Association between Concurrent Substance Use and Genetic Variation in Individuals with Heroin Dependence

K. Uludag (Kadir Uludag), H. Su (Hang Su), M. Zhao (Min Zhao)

Shanghai Mental Health Center, Shanghai Jiao Tong University, School of Medicine, China

Original Article

E-mail address:

kadiruludag233@gmail.com

Reprint address:

Kadir Uludag
Shanghai Mental Health Center
Shanghai Jiao Tong University China
Shanghai
China

Source: Clinical Social Work and Health Intervention *Volume: 15* *Issue: 5*
Pages: 81 – 90 *Cited references: 47*

Reviewers:

Steve Szydlowski
University of Scranton school of education, USA
Andrea Shahum
University of North Carolina at Chapel Hill School of Medicine, USA

Keywords:

Heroin dependence. Drug addiction. Genetics. COMT. Polymorphism. Polydrug use. Methamphetamine, tranquilizer, amphetamine, marijuana, stress.

Publisher:

International Society of Applied Preventive Medicine i-gap

CSWHI 2024; 15(5): 81 – 90; DOI: 10.22359/cswhi_15_5_10 © Clinical Social Work and Health Intervention

Abstract:

Background: Heroin dependence is a condition where an individual develops a compulsive reliance on heroin. It is characterized by various symptoms, including intense drug cravings, inability to control heroin use, tolerance, and withdrawal symptoms when drug use is discontinued. Earlier research has examined the relations between genetics and the subject at hand, but it remains uncertain whether the simultaneous use of drugs is connected to certain genetic factors. To comprehend the potential genetic elements linked to the concurrent use of multiple drugs, further investigation is required. This is crucial because such co-occurrence has the potential to elevate the risk of overdose.

Goal of Study: Our goal of the study was to find an association between polydrug use and genetic factors among individuals with heroin dependence.

Methods: Female individuals with heroin dependence were recruited (n=263). Genetic factors related to Catechol-O-methyltransferase (COMT), and stress were included in the study (rs174696, rs174699, rs4680, rs4818, rs737866, rs933271, rs12953076, and rs44458044).
Results: According to the main results, we found that certain genetic factors are related to amphetamine use (rs174696, rs174699, rs1544325, rs4680, rs4818, rs737866, and rs933271). Furthermore, marijuana use was only associated with CRHBP polymorphism (rs1875999).
Conclusion: In conclusion, amphetamine and heroin comorbidity may be associated with certain genetic factors related to COMT.

Highlights

Certain genetic factors (rs174696, rs174699, rs1544325, rs4680, rs4818, rs737866, and rs933271) are found to be linked to amphetamine use.

Marijuana use is specifically associated with the CRHBP polymorphism (rs1875999).

The comorbidity of amphetamine and heroin may be connected to genetic factors related to COMT.

The most substantial effect size was observed in the relationship between amphetamine use and rs174699.

1. Introduction

Heroin use is related to certain psychiatric and health problems such as structural and cognitive impairments (1), anxiety (2), suicide (3, 4), and certain personality disorders (5). Furthermore, long-term heroin use has detrimental effects on cognitive functioning (6, 7). Decline in cognitive abilities can also result in decreased levels of general well-being.

Moreover, the current policies are inadequate in curbing the issue, as demonstrated by the ongoing epidemic of illicit drug overdose deaths (8). Furthermore, epigenetic and genetic studies have been made to demonstrate the relationship between genetic parameters and heroin use (9). Genetic diversity could potentially contribute to shaping intricate personality traits, such as impulsiveness and sensitivity to stress (10). Multiple studies provide evidence that addiction is influenced by moderate to high genetic factors (11). Nonetheless, individuals who misuse heroin may also engage in the consumption of other substances, and the co-occurrence of polydrug use could be linked to genetic influences. Limited research has thoroughly investigated potential factors that can predict polydrug use (12). Polydrug consumption contributes to fatal overdose in more than half of all polydrug users (13). Moreover, it is common to use it in conjunction with other substances, such as alcohol or additional drugs, which increases the risk of overdose (14). Moreover, given the finding that increased drug usage is associated with heightened mental distress (15), it is crucial to comprehend how genetic risk factors may be connected to the occurrence of polydrug use. In conclusion, the presence of moderate to high genetic factors in addiction, the co-occurrence of polydrug use with heroin misuse, and the increased risk of fatal overdose and mental distress highlight the importance of understanding the genetic influences on polydrug use.

