The European Journal of Psychiatry 36 (2022) 260—270

THE EUROPEAN JOURNAL OF PSYCHIATRY

www.elsevier.es/ejpsy

ORIGINAL ARTICLE

Retinal nerve fiber layer decrease and choroidal layer increase after four weeks of buprenorphine/naloxone maintenance treatment in opioid use disorder

Mehmet Hamdi Orum[a,*], **Aysun Kalenderoglu**[b], **Ayse Sevgi Karadag**[c], **Cicek Hocaoglu**[d]

[a] *Psychiatry, Kahta State Hospital, Adiyaman, Turkey*
[b] *Department of Psychiatry, Adiyaman University, Faculty of Medicine, Adiyaman, Turkey*
[c] *Department of Ophthalmology, Adiyaman University, Faculty of Medicine, Adiyaman, Turkey*
[d] *Department of Psychiatry, Recep Tayyip Erdogan University, Faculty of Medicine, Rize, Turkey*

Received 29 July 2021; accepted 5 April 2022
Available online 18 May 2022

KEYWORDS
Retinal nerve fiber layer;
Opioid use disorder;
Optical coherence tomography;
Buprenorphine-naloxone;
Choroid

Abstract
Background and Objectives: Spectral-domain optical coherence tomography (SD-OCT) findings in substance use disorders have been investigated in recent years. In this study, we compared the retinal nerve fiber layer (RNFL), the ganglion cell layer (GCL), the inner plexiform layer (IPL), and the choroid thickness (CT) of OUD and control groups before and after buprenorphine/naloxone maintenance treatment (BN-MT).
Methods: The OUD group consisted of 46 male subjects and the control group consisted of 49 male subjects. Patients with chronic opioid use and opioid positivity in their urine during the initial SD-OCT application were included in the study. At the end of the fourth week of BN-MT, SD-OCT was repeated and BN positivity was detected in the urine of the patients at this time.
Results: There was a significant difference between OUD and control groups in terms of nasal superior and CT values of both eyes ($p<0.05$) before BN use. The values of RNFL sectors and CT of both eyes before and after BN-MT differed significantly ($p<0.05$); CT increased and RNFL sectors decreased. After BN-MT, psychometric scales differed significantly in favor of the patients ($p<0.05$). The SD-OCT values of the OUD group after BN-MT were compared with the control group: the right IPL ($p=0.003$), the left IPL ($p=0.023$), the right N ($p=0.001$) and the left N ($p<0.001$) values were significantly lower in the OUD group.
Conclusion: This is the first study to show the SD-OCT findings of patients with OUD before and after BN-MT. The findings of this study may indicate possible effects of chronic opioid use in patients and/or possible effects of exogenous opioid or BN present in the body during SD-OCT applications. However, based on our findings, it is not possible to distinguish between the two possible outcomes. The fact that the use of BN acting through opioid receptors has different effects from exogenous opioids may be due to different receptor profiles.

Author indexing: Orum MH, Kalenderoglu A, Karadag AS, Hocaoglu C

* Corresponding author.
E-mail address: mhorum@hotmail.com (M.H. Orum).

https://doi.org/10.1016/j.ejpsy.2022.04.001

Introduction

In addition to endogenous opioids produced naturally in the body such as enkephalins and β-endorphin, there are opiates such as heroin, morphine, and codeine, which are exogenous opioids, and synthetic opioids such as buprenorphine, fentanyl, methadone, tramadol and semi-synthetic opioids such as hydrocodone, oxycodone.[1,2] The endogenous opioid system contains three main types of opioid receptors (μ, κ, δ) which are expressed by peripheral and central neurons, immune, neuroendocrine and ectodermal cells, and has three opioid ligands (β-endorphins, enkephalins, dynorphins).[1,3] Opioids are a class of substances that include illegal drug heroin, pain relievers available legally by prescription, and synthetic opioids such as fentanyl. Opioids exert their effects through the μ, κ, and δ receptors expressed in different parts of the brain.[4,5] Opioid receptor agonists have been used in medical therapy for years due to their pain-relieving properties. However, both opiates such as heroin and opioid receptor agonists elicit severe physical and psychological dependence. Continuation of opioid use causes various changes in the brain.[6]

The effects of exogenous opioids on the body have been revealed by various neuroimaging studies. Structural magnetic resonance imaging (MRI) studies demonstrated that chronic opioid use cause significant grey matter reductions in the temporal and prefrontal cortices.[7] Upadhyay et al.[8] also found decreased amygdala volume and a decrease in fractional anisotropy in white matter pathways in opioid addicts with structural MRI. Wollman et al.[9] reported that patients with heroin addiction have significantly compromised white matter integrity in meta-analysis of diffusion tensor imaging (DTI) studies. In a voxel-wise meta-analysis, Wollman et al.[10] stated that opioid dependency causes significantly less grey matter volumes in some brain regions. The studies also indicate white matter impairments are present in the cerebellum of patients with opioid use disorder (OUD) and OUD may be associated with cerebellar grey matter reduction.[11] Another device where the effects of illicit drugs on brain structures can be observed is spectral-domain optical coherence tomography (SD-OCT).[12]

SD-OCT is an imaging method that can capture biological tissue layers by acquiring high-resolution sections. This technique measures the delay time and intensity of infrared light, which is transmitted to and reflected from different tissue layers. It is a non-invasive and rapid method that can provide the segmentation of retinal layers, such as the ganglion cell layer (GCL), inner plexiform layer (IPL), and retinal nerve fiber layer (RNFL). Another structure that SD-OCT can measure is choroidal thickness (CT).[13,14] In the last decade, its use was expanded to psychiatric disorders because the retina is an anatomical extension of the brain, and retinal changes may occur in parallel with inflammation and central nervous system degeneration.[12] SD-OCT has recently been studied in the field of substance use disorders.[12,15] These studies have focused on alcohol and cannabis.[15-19] While Ozsoy and Alim[15] reported that alcohol does not affect SD-OCT parameters, Orum and Kalenderoglu[19] found a significant correlation between alcohol unit/year and nasal superior, temporal sectors of the RNFL, when the effect of age and liver damage was controlled in the patient group. Dayi et al.,[17] in the study where they compared cannabis use disorder (CUD) and healthy control group, reported that the temporal sector value of the patient group was lower than the control group. However, Kalenderoglu et al.[12] demonstrated that RNFL values were higher in the CUD group than in the control group. In many of these studies, the condition of patients being under drug effect or not was considered as a limitation. Whereas, distinguishing acute and chronic effects may be an important step in overcoming these limitations. These discordant findings regarding cannabis and alcohol suggest that studies in this area are not yet at a satisfactory level.

