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Research Correspondence

Gene polymorphism Mu opioid receptor & its impact on naltrexone treatment response in alcohol-dependent individuals: A pilot study from north India

Sir,

Alcohol dependence (AD) is a chronic disorder, with a relapsing and remitting course. The major challenge in the treatment of alcohol use disorder is the prevention of relapse to heavy drinking. Naltrexone is an FDA approved anti-craving agent for AD and is one of the most well-studied and recommended medications in India[1]. However, it may not be equally effective in all individuals[2]. Naltrexone acts as an opioid agonist with a high affinity for the mu opioid receptor. A single nucleotide polymorphism (SNP) at the mu opioid receptor gene *OPRM1* (A118G) triples the reactivity of the receptor to β-endorphins. It is reported to be responsible for inter-individual variation in naltrexone treatment response[3]. Also, such studies are conspicuous by their absence in the Indian population.

About 5.7 crore Indians are estimated to be affected by alcohol use disorders as per the report Magnitude of Substance Use in India[4]. There are variations in response to naltrexone treatment[5]. In India, where AD is a recognized public health problem, it would be extremely important to study the possible genetic basis of this variation[6]. This study examined the *OPRM1* (A118G) polymorphism and its effect among alcohol-dependent north Indian men seeking naltrexone treatment with an intention-to-treat principle.

A prospective cohort study was conducted at National Drug Dependence Treatment Centre, All India Institute of Medical Sciences, New Delhi. The Institute Ethics Committee cleared the study protocol. The study was carried out for one year from July 2021 to June 2022. The participants were 18-60 yr old males of north Indian origin diagnosed as alcohol dependent (DSM IV), with no known major physical/ psychiatric co-morbidity (self-reported), receiving naltrexone (50 mg once daily) maintenance treatment, and willing to participate. At baseline, information on sociodemographic data, substance use, clinical profile, family history of alcohol use, and past abstinent attempts were recorded. WHO-Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST), Severity of Alcohol Dependence Questionnaire (SADQ), and obsessive compulsive drinking Scale (OCDS) were applied to all the participants. Data on addiction indexes like severity and craving were collected and reported earlier[7]. After obtaining informed consent, 2 ml of blood samples were collected for *OPRM1* genotyping. DNA extraction was carried out using the DNA extraction kit QIAamp from Qiagen GmbH (Germany). The *A118G* genotyping was carried out using TaqMan allelic discrimination assay (Applied Biosystems, Thermo Fisher Scientific). A 20 µl volume reaction mixture consisted 20 ng/µl DNA, primers, and probes (0.1-1 µM). The PCR based amplification of cDNA took place in a real-time PCR machine QS12K Flex (Thermofisher). The genotyping was undertaken using the allelic discrimination assay with QuantStudio 12K Flex optical system software. The personnel performing the reaction were not aware of the clinical details of the study participants.

The consenting study participants were followed up at the end of three months. The clinical data on response to naltrexone treatment was recorded through a questionnaire. This information on response included information on alcohol use (whether alcohol used, days of alcohol use, and whether heavy drinking occurred), craving, and naltrexone intake during the last month. Alcohol use was defined as any single use within the last one month by the participant. Statistical analysis was performed on SPSS 21.0 version (IBM Corp, Armonk, NY). The sociodemographics and clinical data was represented by mean, standard deviation, frequencies, and percentages. The association of allelic variants with response status was assessed through the Chi-square test/ Fischers exact test or Student t-test based on the type of data. A $P< 0.05$ was considered as significant. However, missing value imputation was not done.

Table. The effect of *OPRM1A118G* allele and response to naltrexone treatment at the end of three months (n=45)

S.N.	Item	A Allele n=19 (%)	G Allele n=21 (%)	*P** value
1.	Alcohol use (any single use)	18 (94.7)	12 (57.1)	0.009
2.	No. of abstinence days (last 30 days); Mean (SD)	26.53 (4.1)	23.96 (9.04)	0.26**
3.	Alcohol craving	13 (68.4)	11 (52.4)	0.34
4.	Heavy drinking (more than 5 std. drinks)	16 (84.2)	12 (57.1)	0.06
5.	Naltrexone intake (more than 25 days/month)	19 (100)	21 (100)	1

*Regression analysis, Pearson chi-square, significant $P< 0.05$.**Independent sample t-test. SD, standard deviation

For the study, 89 alcohol dependent participants were recruited. Most of the participants were married (78.9%), employed (92.2%), and educated (77.8%). The mean (SD) age of alcohol use onset was 20.9 (5.27) yr. Alcohol craving was reported by almost all the participants (99%), and most of them were using alcohol despite experiencing harm (98%). In the past three months, the majority (76.7%) of the participants reported daily drinking. A family history of alcohol use was reported by 50 per cent of the study population. A large majority (98%) had made unsuccessful attempts to quit alcohol. As per WHO ASSIST addiction indices, more than 90 per cent of the participants scored in the high-risk category for alcohol, while 87 per cent scored in the moderate-risk category for tobacco. As per SADQ, 64 per cent of participants were in the category of moderate AD. About 60 per cent of participants had mild symptoms as per the OCDS.