The objective of our study was to establish a connection between the simultaneous use of multiple drugs and genetic factors (e.g., COMT) in individuals with heroin dependence.

2. Methods

The collected demographic data included age, gender, educational attainment (classified as completion of secondary school or not), marital status, and employment status. To minimize the influence of potential confounding variables, the study enrolled only female participants (n=263). The average age of the participants was

51% of the participants finished secondary education, while 4.6% of them attained a higher education level.

Table 1 Polydrug Use in individuals with Heroin Dependence

	Amphetamine Use	Marijuana Use	Tranquilizer Use	Inhalation Use	Cocaine Use
rs174696	p<0.05, χ2:11.296	p>0.05	p>0.05	P>0.05	P>0.05
rs174699	p<0.05, χ2:17.791	p>0.05	p>0.05	P>0.05	P>0.05
rs1544325	p<0.05, χ2:10.375	p>0.05	p>0.05	P>0.05	P>0.05
rs4680	p<0.05, χ2:17.214	p>0.05	p>0.05	P>0.05	P>0.05
rs4818	p<0.05, χ2:15.192	p>0.05	p>0.05	P>0.05	P>0.05
rs737866	p<0.05, χ2:16.036	p>0.05	p>0.05	P>0.05	P>0.05
rs933271	p<0.05, χ2:15.176	p>0.05	p>0.05	P>0.05	P>0.05
rs12953076	p>0.05	p>0.05	p>0.05	P>0.05	P>0.05
rs242924	p>0.05	p>0.05	p>0.05	P>0.05	P>0.05
rs4458044	p>0.05	p>0.05	p>0.05	P>0.05	P>0.05
rs17689966	p>0.05	p>0.05	p>0.05	P>0.05	P>0.05
rs1715751	p>0.05	p>0.05	p>0.05	P>0.05	P>0.05
rs3792738	p>0.05	p>0.05	p>0.05	P>0.05	P>0.05
rs32897	p>0.05	p>0.05	p>0.05	P>0.05	P>0.05
rs10062367	p>0.05	p>0.05	p>0.05	P>0.05	P>0.05
rs1875999	p>0.05	P<0.05, χ2:11.503	p>0.05	P>0.05	P>0.05

The study participants consisted of individuals who met the criteria for drug dependence, meaning they had previously relapsed to drug use after being identified as drug users by the public local security system. Therefore, all participants had experienced at least one relapse prior to their enrollment in the compulsory rehabilitation centers at the start of the study. At the time of their participation, the individuals were in a state of abstinence.

The study protocol received approval from the review boards of the Shanghai Jiao Tong University, School of Medicine, Mental Health Center. The research strictly followed the principles stated in the Declaration of Helsinki. Informed consent obtained from the study participants prior to study commencement. Most study participants were of Han Chinese ethnicity. Each subject was interviewed by one psychiatrist.

Participants with a prior history of significant medical conditions that could potentially influence the results of the study, such as neurological disorders or traumatic brain injury, were not included. Moreover, patients who were un-

able to fulfill the study's demands, such as attending scheduled appointments or completing necessary assessments, were also excluded.

Polymerase chain reaction (PCR) was employed to amplify specific DNA sequences. A thorough investigation was undertaken to explore the genetic factors associated with COMT and stress, specifically examining the parameters of rs174696, rs174699, rs4680, rs4818, rs737866, rs933271, rs12953076b, and rs44458044b.

In detail, lymphocytes were employed for the extraction of genomic DNA. Analyzing data from the HAPMAP database for Beijing Han Chinese revealed a conserved pattern without polymorphic distribution in the Chinese population for the CRH genes. Consequently, the research focus shifted towards investigating the CRH receptor 1 (CRHR1) and CRH-binding protein (CRHBP). By screening the CRHR1 and CRHBP genes, along with the upstream region within a range of 10 KB that met the criteria of r2 > 0.8 and MAF > 10%, specific SNPs (CRHR1 rs12953076, rs4458044, rs242924, rs17689966; CRHBP rs1715751, rs3792738, rs32897, rs10062367, rs1875999) were selected. The genotyping of these SNPs was carried out using the ABI Prism 7900 sequence detection system. The stress-related gene genotyping was conducted through the TaqMan SNP genotyping assay, a commonly used and dependable technique in genetic studies.