Buprenorphine is a semisynthetic opioid and has several pharmacological characteristics that account for its unique mechanism of action:[20] (1) It has a high affinity to the μ-opioid receptor competing with other opioids that bind to the same receptor, (2) It produces a prolonged duration of action as compared with other opioids, (3) It functions as a partial μ-opioid receptor agonist, (4) It diminishes the dysphoric and psychotomimetic effects of the opioids via the action of κ-opioid receptor antagonist. Naloxone is a short-acting, broad opioid receptor antagonist. It binds to opioid receptors with high affinity and becomes a competitive antagonist of opioid receptors.[21] Buprenorphine/naloxone is a sublingual combination tablet composed of buprenorphine and naloxone in a fixed 4:1 ratio. Naloxone has no major effect when administered sublingually. Adding naloxone to buprenorphine could prevent intravenous abuse of buprenorphine.[20] Studies show that buprenorphine/naloxone maintenance treatment (BN-MT) has long-term beneficial effects in OUD management.[22] Buprenorphine/naloxone has been used officially in the treatment of OUD in Turkey. According to our best knowledge, no study has assessed the SD-OCT parameters in OUD patients managed by BN-MT. We planned a prospective study in which dependent groups were analyzed in order to reduce limitations and we aimed to compare the SD-OCT parameters of patients diagnosed with OUD with acute opioid effect before and after BN-MT among themselves and with a healthy control group. In this study we targeted the following:

To compare:

1. The RNFL, GCL, IPL and choroidal layer values of the OUD with the control group,
2. The RNFL, GCL, IPL and choroidal layer values of the OUD group before and after BN-MT,
3. The RNFL, GCL, IPL and choroidal layer values of the control group and the OUD group after BN-MT.

Our hypothesis was that SD-OCT findings in OUD before and after BN-MT differ.

Materials and methods

Study sample

In this prospective study, we compared the SD-OCT parameters of patients with OUD who were followed in the Alcohol-Drug Addiction Research Treatment and Training Centre (ADARTTC) outpatient clinic at our hospital with a control group. The OUD patients were consecutive patients who were being followed at our outpatient clinic. After being seen by the treating psychiatrist, each patient's eligibility for the study was evaluated, and if eligible, they were invited to participate in the study. The OUD group consisted of individuals with opioid detected in the urine. The control group consisted of healthy male subjects. Buprenorphine/naloxone 8 mg/2 mg/day sublingual was administered as treatment for the patients in the OUD group. Patients who are started on BN-MT are followed up once a week in the first four weeks of the treatment as required by the practice in our country. At each follow-up, toxic screening test in the urine is applied to the patients and all other illicit drugs except buprenorphine/naloxone are expected to be negative. The treatment process of patients who maintain negativity for illicit drugs continues. In our study, we included patients who had only opioid positivity in toxic screening test in the urine at the baseline and who remained only buprenorphine positivity after BN-MT. All SD-OCT measurements were made at 10.00 am-14.00 pm. Local ethics committee approval was obtained, and all study participants provided written informed consent (University Ethics Committee, Protocol number: 2020/6-45; Date: 23.06.2020).

Inclusion and exclusion criteria

Patients with OUD who were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders-5th Edition (DSM-5)[23] criteria were included. Patients whose toxic screening test in urine was positive for the opioid use only were included in the study. Both the patient and the control groups were examined in the ophthalmology clinic and the patients and the controls with glaucoma and high ametropic ($\pm$5 diopters) were excluded. The healthy control group was selected from the hospital staff. The group of healthy controls did not have any psychiatric disorders according to the structured clinical interview for DSM-5, including any organic illnesses such as hypertension, diabetes mellitus, severe neurological, immunological or systemic diseases which may affect the results. Whether the patient and control groups had a systemic disease was confirmed through the *e-nabiz* national patient registry system. Fifteen patients who were included in the OUD group before BN-MT were not included in the OUD group after BN-MT because they had discontinued the follow-up. The flowchart of the study was shown in Figure 1.

Biochemical measurements

Biochemical analysis was performed in the laboratory of our hospital by means of "Instant-View Multi-Drug Abuse Urine Test Kit". All analyses were performed between 09.00 am and 13.00 pm. In our laboratory, biochemical analysis of drug was performed by immunochromatographic methods. In these analysis findings, the minimum limit for urine; It was accepted as 500 ng/mL for "Methamphetamine", 50 ng/mL for cannabis agent Tetrahydrocannabinol, 200 ng/mL for "Benzodiazepines", 200 ng/mL for "Barbiturates", 300 ng/mL for "Methadone", 1000 ng/mL for "Amphetamine", 25 ng/mL for "Phencyclidine", 300 ng/mL for "Morphine", 500 ng/mL for "Ecstasy", 10 ng/mL for "Acetylmorphine", 20 ng/mL for "Bonsai", 5 ng/mL for "Buprenorphine", 1000 ng/mL for "Ethyl Glucuronide", and 300 ng/mL for "Cocaine".

SD-OCT measurements

A SD-OCT device (SpectralisTM OCT, Version 6.0, Heidelberg Engineering, Germany) was used to assess the RNFL, the CT, the GCL, and the IPL volumes in both eyes. The RNFL includes temporal (T), nasal (N), nasal superior (NS), nasal inferior (NI) temporal superior (TS), temporal inferior (TI) and global (mean) segments. Therefore, seven measurements were made for each eye. Lastly, we measured the GCL and IPL volumes with the SD-OCT device (Fig. 2). All measurements were performed using MATLAB (MathWorks, Natick, MA). The SD-OCT measurements were analyzed by two independent investigators who did not have knowledge of the substance-abusers and the control patients.

Clinical assessment

Sociodemographic form

A form containing sociodemographic and clinical information was filled in by the researcher. Age, education level, marital status, job, smoking, probation history, and family psychiatric history were used as variables in the questionnaire. Each variable was asked directly to the individuals and corroborated by her first-degree relative.

Addiction profile index (API)

API was developed by Ogel et al.[24] and includes the assessment of the six areas related to the addiction: Anger management problems, lack of safe behavior, novelty seeking behavior, impulsivity, depression, anxiety. Self-notification and enforcement forms are available. In our study, API self-notification form was used.

Global assessment scale (GAS)

It is a grading scale that is applied in a short time and covers all aspects (psychological, social and professional functionality) of changes in psychopathology. It was developed by Endicott[25] in 1976 and can be scored between 0-100.

Symptom checklist-90-revised (SCL-90-R)

SCL-90-R is a 90-item self-report of subjects' symptoms and psychopathologic features on subscales: paranoid ideation, interpersonal sensitivity, hostility, psychoticism, phobic anxiety, anxiety, somatization, depression, obsessive-compulsive, additional and global severity index (GSI). It is a measure of the current psychological symptom status with the time