The allelic discrimination assay *A118G* demonstrated that the presence of homozygosity for A and G was in 41 (46.1%) and 12 (13.5%) participants, while 36 (40.4%) were heterozygous. The allele frequency of A (AA) was 59 (66.3%), and G (GG+GA) was 30 (33.7%). This distribution followed the Hardy-Weinberg equation with a *P* value of 0.703. Participants from the two groups, A and G allele carriers, did not differ in terms of sociodemographics, substance use, clinical scores, and follow up data.

At the end of three months, 40 (45%) out of 89 participants reported for the follow up. Further, the effect of the G allele (GG, AG) was examined in clinical parameters like craving, alcohol use, heavy drinking, and naltrexone use. The use of alcohol in the last month was reported by a significantly smaller number of G allele carriers (n=12) as compared to A allele carriers (n=18) (P=0.009). Additionally, the number of heavy drinks in the last month was higher number in A allele participants as compared to G allele participants, although this was not statistically significant (P=0.06) (Table).

This is the first systematic study to observe the possible effect of *OPRM1A118G* genotype on naltrexone treatment response for alcohol dependent individuals in a leading addiction treatment facility in north India. The frequency of A118G was observed to be 66.3 per cent (A) and 33.7 per cent (G), which is in line with earlier studies[3]. At the three months follow up, a significantly lesser number of participants with the G allele reported alcohol use during the last month prior to the start of this study over a short-term (three months) response to naltrexone. Due to the small sample size, no firm conclusion could be drawn from the study. A previous meta-analysis incorporating six studies supported that the G allele moderates the effect of naltrexone in participants with alcohol dependence[8].

These results, however, need to be interpreted in the context of limited sample size and dropouts. This could be explained as the unprecedented outbreak of the pandemic at the start of the study making a substantial impact on the number of dropouts in the follow up. Despite these limitations, this study provides evidence of *A118G* effect on AD participants undergoing naltrexone treatment. The subjects who remain nonresponsive to naltrexone (in terms of number of days of drinking) may be stratified based on the *OPRM1A118G* genotype. Genetic testing for the *OPRM1* gene may be subsequently used in the clinical decision-making for choice of medication, and whether to implement more intensive treatment for alcohol use disorder. However, these are preliminary findings that warrant future studies.

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References

1. Ambekar A, Kattimani S. Anti-Craving Medications in the Treatment of Alcoholism. In: Dhawan A, Jhanjee S, editors. *Manual for long term pharmacotherapy*. National Drug Dependence Treatment Centre, All India Institute of Medical Sciences, developed under WHO, Ministry of Health & Family Welfare, Government of India; 2006. p. 13-23.
2. Del Re A, Maisel N, Blodgett J, Finney J. The declining efficacy of naltrexone pharmacotherapy for alcohol use disorders over time: A multivariate meta-analysis. *Alcohol Clin Exp Res* 2013; *37* : 1064-8.
3. Chamorro A, Marcos M, Mirón-Canelo J, Pastor I, González-Sarmiento R, Laso F. Association of μ-opioid receptor (OPRM1) gene polymorphism with response to naltrexone in alcohol dependence: A systematic review and meta-analysis. *Addict Biol* 2012; *17* : 505-12.
4. Ambekar A, Agrawal A, Rao R, Mishra AK, Khandelwal SK, Chadda RK on behalf of the group of investigators for the National Survey on Extent and Pattern of Substance use in India. Magnitude of substance use in India. New Delhi: Ministry of Social Justice and Empowerment, Government of India; 2019.
5. Anton R, Oroszi G, O'Malley S, Couper D, Swift R, Pettinati H, *et al.* An evaluation of mu-opioid receptor (OPRM1) as a predictor of naltrexone response in the treatment of alcohol dependence: Results from the combined pharmacotherapies and behavioral interventions for alcohol dependence (COMBINE) study. *Arch Gen Psychiatry*2008; *65* : 135-44.
6. De Sousa A, De Sousa A. A one-year pragmatic trial of naltrexone vs disulfiram in the treatment of alcohol dependence. *Alcohol Alcohol* 2004; *39* : 528-31.
7. Kumar R, Quraishi R, Sarkar S, Rao R, Ambekar A. Naltrexone and its effects on craving and alcohol use among patients with alcohol dependence syndrome: A report. *Addict Health* 2024; *16* : 224-7.
8. Deb I, Chakraborty J, Gangopadhyay P, Choudhury S, Das S. Single-nucleotide polymorphism (A118G) in exon 1 of OPRM1 gene causes alteration in downstream signaling by mu-opioid receptor and may contribute to the genetic risk for addiction. *J Neurochem* 2010; *112* : 486-96.