2.2. Statistical Analysis

Each participant was required to participate in a compulsory, standardized rehabilitation program lasting two years. This program included daily physical exercise and educational sessions aimed at relapse prevention. After successfully completing the program, the patients were reintegrated into their respective communities. Statistical analysis was performed using SPSS version 24. Two alleles and both alleles were coded as categoric value, and a chi-square test was conducted to test if there is a significant relationship between categoric parameters.

3. Results

Based on our primary findings, we observed a significant association between amphetamine use and specific genetic variants, including rs174696, rs174699, rs1544325, rs4680, rs4818, rs737866, rs933271, rs12953076, and rs44458044. Additionally, we found that marijuana consumption was associated with the CRHBP polymorphism (rs1875999). Figure 1 includes graphical abstract that summarizes the study. Polydrug use among individuals diagnosed with heroin dependence is presented in Table 1.

Table 2 displays a table indicating the frequencies of alleles. Based on the data presented in the table, it can be observed that the percentage of missing values for all the investigated allele parameters was below 10%. Moreover, to provide information regarding the effect size, the study reported the chi-square value for the significant results.

4. Discussion

According to main findings of our study, we found association between amphetamine use and certain genetic factors such as rs174696, rs174699, rs1544325, rs4680, rs4818, rs737866, rs933271, rs12953076, and rs44458044). The most substantial effect size was observed in the relationship between amphetamine use and rs174699.In addition, the utilization of marijuana was only linked to the CRHBP polymorphism (rs1875999). There was no notable association found between the consumption of heroin and the usage of tranquilizers or cocaine.

A significant number of individuals remain dependent on heroin, facing challenges in regulating their consumption. Hence, it is crucial to explore the genetic factors contributing to individuals' inclination towards drug consumption such as heroin use and cocaine use. Furthermore, the chronic relapse nature of heroin dependence is gaining recognition, yet there remains limited knowledge regarding the recovery journey of individuals who achieve prolonged abstinence (Hser, 2007).

Moreover, using genetic factors can enable the provision of tailored treatment for individuals with heroin dependence. Nevertheless, it is crucial to consider the influence of polydrug use in this context. Due to the potential confounding effects associated with polydrug use, it is imperative to acknowledge its impact on research outcomes.

Table 2 Allele Frequency Table

	Parameter 1	Parameter 2	Parameter 3
rs174696	24%	22.4%	45.6%
rs174699	31.9%	17.9%	42.2%
rs1544325	9.1%	42.2%	40.7%
rs4680	4.2%	44.1%	43.7%
rs4818	37.6%	11%	43.3%
rs737866	8.7%	41.8%	41.4%
rs933271	40.3%	14.1%	37.6%
rs12953076	76.4%	17.5%	N/A
rs242924	0.4%	14.4%	79.1%
rs4458044	9.1%	35.4%	49.8%
rs17689966	62.7%	28.1%	3%
rs1715751	4.9%	41.1%	48.3%
rs3792738	2.7%	30%	61.2%
rs32897	3.4%	30.8%	59.7%
rs10062367	3%	28.9%	61.2%
rs1875999	33.1%	45.6%	15.6%

Psychologically, genetic factors have the potential to influence individuals, impacting various aspects of their mental and emotional well-being. The occurrence of polydrug use, which can signal a higher inclination for risk-taking when compared to using a single drug, implies that genetic factors might play a role in explaining the inclination towards consuming multiple substances. Additionally, polydrug use may be indicative of higher levels of impulsivity, as individuals engaging in such behavior may struggle with self-control.

Moreover, the utilization of a single substance can result in alterations in impulsivity and subsequently lead individuals to engage in the consumption of other drugs. This phenomenon can also be associated with certain genetic factors related to addiction. Additionally, this phenomenon can be associated with stress, as individuals may turn to other substances when one substance alone does not alleviate their stress levels.