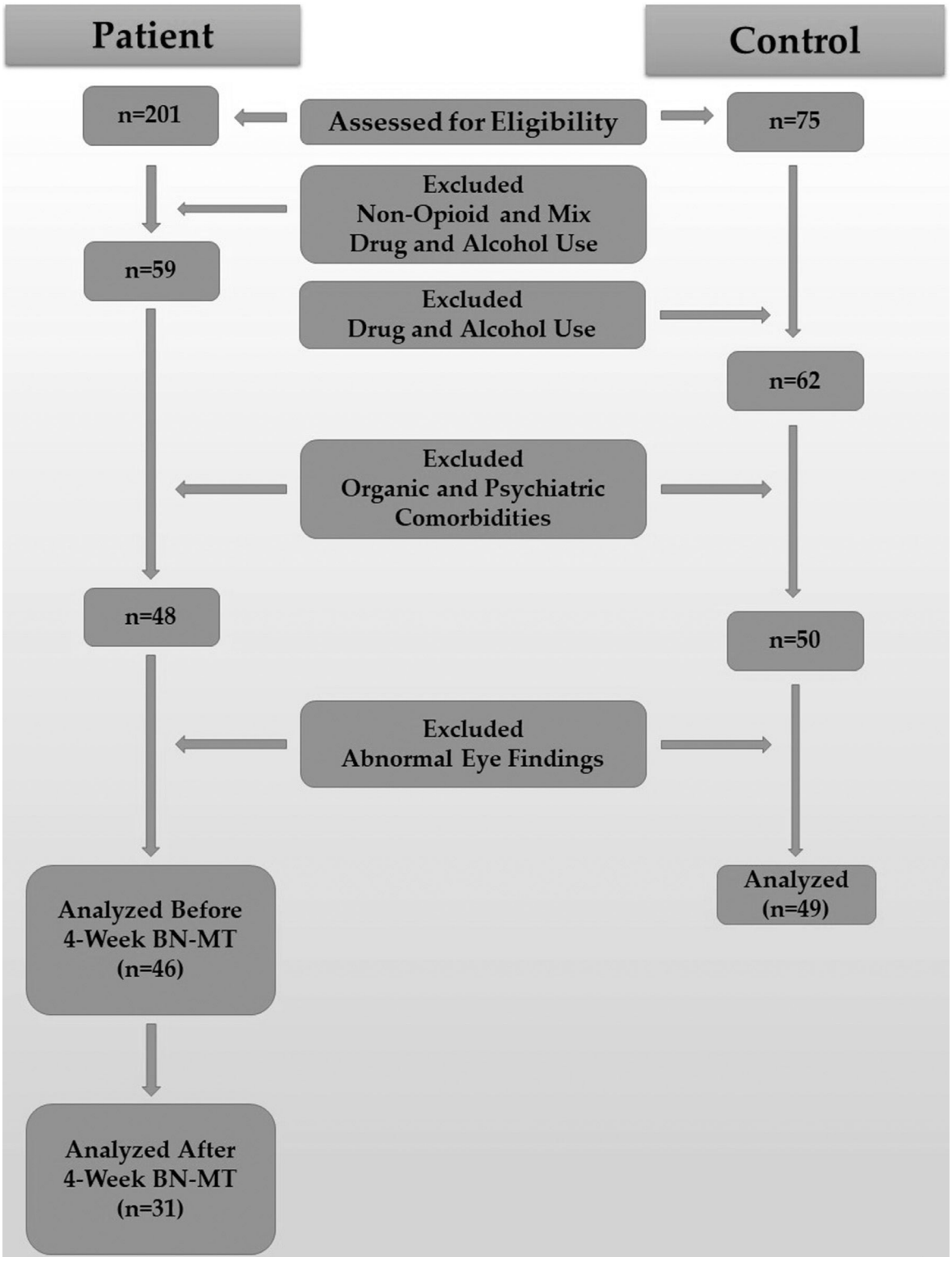

Fig. 1 The flowchart of the study.

reference of "last 7 days, including today". GSI is the average of 90 items. There is a scoring range from zero to four.[26]

Statistical analyses

Statistical analysis was performed using Windows SPSS 22.0 (Statistical Package for the Social Sciences Inc.). Descriptive statistics and continuous variables were given as mean ± standard deviation, and categorical variables were given as frequency and percentage. Chi-square test was used to analyze the categorical data. Normal distribution suitability was assessed using the Kolmogorov-Smirnov test. The diagnosis of SUD and the effect of BN-MT were accepted as the independent variable, sociodemographic and clinical parameters as

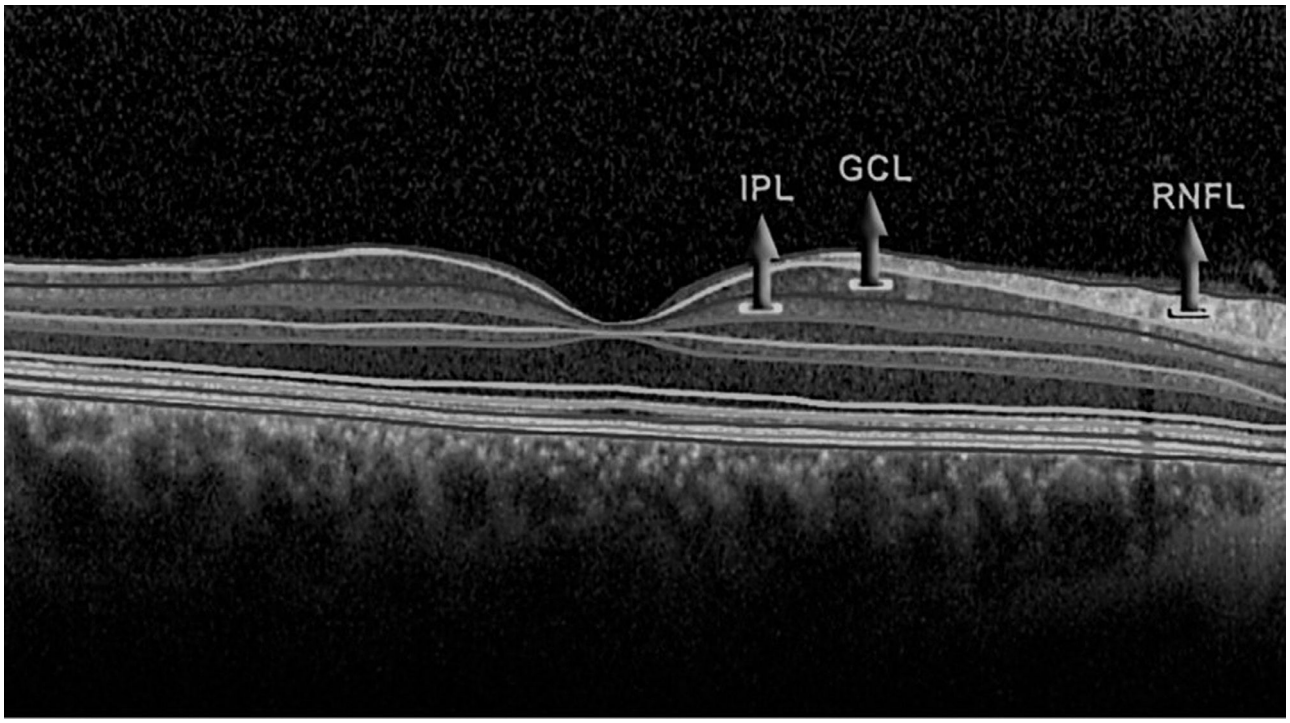

Fig. 2 Measurement of the GCL, IPL, and RNFL (GCL: Ganglion Cell Layer; IPL: Inner Plexiform Layer; RNFL: Retinal Nerve Fiber Layer).

the dependent variable. Independent-samples t-test was used to make comparisons between two groups to determine significant differences between groups. Paired sample t-test was used to make comparisons between dependent variables. Cohen's d and Glass's delta were calculated as the effect size. A value of less than 0.05 (p value) was considered statistically significant.

