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Insurance Companies Fighting the Peer Review Empire without any Validity: the Case for Addiction and Pain Modalities in the face of an American Drug Epidemic

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Abstract

The United States are amid an opioid overdose epidemic; we are challenged to provide non-addicting/non-pharmacological alternatives to assist in pain attenuation. There are proven strategies available to manage chronic pain effectively without opioids. Utilization review providers for insurance companies often ignore medicine based scientific peer-reviewed studies that warn against the chronic use of opioid medications, as well as the lack of evidence to support long-term use of opioids for pain. This paradigm must change if we are to indeed change the drug-embracing culture in American chronic pain management. A barrier to treatment is pushback on the part of insurance companies especially as it relates to fighting against pain relief alternatives compared to classical analgesic agents. Pain specialists in the U.S., are compelled to find alternative solutions to help pain victims without promoting unwanted tolerance to analgesics and subsequent biological induction of the "addictive brain." It is noteworthy that reward center of the brain plays a crucial role in the modulation of nociception, and that adaptations in dopaminergic circuitry may affect several sensory and affective components of chronic pain syndromes. Possibly knowing a patient's genetic addiction risk score (GARS™) could eliminate guessing as it relates to becoming addicted.

Introduction

One hundred and fifty million people suffer from pain conditions, every 14 minutes someone dies from a prescription overdose and 300 million narcotic prescriptions are filled every year with a cost in the 100's of billions. Pain specialists intend to provide needed help to victims of pain. We propose that a critical barrier to treatment relates to potential push-back on the part of insurance companies. It is well-known that prescribing powerful narcotics to relieve pain can lead to high tolerance and severe withdrawal symptoms in a relatively short period [1]. These problems provide the behaviors using objective measures, rather than paper-pencil clinical assessment tools. "Reward Deficiency Syndrome" (RDS) [2], is a genetically based hypodopaminergia known to afflict approximately one-third of people in America [3]. Understanding that while some people can tolerate powerful narcotics and after being treated for pain no longer desire opioids even after withdrawal, others, due to both genetic and

epigenetic insults, become engrossed with additive –like behaviors even after the pain is gone. While seen more easily with acute pain, this is not the case for chronic pain conditions that continue to require powerful narcotics. The double edge sword for the pain specialists is that on the one hand, their patients may not be honest about their true pain level or sensitivity due to being caught up with the "addictive process" possibly linked to polymorphisms of their reward circuitry genes. On the other hand, patients require potent narcotics to overcome disruptive pain symptoms. The issue is to find a way to identify these two types of patients early in their treatment. The answer might be through genetic testing. While this sounds simple and we will explain the concept in more detail, we must consider that although our DNA may predispose addictive –like behaviors it is impacted by our environment or specifically epigenetic processes involving gene expression [4].

However, in today's world even with so many people dying from licit and illicit narcotics, new state laws, governmental agencies and "big pharma" are making it very difficult to continue to treat victims of chronic pain. Possibly knowing a patient's genetic addiction risk score (GARS™), could help to deliver better care, by providing an in-depth view of a patient's risk for addiction, to eliminate guesswork as it relates to becoming addicted.

It is somewhat strange to blame the pain specialist for helping relieve pain and in doing so be responsible for the so-called "bad" behavior of the unwitting individual. With this stated as well as the dilemma of pain specialists in treating both acute and chronic pain this article, will attempt to shed light on:

The role of insurance companies in fighting payment for addiction;

How insurance companies fight non-pharmacological alternatives to powerful analgesics by rejecting peer review articles; and

Provide evidence-based genetic guidance to assist the pain specialists to overcome guessing with "Precision Addiction Management."

The Role of Insurance Companies in Fighting Payment for Addiction

History of parity laws for mental health

The brief history of the Parity laws governing health care as they pertain to addiction in the United States is noteworthy. In the 70s and even 80s, many employers argued against mental health benefits for Substance Use Disorder (SUD) under the Employee Retirement Income Security Act of 1974 (ERISA). Not until 1994 did the Clinton administration propose that Mental Health and SUD services are to be fully integrated into health alliances. Others countered the proposal until in 1996; when the Mental Health Parity Act required insurers and employers to provide benefits, specifically for mental health, and to raise dollar coverage limits on mental health services to the same level as surgery and major medical services. In 2012, Kennison Roy and other ASAM physicians helped form stronger Parity laws specifically, to change the practice activities of addiction physicians, therapists, counselors, nurses, and administrators and service delivery financial personnel. In 2014, T.D. Molfenter pointed out that The Patient Protection and Affordable Care Act (PPACA) would significantly alter addiction treatment service delivery [5].

