Journal of Systems and Integrative Neuroscience

Editorial ISSN: 2059-9781

Opioid and dopamine genes interact to predict precision naltrexone response in alcohol use disorder: Interpretation misfires

Kenneth Blum[1]*, Jean Lud Cadet[2], David Baron[1], Rajendra D, Badgaiyan[3] and Mark S Gold[4]

[1]Graduate College Western University Health Sciences, Pomona, CA USA

[2]Molecular Neuropsychiatry Research Branch, National Institute on Drug Abuse, National Institutes of Health, Bethesda, Maryland, USA

[3]Department of Psychiatry, Icahn School of Medicine Mt Sinai, New York, NY, USA and Department of Psychiatry, South Texas Veteran Health Care System, Audie L. Murphy Memorial VA Hospital, San Antonio, TX, Long School of Medicine, University of Texas Medical Center, San Antonio, TX, USA

[4]Department of Psychiatry, School of Medicine, Washington University, St. Louis, Missouri, USA

Pioneering work reported by Anton, *et al.* [1] in this journal may be an important step in the treatment algorithm of patients with alcohol use disorder (AUD). Identifying patients who need and would benefit from treatment with naltrexone [2] might help to change clinicians' hesitancy to utilize these medications in AUD where twelve step treatment programs have renewed interest and support [3]. Modern therapeutics and personalized medication are predicated on the basis of tests or measures that can provide potential matching of safe and effective medications with the population of patients who are most likely to benefit from these therapeutic interventions. Anton's work might help to improve the utilization of medications in not only in classical AUD but also in a wider spectrum of alcohol misusing patients. The importance of genetic testing to predict Medical Assistance Treatment (MAT) response came to prominence by the initial discovery of the DRD2 Taq A1 allele and its relationship to alcoholism [4]. In addition, it also seems essential to analyze genetic polymorphisms related to opioid and dopaminergic genes as antecedent polymorphic predictors of clinical responses to naltrexone [5].

We also applaud the efforts of Anton's team in evaluating whether response to naltrexone depends on or is predicted by potential interactions of the OPRM1 SNP rs1799971 with the dopamine transporter gene DAT1/SLC6A3 VNTR rs28363170 or the catechol-O-methyltransferase (COMT) gene SNP rs4680. However, their interpretation based on the plethora of genetic literature related to these known polymorphisms seems to be fundamentally erroneous. In their paper, Anton, *et al.* [1] suggest that individuals with AUD that carry more opioid-responsive genotype (OPRM1 G carriers) respond better to naltrexone. Although the latter is true concerning better clinical outcome with naltrexone, their interpretations concerning their results are somewhat perplexing because it is well known that carriers of the OPRM1 G have reduced mu-opioid receptors with blunted functional responses, but not the opposite [6-8]. Specifically, the G allele, the risk variant of the MOR 118A>G (p.Asn40Asp; SNP rs1799971), promotes a low dopamine function because there is a lack of inhibition via the GABA inhibitory control of dopamine release at the nucleus accumbens (NAc), thus inducing hypodopaminergia in this brain region associated with the reward circuitry [9] While Anton, *et al.* [1] characterized the COMT SNP rs4680 with Val /Val homozygous as having reduced dopaminergic tone [10] they mischaracterized the DAT1 DAT1/SLC6A3 VNTR rs28363170 9 allele compared to 10 allele as having higher dopamine tone in comparison to the normal 10 allele. This is, indeed, not the case since it is well known that the 9 allele has a higher transporter availability which translates to increase re-uptake of dopamine back into the axon terminal leading to a hypodopaminergic state, not the other way around [11-13]. The findings relative to the OPRM1 SNP rs1799971 and COMT) gene SNP rs4680 having lower dopamine tone is not unexpected. However, the observation regarding the DAT1 9vs 10 allele is not in agreement with these two polymorphic genes. It should have followed, based on the accumulated evidence, that the 9 allele would have shown better response to naltrexone for AUD. While we are not disputing their results, we are concerned about their interpretation. We believe that they should continue this important work but also consider genotyping for the DRD2 *Taq A1 allele* as well. Our argument is consistent with the findings of Ritchie, *et al.* [14] who reported that, when subjects were grouped by the presence or absence of the A1 (minor) 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. A similar association with the DRD2 A1 allele will further support the hypothesis that lower dopamine tone results in a better treatment outcome with naltrexone. The concept is consistent with the idea that patients with hypodopaminergia will do better than those with normal dopaminergic status as observed earlier from Nobles group [14] Specifically, Lawford, *et al.,* [15] 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 and attrition was highest in the placebo-treated A1 alcoholics.

