ISSN 1018 - 8681

DÜŞÜNEN ADAM
The Journal of Psychiatry and Neurological Sciences

1924 BRSHH

Author's Accepted Manuscript

Cognitive functions in opioid dependent males according to duration of abstinence

Buket Koparal, Ceyda Oktay Yanik, Ismail Volkan Sahiner, Hatice Ayca Kaloglu, Muhammed Hakan Aksu, Cisem Utku, Zehra Arikan

To appear in: *Dusunen Adam The Journal of Psychiatry and Neurological Sciences*

DOI: 10.14744/DAJPNS.2019.00060

Cite this article as: Buket Koparal, Ceyda Oktay Yanik, Ismail Volkan Sahiner, Hatice Ayca Kaloglu, Muhammed Hakan Aksu, Cisem Utku, Zehra Arikan. Cognitive functions in opioid dependent males according to duration of abstinence, *Dusunen Adam The Journal of Psychiatry and Neurological Sciences*, DOI: 10.14744/DAJPNS.2019.00060

Buket Koparal[1], Ceyda Oktay Yanık [2], İsmail Volkan Şahiner[2], Hatice Ayça Kaloğlu[3], Muhammed Hakan Aksu[4], Çisem Utku[5], Zehra Arıkan[5]

[1]Department of Psychiatry, Recep Tayyip Erdogan University Training and Research Hospital, Rize, Turkey

[2]Department of Psychiatry, Ankara Numune Training and Research Hospital, Ankara, Turkey

[3]Department of Psychiatry, Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ankara, Turkey

[4]Department of Psychiatry, Yıldırım Beyazıt University Yenimahalle Training and Research Hospital, Ankara, Turkey

[5]Department of Psychiatry, School of Medicine, Gazi University, Ankara, Turkey

Sorumlu Yazar:

Buket Koparal, Department of Psychiatry, Recep Tayyip Erdogan University Training and Research Hospital, Rize, Turkey

E-mail: bkt_svnc@hotmail.com

Tel: +90 535 670 78 61

Opioid bağımlılığı olan erkek bireylerde temiz kalma sürelerine göre bilişsel işlevlerin değerlendirilmesi

Özet

Amaç: Opioid bağımlılığı, tekrarlayan opioid kullanımı veya kompulsif arama davranışı ile karakterize bir nöro-davranışsal bozukluktur. Bu çalışmada, bilişsel işlevlerin temiz kalma sürelerine göre değerlendirilmesi ve bilişsel işlevleri etkileyen diğer faktörlerin değerlendirilmesini amaçladık.

Gereç ve Yöntem: Çalışma Şubat 2017- Nisan 2017 tarihleri arasında Gazi Üniversitesi Tıp Fakültesi Psikiyatri Anabilim Dalı'nda gerçekleştirildi. Çalışmaya detoksifikasyon tedavisini tamamlamış ve idame tedavisi almakta olan toplam 96 erişkin erkek katıldı. Hastalar temiz kalma sürelerine göre üç gruba ayrıldı. İlk olarak sosyodemografik veri formu ve Beck Anksiyete Envanteri uygulandı. Daha sonra Wisconsin Kart Eşleme Testi, Rey İşitsel-sözel Öğrenme Testi ve Stroop Testi uygulandı.

Bulgular: Bilişsel işlevler açısından norm değerlerle karşılaştırıldığında örneklem grubunda anlamlı bir bozulma olmadığı saptandı. 0-3 ay arası temiz olan hasta grubunda, 1 yıldan daha uzun süre temiz kalma süresi olanlara göre daha iyi bellek skorları mevcuttu. Ayrıca çoklu madde kullanım süresinin, ilk madde kullanım yaşının ve tedavi sayısının bazı bilişsel işlevleri olumsuz yönde etkilendiğini bulundu.

Sonuç: Bu çalışma, Türkiye'de opioid bağımlılığı olan erkeklerde bilişsel işlevlerin değerlendirildiği ilk çalışmadır. Bilişsel işlevleri etkileyen tüm faktörleri kontrol etmek mümkün değildir. Bu nedenle, opioidlerin etkisinin özel olarak incelenebildiği, ileriye dönük çalışmalara ve hayvan çalışmalarına ihtiyaç vardır.

Anahtar kelimeler: Opioid bağımlılığı, bilişsel işlevler, bellek, yürütücü işlevler, dikkat.

Cognitive functions in opioid dependent males according to duration of abstinence

Abstract

Objective: Opioid dependence is neurobehavioral disorder characterized by a repeated compulsive seeking or use of an opioid. In this study, we aimed to evaluate cognitive functions according to the duration of abstinence and other factors affecting cognitive functions.