Are we facing fraud by American health insurance companies?

Mental Health, which includes SUD, may have finally obtained parity with surgery and major medical, but for the most part, American insurance companies still do not understand addiction. Seven years after ASAM redefined addiction as a chronic brain disease the United Behavioral Health telephone prompt says: "If you are calling about substance abuse say 'behavioral."

Parity violations abound. The Office of the New York Attorney General, a national leader in the enforcement of the Mental Health Parity and Addiction Equity Act of 2008, has already successfully prosecuted at least five cases against health insurance companies. The companies had failed to cover residential treatment, improperly evaluated claims, frequently denied medical necessity or charged higher co-payments for outpatient visits. Some of the insurance companies were forced to recalculate years of previously paid claims determined by the Office of the NY Attorney General to most probably been underpaid.

The NY Attorney General sued all the major insurance companies in 2009 for using Ingenix, a re-pricing database owned by United Health Care. Ingenix regularly underpaid out-of-network providers and had bilked their constituents out of millions of dollars. The Commerce Committee of the U.S. Senate decided that consumers across the country have been bilked out of billions. Cuomo used the 2009 settlement monies to create Fair Health, a non-profit database for determining usual, customary and reasonable (UCR) rates for out-of-network providers. Six years later four of the most prominent vendors, each with different "branding," owned by the same New York-based parent, Multiplan were investigated by the NY Attorney General Eric T. Schneiderman for illegally re-pricing claims from out-of-network providers not contracted with them. The same violations of mental health parity, are now occurring in California. Late payments, automated-signed denials of payment for lack of medical necessity, fail first protocols, the likelihood of improvement requirements, refusal of treatment because of patient non-compliance, and limits to the duration and scope of benefits for services provided under the plan or coverage, are also illegally used to deny payment [6]

The primary insurance companies who do not like paying for effective addiction treatment are using companies owned by Multiplan to re-price California's small non-medical treatment facilities using irrelevant data from Medicare. Creative cost

containment vendors help their clients avoid paying the fixed UCR rate of Malibu's 42 treatment centers by expanding the Malibu's 90265 zip code to 902xx. The practice allows them to pit 200 Malibu and Beverly Hills high-end facilities against 200 low-end non- profits facilities in some of Los Angeles' low income, crime-ridden areas, including 100 free Salvation Army beds.

It is Health Net, however, which has taken the lead in trying to destroy effective substance abuse treatment. Health Net had a history of being a bad player. In 2007 a New Jersey federal Judge Faith S. Hochberg agreed to accept a settlement that required Health Net to pay a quarter of a billion dollars to the insured they had cheated in 2008.

Surprisingly, in January 2014 Health Net began offering individual PPO policies through Covered California, and until February 2016 Health Net was hailed by the addiction treatment industry for providing long-term substance abuse benefits that made a difference. Then Health Net merged with the St. Louis Missouri Medicaid company, Centene Health Net and defied Judge Hochberg's decision. Declaring extensive fraud on January 8, 2016, Health Net launched a dragnet audit of all out of network treatment facilities in five states. Most facilities were not paid for 4th quarter 2015 claims and first and second quarter 2016 claims until July 2016. Health Net, which had previously spent 75% of billed, began by trying to pay Medicaid rates of less than $200/day for inpatient and less than $100/day for outpatient. After protests, Health Net settled on 190% of Medicare. Although several Californian Appellate Court decisions confirm that providers have a right to depend on information provided in a telephonic benefit check at least 30 months of benefit checks, have repeatedly stated that there was no linkage to Medicare fee schedules. Health Net also violated several requirements of parity, issuing thousands of cut and pasted denials for lack of medical coverage with an automated signature from Dr. Matthew Wong, a Health Net Medical Director whose addiction credentials Health Net has refused to provide.

The California Department of Insurance launched an investigation in April 2016 into the illegality of Health Net's actions but had not decided by early August, thus caused treatment facilities struggling to survive financially to sue Health Net in large multi-plaintiff actions. Arizona facilities filed a similar motion in late July.