The idea that lower dopamine tone not higher dopamine tone displays a preferential better clinical outcome has been shown by others [16] revealing that carriers of the DRD2 A1 allele show a higher

Correspondence to: Kenneth Blum, Graduate College, Western University, Health Sciences, Pomona, CA, USA, E-mail: drd2gene@gmail.com

Received: February 22, 2021; **Accepted:** February 26, 2021; **Published:** March 02, 2021

Pearson's Correlation with improved compliance in the number of days of treatment with pro-dopamine regulation therapy for addictive behavior. The notion that lowers dopamine tone due to certain genetic polymorphisms including the 9 allele rather than the 10 allele of the DAT1 gene is evident from the existing literature. Thus, to reiterate, specially showing increased frequency of individuals carrying the allele A9 [f(A9+)] displaying significantly higher in the group of alcoholics [f(A9+) compared with healthy controls [17,18] raises these obvious interpretative concerns. Once again, our group applaud the work of Anton, *et al.* [1], and encourage more work from them and other researchers in the field to personalized treatment for substance use disorders in general [19] and AUDs as described in their study. Personalized or Precision medicine can be applied to AUD and simplify the conflicting guidance and treatment algorithms in use today. Genetic addiction risk testing as a front line tool to reduce guesswork in terms of treatment choice and conviction for MAT therapy.

References

1. Anton RF, Voronin KE, Book SW, Latham PK, Randall PK, et al. (2020) Opioid and Dopamine Genes Interact to Predict Naltrexone Response in a Randomized Alcohol Use Disorder Clinical Trial. *Alcohol Clin Exp Res* 44: 2084-2096. [Crossref]
2. Srivastava AB, Gold MS (2018) Naltrexone: A History and Future Directions. *Cerebrum* 2018 Sep 1;2018: cer-13-18. [Crossref]
3. Kelly JF, Humphreys K, Ferri M (2020) Alcoholics Anonymous and other 12-step programs for alcohol use disorder. *Cochrane Database Syst Rev* 3: CD012880. [Crossref]
4. Blum K, Noble EP, Sheridan PJ, Montgomery A, Ritchie T, et al. (1990) Allelic association of human dopamine D2 receptor gene in alcoholism. *JAMA* 263: 2055-2060.
5. Blum K, Chen ALC, Thanos PK, Febo M, Demetrovics Z, et al. (2018) Genetic addiction risk score (GARS) ™, a predictor of vulnerability to opioid dependence. *Front Biosci (Elite Ed)* 10: 175-196.
6. Hendershot CS, Claus ED, Ramchandani VA (2016) Associations of OPRM1 A118G and alcohol sensitivity with intravenous alcohol self-administration in young adults. *Addict Biol* 21: 125-35. [Crossref]
7. Hirasawa-Fujita M, Bly MJ, Ellingrod VL, Dalack GW, Domino EF, et al. (2017) Genetic Variation of the Mu Opioid Receptor (OPRM1) and Dopamine D2 Receptor (DRD2) is Related to Smoking Differences in Patients with Schizophrenia but not Bipolar Disorder. *Clin Schizophr Relat Psychoses* 11: 39-48.
8. Gong XD, Wang JY, Liu F, Yuan HH, Zhang WY, et al. (2013) Gene polymorphisms of OPRM1 A118G and ABCB1 C3435T may influence opioid requirements in Chinese patients with cancer pain. *Asian Pac J Cancer Prev* 14: 2937-2943. [Crossref]
9. Ray LA (2011) Stress-induced and cue-induced craving for alcohol in heavy drinkers: Preliminary evidence of genetic moderation by the OPRM1 and CRH-BP genes. *Alcohol Clin Exp Res* 35: 166-174.
10. Nogueira NGHM, Bacelar MFB, Ferreira BP, Parma JO, Lage GM, et al. (2019) Association between the catechol-O-methyltransferase (COMT) Val158Met polymorphism and motor behavior in healthy adults: A study review. *Brain Res Bull* 144: 223-232.
11. Van Dyck CH, Malison RT, Jacobsen LK, Seibyl JP, Staley JK, et al. (2005) Increased dopamine transporter availability associated with the 9-repeat allele of the SLC6A3 gene. *J Nucl Med* 46: 745-51. [Crossref]
12. Van de Giessen E, De Win MM, Tanck MW, van den Brink W, Baas F, et al. (2008) Striatal dopamine transporter availability associated with polymorphisms in the dopamine transporter gene SLC6A3. *J Nucl Med* 50: 45-52. [Crossref]
13. Faraone SV, Spencer TJ, Madras BK, Zhang-James Y, Biederman J, et al. (2014) Functional effects of dopamine transporter gene genotypes on in vivo dopamine transporter functioning: a meta-analysis. *Mol Psychiatry* 19: 880-889.
14. Ritchie T, Noble EP (1996) [3H] naloxone binding in the human brain: alcoholism and the TaqI A D2 dopamine receptor polymorphism. *Brain Res* 718: 193-197. [Crossref]
15. 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: 337-341. [Crossref]
16. Blum K, Chen AL, Chen TJ, Rhoades P, Prihoda TJ, et al. (2008) LG839: anti-obesity effects and polymorphic gene correlates of reward deficiency syndrome. *Adv Ther* 25: 894-913. [Crossref]
17. Köhnke MD, Batra A, Kolb W, Köhnke AM, Lutz U, et al. (2005) Association of the dopamine transporter gene with alcoholism. *Alcohol* 40: 3339-3342. [Crossref]
18. Oesterle TS, Thusius NJ, Rummans TA, Gold MS (2019) Medication-Assisted Treatment for Opioid-Use Disorder. *Mayo Clin Proc* 94: 2072-2086. [Crossref]