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Buprenorphine Response as a Function of Neurogenetic Polymorphic Antecedents: Can Dopamine Genes Affect Clinical Outcomes in Reward Deficiency Syndrome (RDS)?

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Abstract

There is a plethora of research indicating the successful treatment of opioid dependence with either buprenorphine alone or in combination with naloxone (Suboxone®). However, we encourage caution in long-term maintenance with these drugs, albeit, lack of any other FDA approved opioid maintenance compound to date. Our concern has been supported by severe withdrawal (even with tapering of the dosage of for example Suboxone® which is 40 times more

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Conflict of Interest:
Kenneth Blum, PhD is the holder of a number of US and Foreign patents issued and pending related to Nutrigenomics and Nutraceuticals. Through IGENE LLC., Dr. Blum exclusively licensed the Genetic Addiction Risk Score (GARS)™ to Dominion Diagnostics, LLC. Dr. Blum is also an officer and stock holder of IGENE, LLC and is a paid consultant of Dominion Diagnostics, LLC, IGENE, Malibu Recovery Center. Dr. Blum is a member of the scientific advisory board of Dominion Diagnostics, LLC and is Chief Scientific Advisor of Dominion Diagnostics, LLC.

potent than morphine) from low dose of buprenorphine (alone or with naloxone). In addition our findings of a long-term flat affect in chronic Suboxone® patients amongst other unwanted side effects including diversion and suicide attempts provides impetus to reconsider long-term utilization. However, it seems prudent to embrace genetic testing to reveal reward circuitry gene polymorphisms especially those related to dopaminergic pathways as well as opioid receptor(s) as a way of improving treatment outcomes. Understanding the interaction of reward circuitry involvement in buprenorphine effects and respective genotypes provide a novel framework to augment a patient's clinical experience and benefits during opioid replacement therapy.

Keywords

Buprenorphine; Naloxone; Suboxone; Dopamine & Opioid polymorphic genes; Reward Deficiency Syndrome (RDS)

Introduction

The main purpose of this commentary is to point out that while the United States government Food and Drug Administration (FDA) has approved the utilization of buprenorphine alone or in combination with Naloxone (Suboxone®), to treat acute pain and as an a opioid maintenance modality, our laboratory has cautioned against its long-term use to treat opioid addicted patients. We have provided evidence to support an anti-reward component supporting its benefit in the short term but not in the long-term. This cautionary note is further enlightened by recent genetic information showing that outcome with buprenorphine alone and in combination with naloxone depends in-part on certain reward gene polymorphisms including genes that regulate both opiate and dopamine receptors. This is underscored when one considers the “deficit theory” and the need for dopamine agonist therapy as proposed for all addictive behaviors as espoused in our initial concepts on “Reward Deficiency Syndrome (RDS) [1].

The National Institute on Drug Abuse (NIDA) established the National Drug Abuse Treatment Clinical Trials Network (CTN) in 1999 to bring researchers and treatment providers together to develop a clinically relevant research program. CTN efforts addressed the use of buprenorphine, a mu-opioid partial agonist, as treatment for opioid dependence. Strong evidence of buprenorphine's therapeutic efficacy was demonstrated in clinical trials involving several thousand opioid-dependent participants. This data resulted in 2002, the Food and Drug Administration approved buprenorphine for maintenance treatment of opioid dependence.

Following this approval, buprenorphine, alone or in combination with naloxone known as Suboxone®, has been used successfully for opioid replacement therapy and maintenance. To some in the addiction clinical space it is considered a “Gold Standard”; to others a concern having anti-reward properties [1-3]. We are cognizant that at the present time there is no real replacement for opioid dependence, although we caution the long term use of this combination. It is well known that dependence to illicit drugs, especially opioids, is among the nation's most critical public health and societal problems.