How Insurance Companies Fight Non-Pharmacological Alternatives to Powerful Analgesics by Rejecting Peer Review Articles

Issues with insurance companies fighting the peer review empire

Peer review is defined as the merit-based evaluation of work by one or more researchers of similar competence to the creators of the work (peers). It constitutes a type of self-regulatory process by qualified members within a profession from a relevant field. The methods are employed to maintain standards of quality, improve performance, and provide credibility.

It is noteworthy that the peer review process has been a formal part of the scientific literature since The Philosophical Transactions of the Royal Society was the first journal to formalize the peer review process over 300 years ago. More recently, the major publishing firm Elsevier in 2009 launched with "Sense about Science" an international survey of both authors and reviewers called 2009 Peer Review Study. The primary reason for this survey was to help educate the public's understanding of "sound science" [7,8]

Scientific peer review of scholarly publishing is a well-established practice. While not being a perfect system, peer review helps validate research, including creating a method for evaluation of scientific discourse before publication. Certainty, despite criticism peer review, is widely accepted as the validation method for research. Studies of Peer Review have demonstrated that most rejected papers will go on to be published in other journals. However, occasional errors of peer review are not reasons for abandoning the process altogether – the mistakes would be worse without it. Eighty-Four percent of scientists believe that without peer review there will be no control related to scientific communication. Nine out of ten authors think that stringent peer review increases the credibility of their publications. Quality and speed of peer review are the two most important factors in attracting authors to publish in a journal [9]. Understanding these facts consensus shows that most prestigious journals and many others want to improve the efficiency of the process and suggest the following:

Synopsis of the fate of rejected papers

Previous studies of rejected manuscripts outcome initially examined the effect of rejections in delaying publication and potential editorial bias. To understand authors' publication strategies the relationship between the impact factor of the rejecting journal and that of the journal that eventually published the manuscript was considered. For example, sending manuscripts to a highly ranked journal first and then successively in less prestigious ones. Some studies have also attempted to estimate whether peer review could help authors to increase the quality of their rejected submissions by understanding what authors modified when targeting subsequent journals [10]. This latter part is significant, and many authors rely on these comments for future submissions of the same work. Not all rejected articles are subsequently published, and sometimes the impact factor could be higher in the journal that finally accepts the submission. Armstrong et al. [11] examined the evidence of 489 manuscripts rejected by the Journal of the American Academy of Dermatology in 2004-2005 to look at whether suggested changes were adopted in final publications. Among the 101 subsequently published manuscripts for which full texts were available, 82% of the authors incorporated at least one change suggested by the

original reviewers. These manuscripts were eventually published in journals with higher impact factors than those that did not include any reviewer suggestions (p = 0.0305)[12]. A more in depth-study on Angewandte Chemie International Edition by Bornmann and Daniel [13], who applied content analysis to referee reports on 1899 manuscripts that were reviewed in 2010, confirmed a relation between original peer review and later publication of rejected manuscripts. While 94% of the 1021 rejected manuscripts were published almost unchanged within another journal, they found that previously rejected manuscripts were more likely to be published in journals of higher impact factor when there were no adverse comments by reviewers on essential aspects of the submission, such as the relevance of contribution and research design.

However, given that evaluation and publication time delays are field-dependent and that the publishing market is highly stratified and segmented between fields, these studies may only be relevant to research in medicine and related areas. Furthermore, these studies were constrained within a limited time frame, typically following papers for only a couple of years. This may be sufficient time in fields such as medicine, but not for others, like social science, computer science, and humanities, where there are more types of publication outlet, including conference proceedings and books, and more extended publication trajectories [14].

The Case for Electrotherapy for Pain

Iatrogenic prescription drug abuse is the fastest growing drug problem in the United States. About 64,000 unintentional drug overdose deaths occurred in the United States, in 2017. The two primary US populations at risk for prescription drug overdose are the approximately 9 million individuals who report the long-term medical use of opioids, and about 5 million individuals who report nonmedical use, without a prescription or medical need. The twenty percent of patients, who are prescribed high daily doses and seek care from multiple clinicians, account for 80% of opioid overdoses and are likely to divert drugs to others, who use them without prescription.