Methods: The study was carried out between February 2017- April 2017 in Gazi University Medical Faculty Psychiatry Department. A total of 96 adult males participated and all participants received detoxification treatment, underwent maintenance treatment. Patients were divided into three groups according to the duration of abstinence. First, sociodemographic data form and Beck Anxiety Inventory were administered. Afterwards, the Wisconsin Card Sorting Test, Rey Auditory-Verbal Learning Test and Stroop Test were applied.

Results: It was found that the sample group showed no significant impairment in terms of cognitive functions when compared to the norm values. The group of patients with 0-3 months abstinence had longer memory scores than those who were abstinent for longer than 1 year. We also found that duration of multiple substance use, age of first substance use and the number of treatments affected some of the cognitive functions negatively.

Conclusion: This study is the first study in which cognitive functions are evaluated in opioid dependent males in Turkey. It is not possible to control all of the factors affecting cognitive functions. So that prospective studies and animal studies in which the effect of opioid can be examined exclusively are needed.

Key words: Opioid dependence, cognitive functions, memory, executive functions, attention.

INTRODUCTION

Opioid dependence primarily reflects a pattern of compulsive, prolonged self-administration of opioid substances with continuing use of opioids despite significant substance-related problems such as physiological, behavioral and cognitive indications (1). Opioid use disorders are growing public health problem. In Turkey, approximately 381 200 people with substance use disorders in 1990, this number rose to 664 906 people in 2016 (2). When we rate the population; The rate increased from 0.0070 in 1990 to 0.0082 in 2016(2). The size of the addiction problem globally becomes more apparent when considering that 1 out of every 10 people with substance use has substance use disorder or dependence (3).

Long-term opioid use leads to physical, mental and social impairments as well as opioid related death rates. In Turkey, there were 920 deaths reported due to substance use in 2016 (2). Studies have shown the decrease in the frequency and amount of opioid use leads to a decrease in criminal behavior and the risk of infection, and it increases well-being from a psychosocial aspect (4, 5).

Cognitive functions generally include executive functions, attention, memory, and visual-spatial functions (6). Imagination, learning, memory, ability to make decisions and conscience are also components of cognitive functions (6, 7). They have very important roles in the treatment of addiction. It is thought that in addition to the mental performance of the patients, they affect the treatment compliance and the course of the disease. Learning, retaining and implementing new skills to prevent relapse, controlling impulsive responses and automatic thoughts and developing problem-solving strategies are critical in adapting a new lifestyle and keeping away from substance (8-10).

Studies evaluating cognitive functions in opioid addicts are limited. Before using opioids, different substances are usually used for a long time, and heroin is usually the last substance used. So that, the number of studies only investigating the effects of opioids is limited (11-13). Some of the studies show that individuals with opioid dependence have impaired brain function when compared to normal subjects. Dysfunction is particularly found in executive functions, including processing memory, planning, impulse control, and decision making (8, 14, 15). In addition to studies reporting that cognitive

impairment is persistent in individuals with opioid dependence, there are studies reporting that the disorder is due to the toxic effect of the substance and that cognitive functions return to normal after substance use is stopped (16-19). The methodological characteristics of the studies limit the generalizability of the results.

In the literature review, there was no study in our country investigating the relationship between opioid dependence and cognitive functions. In this study, the aim was to evaluate the relationship between cognitive functions and duration of abstinence in opioid dependence and to investigate other factors affecting cognitive functions. We hypothesized that; (1) opioid dependent patients have worse cognitive functions when compared to norm values of these tests. (2) opioid dependent patients who have longer abstinence have better cognitive functions than the patients who have shorter abstinence.

MATERIAL AND METHODS

Participants

The study was carried out in Gazi University Medical Faculty Hospital with male subjects between the ages of 15-40 who applied to the psychiatric outpatient clinic and who were diagnosed with opioid dependence according to ICD-10 diagnostic criteria. In Turkey the *ICD-10* medical classification system is used for procedural coding for the patient tracking system in all the hospitals and health care services, so we choosed the ICD-10 diagnostic criterias instead of the DSM 5 criterias. All patients who were diagnosed as opioid dependence were using heroin. Those who had any drug use in the last 14 days, degenerative neurological disease, mental retardation, cerebral tumor or cerebrovascular disease, psychiatric comorbid illness except nicotine dependence (past and now), and who were illiterate were not included in the study. All participants participating in the study were given an informed consent form which was approved by GÜTF Clinical Research Ethics Committee before clinical interviews and applications. Detailed information was provided about the study and signed consent was obtained from all participants.