Our group's concerns about the current opioid prescription epidemic and the need for buprenorphine/naloxone (Suboxone®; SUBX) as an opioid maintenance option, and its growing street diversion provided impetus to determine affective states (“true ground emotionality”) in long-term SUBX patients. We utilized emotion-detection in speech as a measure of “true” emotionality in 36 SUBX patients compared to 44 individuals from the general population (GP) and 33 members of Alcoholics Anonymous (AA). We found in long-term SUBX patients (average 1.66 years) a significantly flat affect ($p<0.01$), and they had less self-awareness of being happy, sad, and anxious compared to both the GP and AA groups. Understanding this we have encouraged continued research strategies in SUBX patients to target the specific brain regions responsible for relapse prevention of opioid addiction [4]. Unfortunately, Buprenorphine does not have any effects at the PFC-Cingulate Gyrus and as such does not offer any relapse preventive influence on subsequent opioid seeking behavior even during treatment for almost 50% of subjects [5,6].

While it is well established that dopamine deficiency or a hypodopaminergic trait/state leads to aberrant substance seeking behaviors (RDS) and intact mu opiate receptors are important for maintaining “dopamine homeostasis”, we have suspected that opioiddopaminergic interaction must be involved in buprenorphine response. In this regard we have provided some evidence that a putative dopamine agonist (KB220Z) shows long-term potential as an opioid replacement compound especially in subjects having a genetically determined hypodopaminergic trait (e.g. RDS) [7].

RDS was first defined by our lab in 1996 as a putative predictor of impulsive and addictive behaviors. The D2 receptor has been associated with pleasure, and the DRD2 has been referred to as a reward gene [8-10]. Although the DRD2 gene and especially the Taq1 A1 allele, has been most associated with neuropsychiatric disorders in general and in alcoholism, other addictions (carbohydrate) and /or reward behaviors, it may also be involved in co-morbid antisocial personality disorder symptoms [especially in children and adults with attention deficit hyperactivity disorder (ADHD) or Tourette's Syndrome and high novelty seeking] .

Dopamine has been called the “anti-stress molecule” and/or the “pleasure molecule.’ When dopamine is released into the synapse, it stimulates a number of receptors (D1–D5) which results in increased feelings of well-being and stress reduction [11]. The mesocorticolimbic dopaminergic pathway plays an especially important role in mediating the reinforcement of natural rewards like food and sex, as well as unnatural rewards like drugs of abuse [12]. Natural rewards include satisfaction of physiological drives (e.g. thirst, hunger and reproduction) and unnatural rewards are learned and involve satisfaction of acquired pleasures such as hedonic sensations derived from alcohol and other drugs, as well as from gambling and other risk-taking behaviors [13].

In discussing RDS, we refer specifically to an insensitivity and inefficiency in the reward system. There may be a common neuro-circuitry, neuroanatomy and neurobiology for multiple addictions and for a number of psychiatric disorders. Due to specific genetic antecedents and environmental influences a deficiency of the D2 receptors may predispose individuals to a high risk for multiple addictive, impulsive, and compulsive behaviors. It is

well known that alcohol and other drugs of abuse, as well as other reinforcers (i.e. sex, food gambling, aggressive thrills) cause activation and neuronal release of brain dopamine which can decrease negative feelings and satisfy abnormal cravings for alcohol, cocaine, heroin and nicotine which among others are linked to low dopamine function [14].

In doing association studies for which an investigator requires a representative control sample for a single RDS psychiatric diagnosis or for potential subsets of RDS [Table 1], the obvious limitation relates to controls poorly screened for multiple RDS behaviors and other related psychiatric disorders.

Modified from Blum et al. [15]

Missing behaviors that are part of the RDS subset may be the reason for spurious results when genotyping for single subsets of RDS behaviors. For example an individual may not drink or use drugs but may have other RDS behaviors like overeating or intensive video gaming. In support of this notion, we found a very strong association of the dopamine D2 receptor A1 allele (100%) in a family genotyped for five generations [16] that displayed multi-RDS like behaviors especially substance –related disorders consistent with DSM 5 criteria.