4.1. Genetics and Heroin Dependence

Heroin dependence is a chronic complex disease with a genetic contribution (Levran et al., 2008). Previous studies have shown that there is a relationship between heroin dependence and genetic factors such as BDNF (16-18), Furthermore, addiction mechanism involves pathways mediated by the dopamine D3 receptor (19). In addition, the findings from one study mentioned an interaction between the *ALDH2 gene* and novelty seeking in individuals who are dependent on heroin (20). In addition, heroin-dependent patients and controls have demonstrated an association between the COMT and the temperament scale (21). Stress fuels the start and reoccurrence of addiction: it drives drug craving and overconsumption, while withdrawal ramps up stress (22). Among all drug users, those who use multiple drugs showed the strongest link to psychological distress (23). Hence, it is reasonable to infer that genetic polymorphisms linked to stress response may be associated with addiction process. Furthermore novelty seeking and antisocial behavior related genetic factors may be related to heroin dependence.

Moreover, variances were observed in the distribution of genotype and allele frequencies of the PDYN gene 68-bp VNTR between indi-

viduals with heroin dependence and in a healthy control). In detail, the prevalence of the H allele among heroin-dependent subjects was notably higher when compared to the control group (24).

Previous study presents evidence suggesting that three specific genetic variants (rs696522, rs1381376, and rs3778151) are linked to an elevated susceptibility to experiencing positive responses upon initial heroin use (25). Consequently, these positive responses could contribute to the development of dependence, and future studies should also investigate the precise relationship between these factors. Other findings support a contribution of the *5-HT2A gene* to susceptibility to heroin dependence (26). Nevertheless, our study did not incorporate the analysis of the *5-HT2A gene*, which would have enabled us to make comparisons with other studies. While various gene variants have been discovered, there is ongoing debate about how specific alleles and combinations of alleles contribute to the risk of psychiatric diseases such as schizophrenia (27).

Overall, our investigation revealed a connection between amphetamine use and genetic factors associated with COMT. Moreover, our study included stress and COMT related genetic parameters. Furthermore, there is a limited literature on polydrug use and genetic factors. When exploring the association between genetics and heroin, it is essential for studies to consider the influence of comorbid amphetamine use.

4.1.1. Catechol-O-methyltransferase and Heroin Use

COMT is an enzyme responsible for the metabolism of catecholamines (28). The *COMT gene* has been found to be associated with various factors relevant to addiction (29). Certain studies specifically focused on examining the correlation between the *COMT gene* and heroin dependence.

For example, a previous study found that individuals carrying the C allele of ADRA1A rs3808585 are more susceptible to memory impairment after heroin use and subjects with G allele of COMT rs769224 are more likely to take a higher dose of heroin (30). Furthermore, a previous study found no association between heroin dependence and the 108 val/met polymorphism or the 900 Ins C/Del C polymorphism of the *COMT gene* (31). In an animal study, modulations in COMT affect dopamine metabolism (32) and therefore COMT may be related to heroin dependence related factors since heroin dependence is associated with genes related to the dopaminergic system (33). Furthermore, other studies also investigated the relationship between dopamine and addiction (34, 35).

In a different study, the presence of the A allele in ADRA1A rs1048101 is linked to a reduced duration of transition from initial drug use to addiction. Individuals with the C allele of ADRA1A rs3808585 exhibit increased vulnerability to memory impairment following heroin use disorder (30). The severity of dependence may be associated with memory impairment. In conclusion, the *COMT gene*, responsible for catecholamine metabolism, has been found to be associated with various addiction-related factors, including heroin dependence.

4.1.2. Catechol-O-methyltransferase and Amphetamine Use

Amphetamine was first identified more than a century ago (36). Amphetamine triggers a cascade of biochemical changes (37). There are a few studies made on amphetamine and heroin use comorbidity.

COMT is an enzyme involved in the breakdown of neurotransmitters such as dopamine and norepinephrine. Variations in the *COMT gene* can lead to differences in COMT enzyme activity, affecting the levels of these neurotransmitters in the brain. The *COMT gene* has been associated with a range of human characteristics, such as cognition, anxiety, pain sensitivity, and psychosis (38).

Research has indicated that certain genetic variations in the *COMT gene* may influence an individual's response to amphetamine use. For example a previous study showed that, people who possess the met/met COMT genotype seem to have a higher likelihood of experiencing a negative reaction to amphetamine (39). However, a previous study showed that the COMT val158met polymorphism did not show any association with initial performance or the impact of d-amphetamine on two executive functioning tasks (40).

