obama emphasized that the profile of heroin addiction has transmogrified with a socioeconomic shift and altered public opinions: specifically, heroin addiction is no longer an affliction of the urban poor nor due to presumed moral ineptitude, but rather affects every day folk - sons and daughters, aunts and uncles, and even grandparents residing in suburbia.

The FDA has increased warnings on immediate-release opioid prescription medications to warn patients about abuse, potential overdose, and complications. Previously, in 2013, the FDA relabelled thirty-four brands of extended-release medications. This latest change includes the relabelling of 288 medications. New CDC guidelines attempt to restrict the prescribing of opioids to cases in which no other option exists. Thus, these new warnings labels and guidelines will remain integral in combating opioid dependency and addiction [7].

Understanding the role of genetic testing in addiction medicine

Over 100 million Americans with addictive personalities have a genetic predisposition for addiction, which is called the Reward Deficiency Syndrome (RDS) [8–20]. They have a lower utilization level of the pleasure chemicals in the brain called neurotransmitters, known as “neurotransmitter deficits,” than those with normal counts. This puts them at a disadvantage and makes them prone to accidents, aberrant cravings, and drug-seeking behaviours, which overburdens the health care delivery system as a whole.

The etiology of drug addiction is highly complex. The primary consideration is how the patient is to be treated. These individuals are prescribed behavioral or psychiatric modification instead of being treated for the underlying medical condition. Drug addicts are relatively easy to detoxify with careful professional oversight and management [21]. However, to prevent drug relapse and the intense psychological cravings are another matter. Most drug-seeking behaviours originate in the dopaminergic centres of the mesolimbic brain.

These pathways are responsible for the feelings of pleasure and a sense of well-being. Any deficits or decrease in the dopaminergic system will lead to a loss of pleasure and eventually lead to drug-seeking or high-risk behaviours [22]. Our laboratory now documented, and it is widely known and accepted, that there is a genetic relationship between RDS and the dopaminergic system. The RDS is based on deficits in the ‘brain reward cascade’ and

originates primarily from a relatively common genetic deficiency in the dopamine D2 receptors and other genes. A genetically-dependent decline in the number of receptors for neurotransmitters will lessen or attenuate the neurological reward/pleasure signal to the affected target organs, known as “dopamine resistance.” The dopamine resistance creates a lower sense of well- being. DNA gene testing can identify these individuals who carry the affected Reward Deficiency Genes [23].

Can we predict risk using genetic testing?

Various alleles in the P450 system are currently utilized in pain medicine clinics to evaluate metabolic concerns to help identify high and low metabolizers.

Genetic Addiction Risk Score™

Molecular genetic or DNA testing is critical for examining the genetic link of aberrant behaviours to specific individual. Blum’s laboratory proposed [24] that disturbances along the brain reward cascade may be due to gene variations (polymorphisms) and/or environment (epigenetics) resulting in aberrant-addictive behaviours or Reward Deficiency Syndrome (RDS). In spite of a global genome-wide search to divulge candidate or specific genes, or even clusters of genes, it is well-known that many attempts have either not replicated or have been inconclusive. However, Palmer et al. [25] recently showed that between 25–36% of the genetic variance in vulnerability to substance dependence/abuse might be attributable to relatively common single-nucleotide polymorphisms (SNPs). Additionally, the additive effect of common SNPs may be shared across comorbid drug dependency/addiction. Finally, recent evidence has revealed that specific candidate gene variants account for risk prediction.

Adopting a Bayesian approach, earlier studies from Blum’s laboratory divulged a Positive Predictive Value (PPV) of 74% specifically for the DRD2 A1 variant associated with a lower amount of D2 receptors. A newborn with this polymorphism is at substantially higher risk of becoming addicted to either drug, food, or aberrant behaviours at some point in his/her future [26, 27]. Since this finding in 1990 by Blum and Noble of the association of the DRD2 A1 variant and severe alcoholism, various laboratories and research centres across the globe, including those associated with or funded by NIDA and NIAAA, not only have confirmed this finding [9], but have extended the magnitude of candidate genes and second messengers located in the reward circuitry of the brain [28].

Examples include Moeller et al. [29], who suggested drug-cues substantially contribute to relapse. Neurogenetic results have revealed the DAT1R 9R-allele as a vulnerability allele for potential relapse, especially during early abstinence (e.g., detoxification) in treatment. The DAT1 9 allele impacts the fast acting reuptake-transport of dopamine sequestered from the synapse leading to a hypodopaminergic trait.

It seems shrewd to utilize genetic testing to reveal reward circuitry gene polymorphisms, especially those related to dopaminergic pathways, as well as the opioid receptors, with the intention of improving treatment outcome. It is imperative to understand the interaction of reward circuitry’s involvement in buprenorphine treatment effects and their respective

genotypes to provide a novel framework to augment a patient's clinical experience and benefits during opioid replacement therapy [30].

Our laboratory is developing a genetic risk score that represents a panel of known reward genes and associated risk polymorphisms providing the genetic risk for addiction and other behaviours including medical monitoring and clinical outcome response.

Pharmacogenomics – Precision addiction medicine (PAM™)

Blum and Kozlowski have published on the "Brain Reward Cascade" (BRC) [31]. This concept served as a blueprint for how neurotransmitters interact in the reward system of the brain. Also, it has been firmly established that reward-related genes that regulate chemical messengers mediate the quantity of dopamine released into the reward circuit and in other regions of the brain. Moreover, it is well established that resting-state functional connectivity integrity is essential for healthy homeostatic functioning. Zhang et al. [32] recently revealed that in heroin addicts there was a significant reduction of connectivity between the rostral anterior cingulate (rACC) and the dorsal anterior cingulate cortex (dACC), as well as reduced connectivity between the dACC and subcallosal (sACC). These findings of variations in the functional connectivity within three sub regions of the ACC within heroin addicts has implied that these sub regions, together with crucial other brain areas (such as the putamen, dorsal striatum, orbital frontal cortex, dorsal striatum, cerebellum, amygdala, etc.) may play essential aspects in heroin addiction. More recently, in Blum's laboratory, and along with Zhang's group [33] in abstinent heroin addicts showed that KB220Z™ (Pro-Dopamine Regulator) a complex dopamine agonist, induced a significant increase in MRI BOLD activation within the caudate-accumbens-dopaminergic pathways compared to placebo following one-hour acute administration. Additionally, KB220Z™ also reduced resting-state activity in the cerebellum of abstinent heroin addicts in recovery. In the second tier of this pilot study, all ten abstinent heroin-dependent subjects, three brain regions of interest (ROIs) were observed to be significantly activated in resting state by KB220Z™ contrasted with placebo ($p < 0.05$). This increased functional connectivity was observed in a presumed network which encompassed the dACC, posterior cingulate, nucleus accumbens, medial frontal gyrus, occipital cortical areas, and cerebellum.

SUMMARY

The development of a polymorphic gene panel [34–43] has enabled customized (personalized) anti-obesity compounds [44] and now could provide personalized induction of "*dopamine homeostasis*." This serves as the basis of futuristic personalized addiction medicine utilizing the Genetic Addiction Risk Score (GARS).

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HIGHLIGHTS

- The opioid-addiction epidemic is a plague to modern society.
- Genetic Addiction Risk Score (GARS™), paired with potential precision or personalized medicine (i.e., nutrigenomics) to induce “dopamine homeostasis” is essential in treating addiction.
- The compounds KB220Z/KB220ZBR/KB220PAM™ (Pro-Dopamine Regulators) are complexes with known dopamine agonistic qualities that successfully mediates “dopamine homeostasis”.