In addition to the main pain pathways that ascend from the dorsal horn of the spinal cord to the medulla, several genes and their polymorphisms that reside in the mesolimbic reward center of the brain have a role in the moderation of pain sensitivity and tolerance [15-17].

The identification of these genes and polymorphisms can provide unique therapeutic targets for non-narcotic pharmacogenomic solutions that can be used to treat pain. The Genetic Addiction Risk Score (GARS™) test (reward genes such as DRD2 for risk for narcotic addiction predisposition) [18] can identify patients with a predisposition to addiction in the early stages of treatment. Those are the patients who will need a non-addictive alternative treatment for pain. The electrotherapeutic H-Wave® device developed by Electronic Waveform Lab, Inc., Huntington Beach, CA is one such alternative.

The Characteristic of H-Wave Electrotherapy include

The physiological mechanisms of action of H-Wave device stimulation (HWDS) have been examined in animals. The device has been shown to reduce edema due to the stimulation of smooth muscle fibers within the lymphatic vessels [19]. Moreover, using HWDS benefits tissue healing by the induction of nitric oxide (NO)-dependent microcirculation augmentation and angiogenesis (new blood vessels formation) [20].

The characteristic of H-Wave Electrotherapy include:

- Contraction of smooth muscle and skeletal muscle (red, slow twitch) fibers via low frequency (1-2Hz) stimulation, resulting in loading of tissue while maintaining the low muscle force tension characteristics; being non-tetanizing and non-fatiguing.
- Arteriolar vasodilation accompanying HWDS is due to a nitric –oxide mechanism demonstrated in rat studies.
- Increase in new blood vessels which proving angiogenesis using bromouridine staining in repetitive stimulation in rats.
- HWDS specifically and directly stimulates the smooth muscle fibers within the lymphatic vessels ultimately leading to fluid shifts and reduce edema as well as protein clearance.

There is a need for non-pharmacological alternatives to treat pain in the face of the opioid crisis. The published peer-reviewed evidence regarding the positive effects of H-Wave includes a total of 18 published works. These original studies, reviews, and abstracts represent an essential, evidence-based series showing significant pain relief and mechanisms of action. This significant body of literature has been published in peer review and impact, PUBMED journals including BMC Musculoskeletal Disorders; Diabetes Care; Journal of Surgical Orthopaedic Advances; Journal of Orthopaedic Research; Medical Hypothesis; Advances in Therapy; Physician and Sportsmedicine, J Foot Ankle Surgery; J Manipulative Physiol Ther; Cases Journal. Bio Med Central, Anesthesia & Analgesia, and J Addict Res Ther [18-27]. Other studies indicate a critical role for electrotherapy for pain [27-29].

The main issue is that despite clear evidence in peer-reviewed journals, that demonstrates the positive anti-nociceptive benefits using H-wave a well researched electrotherapeutic pain treatment modality many large insurance carriers including California Workers Compensation ignored these studies. They argued that these articles not be considered as scientifically sound, to try to justify their contention for non-payment for H-Wave and other deserving therapeutic non-narcotic modalities. The rejection of therapeutic non-narcotic modalities is a hazardous pattern, inappropriately used, by third-party payers to save costs. We retort that this represents

an infraction on the part of insurance companies and their Utilization Review (UR) provider examiners wittingly offering biased views without any validity against a very well-established peer review system as carefully described above. Notably, in the face of our worst drug epidemic ever, with many lives being lost daily, the entire pain community should embrace an alternative to potent pain medications.

Providing Evidence-Based Genetic Guidance to Assist Pain Specialists to Overcome Guessing with "Precision Addiction Management

It is noteworthy that any pain specialist would welcome a non-addicting way to achieve attenuation of both acute and chronic pain for their patients. The recommendation is that if patients present with a history of chronic pain and show a high genetic risk for addiction an alternative approach that includes both electrotherapy like H-Wave and pro-dopamine regulation to induce dopamine balance (Homeostasis). Along these lines, it is well-known that the chemical messenger Nitric Oxide (NO) increases circulation to the brain concomitantly with increased oxygenation. It is also now known that the mechanism by which H-Wave achieves increased circulation is via a NO mechanism [21]. Concomitantly, Blum's group using a left ventricular injection of radiolabeled 15-micron spheres, in swine, that recorded cerebral blood flow (CBF) to systemically evaluate the effect of the putative neurotransmitter methionine-enkephalin on regional brain areas seems very relevant CBF [30]. The results divulged that the infusion of methionine enkephalin peripherally into miniature swine remarkably increased CBF in the cerebellum, basal ganglia, pons, frontal cortex and inferior parietal cortex. Insignificant increases were observed in areas including the occipital cortex, hippocampus, and medulla oblongata while there was no effect in the pituitary gland. These results provide the rationale for a potential role of methionine enkephalin as a modulator of blood flow to the brain[30]. When one considers that D-phenylalanine an enkephalinase inhibitor can increase brain CBF combined with analgesic properties of H-Wave might provide an attractive front-line option for people with a high GARS.