Results

The OUD group consisted of 46 males and the control group consisted of 49 males. The mean age was 24.21±3.81 years in the OUD group and 25.18±3.19 years in the control group (p=0.119). The mean duration of education was 10.19± 2.82 years in the patient group, and was 13.79±1.45 years in the control group (p<0.001). All patients had used buprenorphine/naloxone in the past. Twenty-eight (60.86%) of the patients had a history of intravenous opioid administration. In the OUD group, the first substance used in 27 subjects was cannabis, in 12 subjects was alcohol, in 5 subjects was ecstasy, and in 2 subjects was opioid. These were illicit drugs that patients used in the past and were not actively using them. The sociodemographic data of the groups and substance use characteristics of the patient group were shown in Table 1 and Table 2.

When the SD-OCT findings of the OUD group before BN-MT and the control group were compared, it was seen that the right and left NS and CT values showed significant differences. While the NS values of the OUD group were found to be increased compared to the control group, the CT values were found to be decreased. The SD-OCT findings and comparison of the OUD and the control groups were shown in Table 3.

The comparison of clinical variables before and after BN-MT was shown in Table 4. It was determined that the functionality of the patients increased, their somatic complaints decreased, and their social adjustment increased after four weeks of BN-MT treatment.

After BN-MT, a decrease in RNFL values and an increase in CT values were detected in both eyes of the patients. The comparison of SD-OCT parameters before and after BN-MT in the OUD group was shown in Table 5. Also, the comparison of SD-OCT parameters of OUD group after BN-MT and the control group was shown in Table 6.

Discussion

The similarity of the groups in terms of age, gender, and smoking status facilitated the interpretation of the findings. The NS value of the OUD group before BN-MT was significantly higher than the control group. The choroidal value of the OUD group before BN-MT was significantly lower than the control group. In the OUD group, after four weeks of BN-MT, a drop in RNFL sectors and rise in CT values were detected. IPL values of the OUD group after four weeks of buprenorphine/naloxone were significantly lower than the control group.

Chronic opioid use induces opioid addiction, which is characterized by extremely unpleasant physical and emotional consequences after substance use is ceased. The rewarding effects and withdrawal symptoms of opioids ensure continued use, and the nucleus accumbens is important for orchestrating both processes.[27] The paraventricular nucleus of the thalamus orchestrates the acquisition and maintenance of opioid-associated memories via projections

Table 1 Sociodemographic data of OUD and control groups.

Variables		OUD (n=46) Mean±SD	Control (n=49) Mean±SD	*p* value
Age (years)		24.21±3.81	25.18±3.19	0.119
Education (years)		10.19±2.82	13.79±1.45	<0.001**
Monthly Income (Turkish Lira)		1618±825	3208±681	<0.001**
Smoking (package/year)		12.78±5.45	11.41±4.95	0.216
Variables		**OUD n (%)**	**Control n (%)**	**p value**
Regular Working Status	**Yes**	25 (54.34%)	41 (83.67%)	0.002*
	No	21 (45.66%)	8 (16.33%)	
Marital Status	**Married**	9 (19.56%)	6 (12.24%)	0.189
	Single	35 (76.08%)	43 (87.76%)	
	Widow	2 (4.36%)	0 (0.0%)	
Psychiatric History	**Yes**	46 (100.0%)	4 (8.16%)	<0.001**
	No	0 (0.0%)	45 (91.84%)	
Psychiatric History in the Family	**Yes**	23 (50.0%)	11 (22.44%)	0.005*
	No	23 (50.0%)	38 (77.56%)	
Illicit Drug Use in the Family	**Yes**	17 (36.95%)	4 (8.16%)	0.001*
	No	29 (63.05%)	45 (91.84%)	
Psychiatric Hospitalization History	**Yes**	9 (19.56%)	0 (0.0%)	<0.001**
	No	37 (80.44%)	49 (100.0%)	
Probation Implementation History	**Yes**	33 (71.73%)	0 (0.0%)	<0.001**
	No	13 (28.27%)	49 (100.0%)	
Prison History	**Yes**	8 (17.39%)	0 (0.0%)	<0.001**
	No	38 (82.61%)	49 (100.0%)	
Additional Organic Disease	**Yes**	3 (6.52%)	4 (8.16%)	0.760
	No	43 (93.48%)	45 (91.84%)	
Buprenorphine/Naloxone Use History	**Yes**	46 (100.0%)	0 (0.0%)	<0.001**
	No	0 (0.0%)	49 (100.0%)	
Intravenous Opioid Use History	**Yes**	28 (60.86%)	0 (0.0%)	<0.001**
	No	18 (39.4%)	49 (100.0%)	

* p<0.05,
** p<0.001; Chi-square test was used;
Abbreviations: OUD: Opioid Use Disorder; SD: Standard Deviation

to the central nucleus of the amygdala and nucleus accumbens.[28] Studies show that nucleus accumbens and thalamus are structurally affected by opioid use.[29-31] Seifert et al.[29] demonstrated that heroin addiction causes reduced volume of the nucleus accumbens in heroin addiction. Müller et al.[30] conducted a postmortem study to assess the possible differences in nucleus accumbens volume between heroin-addicted patients and healthy non-addicted control subjects and found that the mean volume of the nucleus accumbens in heroin addicts was smaller than in controls. Reid et al.[31] studied abstinent heroin-dependent subjects with no comorbid use of other psychoactive substances except nondependent use of alcohol and they reported reduction of thalamic grey matter volume. According to the Shi et al.,[32] the atrophy of mesolimbic dopaminergic regions, especially bilateral nucleus accumbens and thalamus, as well as the trend of negative correlation between bilateral nucleus accumbens and duration of heroin use suggested the close relationship between deficits of reward system and heroin use. Studies on the nucleus accumbens and thalamus pathways help us understand why clinicians have difficulty treating opioid addiction. However, structural changes associated with opioid use may be associated with many regions of the brain.[7-10] Calling the retina as "a window into the brain" has prompted many researchers to investigate the findings of OCT in psychiatric disorders.[33] Kalenderoglu et al.[12] investigated the effects of marijuana on OCT parameters. Ozsoy and Alim,[15] Ahuja et al.,[16] Dayi et al.,[17] Das,[18] and Orum and Kalenderoglu[19] studied the effects of alcohol on OCT

Table 2 Substance use characteristics of OUD group (n=46).