In addition, every individual in the second family also genotyped for five generations also had at least one dopaminergic high risk allele (100%) [48% carried the DRD2 A1 allele]. Moreover, in the second family, only three adult individuals had no addictive behaviors. When we compared our results in which 55 RDS subjects carried the DRD2 A1 allele at (78.2%) with the results of Noble et al. [17] study in which 597 severe alcoholics at (49.3%) carried the A1 allele, there was a significant difference between these two groups (X^2=16.9, $p<0.001$). This demonstrated that the A1allele prevalence increases with multiple RDS behaviors. We also found significant association with the polymorphisms of the dopamine transporter gene (DAT1) as well [16].

Here we propose that multifaceted non-specific RDS behaviors should be considered as the true “reward” phenotype (endophenotype) instead of a single subset RDS behavior such as alcoholism [16]. This may indeed be a paradigm shift in future association and linkage studies and may even be important for the clinical effects of buprenorphine.

Understanding the role of reward gene polymorphisms for both buprenorphine and naloxone should allow an important model to target therapy especially in dosing with Suboxone® in short term treatment.

Neurogentics of Buprenorphine Clinical Response

It is important to realize that clinical outcome in drug addicted patients including alcoholism may depend upon dopaminergic genes and associated polymorphisms. In 1995, Lawford et al. showing that when in a double-blind study, bromocriptine (a DRD2 agonist) or placebo was administered to alcoholics with either the A1 (A1/A1 and A1/A2 genotypes) or only the A2 (A2/A2 genotype) allele of the DRD2 gene, the greatest improvement in craving and anxiety occurred in the bromocriptine-treated A1 alcoholics. Importantly, the attrition was

highest in the placebo-treated A1 alcoholics suggesting treatment outcome is a function of genotype [17,18].

The concept of the feasibility of treating RDS based on pharmacogenetics has been further underscored by Blum et al. [19] They found that the DRD2 gene polymorphism (A1 allele vs A2 al0lele) had a significant Pearson correlation with days in treatment (r=0.42). Compared to the DRD2 A1- carriers the number of days in treatment with the putative natural dopamine agonist KB220 was 51.9 ± 9.9 SE (95%CI, 30.8 to 73.0) and for the DRD2 A1+ carriers the number of days on treatment with KB220 was 110.6 ± 31.1 (95% CI, 38.9 to 182.3). Once again the attrition was highest in the $A1^{-}$ genotype group. It was suggested that the genotype may be a predictor of treatment persistency and compliance. Moreover, even relapse may depend on the DRD2 A1 allele which could affect treatment response. Dahlgren et al. [20] provided the first report of an association between the TaqI A1 allele and a substantially increased relapse rate in alcohol dependent patients.

Along similar lines, Noble & Ritchie [21] measured [3H] Naloxone binding in frontal gray cortex, caudate nucleus, amygdala, hippocampus and cerebellar cortex obtained post mortem from human alcoholic and non-alcoholic subjects. When subjects were grouped by the presence or absence of the A1 allele of the D2 dopamine receptor gene, [3H] naloxone binding was lower in all brain regions examined of subjects with the A1 allele than in those without this allele, with a significant difference in the caudate nucleus. It was suggested that the decreased [3H] naloxone binding observed in subjects with the A1 allele may be a compensatory response to their decreased dopaminergic modulation of opiate receptor activity.

Interestingly, Gerra et al. [22] provided clear evidence that the dopaminergic system is linked to buprehorphine treatment response in heroin addicted humans. Surprisingly, they found no difference between responders and non-responders to buprehorphine in the frequency of kappa opioid receptor (OPRK1) 36G>T SNP. However, the frequency of dopamine transporter (DAT) gene polymorphism (SLC6A3/DAT1), allele 10, was much higher in “non-responder” than in “responder” individuals (64.9% vs. 55.93%) whereas the frequency of the category of other alleles was higher in responder than in non-responder individuals (11.02% vs. 2.13% respectively). Our own interpretation of these results dove tail with the work of others [17,18] showing better treatment outcome and compliance based on dopaminergic polymorphisms whereby hypodopaminergic traits mediate a better response during treatment. We hypothesize that carriers of the 9 allele of the DAT1 would confer a better treatment response with buprehorphine due to its faster transport activity resulting in a hypodopaminergic trait.