There is a significant body of evidence indicating that malfunctioning of the dopamine transporter could play a role in the development of amphetamine dependence (41). Furthermore, distinct categories were established for individuals who inject heroin based on their patterns of methamphetamine and cocaine use (42).

In conclusion, the *COMT gene* has been found to be associated with various addiction-related factors, including amphetamine usage, in individuals with heroin dependence.

4.2. Confounding Factors in Heroin Dependence literature

There are numerous confounding factors associated with heroin dependence. For example, age is one of the main confounding factors. In a previous study, older individuals who use substances at a young age and continue to do so as they get older, along with the natural effects of aging on health conditions, are susceptible to experiencing negative substance use outcomes (43). Furthermore, Gender disparity persists in heroin use, with men roughly twice as likely to be affected (44). Epigenetic mechanisms play a role in governing gene expression (6) and thus one of the potential confounding factors in addiction studies. Other study found proof of structural irregularities in individuals dependent on heroin, indicating that the length of heroin use plays a crucial role in causing harm to the brain (45). Therefore, length of heroin use is one of the confounding factors of the study.

Numerous confounding factors are associated with heroin dependence, including age, with older individuals who initiate substance use at a young age being susceptible to negative outcomes, gender disparity, epigenetic mechanisms influencing gene expression, and the length of heroin use contributing to structural harm in the brain.

4.3. Polydrug Use and Heroin Use

Polydrug use refers to the simultaneous or concurrent use of multiple drugs by an individual. This practice is commonly observed among substance users and can involve a combination of illicit drugs, prescription medications, and/or alcohol. One specific form of polydrug use that poses significant risks and challenges is the co-occurring use of multiple substances alongside heroin such as cocaine use and marijuana use.

4.4. Marijuana Use and Heroin Use

Marijuana use disorder, the leading illegal drug misuse issue, casts a growing shadow of psychiatric concerns (46). There is a limited amount of available literature regarding the co-occurrence or simultaneous use of marijuana and heroin. In this study, we found that marijuana use was only associated with CRHBP polymorphism (rs1875999). Genetic variation is linked to stress. The strongest association with psychological distress was found among individuals who use multiple drugs, indicating that genetic variations associated with stress response may play a role in the addiction process.

Hence, the use of marijuana could potentially be connected to genetic factors related to stress.

4.5. Suggestions for Further Studies

As mentioned in the previous study, preventive measures should consider the patterns of polysubstance use among adolescents who use heroin (47). Furthermore, in the future, researchers can explore multiple novel genes that might play a role in determining a person's susceptibility to developing heroin dependence, particularly when considering the concurrent use of multiple drugs.

Moreover, additional research can consider the influence of the method of heroin administration.

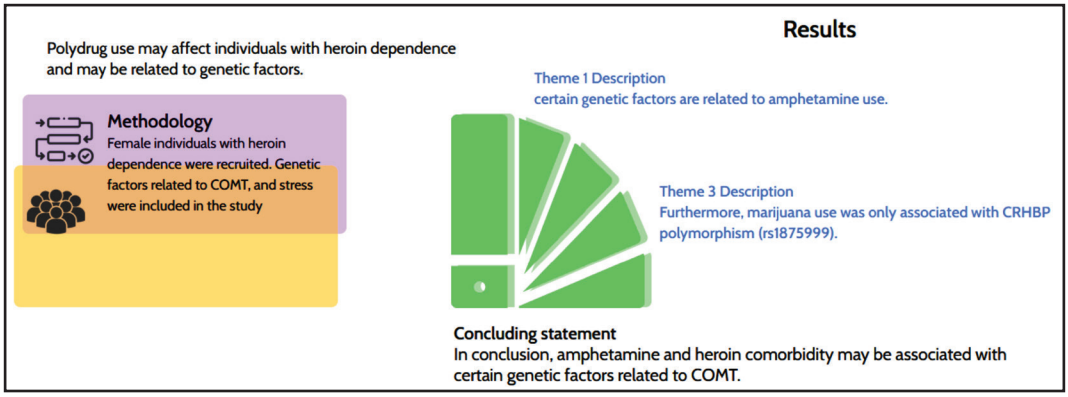
4.6. Limitations:

Some studies depended on clinical diagnoses assigned by healthcare providers (46). Our research does not include information on smoking habits, which could potentially be a confounding variable. Additionally, both age and the extent of exposure to heroin represent confounding factors in our study. Extended exposure to heroin has the potential to influence genetic alterations. Furthermore, our study lacks smoking data which may affect individuals with heroin dependence. Moreover, the route of administration is also one of the major confounding factors in our study. Also, cross sectional design may limit the generalizability of the study.