Variables	Mean±SD (minimum; maximum)
Onset of Opioid Use (year)	16.32±3.19 (min: 11; max: 26)
Diagnosis of SUD for the First (year)	19.21±2.88 (min: 14; max: 26)
Duration of Opioid Use (year)	3.04±2.03 (min: 1; max: 9)
Money Spent on Alcohol (Turkish Lira)	1195±484 (min: 450; max: 2100)
Attempt to Quit Opioid	3.63±2.79 (min: 1; max: 10)
Longest Time to Avoid Alcohol (week)	10.52±8.52 (min: 1; max: 32)
The Last Day of Opioid Use	2.26±1.78 (min: 1; max: 4)

Abbreviations: OUD: Opioid Use Disorder; SUD: Substance Use Disorder; SD: Standard Deviation

Table 3 Comparison of RNFL, GCL, IPL, CT values between the OUD and the control groups before the BN-MT.

Parameters	Groups	Mean±SD	*p* value	Cohen's *d*
Right NS	**OUD**	125.39±13.92	<0.001**	1.01
	Control	109.22±18.11		
Right N	**OUD**	79.04±10.53	0.022*	0.47
	Control	84.34±11.62		
Right NI	**OUD**	120.02±24.12	0.526	0.13
	Control	117.20±21.83		
Right TI	**OUD**	147.54±21.28	0.080	0.37
	Control	140.45±16.54		
Right T	**OUD**	75.02±9.73	0.142	0.35
	Control	72.20±8.78		
Right TS	**OUD**	138.04±22.54	0.700	0.05
	Control	139.61±16.79		
Right Mean	**OUD**	103.97±10.16	0.391	0.18
	Control	102.46±6.63		
Right CT	**OUD**	330.52±61.13	<0.001**	0.95
	Control	392.51±68.45		
Right GCL	**OUD**	1.19±0.06	0.711	0.05
	Control	1.19±0.05		
Right IPL	**OUD**	0.93±0.03	0.098	0.35
	Control	0.95±0.04		
Left NS	**OUD**	126.02±25.56	0.001*	0.66
	Control	111.85±20.54		
Left N	**OUD**	78.08±20.00	0.085	0.38
	Control	84.04±12.02		
Left NI	**OUD**	124.78±28.60	0.132	0.36
	Control	116.34±25.52		
Left TI	**OUD**	146.78±21.08	0.390	0.17
	Control	150.57±21.59		
Left T	**OUD**	72.93±9.15	0.131	0.35
	Control	70.20±8.29		
Left TS	**OUD**	144.82±22.73	0.078	0.55
	Control	134.08±13.31		
Left Mean	**OUD**	105.60±11.34	0.068	0.57
	Control	101.95±6.62		
Left CT	**OUD**	345.25±71.14	0.001*	0.68
	Control	393.94±69.94		
Left GCL	**OUD**	1.19±0.05	0.346	0.35
	Control	1.18±0.05		
Left IPL	**OUD**	0.93±0.03	0.121	0.36
	Control	0.95±0.04		

* $p<0.05$,

** $p<0.001$; n=46 for patient group and n=49 for control group; Independent-samples t-test was used;

Abbreviations: BN-MT: Buprenorphine/Naloxone Maintenance Treatment; RNFL: Retinal Nerve Fiber Layer; GCL: Ganglion Cell Layer; IPL: Inner Plexiform Layer; CT: Choroidal Thickness; OUD: Opioid Use Disorder; SD: Standard Deviation; NS: Naso-Superior; NI: Naso-Inferior; N: Nasal; TS: Temporo-Superior; TI: Temporo-Inferior; T: Temporal

parameters. The current study is important in terms of investigating the OCT parameters of individuals affected by opioids, as well as showing the changes caused by BN-MT in OCT parameters.

Although the number of OCT studies in substance use disorder (SUD) is limited, Kalenderoglu et al.[12] reported that substance use may cause an increase in RNFL. Kalenderoglu et al.[12] demonstrated that chronic use of cannabis, another illicit drug, may result in an increase in RNFL, which may be related to the neuroprotective property of cannabis. The substance investigated in the present study was exogenous opioid, and opioids were detected in the patient's urine during the initial OCT application. That is, the study was performed while the patient had exogenous opioids in their body. However, the patient group consisted of individuals who had been using substances for many years. Based on the findings of this study, it is not possible to distinguish between chronic opioid use and the possible changes in the body due to the opioid currently available. Initial OCT findings at the patient's admission may reflect both the chronic effects of opioids and the effects of opioids currently in the body. The same can be said for OCT findings after BN-MT. Because the OCT findings after four weeks of treatment may also reflect the possible effects of chronic opioid use; it may also reflect

Table 4 Comparison of clinical variables before and after BN-MT in the OUD group (n=31).

Variables	Before BN-MT (Mean±SD)	After BN-MT (Mean±SD)	*p* value
API	16.38±0.92	14.83±0.66	<0.001**
GAS	57.22±9.83	64.32±8.61	<0.001**
SOM	1.80±0.51	1.56±0.44	<0.001**
ANX	1.91±0.57	1.72±0.56	0.012*
O-C	2.18±0.70	2.21±0.54	0.663
DEP	1.88±0.72	1.65±0.59	0.005*
I-S	2.53±0.49	2.15±0.47	<0.001**
PSY	0.65±0.34	0.59±0.23	0.329
PAR	2.23±0.64	2.19±0.45	0.667
HOS	2.91±0.33	2.71±0.27	0.005*
PHOB	1.01±0.78	1.19±0.83	0.172
AD	2.37±0.44	2.02±0.30	<0.001**
GSI	2.15±0.56	1.84±0.35	<0.001**

* p<0.05,
** p<0.001; Paired sample t-test was used;
Note: Four weeks from baseline to second application;
Abbreviations: BN-MT: Buprenorphine/Naloxone Maintenance Treatment; OUD: Opioid Use Disorder; SD: Standard Deviation; API: Addiction Profile Index; GAS: Global Assessment Scale; SOM: Somatization; O-C: Obsessive-Compulsive; I-S: Interpersonal Sensitivity; DEP: Depression; ANX: Anxiety; HOS: Hostility; PHOB: Phobic; PAR: Paranoid; PSY: Psychotic; AD: Additional; GSI: Global Severity Index

the possible effects of buprenorphine present in the body at that time. Whether chronic effects of opioid use or due to the effects of existing opioids in the body, this study demonstrated that opioid use has significant effects on RNFL and choroid. Contrary to the studies that opioids cause neuronal damage,[34] there are studies reporting that opioids have neuroprotective effects.[35,36] Opioids lead to long-lasting changes, which influence many different forms of neural plasticity.[37] In the eye, clinical and/or experimental evidence suggested that opioid receptors regulate the accommodation and iris function, retinal development, neuronal protection, and aqueous humor dynamics.[38] Husain et al.[38] reported that both endogenous and exogenous opioids trigger neuroprotective events in the ischemic retina. This effect occurs through δ, κ, and μ opioid receptors expressed at different rates in the retina. Immunohistochemistry

Table 5 Comparison of SD-OCT parameters before and after BN-MT in the OUD group (n=31).