About the development of the GARS test

An unpublished pilot study of genetic severity conducted in 70 patients attending two independent addiction treatment centers, the percentage of prevalence of risk alleles was calculated. The prevalence of the risk alleles of the DRD1-4, SLC6A3, DAT1, 5HTTLPR, MAO, COMT, mu opioid receptor, and GABA receptor genes provided an arbitrary severity score based on the percentage of risk alleles present. Blum's group found that 14% had low risk; 81% had a moderate risk, and 5% had a high genetic risk. A multi-centered study of 450 patients now completed will report on a subsequent analysis utilizing GARS and the Addiction Severity Index (ASI) in SUD clinics that evaluated genetic risk for Reward Deficiency Syndrome (RDS) in patients presenting with pain and addiction.

These positive associations support the incorporation of GARS tests for pain patients at risk for opiate addiction upon entry to pain clinics. The take home message is that following careful analysis patients that carry four or more of any risk allele in the GARS test predict ASI severity for drug abuse (including opioids), whereas carrying seven or more risk alleles of GARS predicts ASI alcohol severity.

Pro-dopamine regulation

Neuroimaging tools including fMRI and QEEG in humans and most recently, fMRI in rodent models were used to evaluate a well-known neuro-nutrient dopaminergic agonist. BOLD activation of dopaminergic pathways and regulation of PFC – cingulate gyrus activity [31] in abstinent heroin [32] and psychostimulant abusers [33] were observed.

"Gene Guided Precision Nutrition™" and KB220 variants (a complex mixture of amino acids, herbals, and trace metals) are the pioneers and standard-bearers for a state of the art DNA customization [34]. Findings by both, Kenneth Blum, Ph.D. and Ernest Noble, Ph.D. and others demonstrated the genetic role of shaping our cravings and pleasure-seeking, has opened the doors to the comprehension of how genetics control our behaviors and effect our mental and physical health [35]. Moreover, the technology that is related to KB220 variants to decrease or ameliorate extreme cravings via influencing genetics may be the cornerstone of the practical applications of neurogenetics/nutrigenomics [36]. Continuing research discoveries are a principle catalyst for the expansion, evolution and the scientific recognition for the significance of nutrigenomics. There are potentially remarkable contributions to medicine and human health. Neuro-Nutrigenomics is now a vital field of scientific investigation that offers great promise to improve the flawed human condition. The development of the GARS which has noted predictive value for the severity of drug and alcohol use disorders as well as other non-substance related addictive behaviors is at the forefront of neuro-nutrigenomics. Backed by evidence of obesity [37] individual customization of neuronutrients has been commercialized and could have a profound impact on both addiction medicine and pain management.

"Precision Addiction Management" that includes genetic testing of both metabolism and narcotic risk; electrotherapy a non-addicting alternative to pain opioid prescription, dopaminergic activation with KB220PAM; medical monitoring with CARD (developed by Dominion Diagnostics LLC.)and 12 step self-help programs is proposed.

Both substance and non- substance use disorders are considered a brain disorder with genetic and epigenetic impairments by the American Society of Addiction Medicine (ASAM). How can a brain disorder be fixed in weeks or months, let alone in 7-30 days or even two years? Without considering genetic predisposition as a factor, evidence

emerging from neuroscience now suggests that it will take at least three years of abstinence for the brain to heal in high opioid use disorders (OUD) patients [38]. For example, neuroimaging studies show that in abstinent heroin addiction there is a protracted reduction of resting-state functional connectivity (where one brain region cross-talks with a distant brain region). Lack of crosstalk has been observed in a vital network that includes: dorsal anterior cingulate, medial frontal gyrus, nucleus accumbens, posterior cingulate, occipital cortical areas, and cerebellum [39]. Decreased rsFC together with genetic and other environmental influences like stressors and ques, will promote the "revolving door" and relapse. We also now know that specific genetic variations such as the A1 form of the dopamine D_2 receptor gene will have 30-40 % less D_2 receptors is associated with a high risk for relapse, hospitalization and even fatality. It is noteworthy that over 100 million people in the United States alone carries this gene form [35].