Competing Interests

None.

Figure 1 Graphical Abstract



References

1. TOLOMEO, S., STEELE, JD., EKHTIARI, H., BALDACCHINO, A. 2020. Chronic heroin use disorder and the brain: Current evidence and future implications. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2020:110148.
2. HURD, YL., SPRIGGS, S., ALISHAYEV, J., WINKEL, G., GURGOV, K., KUDRICH, C., et al. 2019. Cannabidiol for the reduction of cue-induced craving and anxiety in drug-abstinent individuals with heroin use disorder: a double-blind randomized placebo-controlled trial. American Journal of Psychiatry. 2019;176(11):911-22.
3. DARKE, S., ROSS, J. 2002. Suicide among heroin users: rates, risk factors and methods. Addiction. 2002;97(11):1383-94.
4. CHEN, W-T., WANG, S-C., WANG, IA., TSAY, J-H., CHEN C-Y. 2020. Suicide attempts and death among heroin-involved women seeking methadone treatment in Taiwan. Drug and Alcohol Dependence. 2020;217:108277.
5. FASSINO, S., ABBATE, DAGA, G., DELSEDDIME, N., ROGMA, L., BOGGIO, S. 2004. Quality of life and personality disorders in heroin abusers. Drug and Alcohol Dependence. 2004;76(1):73-80.
6. MA, B., MEI, D., WANG, F., LIU, Y., ZHOU, W. 2019. Cognitive enhancers as a treatment for heroin relapse and addiction. Pharmacological Research. 2019;141:378-83.
7. GHOSH, A., SHAKTAN, A., NEHRA, R., BASU, D., VERMA, A., RANA, DK., et al. 2023 Heroin use and neuropsychological impairments: comparison of intravenous and inhalational use. Psychopharmacology. 2023;240(4):909-20.
8. BOYD, S. 2021. Heroin and the illegal drug overdose death epidemic: A history of missed opportunities and resistance. International Journal of Drug Policy. 2021;91:102938.
9. NAZMARA, Z., SHIRINBAYAN, P., REZA ASGARI, H., AHADI, R., ASGARI, F., MAKI, CB., et al. 2021. The epigenetic alterations of human sperm cells caused by heroin use disorder. Andrologia. 2021;53(1):e13799.
10. KREEK, MJ., NIELSEN, DA., BUTELMAN, ER., LAFORGE, KS. 2005. Genetic influences on impulsivity, risk taking, stress responsivity and vulnerability to drug abuse and addiction. Nature Neuroscience. 2005;8(11):1450-7.
11. AGRAWAL, A. (2008) Lynskey MT. Are there genetic influences on addiction: evidence from family, adoption and twin studies. Addiction. 2008;103(7):1069-81.
12. JONGENELIS, M., PETTIGREW, S., LAWRENCE, D., RIKKERS, W. 2019. Factors Associated with Poly Drug Use in Adolescents. Prevention Science. 2019;20(5):695-704.
13. LOGANATHAN, K, LV, J., CROPLEY, V., ZALESKY, A., HO, ETW. 2021. Valuation system connectivity is correlated with poly-drug use in young adults. Neuroscience Research. 2021;173:114-20.