Variables	Before BN-MT (Mean±SD)	After BN-MT (Mean±SD)	*p* value
Right NS	126.48±13.79	106.16±13.88	<0.001**
Right N	79.54±10.38	75.45±11.10	<0.001**
Right NI	120.12±23.92	116.87±22.41	0.082
Right TI	146.06±21.02	148.25±20.61	0.308
Right T	73.96±9.97	71.61±9.35	0.034*
Right TS	135.74±23.53	142.06±14.84	0.068
Right Mean	103.54±9.97	101.16±8.77	0.018*
Right CT	322.32±56.17	383.09±55.22	<0.001**
Right GCL	1.19±0.06	1.18±0.05	0.262
Right IPL	0.93±0.03	0.92±0.04	0.127
Left NS	124.77±23.83	115.87±19.54	0.001*
Left N	78.32±18.96	69.22±17.43	<0.001**
Left NI	124.77±26.92	114.29±25.81	<0.001**
Left TI	146.22±20.33	151.61±22.62	0.016*
Left T	72.22±8.62	75.48±8.86	0.002*
Left TS	144.54±23.11	141.25±22.03	0.104
Left Mean	105.16±11.41	102.25±9.66	0.001*
Left CT	338.83±67.39	386.09±63.73	<0.001**
Left GCL	1.19±0.05	1.19±0.05	0.578
Left IPL	0.93±0.03	0.93±0.03	0.196

* p<0.05,
** p<0.001; Paired sample t-test was used;
Note: Four weeks from baseline to second application;
Abbreviations: SD-OCT: Spectral-Domain Optical Coherence Tomography; BN-MT: Buprenorphine/Naloxone Maintenance Treatment; OUD: Opioid Use Disorder; SD: Standard Deviation; NS: Nasal Superior; NI: Nasal Inferior; N: Nasal; TS: Temporal Superior; TI: Temporal Inferior; T: Temporal; GCL: Ganglion Cell Layer; IPL: Inner Plexiform Layer; CT: Choroidal Thickness

Table 6 Comparison of SD-OCT parameters of OUD group after BN-MT and control group.

Variables	OUD After BN-MT (n=31) (Mean±SD)	Control (n=49) (Mean±SD)	*p* value	Cohen's *d*	Glass's *delta*
Right NS	106.16±13.88	109.22±18.11	0.424	0.19	0.23
Right N	75.45±11.10	84.34±11.62	0.001*	0.78	0.80
Right NI	116.87±22.41	117.20±21.83	0.977	0.04	0.04
Right TI	148.25±20.61	140.45±16.54	0.076	0.44	0.40
Right T	71.61±9.35	72.20±8.78	0.776	0.05	0.06
Right TS	142.06±14.84	139.61±16.79	0.508	0.19	0.21
Right Mean	101.16±8.77	102.46±6.63	0.451	0.21	0.20
Right CT	383.09±55.22	392.51±68.45	0.516	0.19	0.20
Right GCL	1.18±0.05	1.19±0.05	0.596	0.19	0.18
Right IPL	0.92±0.04	0.95±0.04	0.003*	0.75	0.75
Left NS	115.87±19.54	111.85±20.54	0.297	0.19	0.21
Left N	69.22±17.43	84.04±12.02	<0.001**	0.98	0.85
Left NI	114.29±25.81	116.34±25.52	0.728	0.05	0.05
Left TI	151.61±22.62	150.57±21.59	0.837	0.03	0.03
Left T	75.48±8.86	70.20±8.29	0.010*	0.61	0.59
Left TS	141.25±22.03	134.08±13.31	0.101	0.38	0.31
Left Mean	102.25±9.66	101.95±6.62	0.870	0.03	0.03
Left CT	386.09±63.73	393.94±69.94	0.614	0.18	0.19
Left GCL	1.19±0.05	1.18±0.05	0.787	0.06	0.08
Left IPL	0.93±0.03	0.95±0.04	0.023*	0.56	0.66

* $p<0.05$,
** $p<0.001$; Independent-samples t-test was used;
Note: Four weeks from baseline to second application;
Abbreviations: SD-OCT: Spectral-Domain Optical Coherence Tomography; BN-MT: Buprenorphine/Naloxone Maintenance Treatment; OUD: Opioid Use Disorder; SD: Standard Deviation; NS: Nasal Superior; NI: Nasal Inferior; N: Nasal; TS: Temporal Superior; TI: Temporal Inferior; T: Temporal; GCL: Ganglion Cell Layer; IPL: Inner Plexiform Layer; CT: Choroidal Thickness

showed that these receptors are in the inner retinal layers, especially RNFL and GCL. Hence, inner layers of the retina are more affected by ischemia.[38] Also, in this study, a thinning was found in the choroidal layer before BN-MT. The choroid is one of the most vascularized tissues of the human body and it plays important roles in nutrition and oxygenation of outer retina, disposal of waste products out of retina and secretion of growth factors. Choroid tissue is affected by any inflammatory or autoimmune conditions affecting blood flow.[12] We thought that the thinning of the choroidal layer was due to the anti-edematous effects of opioids.[39,40] On the other hand, buprenorphine also exerts its effects through opioid receptors. The changes in choroidal thickness after the exogenous opioid effect disappeared and the patient was under the effect of buprenorphine can be explained by the different receptor profiles of exogenous and semi-synthetic buprenorphine.[20] Previous studies have found that RNFL damage can be detected by ophthalmologic examination only after 50% of the ganglion cells were damaged. Therefore, RNFL damage may be expected to occur after more ganglion cell damage takes place.[20] In our study, RNFL values were found to be increased in the OUD group before BN-MT. The above-mentioned mechanisms may be possible reasons for this finding. There was no difference between the GCL and IPL values of the OUD group and the control group. However, initial IPL values were found to be significantly lower than the control group.

Endogenous and exogenous opioids have similar and different properties. While it is a common feature that they act through opioid receptors, this receptor interaction shows differences among opioids.[1-3] Agonist, antagonist or partial agonist binding of opioids to receptors, affinities, and the systems in which their effects are seen in the body show changes.[20] For instance, in vitro, buprenorphine is one of the most affine ligand of the human μ-opioid receptor (μ-OR, *Ki* = 0.9 nM) and was compared with other opioid such as naloxone (*Ki* = 14 nM), morphine (*Ki* = 74 nM) or oxycodone (*Ki* = 780 nM) in the same conditions. Buprenorphine is also described as an antagonist of κ-OR and δ-OR, and an agonist of nociceptin/ORL-1 receptors.[41] It is therefore difficult to predict the in vivo dynamics of the interaction of buprenorphine with its central nervous system targets from this complex in vitro profile. It is known that opioids differ in terms of their effects on the brain. Lorenzetti et al.[42] examined heroin users on stable doses of either methadone or buprenorphine and matched healthy controls. They demonstrated that heroin users exhibited larger pituitary gland volumes than healthy controls; this was particularly evident among the buprenorphine-treated group. Lorenzetti et al.[42] stated that this difference between buprenorphine and methadone may be related to the differing pharmacological profile. Some studies showing that the effects of exogenous and endogenous opioids in the body may differ have indicated that methadone may aggravate, not ameliorate the white matter impairment[43] and cerebral metabolism[44] associated with chronic heroin use. However, there are also studies reporting that exogenous and endogenous opioids have similar effects.[45] Bora et al.[45] found that there were no significant between-group differences between methadone and buprenorphine users for mean fractional anisotropy. It is thought that these differences or similarities are difficult to interpret. It is obvious that many factors such as the

structural (e.g., MRI) or functional (e.g., fMRI) devices, methods, the doses and route of administration of the drugs used, the characteristics of the subjects, etc. have the potential to affect the results.