Finally, Barratt et al. [23] while not showing significant differences in methadone or buprenorphine outcomes in terms of maintenance with carriers of the Taq1 A1 allele, did show in successful methadone subjects, significantly fewer A(1) allele carriers experienced withdrawal than non-A (1) carriers ($P = 0.04$). Moreover, our laboratory [7] found in a genetically determined hypodopaminergic trait patient at 432 days post Suboxone® withdrawal being maintained on a putative dopamine agonist KB220Z, has been urine tested and is opioid free. Genotyping data revealed a moderate genetic risk for addiction showing a

hypodopaminergic trait. In agreement with these findings, Makhinson and Gomez-Makhinson [24] observed in a case report that buprenorphine withdrawal syndrome with predominant symptoms of restlessness resistant to clonidine and benzodiazepines, was successfully treated with the dopamine agonist pramipexole.

The constant controversy over either dopamine antagonistic compared to dopamine agonistic therapy or simply put treating the dopaminergic surfeit or deficit has been the recent subject of paper published in Nature Neuroscience [25]. Specifically, Willuhn et al. [25] found that phasic dopamine decreased as the rate of cocaine intake increased, with the decrement in dopamine in the ventromedial striatum (VMS) significantly correlated with the rate of escalation. This work suggests that the “deficit” relative to “surfeit” theory requires dopaminergic agonistic rather than antagonistic treatment.

As has been proposed previously, activation rather than blocking mesolimbic dopaminergic reward circuitry in the long-term treatment of RDS is the preferred modality [26]. Although, the acute treatment should consist of preferential blocking of postsynaptic NAc DA receptors (D1-D5), the long-term mesolimbic activation of the dopaminergic system should involve the release and/or activation of DA at the NAc site. This theory suggests that excessive craving behavior can be attributed to reduced number of DA D2 receptors an effect of carrying, for example, the DRD2 A1 allelic genotype, whereas a normal or sufficient density of D2 receptors results in reduced craving. A goal, in terms of preventing substance abuse, could be to induce a proliferation of D2 receptors in individuals who are genetically vulnerable. While, in vivo experiments that used a typical D2 receptor agonist induce down-regulation [27] in vitro experiments have shown that in spite of genetic antecedents, constant stimulation with a known D2 agonist, bromocriptine, results in significant proliferation of D2 receptors within the DA system but chronic treatment results in down-regulation instead of up-regulation proposed for KB220Z and that is a reason for failure in treatment.

Conclusion

The importance of utilization of buprenorphine alone or in combination with naloxone to treat opioid addiction as a maintenance drug is well researched and established. However, due to significant alteration of mood and emotion, we encourage caution in long-term maintenance with these drugs, albeit, lack of any other compounds FDA approved to date. Previously, we and others have documented severe withdrawal from buprenorphine alone or in combination in human addicts [7,24]. Here we point out that since it is known that certain dopaminergic/opiate gene polymorphisms significantly influence clinical outcomes linked to buprenorphine alone or in combination with naloxone, it seems prudent to embrace genetic testing. Genetic addiction risk stratification will help reveal reward circuitry gene polymorphisms as a way of improving treatment outcomes.

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Table 1

The Reward Deficiency Syndrome Behaviors (RDS)

Addictive Behaviors		**Impulsive Behaviors**		**Obsessive Compulsive Behaviors**	**Personality Disorders**
Substance Related	Non Substance Related	Spectrum Disorders	Disruptive Impulsive		
Alcohol	Thrill seeking (novelty)	Attention-deficit Hyperactivity	Anti-social	Body Dysmorphic	Paranoid
Cannabis	Sexual Sadism	Tourette and Tic Syndrome	Conduct	Hoarding	Schizoid
Opioids	Sexual Masochism	Autism	Intermittent Explosive	Trichotillo-mania (hair pulling)	Borderline
Sedatives/Hypnotics	Hypersexual		Oppositional Defiant	Excoriation (skin picking)	Schizotypal
Stimulants	Gambling		Exhibitionistic	Non-suicidal Self-Injury	Histrionic
Tobacco	Internet Gaming				Narcissistic
Glucose					Avoidant
Food					Dependent