14. KHAN, A., ZAMAN, G., ULLAH, R., NAVEED, N. 2021. Optimal control strategies for a heroin epidemic model with age-dependent susceptibility and recovery-age. AIMS Math. 2021;6(2):1377-94.
15. BURDOVICZ, A. J., LAURITZEN, G., NORDFJAERN, T. 2015. Co-occurrence between mental distress and poly-drug use: A ten year prospective study of patients from substance abuse treatment. Addictive behaviors. 2015;48:71-8.
16. JIA, W., SHI, JG., WU, B., AO, L., ZHANG, R., ZHU, YS. 2011. Polymorphisms of brain-derived neurotrophic factor associated with heroin dependence. Neuroscience Letters. 2011;495(3):221-4.
17. CHEN, S-L., LEE, S-Y., CHANG, Y-H., WANG, T-Y., CHEN S-H., CHU, C-H., et al. 2015. The BDNF Val66Met polymorphism and plasma brain-derived neurotrophic factor levels in Han Chinese heroin-dependent patients. Scientific Reports. 2015;5(1):8148.
18. GREENWALD, MK., STEINMILLER, CL., SLIWERSKA, E., LUNDAHL, L., BURMEISTER, M. 2013. BDNF Val66Met genotype is associated with drug-seeking phenotypes in heroin-dependent individuals: a pilot study. Addiction biology. 2013;18(5):836-45.
19. KUO, S-C., YEH, Y-W., CHEN, C-Y., HUANG, C-C., CHANG, H-A., YEN, C-H., et al. 2014. DRD3 variation associates with early-onset heroin dependence, but not specific personality traits. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2014;51:1-8.
20. LEE, S-Y., WANG, T-Y., CHEN, S-L., HUANG, S-Y., TZENG, N-S., CHANG, Y-H., et al. 2013. Interaction between novelty seeking and the aldehyde dehydrogenase 2 gene in heroin-dependent patients. Journal of clinical psychopharmacology. 2013;33(3):386-90.
21. MEDETROVICS, Z., VARGA, G., SZEKELY, A., VERECZKEI, A., CSORBA, J., BALASZ, H., et al. 2010. Association between Novelty Seeking of opiate-dependent patients and the catechol-O-methyltransferase Val158Met polymorphism. Comprehensive Psychiatry. 2010;51(5):510-5.
22. LEVRAN, O., PELES, E., RANDESI, M., LI, Y., ROTROSEN, J., OTT, J., et al. 2014. Stress-related genes and heroin addiction: A role for a functional FKBP5 haplotype. Psychoneuroendocrinology. 2014;45:67-76.
23. KELLY, AB., CHAN, GC., MASON, WA., WILLIAMS, JW. 2015. The relationship between psychological distress and adolescent polydrug use. Psychology of Addictive Behaviors. 2015;29(3):787.
24. WEI, S., ZHU, Y., LAI, J., XUE, H., CHAI, Z., LI, S. 2011. Association between heroin dependence and prodynorphin gene polymorphisms. Brain research bulletin. 2011;85(3-4):238-42.
25. ZHANG, D., SHAO, C., SHAO, M., YAN, P., WANG, Y., LIU, Y., et al. 2007. Effect of μ-Opioid Receptor Gene Polymorphisms on Heroin-Induced Subjective Responses in a Chinese Population. Biological Psychiatry. 2007;61(11):1244-51.
26. SAIZ, PA., GARCIA-PORTILLA, MP., ARANGO, C., MORALES, B., MARTINEZ-BARRONDO, S., ALVAREZ, C., et al. 2008. Association between Heroin Dependence and 5-HT2A Receptor Gene Polymorphisms. European Addiction Research. 2008;14(1):47-52.
27. MEYER-LINDENBERG, A, NICHOLS, T., CALLICOTT, JH., DING, J., KOLACHANA, B., BUCKHOLTZ, J., et al. 2006. Impact of complex genetic variation in COMT on human brain function. Molecular Psychiatry. 2006;11(9):867-77.
28. HAMIDOVIC, A., DLUGOS, A., PALMER, AA., DE WIT, H. 2010. Catechol-O-methyltransferase val158met genotype modulates sustained attention in both the drug-free state and in response to amphetamine. Psychiatr Genet. 2010;20(3):85-92.
29. TAMMIMAKI, AE., MANNISTO, PT. 2010. Are genetic variants of COMT associated with addiction? Pharmacogenetics and genomics. 2010;20(12):717-41.
30. DEJI, C., LI, Y., CHEN, Y., LAI, J., WEI, S. 2021. Association study of Catechol-o-methyltransferase and Alpha-1-adrenergic receptor gene polymorphisms with multiple phenotypes of heroin use disorder. Neuroscience Letters. 2021;748:135677.

