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Editorial *Volume 1; Issue 2*

Introducing "Precision Addiction Management (PAM®)" as an Adjunctive Genetic Guided Therapy for Abusable Drugs in America

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Abbreviations: PAM: Precision Addiction Management; DRD2: Dopamine Receptor D2; FDA: Food Drug Administration; RDS: Reward Deficiency Syndrome; DAT: Dopamine Transporter; VMS: Ventromedial Striatum; GARS: Genetic Addiction Risk Score; OPRK: Kappa Opioid Receptor

Editorial

While the heroin and opioid epidemic has been front and center in the US, it appears that cocaine is making a comeback. Since 1913 the expansion of Colombia's illegal coca crop has driven demand on US streets. The 2015 amphetamine users increased globally, reaching 37 million, and new cocaine use expanded to 2 percent of the US population last year. Unlike for opioids and alcohol, there is no FDA medication approval for psychostimulants. However, gene-guided therapy presented herein may be useful in treatment and relapse prevention for Abusable drugs [1].

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. [2] showed that 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, with the greatest improvement in craving and anxiety occurring 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 [3].

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The concept of the feasibility of treating Reward Deficiency Syndrome (RDS) based on pharmacogenetics and or pharmacogenomics has been further underscored by Blum et al. [4]. They found that the DRD2 gene polymorphism (A1 allele vs A2 allele) 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. [5] 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 [6] measured [3H] Naloxone binding in frontal gray cortex, caudate nucleus, amygdala, hippocampus and cerebellar cortex. Samples were 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 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. [7] provided clear evidence that the dopaminergic system is linked to buprenorphine treatment response in heroin addicted humans. Surprisingly, they found no difference between responders and non-responders to buprenorphine 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 showing better treatment outcome and compliance based on dopaminergic polymorphisms whereby hypodopaminergi c 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 buprenorphine due to its faster transport activity resulting in a hypodopaminergic trait [1,3].

Finally, Barratt et al. [8] 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 that significantly fewer A (1) allele carriers experienced withdrawal than non-A (1) carriers (P = 0.04). Moreover, our laboratory found in a genetically determined hypodopaminergic trait patient at 432 days post Buprenorphine –naloxone (Suboxone®) withdrawal being maintained on a putative dopamine agonist KB220Z, has been urine tested and is opioid free [9]. Genotyping data revealed a moderate genetic risk for addiction showing a hypodopaminergic trait. In agreement with these findings, Makhinson & Gomez-Makhinson [10] 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. Specifically, Willuhn et al. [11] 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 [12]. 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, associated with 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 induced proliferation of D2 receptors in individuals who are genetically vulnerable. While in vivo experiments that used a typical D2 receptor agonist induce down-regulation, 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. However, chronic treatment results in down-regulation instead of up-regulation proposed for KB220Z, and that is a reason for failure in treatment. Following almost three decades of research, our group has embarked on a novel approach based on gene guided therapy we designate Precision Addiction Management (PAM®) [13].

The technology uses an individual's Genetic Addiction Risk Score (GARS) result to formulate precision pro–dopamine neuro-nutrient. Nobel & Blum's group was the first to report the association of the A1 allele of the Dopamine D2 receptor gene and cocaine dependence in 1993. The A1 allele of the DRD2 gene causes a reduction in the production of dopamine receptors, and almost 300 association studies have looked at the A1 polymorphism (PUBMED 7/13/18). Dopamine is the neurotransmitter responsible for stress reduction and feelings of well-being. The GARS test is based on hundreds of studies that identified dysfunctional polymorphic risk alleles of genes and second messengers within the brain reward circuitry. Those selected for GARS induce low dopamine (hypodopaminergia). The panel includes alleles of the D1-D4, DAT1, Mu opioid receptor, Serotonin transporter, COMT, MOA-A, and GABAB3 receptor. In conjunction with Geneus Health, Dominion Diagnostics carried out a comparative analysis of the ASI (MV) and GARS (N=273), which revealed a significant predictive risk for drug severity at ≤ 4 alleles ($P<0.05$) and alcohol severity at ≤ 7 alleles ($P< 0.004$). Clinical benefit of GARS test results for people in treatment for psychostimulant and poly-drug dependence include removal of denial, guilt and shame, genogram confirmation, relapse information and better resource allocation. Importantly, the GARS result can be used to formulate a precision DNA directed pro–dopamine neuro-nutrient therapeutic KB220 PAM.