Ninety-six patients who agreed to participate in the study and who met the inclusion criteria were divided into 3 groups as those abstinent for between 0-3 months, abstinent for between 3 months and 1 year, and abstinent for longer than 1 year according to their abstinence time. Their abstinence time was evaluated according to their statement.

At the beginning of the study, no intelligence test was performed to determine the intelligence scores; patients who were considered mentally retarded clinically were excluded.

When the patient group was created, the patients' urine metabolite analyses were obtained and screened for the substances in addition to self-report of the participants.

The sociodemographic data form and Beck Anxiety Inventory (BAI) were administered before the neuropsychological test. Afterwards, during approximately 45 minutes, patients completed the Wisconsin Card Sorting Test (WCST), Rey Auditory-Verbal Learning Test (AVLT) and Stroop Test (ST). These tests are commonly used tests that evaluate cognitive functions in Turkey and also our clinic. Most of the cognitive functions can be evaluated by these tests. We used BAI in order to compare their cognitive functions and anxiety scores. Even if they do not have an anxiety disorder, high anxiety levels could be affect their performance scores.

The study did not include a control group and the norm values of the BIL-NOT battery were used for comparison with normal individuals as a control group. BIL-NOT battery is a data tool which includes norm values of some neurocognitive tests for Turkish people (20).

Data Collection Tools

Sociodemographic data form: This form inquiring about sociodemographic characteristics of the disease was prepared by the investigator.

Beck Anxiety Inventory: The scale developed by Beck has been tested for validity and reliability in our country (21, 22). The total score indicates the height of the anxiety experienced by the person.

Cognitive Assessment

All participants were examined by one researcher who participated in a training course to ensure uniform procedures for administration and scoring.

After the clinical interview with the participants, AVLT, WCST and ST were applied during approximately 45 minutes to evaluate cognitive functioning. A validity-reliability study was conducted for each test(23-25).

Stroop 5 indicy were calculated for ST. It evaluates selective attention, as well as complex attention.

Four indices of WCST were calculated; including number of categories completed (CC), number of total errors (TE), number of perseverative errors (PE) and number of non-perseverative errors (NPE). WCST evaluates complex attention, perseveration, working memory and conseptualization.

Three indices of AVLT were calculated; Rey 1 for short-time memory, Rey 8 for long-term memory and Rey 5 for auditory- verbal learning.

Statistical Analysis

Statistical evaluations were performed using SPSS 15 package program. Parametric tests were used for all evaluations. Descriptive analysis methods were used for the evaluation of sociodemographic data; T-Test, Chi-Square and One-way ANOVA were used for comparison between groups; and Pearson Correlation analysis methods were used to examine the relationship between dependent variables. The Mann-Whitney U analysis method was used for comparison of the groups when the number of the persons included in the sample group was less than 30.

RESULTS

Sociodemographic and clinical data of participants are shown in Table 1.

Patients with opioid dependence were divided into three groups according to the duration of abstinence. There was no significant difference between the groups in terms of educational status (X2 =

1.409, p = .843), age (F2-95 = 0.100, p = .905) and income (F2-95 = 0.465, p = .630). There was significant difference between groups in terms of working status (p=0.01).

Information about the disease for the sampling groups is given in Table 1. There were no significant differences in terms of the duration of opioid use (F2-95 = 0.344, p = .710) and duration of multiple substance use (F2-95 = 0.541, p = .584). All patients had maintenance treatment either naltrexone or buprenorphine/naloxane. The doses are given in Table 1.

The sampling groups were compared in terms of the clinical scales applied and the results are shown in Table 2.

There was significant difference between the groups in terms of Rey 8 Recall scores (F2-95 = 3.157, p <.05) and there was no significant difference between the groups in terms of the other AVLT scores.

There was no significant difference between groups in terms of ST scores and WCST scores (p>0.05).

Table 2 shows whether there are significant differences between the groups and the neuropsychological tests performed.

DISCUSSION

In this study, we evaluated cognitive functions in opioid dependent male patients according to duration of abstinence. We couldn't find significant difference between patients' values and norm values. When we compared groups in between, we found that the group who has abstinence 0-3 months had better long-term memory scores than others. These results does not support our hypothesis that opioid dependent patients has worse cognitive functions than healthy people and also the patient who has longer abstinent has better cognitive functions.