The lack of knowledge of the blood levels of the exogenous opioids and buprenorphine used by the patients is an important limitation. After four weeks of BN-MT, while SD-OCT was applied, patients had buprenorphine/naloxone in their body. The effect of this buprenorphine/naloxone on SD-OCT values was not excluded. Only the current diagnosis is known and there is no information about which substance they used in the past and how much. The irreversible effects of possible substances used in the past were not excluded. Another limitation of our study is lack of control measurements to increase validity and reliability of SD-OCT to detect the neuronal degeneration. Further studies in which SD-OCT is used together with other neuroimaging methods such as pharmacological magnetic resonance imaging will provide better clues about the utility of SD-OCT as a tool in OUD. Deep chamber, thick lens and axial length parameters are considered to be able to influence the measurements made and their absence is considered as a limitation. It may be helpful to report diet habits of patients. As some of the information such as duration of opioid use has self-report feature, it may be wrong recall. Although the implementation is more difficult, studies involving more patient groups can reduce the limitations considerably. For instance, the group that was opioid-negative at the time of testing with chronic opioid use, the group who used opioids for the first time and whose current test was positive for opioids; etc. *E-nabiz* includes all medical records of the patients after 2015. However, information prior to 2015 may have false connotations due to memory factor. In addition, possible undiagnosed medical conditions are another limitation. Further studies are needed to clarify the limitations.

In conclusion, this study is the first to prospectively examine the effects of opioid use before and after BN-MT on SD-OCT parameters. We have suggested that there was a significant difference between the patient and the control groups in terms of choroidal thickness and nasal sectors of the RNFL values of both eyes. After BN-MT, CT and RNFL values were similar to the control group, but a significant decrease was observed in IPL values. Further studies are needed to reveal the relationship of SD-OCT findings with chronic opioid use, existing exogenous opioids in the body, and buprenorphine used for treatment.

Funding

No funding was received for this research.

Ethical considerations

All procedures performed in studies involving human participants were in accordance with the ethical standards of the (place name of institution and/or national research committee) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Institutional Board Review (IRB) approval was obtained from Adıyaman University Ethics Committee (Protocol number: 2020/6-45; Date: 23.06.2020).

Informed consent was obtained from all individual participants included in the study.

Conflict of interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements).

References

1. Corder G, Castro DC, Bruchas MR, Scherrer G. Endogenous and exogenous opioids in pain. Annu Rev Neurosci. 2018;41:453—73. https://doi.org/10.1146/annurev-neuro-080317-061522.
2. Stein C. Opioid receptors. Annu Rev Med. 2016;67:433—51. https://doi.org/10.1146/annurev-med-062613-093100.
3. Holden JE, Jeong Y, Forrest JM. The endogenous opioid system and clinical pain management. AACN Clin Issues. 2005;16 (3):291—301. https://doi.org/10.1097/00044067-200507000-00003.
4. Darcq E, Kieffer BL. Opioid receptors: drivers to addiction? Nat Rev Neurosci. 2018;19(8):499—514. https://doi.org/10.1038/s41583-018-0028-x.
5. Contet C, Kieffer BL, Befort K. Mu opioid receptor: a gateway to drug addiction. Curr Opin Neurobiol. 2004;14(3):370—8. https://doi.org/10.1016/j.conb.2004.05.005.
6. Wang SC, Chen YC, Lee CH, Cheng CM. Opioid addiction, genetic susceptibility, and medical treatments: a review. Int J Mol Sci. 2019;20(17):4294. https://doi.org/10.3390/ijms20174294.
7. Lyoo IK, Pollack MH, Silveri MM, Ahn KH, Diaz CI, Hwang J, et al. Prefrontal and temporal gray matter density decreases in opioid dependence. Psychopharmacology. 2006;184:139—44. https://doi.org/10.1007/s00213-005-0198-x.
8. Upadhyay J, Maleki N, Potter J, Elman I, Rudrauf D, Knudsen J, et al. Alterations in brain structure and functional connectivity in prescription opioid-dependent patients. Brain. 2010;133(Pt 7):2098—114. https://doi.org/10.1093/brain/awq138.
9. Wollman SC, Alhassoon OM, Stern MJ, Hall MG, Rompogren J, Kimmel CL, et al. White matter abnormalities in long-term heroin users: a preliminary neuroimaging meta-analysis. Am J Drug Alcohol Abuse. 2015;41(2):133—8. https://doi.org/10.3109/00952990.2014.985829.
10. Wollman SC, Alhassoon OM, Hall MG, Stern MJ, Connors EJ, Kimmel CL, et al. Gray matter abnormalities in opioid-dependent patients: a neuroimaging meta-analysis. Am J Drug Alcohol Abuse. 2017;43(5):505—17. https://doi.org/10.1080/00952990.2016.1245312.
11. Moreno-Rius J. Opioid addiction and the cerebellum. Neurosci Biobehav Rev. 2019;107:238—51. https://doi.org/10.1016/j.neubiorev.2019.09.015.
12. Kalenderoglu A, Orum MH, Karadag AS, Kustepe A, Celik M, Egilmez OB, et al. Increases in retinal nerve fiber layer thickness may represent the neuroprotective effect of cannabis: an optical coherence tomography study. J Addict Dis. 2020;38(3): 280—90. https://doi.org/10.1080/10550887.2020.1754109.
13. Drexler W, Morgner U, Ghanta RK, Kärtner FX, Schuman JS, Fujimoto JG. Ultrahigh-resolution ophthalmic optical coherence tomography. Nat Med. 2001;7(4):502—7. https://doi.org/10.1038/86589. Erratum in: Nat Med. 2001;7(5):636.