31. CAO, L., LI, T., LIU, X. 2003. [Association study of heroin dependence and catechol-O-methyltransferase gene]. Zhonghua yi xue yi chuan xue za zhi = Zhonghua yixue yichuanxue zazhi = Chinese journal of medical genetics. 2003;20(2):127-30.
32. HUOTARI, M., GARCIA-HORSMAN, JA., KARAYIORGOU, M., GOGOS, JA., MANNISTO, PT. 2004. d-Amphetamine responses in catechol-O-methyltransferase (COMT) disrupted mice. Psychopharmacology. 2004;172(1):1-10.
33. LEVRAN, O., PELES, E., RANDESI, M., CORREA, DA ROSA, J., OTT, J., ROTROSNE, J. et al. 2014. Dopaminergic pathway polymorphisms and heroin addiction: further support for association of CSNK1E variants. Pharmacogenomics. 2014;15(16):2001-9.
34. WISE, RA., ROBBLE, MA. 2020. Dopamine and Addiction. Annual Review of Psychology. 2020;71(1):79-106.
35. SAMAHA, A-N., KHOO, SYS., FERRARIO, CR., ROBONSON, TE. 2021. Dopamine ‘ups and downs’ in addiction revisited. Trends in Neurosciences. 2021;44(7):516-26.
36. HEAL, DJ., SMITH, SL., GOSDEN, J., NUTT, DJ. 2013. Amphetamine, past and present – a pharmacological and clinical perspective. Journal of Psychopharmacology. 2013;27(6):479-96.
37. HAYLEY, AC, SHIFERAW, B., DOWNEY, LA. 2021. Amphetamine-induced alteration to gaze parameters: A novel conceptual pathway and implications for naturalistic behavior. Progress in Neurobiology. 2021;199:101929.
38. PAPALEO, F., CRAWLEY, JN., SONG, J., LIPSKA, BK., PICKEL, J., WEINBERGER, DR., et al. 2008. Genetic dissection of the role of catechol-O-methyltransferase in cognition and stress reactivity in mice. Journal of Neuroscience. 2008;28(35):8709-23.
39. MATTAY, VS., GOLDBERG, TE., FERA, F., HARIRI, AR., TESSITORE, A. TESSITORE, A., EGAN, MF., et al. 2003. Catechol O-methyltransferase val 158-met genotype and individual variation in the brain response to amphetamine. Proceedings of the National Academy of Sciences. 2003;100(10):6186-91.
40. WARDLE, MC., HART, AB., PALMER, AA., DE WIT, H. 2013. Does COMT genotype influence the effects of d-amphetamine on executive functioning? Genes, Brain and Behavior. 2013;12(1):13-20.
41. TZENG, N-S., LU, R-B., YEH, H-W., YEH, Y-W., HUANG, C-C., YEN, C-H., et al. 2015. The dopamine transporter gene may not contribute to susceptibility and the specific personality traits of amphetamine dependence. Drug and Alcohol Dependence. 2015;149:100-7.
42. MEACHAM, MC., RUDOLPH, AE., STRATHDEE, SA., RUSCH, ML, BROUWER, KC., PATTERSON, TL, et al. 2015. Polydrug Use and HIV Risk Among People Who Inject Heroin in Tijuana, Mexico: A Latent Class Analysis. Substance Use & Misuse. 2015;50(10):1351-9.
43. WU, L-T., BLAZER, DG. 2013. Substance use disorders and psychiatric comorbidity in mid and later life: a review. International journal of epidemiology. 2013;43(2):304-17.
44. MCHUGH, RK., NGUYEN, MD., CHARTOFF, EH., SUGARMANN, DE., GREENFIELD, SF. 2015. Gender differences in the prevalence of heroin and opioid analgesic misuse in the United States, 2015–2019. Drug and Alcohol Dependence. 2021;227:108978.
45. YUAN, Y., ZHU, Z., SHI, J., ZOU, Z., YUAN, F., LIU, Y. et al. 2009. Gray matter density negatively correlates with duration of heroin use in young lifetime heroin-dependent individuals. Brain and Cognition. 2009;71(3):223-8.
46. CAMPBELL, CI., BAHORIK, AL., KLINE-SIMON, AH., SATRE, DD. 2017. The role of marijuana use disorder in predicting emergency department and inpatient encounters: A retrospective cohort study. Drug and Alcohol Dependence. 2017;178:170-5.
47. PALAMAR, J.J, LE, A., MATEU-GELABERT, P. 2018.Not just heroin: Extensive polysubstance use among US high school seniors who currently use heroin. Drug and Alcohol Dependence. 2018;188:377-84.