Patients in the study were divided into 3 groups: abstinent between 0-3 months, abstinent between 3 months and 1 year and abstinent for longer than 1 year. Different durations were chosen in

different studies which evaluated cognitive functions according to the duration of abstinence in opioid addicts. For example, Zhang et al. in their study of the effect of stress on decision-making divided opioid dependent patients into groups as 3-7-15-30 days, 3-6-12-24 months, according to their duration of abstinence (26). Li et al. (2013) in their studies investigating long-term and short-term decision-making disorders in opioid addicts, differentiated three groups as short-term (6 months short), mid-term (6-16 months) and long-term (16 months long) abstinence (12). In our study, patients were separated according to early remission (between 3 months and 12 months) and continuous remission (over 12 months) in DSM 5; patients who completed detoxification treatment even if they did not meet early remission criteria and who did not use heroin for at least 14 days were included as a third group. In the other studies, we couldn't see any criteria for abstinence time. We used DSM 5, in order to make a standardization for remission criteria. We thought that if one person is accepted as continuous remission, his environment, health, nutrition and social lifes get better and all of these affect cognitive tests.

There was no significant difference between the groups in terms of age, socio-economic status (except for working status), age at onset of substance abuse, duration of multiple substance use, duration of heroin use and number of treatment applications ($p > 0.05$). All of these factors influence cognitive functioning and may be confounding factors. In this study, we could eliminate these confounding factors. As heroin quantity and purity in each pack may vary, the amount of heroin that patients use daily cannot be clearly determined in the study. For this reason, the amount of substances used by patients on a daily basis is evaluated considering how much substance they are exposed to. Of patients, 87.5% reported that they were under the influence of substance close to every day.

When the groups are compared with the norm values in terms of WCST, ST and AVLT, there was no significant difference in any test subscore statistically.

Studies in which opioid dependence is compared with healthy individuals in the literature have provided different results. Some authors report that after the toxic effects of opioids have resolved, cognitive functions return to their original state (16-19). On the other hand, some authors suggest that the damage is persistent. For example, McDonald et al. (2013) found statistically significant

differences between the control group and non-users who did not receive maintenance treatment, and 50 control group subjects who received 125 methadone maintenance treatments in 2013. They evaluated the executive functions, working memory, data processing speed, learning, social perception and interaction and did not find a significant difference (27). Darke et al. (2012) found that executive functioning, speed of information processing and maintenance treatment in verbal learning were poor in the study they conducted with 125 older patients, 50 older users and 50 healthy controls. They did not find any significant difference in cognitive performance between old users who did not receive maintenance treatment and the control group(28). Authors think that, even if there is a persistent deterioration, the brain can fix it and cognitive functions improves over time. Some authors suggest that opioids lead to persistent cognitive impairment; but there is no clear evidence for which cognitive function is more distorted. It has been considered that memory was not significantly degraded in some studies, while memory was found to be impaired in many studies (13, 14, 29-31). While most executive dysfunctions are reported in cognitive functions, results are inconsistent. Some studies have found dysfunction in cognitive flexibility (29, 31), others in strategic plans (13, 14, 30) and others in decision-making (18, 32). The methodological characteristics of the studies make it difficult to generalize the results. For example, some studies were conducted with a very small sample group. When we look at the sample sizes of the studies, there are small sample groups like 18 patients as well as studies with more than 100 patients. The number of controlled studies is also very low. The inclusion and exclusion criteria in each study are not clearly defined. Education, age, duration of multiple substance use, age at onset of substance use, head trauma, opioid overdose, etc. confounding factors cannot be controlled in each study. Differences in the tests used to assess cognitive functioning in studies may have led to different results. Our study supports studies in which individuals with opioid dependence do not differ from cognitively healthy controls. This is inconsistent with our hypothesis. This can be explained some ways. In Turkey heroin is self administered by small amounts and doesn't have much purity. Even tough patienst have been using heroin for along time, the amount and the purity of the heroin may not be enough to detoriate the brain functions. Also as it's considered

before by several researchers, the effect of the heroin can be transient or brain can repair itself over time(16, 18, 19).

When we compared groups within each test; Rey 8 recall scores were higher ($p = 0.047$) in 0-3 months abstinent group. No significant difference was found between the groups in other tests in which cognitive functions were evaluated ($p > 0.05$).

Memory is one of the basic components of cognitive functions. The AVLT was used in our study to evaluate the short-term and long-term memory and learning. The Rey 8 recall score is associated with long-term memory. The better long-term memory of patients although they are abstinent for shorter duration may be explained in a few ways. Although there was no statistically significant difference at first, the education level is higher in the first group. Of the patients in the first group, 20 had high school education and above, while the group abstinent for 1 year and above contained 13 high school or above graduates. The effect of education on cognitive functions is well described in the literature (14, 20, 33). This can be one of the reasons for the difference between the groups. Second, there is a difference in the duration of maintenance treatment among the groups.