The basic tenet is that most people entering a SUD treatment facility, and many entering a pain clinic possess a hypodopaminergic trait (genetic) or state (epigenetic). This reward deficiency is crucial regarding continued motivation to misuse alcohol or other drugs, or participate in non-substance compulsive behaviors like gambling, gaming, food excesses and can lead to relapse. Refusals of intensive treatment for all RDS behaviors from health insurance companies is equivalent to denying therapy for other inheritable disorders like diabetes and cancer [40].

Dopamine homeostasis "aftercare" –a long-term goal to prevent relapse and enhance recovery quality

Analysis of thousands of urine specimens, developed by Dominion Diagnostics, LLC., data from the Comprehensive Analysis of Reported Drugs (CARD™), revealed a significant difference in both compliance and abstinence rates. Opioid replacement programs show the best compliance with a range of 88% to 92%; Methadone and Suboxone respectively, but also show high drug abuse during treatment approximately 47% [41]. Can the treatment programs be improved?

Presently, "aftercare" refers to any program or therapy that follows primary treatment including 12-Step programs [42]. Unfortunately, very few programs provide any evidenced-based treatment approaches during this, most vulnerable, recovery period. While there is evidence of benefit from a short-term dopamine blockade preferred by FDA approved medications for the treatment of drug addiction (e.g., alcohol, opiates, nicotine) there is also evidence that supports "dopamine homeostasis" as a goal of treatment for long-term recovery. Dopamine balance can be accomplished through many holistic modalities including, but not limited to, brain neurotransmitter balancing with geentically guided neuro-nutrients such as the KB220PAM variant [43]. Other modalities include dopamine-boosting diets, hyper-oxygenation, heavy metal detoxification, exercise, mindfulness, meditation, yoga, biofeedback, cognitive behavioral therapy, and trauma therapy, Especially during aftercare, 12-step programs and fellowships and group activities like for example, singing in a choir are helpful. It is imperative that clinical professionals begin to understand healthy resting state functional connectivity (rsFC) as being a cornerstone goal concerning the treatment of addiction, RDS and pain [44].

Insurance companies should begin to realize that like in cancer treatment, prevention is the most beneficial tactic in the long-term. The cost of addiction treatment can be lowered by preventing and reducing relapse. Drugs, food, smoking, gambling, and even compulsive sexual behavior and even major depressive disorder (MDD) have been shown in many studies to reduce rsFC. Modalities that can restore this impaired cross-talk between brain areas like the cingulate gyrus, nucleus accumbens, and hippocampus, should all be included in the aftercare plan in all treatment programs in America [45].

While this is a laudable goal anything, less will ultimately lead to the so-called "revolving door" for as many as 90% of treatment participants. "Love needs care," and it must start with the gatekeepers of treatment- the insurance companies [46]. Finally, our unique challenge is to re-educate the top decision-makers in the insurance world. Instead of threats related to possible criminal action provide new guidance that reflects evidence-based facts. The insurance companies should understand the etiological factors linked to RDS as a biological, genetic disorder should have actual parity with medical benefits for other chronic diseases like Diabetes, Hypertension Asthma, COPD and Cystic Fibrosis that require life-long treatment -not just seven days of detoxification [47].

To reiterate there is a general understanding that at least in the addiction and pain field many examples, of insurance non-payment are because of inappropriate utilization of articles with no validity carefully selected to provide evidence to refute a therapeutic modality and support their refusal of payment. In many cases, a number of these articles are not listed in PubMed. One example includes patients in SUD programs whereby "suicide ideation" must be present to receive third-party payment despite parity laws protecting SUD.

The smart insurance executives will heed these remarks and adopt a new approach embracing Parity laws and focus instead on a plausible preventive tactic to reducing costs long-term and instead of being chastised, become a hero!

Can we overcome the Opioid Crisis?