Previously KB220 variants in human trials demonstrated clinical benefit:

a. Significantly reduced relapse rates and enhanced recovery outcomes in 73% of alcoholics and 53% of cocaine-dependent patients, in a ten-month DUI-out-patient study.

b. A triple-blind, placebo-controlled, crossover study of abstinent psychostimulant use disorder patients found regulation of qEEG widespread theta, increased alpha and low beta, and reduced high beta activity in the parietal brain region.

c. A significant difference between placebo and KB220 in cocaine abusers regarding AMA rate (over the first five days) was 37.5% compared to only 4.2% in a 30-day hospital program.

d. Naive rats significantly increased resting-state functional connectivity (rsFC) volume across various brain regions (neuroplasticity) in a triple-blind, placebo-controlled, crossover study.

Summary

We believe GARS may provide valuable information to those with genetically induced dopamine deficiency. With the use of precision KB220 as a treatment adjunct to putatively induce dopamine regulation, "Dopamine Homeostasis" and improvement in the recovery of individuals with, for example, psychostimulant and poly drug abuse problems may be achievable. Given the complexity of RDS behaviors, especially related to drug-seeking, our knowledge regarding the interrelatedness of 85 billion neurons in the human brain is in a pioneering stage. However, this reductionist view as presented herein is an imperative piece of the puzzle and must be considered as we move forward in the current arena of neuroimaging and genetic interface.

References

1. Blum K, Oscar-Berman M, Jacobs W, Mc Laughlin T, Gold MS (2014) Buprenorphine response as a function of neurogenetic polymorphic antecedents: Can dopamine genes affect clinical outcomes in Reward Deficiency Syndrome (RDS)? J Addict Res Ther 5: pii: 1000185.

2. Lawford BR, Young RM, Rowell JA, Qualichefski J, Fletcher BH, et al. (1995) Bromocriptine in the treatment of alcoholics with the D2 dopamine receptor A1 allele. Nat Med 1(4): 337-341.

3. Noble EP (2003) D2 dopamine receptor gene in psychiatric and neurologic disorders and its phenotypes. Am J Med Genet B Neuropsychiatr Genet 116B(1): 103-125.

4. Blum K, Chen TJH, Chen LC, Rhoades P, Prihoda TJ, et al. (2008) Dopamine D2 Receptor Taq A1 allele predicts treatment compliance of LG839 in a subset analysis of pilot study in the Netherlands. Gene Ther Mol Biol 12: 129-140.

5. Dahlgren A, Wargelius HL, Berglund KJ, Fahlke C, Blennow K, et al. (2011) Do alcohol-dependent individuals with DRD2 A1 allele have an increased risk of relapse? A pilot study. Alcohol Alcohol 46(5): 509-513.

6. Ritchie T, Noble EP (1996) [3H] naloxone binding in the human brain: alcoholism and the TaqI A D2 dopamine receptor polymorphism. Brain Res 718(1-2): 193-197.

7. Gerra G, Somaini L, Leonardi C, Cortese E, Maremmani I, et al. (2014) Association between gene variants and response to buprenorphine maintenance treatment. Psychiatry Res 215(1): 202-207.

8. Barratt DT, Coller JK, Somogyi AA (2006) Association between the DRD2 A1 allele and response to methadone and buprenorphine maintenance treatments. Am J Med Genet B Neuropsychiatr Genet 141B (4): 323-331.

9. Blum K, Oscar-Berman M, Femino J, Waite RL, Benya L, et al. (2013) Withdrawal from Buprenorphine/Naloxone and Maintenance with a Natural Dopaminergic Agonist: A Cautionary Note. J Addict Res Ther 4(2) doi: 10.4172/2155-6105.1000146.

10. Makhinson M, Gomez-Makhinson J (2014) A successful treatment of buprenorphine withdrawal with the dopamine receptor agonist pramipexole. Am J Addict 23(5): 475-477.

11. Willuhn I, Burgeno LM, Groblewski PA, Phillips PE (2014) Excessive cocaine use results from decreased phasic dopamine signaling in the striatum. Nat Neurosci 17(5): 704-709.

12. Blum K, Chen AL, Chen TJ, Braverman ER, Reinking J, Blum SH et al. (2008) Activation instead of blocking mesolimbic dopaminergic reward circuitry is a preferred modality in the long term treatment of reward deficiency syndrome (RDS): a commentary. Theoretical Biology & Medical Modelling 5: 24.

13. Boundy VA, Pacheco MA, Guan W, Molinoff PB (1995) Agonists and antagonists differentially regulate the high affinity state of the D2L receptor in human embryonic kidney 293 cells. Mol Pharmacol 48: 956-964.