All three groups received maintenance treatment with naltrexone or buprenorphine/naloxone. Methadone is not prescribed legally in Turkey, so no patient received methadone maintenance treatment. Even though there is no significant difference between the doses of the medicines used by the patients, the group that is abstinent longer than 1 year is more likely to have been exposed to these medications for longer. The results of studies investigating the effect of maintenance treatment on cognitive functioning in the literature are confusing. The effect of studies on the cognitive functions of the majority of the meta-identities has been investigated. The nature of the medicines used in the maintenance treatment should be noted. Methadone is a full receptor agonist, while buprenorphine is a partial agonist and naltrexone is a full antagonist. It is therefore expected that the effects on cognitive functions of all three drugs will be different. Compared with methadone, buprenorphine and naltrexone are expected to have fewer negative effects on cognitive performance. The number of studies investigating the effects of buprenorphine and naltrexone on cognitive performance is limited. It is reported that some of these studies showed positive effects of drugs. For example; Pirastu et al (2006) found that buprenorphine

increased cognitive performance in long-term opioid use (31). In some studies, it was reported that medicines adversely affected neurocognitive performance. Zacny et al. (1997) studied the effects of buprenorphine, morphine, and placebo on psychomotor and cognitive performance in 16 healthy volunteers. Surprisingly, they found that buprenorphine dose-dependently leads to impairment in 5/6 of the tests. Memory is also one of the cognitive functions that are impaired in this study (34). Rapeli et al. (2007) prospectively compared buprenorphine/naloxone and methadone in their study of impairment in both groups compared to healthy controls and found that most of the time deterioration persisted on neuropsychological tests (35). Arias et al. (2016) found 38% of patients had global neurocognitive impairment, and more than a third of patients had impaired learning, memory, executive functions, and verbal fluency in their study of 38 patients who received buprenorphine treatment (36). Soyka et al. (2005) divided 62 patients with opioid dependence into 2 groups as buprenorphine and methadone and compared psychomotor performances at the beginning of treatment and in the 10th week. As a result, they reported that there was less disruption in the buprenorphine group (37). In our study, the effect of drugs on neuropsychological tests was not investigated as a primary outcome, but there was no significant difference for medications between the groups. This situation seems to explain the fact that the patients complain about forgetfulness while using medication. It is known that conditions such as head trauma, heroin overdose, poor nutrition, and poor physical health also affect cognitive function (29, 38). Most of the factors thought to influence cognitive function were not questioned in this study and there was no difference between the groups, but head trauma and opioid overdose were not questioned. This may be another factor explaining differences between groups.

Anxiety can be seen in opioid dependence before the addiction and can cause opioid use or it may occur in relation to the toxic effect of the substance within the addiction, withdrawal symptoms, engorgement or vital events. Anxiety levels were found to be significantly higher in the groups that were 0-3 months abstinent compared to the ones who were abstinent longer than 1 year ($p = 0.011$). Patients often express anxiety symptoms such as internal stress, anxiety, and feelings of badness during the detoxification period. This situation is often associated with the deprivation of the substance, and the decrease in symptoms in the following period supports the idea that the anxiety is seen as a symptom of

substance abstraction rather than anxiety disorder. In this study, this can explain the higher anxiety levels of individuals who recently completed detoxification treatment with a 0-3-month abstinence period compared to those who were abstinent for over one year.

Limitations of the study

There are some limitations of our study, in spite of the fact that the strengths of the study are a large sample group, a large number of tests applied to evaluate different cognitive features, and the exclusion of the toxic effect of heroin.

1. The inclusion of only male individuals in the study limits the generalization of the study due to the lack of female patients.

2. Although norm values are compared, norm values have a wide range according to age and educational level. One of the most important limitations is that there was no control group.

3. There are many factors that affect cognitive functioning. Some factors suggested to affect cognitive functions in individuals with opioid dependence in the literature, such as head trauma and opioid overdose, depression were not included in this study.

4. Most of the opioid dependent patients have a history of multiple substance use in the past. Since the study was not performed on individuals who used opioids as the first and only substance, the results are not generalizable as the effect of opioids alone.

5. All of the patients were admitted to treatment with buprenorphine or naltrexone. Patients receiving buprenorphine were not questioned about whether they took their daily doses during the test. Although physical withdrawal was not observed, testing was done before patients took their medications, but the likelihood of being deprived is present, and therefore test performance is likely to be affected.