The role of neurogenetics of opioids in pain mechanisms has been extensively studied and published. Results indicated that both sensitivity and tolerance to morphine were found to be dependent on genotype, with inheritance characterized by dominance or partial-dominance. Unfortunately, the enactment of the 1994 law that opened the doors to opioid prescription writing for chronic pain was based on a concise letter in New

England Journal of Medicine [48] suggesting that opioid used chronically does not cause addiction has been cited 600 times since its publication.

Several groups are setting goals and determining guidelines, and regulations to address the eschewing opioid crisis. These include the Joint Commission, the Institute of Medicine (IOM), the Federal Drug Administration (FDA), the Centers of Medicare and Medicaid Services (CMS), the Department of Health and Human Services, the Centers for Disease Control and Prevention, and other federal and state government agencies. In 2011, the IOM published "Relieving Pain in America," which advocates for a multidisciplinary and multimodal approach to pain management, and includes an emphasis on prevention, not just treatment [49].

Over the past decade, the Joint Commission decidedly reexamined and thus modified its view of the standard of pain management starting with the elimination of assessments as a fifth vital sign in 2009 [50]. The CMS and the Department of Health and Human Services combined efforts to set priorities including addressing opioid prescribing practices and implement more efficient population-based, person-centered strategies, to decrease the risk of opioid disorders. They recommended increasing the use of naloxone and injectable naltrexone and medication-assisted treatments to reduce opioid disorders and thus encouraged the use of evidence-based practices for both acute and chronic pain management [50,51].

The CMS also is transitioning to new questions regarding pain in the HCAPHS Survey. Starting in January 2018, the new questions are as follows: (1) during this hospital stay did you have pain? (2) During this hospital stay did the hospital staff talk with you about how much pain you had? And (3) during this hospital stay, how often did hospital staff talk with you about how to treat your pain [51,52]? Many are recommending investment in research to understand the neurobiology of pain and opioid use disorders better to find better non-opioid treatments and other interventions that identify unique factors for specific opioid using populations [53]. The Centers for Disease Control and Prevention has created guidelines for prescribing opioids for chronic pain [54]. Various states are also addressing this same crisis. Most have extensive databases that providers may access, divulging previous prescriptions of opioids dispensed to patients. This measure is correlated with a modest and sustained decrease in opioid prescriptions as has been found by the mandatory prescribing drug monitoring program on opioid prescriptions by dentists in New York [36,55].

As of April 2017, specific federal legislation was introduced to limit the supply of opioid prescription for acute pain to 7 days [56]. By August of that same year, some 24 states enacted legislation with a limit, guidance, or requirement related to opioid prescribing [57]. Despite advances, there are still significant gaps that remain unaddressed, for example, reimbursement of hospitals and physicians for pain control and patient satisfaction data that neither consistently rewards nor reflects the provision of the best care practices.

Insurance companies and retail pharmacies should also reassess how opioid medications are supplied to patients and how the cost of opioid versus non-opioid pain medications is determined. Potent, synthetic illegal opioids such as heroin, carfentanil, and many others entering the United States from outside markets must be eliminated.

Differences in human response to opioids have been well documented. For example, a specific opioid may provide better analgesia for one individual and not another. Individual responses differences are not unique to the analgesic effect. They are often found with other opioid effects. These include things like side effects, interactions, and toxicities. As research gains from databases on knockout rodents, pharmacogenetics, and gene polymorphisms, unravel various biochemical differences of opioid responses in humans and genetic receptor interactions, such differences may be used to provide better care. Testing may become more cost-effective and readily available to aid clinicians. Instead of simply relying on patient feedback, clinical judgments and trial and error, clinicians should be able to predict patient responses to specific doses of specific opioids. This will allow individualization of opioid analgesic therapy which will allow opioid rotation strategies. Information of this type should translate into improved patient care, as clinicians become adept at tailoring appropriate opioid therapy. Although presently perfect candidate genes for gene-directed opioid therapy are not obvious, specific candidate genes have been studied [58], and some associations with analgesic requirements for acute and chronic pain states, as well as with sensitivity to the pain, have been found and included in the GARS.