6. There are conflicting results regarding the effects of drugs used in maintenance treatment on cognitive functions. Patients who received maintenance treatment were included in the study because it was difficult to find a patient who did not receive maintenance treatment.

CONCLUSION

In this study, in which cognitive functions were evaluated according to the duration of abstinence, there was no statistically significant deterioration in executive functions, attention, learning, memory, and working memory when compared with the norm values for individuals.

When assessed within the groups, the group that was abstinent for 0-3 months was found to have a longer memory scores and anxiety levels compared to the group who were abstinent for longer than 1 year.

This study is very important as the studies which cognitive functions are evaluated in opioid dependency are limited and this study contributes to the literature.

Because it is not possible to control all of the factors affecting cognitive functions in opioid dependence, prospective studies in which the same group of patients are assessed cognitively before and after treatment are needed, rather than cross-sectional investigations and animal studies in which the effect of heroin can be examined exclusively.

Role of Funding Source

Nothing declared.

Conflict of Interest

No conflict declared

REFERENCES

1. Sadock B, Sadock V.A, Ruiz P: Kaplan& Sadock Synopsis of Psychiatry: Behavioral Science/Clinical psychiatry. Bozkurt A (Translation Editor) 11th edition, Ankara: Güneş Kitabevi Ltd. Sti., 2016; 659-666. (Turkish)

2. Turkey Drug Report- datas of 2016. Ankara, Turkey Drug and Drug Addiction Monitoring Center; 2017. (Turkish)

3. United Nations Office on Drugs and Crime, World drug report 2016 (United Nations publication, Sales No, E.16.XI.7). 2016.

4. Bukten A, Skurtveit S, Gossop M, Waal H, Stangeland P, Havnes I, Clausen T. Engagement with opioid maintenance treatment and reductions in crime: a longitudinal national cohort study. Addiction. 2012; 107:393-399.

5. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Cochrane Database Syst Rev. 2009:CD002209.

6. Lezak M: Neuropsychological testing. Oxford, University Press; 1995.

7. Pennington BF, Ozonoff S. Executive functions and developmental psychopathology. J Child Psychol Psychiatry. 1996; 37:51-87.

8. Ersche KD, Sahakian BJ. The neuropsychology of amphetamine and opiate dependence: implications for treatment. Neuropsychol Rev. 2007; 17:317-336.

9. Baldacchino A, Balfour DJ, Passetti F, Humphris G, Matthews K. Neuropsychological consequences of chronic opioid use: a quantitative review and meta-analysis. Neurosci Biobehav Rev. 2012; 36:2056-2068.

10. Soyka M. Cognitive Functioning in Methadone Use. Neuropathology of Drug Addictions and Substance Misuse. Edited by Preedy V, Academic Press; 2016; 603-606.

11. Fields FR, Fullerton JR. Influence of heroin addiction on neuropsychological functioning. J Consult Clin Psychol. 1975; 43:114.

12. Li X, Zhang F, Zhou Y, Zhang M, Wang X, Shen M. Decision-making deficits are still present in heroin abusers after short- to long-term abstinence. Drug Alcohol Depend. 2013; 130:61-67.

13. Fishbein DH, Krupitsky E, Flannery BA, Langevin DJ, Bobashev G, Verbitskaya E, Augustine CB, Bolla KI, Zvartau E, Schech B, Egorova V, Bushara N, Tsoy M. Neurocognitive characterizations of Russian heroin addicts without a significant history of other drug use. Drug Alcohol Depend. 2007; 90:25-38.

14. Ornstein TJ, Iddon JL, Baldacchino AM, Sahakian BJ, London M, Everitt BJ, Robbins TW. Profiles of cognitive dysfunction in chronic amphetamine and heroin abusers. Neuropsychopharmacology. 2000; 23:113-126.

15. Fernandez-Serrano MJ, Perez-Garcia M, Verdejo-Garcia A. What are the specific vs. generalized effects of drugs of abuse on neuropsychological performance? Neurosci Biobehav Rev. 2011; 35:377-406.

16. Pau CW, Lee TM, Chan SF. The impact of heroin on frontal executive functions. Arch Clin Neuropsychol. 2002; 17:663-670.

17. Mintzer MZ, Copersino ML, Stitzer ML. Opioid abuse and cognitive performance. Drug Alcohol Depend. 2005; 78:225-230.

18. Verdejo-Garcia AJ, Perales JC, Perez-Garcia M. Cognitive impulsivity in cocaine and heroin polysubstance abusers. Addict Behav. 2007; 32:950-966.