These associations with analgesia and chronic pain were a consequence of an intense investigation of the candidate genes for the catechol-O-methyl-transferase, melanocortin-1 receptor, guanosine triphosphate glycohydrolase (involved with Nicotinamide Adenine Dinucleotide (NAD) metabolism), and the mu-opioid receptor [59, 60].The genetic variants of drug-metabolizing enzymes, in contrast, have well known and described impacts on responses to pharmacotherapy. The analgesic efficacy of codeine, tramadol, nonsteroidal anti-inflammatory drugs and tricyclic antidepressants are influenced by polymorphisms of the cytochrome P450 enzymes. For example, genetically caused cytochrome P450 (CYP) 2D6 inactivity, renders codeine ineffective due to lack of morphine formation, slightly decreases the clearance of methadone and the efficacy of tramadol due to lack of formation of the active O-desmethyl-tramadol [61].

In an animal genetic experiment, Mogil's group [59,61] investigated tolerance and sensitivity to morphine. They did this using two strains of mice (C57BL/6By and BALB/cBy) and the addition of seven recombinant inbred strains of their

reciprocal F1 hybrids. After administering of 20 mg/kg of saline or morphine HCL, sensitivity was measured via locomotive activity. The 'hot plate' method was employed to assess tolerance following repeated or single administration of 20 mg/kg of saline or morphine HCL. Results indicated that both sensitivity and tolerance to morphine were found to be dependent on genotype, with inheritance characterized by dominance or partial dominance. Ongoing research with our group using GARS testing will target candidate gene polymorphisms and the drug metabolizing enzyme genetic variants, all to search for any associations between an individual's genetic profile and drug response (pharmacogenetics).

The gene for the mu-opioid encodes the receptor targets for various endogenous opioids. Studies of polymorphisms in the receptors have contributed substantially to knowledge about genetic influences on cocaine and opiate addiction (including heroin, morphine, and synthetic opioids) [62]. Genes for monoamines and endogenous opioid system, particularly genes encoding the dopamine, serotonin, and norepinephrine transporters, and dopamine β-hydroxylase, have also been studied [63].

Currently, in the US, we are in the midst of an opioid epidemic. The primary gateway to opioid addictions/abuse often commences with prescribing of powerful analgesics (e.g., OxyContin®) for illness and related pain. One way to prevent this dilemma is to employ the use of GARS. By illuminating and unraveling opioid dependence risk and encouraging patients and clinicians to seek out other non-opioid pain relievers like electrotherapies [20,24,25,27] and non -steroid analgesics [64] as well as precision KB220PAM prevention of OUD is possible.

Conclusion

There is a devastating opiate/opioid epidemic in the United States. As stated by the CDC, adulterated heroin overdose is on the rise and approximately 100 people, young and old, are dying every day due to narcotic overdose. The FDA has approved some Medication-Assisted Treatments (MATs) for alcoholism, opiate and nicotine dependence, but nothing for psychostimulant and cannabis abuse. While these pharmaceuticals are essential for the short-term induction of "psychological extinction," in the long-term caution is necessary because their use favors blocking dopaminergic function indispensable for achieving normal satisfaction in life and reduced hyperalgesia [65]. The two institutions devoted to alcoholism and drug dependence (NIAAA & NIDA) realize that MATs are not optimal and continue to seek better treatment options. Blum's group has developed a glutaminergic-dopaminergic optimization complex called KB220 that can provide for the eventual balancing of the brain reward system and create "dopamine homeostasis" [66] together with H-Wave therapy should be carefully considered. This system may provide substantial clinical benefit to the victims of RDS who can be identified using. "Precision Addiction Management (PAM)" based on the GARS test. High risk for addiction and electrotherapeutic pain treatment could assist in prevention and recovery from iatrogenically induced opioid addictive behaviors.

Non-pharmacological alternatives to potent narcotics, diagnosis of the risk for subsequent OUD, fatal overdoses and awareness of the unwanted pushback from the insurance companies in arguing studies that meet peer review criteria as in the case of H-Wave, must be embraced. With this knowledge of the interaction of the reward center and the need for balanced dopamine tone regarding pain, we encourage the scientific community, and especially pain specialists, to consider electrotherapeutic modalities along with other non-addicting alternatives, as a front-line approach to combat the ongoing opioid epidemic.

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Conflict of Interests

K. Blum is 100% owner of Synaptamine Inc. holding a number of nutrigenomic patents worldwide including Geneus Health holding genetic testing for RDS. All other authors have no conflict of interest to report.

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