19. Fernandez-Serrano MJ, Perez-Garcia M, Schmidt Rio-Valle J, Verdejo-Garcia A. Neuropsychological consequences of alcohol and drug abuse on different components of executive functions. J Psychopharmacol. 2010; 24:1317-1332.

20. Karakaş S, Erdoğan E, Dinçer Doğutepe E. BİL-NOT YETİŞKİN: Nöropsikolojik Testlerin Yetişkinler İçin Araştırma ve Geliştirme Çalışmaları. Ankara, Eğitim Yayınevi; 2013 (CrossRef)

21. Ulusoy M, Sahin N, Erkmen H. Turkish version of Beck Anxiety inventory: Psychometric Properties. Journal of Cognitive Psychotherapy: An international Cjuaterly. 1998; 12:163-172.

22. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol. 1988; 56:893-897.

23. Karakaş S, Başar E. Nöropsikolojik Testlerin Türk Örneklemi Üzerinde Değişik Yaş ve Eğitim Düzeylerine Göre Standardizasyonu. Kriz Dergisi. 1993; 159-166. (Turkish)

24. Karakaş S, Erdoğan E, Sak L, Soysal A.Ş, Ulusoy T, Ulusoy İ.Y, Alkan S. Stroop Testi TBAG Formu: Türk Kültürüne Standardizasyon Çalışmaları, Güvenirlik ve Geçerlik. Klinik Psikiyatri. 1999. (Turkish)

25. Karakaş S, Doğutepe Dinçer E. BİLNOT Bataryası El Kitabı: Nöropsikolojik Testlerin Çocuklar için Araştırma ve Geliştirme Çalışmaları: BİLNOT-Çocuk. Ankara, Nobel Tıp Kitabevleri. 2011. (Turkish)

26. Zhang XL, Shi J, Zhao LY, Sun LL, Wang J, Wang GB, Epstein DH, Lu L. Effects of stress on decision-making deficits in formerly heroin-dependent patients after different durations of abstinence. Am J Psychiatry. 2011; 168:610-616.

27. McDonald S, Darke S, Kaye S, Torok M. Deficits in social perception in opioid maintenance patients, abstinent opioid users and non-opioid users. Addiction. 2013; 108:566-574.

28. Darke S, McDonald S, Kaye S, Torok M. Comparative patterns of cognitive performance amongst opioid maintenance patients, abstinent opioid users and non-opioid users. Drug Alcohol Depend. 2012; 126:309-315.

29. Darke S, Sims J, McDonald S, Wickes W. Cognitive impairment among methadone maintenance patients. Addiction. 2000; 95:687-695.

30. Ersche KD, Clark L, London M, Robbins TW, Sahakian BJ. Profile of executive and memory function associated with amphetamine and opiate dependence. Neuropsychopharmacology. 2006; 31:1036-1047.

31. Pirastu R, Fais R, Messina M, Bini V, Spiga S, Falconieri D, Diana M. Impaired decision-making in opiate-dependent subjects: effect of pharmacological therapies. Drug Alcohol Depend. 2006; 83:163-168.

32. Brands B, Blake J, Marsh DC, Sproule B, Jeyapalan R, Li S. The impact of benzodiazepine use on methadone maintenance treatment outcomes. J Addict Dis. 2008; 27:37-48.

33. Zeng H, Lee TM, Waters JH, So KF, Sham PC, Schottenfeld RS, Marienfeld C, Chawarski MC. Impulsivity, cognitive function, and their relationship in heroin-dependent individuals. J Clin Exp Neuropsychol. 2013; 35:897-905.

34. Zacny JP, Conley K, Galinkin J. Comparing the subjective, psychomotor and physiological effects of intravenous buprenorphine and morphine in healthy volunteers. J Pharmacol Exp Ther. 1997; 282:1187-1197.

35. Rapeli P, Fabritius C, Alho H, Salaspuro M, Wahlbeck K, Kalska H. Methadone vs. buprenorphine/naloxone during early opioid substitution treatment: a naturalistic comparison of cognitive performance relative to healthy controls. BMC Clin Pharmacol. 2007; 7:5.

36. Arias F, Arnsten JH, Cunningham CO, Coulehan K, Batchelder A, Brisbane M, Segal K, Rivera-Mindt M. Neurocognitive, psychiatric, and substance use characteristics in opioid dependent adults. Addict Behav. 2016; 60:137-143.

37. Soyka M, Hock B, Kagerer S, Lehnert R, Limmer C, Kuefner H. Less impairment on one portion of a driving-relevant psychomotor battery in buprenorphine-maintained than in methadone-maintained patients: results of a randomized clinical trial. J Clin Psychopharmacol. 2005; 25:490-493.

38. Soyka M. Neuropathology of Drug Addictions and Substance Misuse Volume 1: Foundations of Understanding, Tobacco, Alcohol, Cannabinoids and Opioids. Boston: Elsevier, 2016.

TABLES

Table 1. Sociodemographic and clinical characteristics of participants

	Duration of Abstinence						**p**
	0-3 Months (N=35)		**3 Months -1 Year (N=31)**		**More than 1 year (N=30)**		
	N	**%**	**N**	**%**	**N**	**%**	
Marital Status							
Married	2	5.7	5	16.1	6	20	-*
Single	33	94.3	26	83.9	24	80	
Working Status							
Not working	23	65.7	12	38.7	6	20	**0.01**
Working	12	34.3	19	61.3	24	80	

Educational Status							
Middle School	15	42.9	15	48.4	17	56.7	-*
High School	18	51.4	14	45.2	12	40	
University	2	5.7	2	6.5	1	3.3	
Age (year) (mean ±SD)	23.37	3.34	23.55	3.12	23.2	2.56	0.905
Monthly Income (Turkish Lira) (mean ±SD)	1615.15	1003.78	1931.48	1862.65	1693.33	917.24	0.630
First used substance							
Cannabis	30	85.7	26	83.9	25	83.3	
Volatiles	1	2.9	1	3.2	3	10	
Heroin	1	2.9	4	12.9	2	6.7	
Pills	1	2.9	0	0	0	0	-*
Others	2	5.7	0	0	0	0	
Method of substance use							
Inhalation	30	85.7	26	83.9	23	76.7	
Intravenosis	5	14.3	3	9.7	4	13.3	-*
Others	0	0	1	3.2	0	0	
Both intravenosis and inhalation	0	0	1	3.2	3	10	
Frequency							
Everyday	34	97.1	31	100	29	96.7	-*
A few days in a week	1	2.9	0	0	1	3.3	
Treatment							
Buprenorfin/naloxane	23	65.7	24	77.4	22	73.3	
Naltrekson subdermal pellet	4	11.4	4	12.9	2	6.7	-*
Naltrekson oral	8	22.9	3	9.7	6	20	
Age of first substance use (year) (mean ±SD)	15.86	3.32	16.77	3.01	15.47	2.34	0.207
Duration of heroin use (months)	40.46	23.21	39.29	21.57	43.8	21.15	0.710

(mean ±SD)							
Number of treatment (mean ±SD)	3.6	1.56	3.67	2.22	3	1.36	0.201

*p value can not be evaluated statistically because some cells count less than 5 patients.

SD: Standart deviation.

Table 2: Comparison of neuropsychological and clinical tests

Scales		**Source of variance**	**Sum of squares**	**SD**	**Averages of squares**	**F**	**p**	**Post Hoc**
BAI		Intra-groups	1043.75	2	521.88	4.773	0.011	0-3 month> more than 1 year
		Inter-groups	10168.75	93	109.34			
		Total	11212.5	95				
Stroop	**Stroop 5**	Intra-groups	166.68	2	83.34	2.149	0.122	-
		Inter-groups	3606.06	93	38.78			
		Total	3772.74	95				
WCST	**Number of total errors**	Intra-groups	39.52	2	19.76	0.065	0.937	-
		Inter-groups	28422.44	93	305.62			
		Total	28461.96	95				
		Intra-groups	0.13	2	0.07			-

	Number of categories completed	Inter-groups	93.49	93	1	0.067	0.936	
		Total	93.62	95				
	Number of perseverative errors	Intra-groups	130.67	2	65.33	0.619	0.541	-
		Inter-groups	9816.96	93	105.56			
		Total	9947.62	95				
	Number of non-perseverative errors	Intra-groups	5.27	2	2.63	0.030	0.971	-
		Inter-groups	8206.69	93	88.24			
		Total	8211.96	95				
AVLT	**Short-time memory scores**	Intra-groups	0.84	2	0.42	0.201	0.819	-
		Inter-groups	194.78	93	2.09			
		Total	195.62	95				
	Auditory-verbal learning scores	Intra-groups	3.53	2	1.77	0.535	0.588	-
		Inter-groups	307.42	93	3.31			
		Total	310.96	95				
	Long-term memory scores	Intra-groups	44.62	2	22.31	3.157*	0.047	0-3 month> more than 1 year
		Inter-groups	657.22	93	7.07			
		Total	701.83	95				

F: One-way analysis of varience, SD: Standart deviation, BAI: Beck Anxiety Inventory, WCST: Wisconsin card sorting test, AVLT: Rey Auditory-verbal learning test.