14. Fujimoto JG. Optical coherence tomography for ultrahigh resolution in vivo imaging. Nat Biotechnol. 2003;21(11):1361–7. https://doi.org/10.1038/nbt892.
15. Özsoy F, Alim S. Optical coherence tomography findings in patients with alcohol use disorder and their relationship with clinical parameters. Cutan Ocul Toxicol. 2020;39(1):54–60. https://doi.org/10.1080/15569527.2019.1700379.
16. Ahuja S, Kumar PS, Kumar VP, Kattimani S, Akkilagunta S. Effect of chronic alcohol and tobacco use on retinal nerve fibre layer thickness: a case-control study. BMJ Open Ophthalmol. 2016;1 (1):e000003. https://doi.org/10.1136/bmjophth-2016-000003.
17. Dayi A, Dayi Ö, Kurt E, Yorguner N. Optical coherence tomography findings in cannabis users. Turk Psikiyatri Derg. 2020;31 (4):239–43. https://doi.org/10.5080/u25205.
18. Das D. The effect of chronic alcohol use on retinal nerve fiber layer thickness. Int J Sci. 2019;8(12):1–3. https://doi.org/10.36106/ijsr/0520260.
19. Orum MH, Kalenderoglu A. Decreases in retinal nerve fiber layer thickness correlates with cumulative alcohol intake. J Addict Dis. 2020;38(4):400–10. https://doi.org/10.1080/10550887.2020.1776083.
20. Chen KY, Chen L, Mao J. Buprenorphine-naloxone therapy in pain management. Anesthesiology. 2014;120(5):1262–74. https://doi.org/10.1097/ALN.0000000000000170.
21. van Dorp E, Yassen A, Dahan A. Naloxone treatment in opioid addiction: the risks and benefits. Expert Opin Drug Saf. 2007;6 (2):125–32. https://doi.org/10.1517/14740338.6.2.125.
22. Parran TV, Adelman CA, Merkin B, Pagano ME, Defranco R, Ionescu RA, et al. Long-term outcomes of office-based buprenorphine/naloxone maintenance therapy. Drug Alcohol Depend. 2010;106(1):56–60. https://doi.org/10.1016/j.drugalcdep.2009.07.013.
23. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Arlington, VA: APP; 2013.
24. Ogel K, Evren C, Karadağ F, Gürol DT. The development, validity, and reliability of the Addiction Profile Index (API). Turk Psikiyatri Derg. 2012;23(4):263–75.
25. Endicott J, Spitzer RL, Fleiss JL, Cohen J. The global assessment scale. A procedure for measuring overall severity of psychiatric disturbance. Arch Gen Psychiatry. 1976;33(6):766–71. https://doi.org/10.1001/archpsyc.1976.01770060086012.
26. Derogatis LR, Ceary PA. Confirmation of the dimensional structure of the SCL-90: a study in construct validation. J Clin Psychol. 1977;33(4):981–9. https://doi.org/10.1002/1097-4679(197710)33. 4<981::AID-JCLP2270330412>3.0.CO;2-0.
27. Zhu Y, Wienecke CF, Nachtrab G, Chen X. A thalamic input to the nucleus accumbens mediates opiate dependence. Nature. 2016;530(7589):219–22. https://doi.org/10.1038/nature16954.
28. Keyes PC, Adams EL, Chen Z, Bi L, Nachtrab G, Wang VJ, et al. Orchestrating opiate-associated memories in thalamic circuits. Neuron. 2020;107(6):1113–23. https://doi.org/10.1016/j.neuron.2020.06.028.
29. Seifert CL, Magon S, Sprenger T, Lang UE, Huber CG, Denier N, et al. Reduced volume of the nucleus accumbens in heroin addiction. Eur Arch Psychiatry Clin Neurosci. 2015;265(8):637–45. https://doi.org/10.1007/s00406-014-0564-y.
30. Müller UJ, Truebner K, Schiltz K, Kuhn J, Mawrin C, Dobrowolny H, et al. Postmortem volumetric analysis of the nucleus accumbens in male heroin addicts: implications for deep brain stimulation. Eur Arch Psychiatry Clin Neurosci. 2015;265(8):647–53. https://doi.org/10.1007/s00406-015-0617-x.
31. Yuan Y, Zhu Z, Shi J, Zou Z, Yuan F, Liu Y, et al. Gray matter density negatively correlates with duration of heroin use in young lifetime heroin-dependent individuals. Brain Cogn. 2019;71 (3):223–8. https://doi.org/10.1016/j.bandc.2009.08.014.
32. Shi H, Liang Z, Chen J, Li W, Zhu J, Li Y, et al. Gray matter alteration in heroin-dependent men: an atlas-based magnetic resonance imaging study. Psychiatry Res Neuroimaging. 2020;304:111150. https://doi.org/10.1016/j.pscychresns.2020.111150.
33. Appaji A, Nagendra B, Chako DM, Padmanabha A, Hiremath CV, Jacob A, et al. Retinal vascular abnormalities in schizophrenia and bipolar disorder: a window to the brain. Bipolar Disord. 2019;21(7):634–41. https://doi.org/10.1111/bdi.12779.
34. Büttner A. Review: the neuropathology of drug abuse. Neuropathol Appl Neurobiol. 2011;37(2):118–34. https://doi.org/10.1111/j.1365-2990.2010.01131.x.
35. Jeong S, Kim SJ, Jeong C, Lee S, Jeong H, Lee J, et al. Neuroprotective effects of remifentanil against transient focal cerebral ischemia in rats. J Neurosurg Anesthesiol. 2012;24(1): 51–7. https://doi.org/10.1097/ANA.0b013e3182368d70.
36. Lv MR, Li B, Wang MG, Meng FG, Yu JJ, Guo F, et al. Activation of the PI3K-Akt pathway promotes neuroprotection of the δ-opioid receptor agonist against cerebral ischemia-reperfusion injury in rat models. Biomed Pharmacother. 2017;93:230–7. https://doi.org/10.1016/j.biopha.2017.05.121.
37. Zhang Y, Loh HH, Law PY. Effect of opioid on adult hippocampal neurogenesis. Sci World J. 2016:2601264. https://doi.org/10.1155/2016/2601264.
38. Husain S, Potter DE, Crosson CE. Opioid receptor-activation: retina protected from ischemic injury. Invest Ophthalmol Vis Sci. 2019;50(8):3853–9. https://doi.org/10.1167/iovs.08-2907.
39. Vaidya B, Sifat AE, Karamyan VT, Abbruscato TJ. The neuroprotective role of the brain opioid system in stroke injury. Drug Discov Today. 2018;23(7):1385–95. https://doi.org/10.1016/j.drudis.2018.02.011.
40. Silvia RC, Slizgi GR, Ludens JH, Tang AH. Protection from ischemia-induced cerebral edema in the rat by U-50488H, a kappa opioid receptor agonist. Brain Res. 1987;403(1):52–7. https://doi.org/10.1016/0006-8993(87)90121-1.
41. Auvity S, Goutal S, Caillé F, Vodovar D, Pruvost A, Wimberley C, et al. Pharmacokinetic neuroimaging to study the dose-related brain kinetics and target engagement of buprenorphine in vivo. Neuropsychopharmacology. 2021;46(6):1220–8. https://doi.org/10.1038/s41386-021-00976-w.
42. Lorenzetti V, Lubman DI, Velakoulis D, Yücel M. Pituitary gland volume among heroin users stabilised on substitution pharmacotherapy. Drug Alcohol Depend. 2010;110(1-2):164–6. https://doi.org/10.1016/j.drugalcdep.2010.02.012.
43. Lin WC, Chou KH, Chen CC, Huang CC, Chen HL, Lu CH, et al. White matter abnormalities correlating with memory and depression in heroin users under methadone maintenance treatment. PLoS One. 2012;7(4):e33809. https://doi.org/10.1371/journal.pone.0033809.
44. Shi J, Zhao LY, Copersino ML, Fang YX, Chen Y, Tian J, et al. PET imaging of dopamine transporter and drug craving during methadone maintenance treatment and after prolonged abstinence in heroin users. Eur J Pharmacol. 2008;579(1-3):160–6. https://doi.org/10.1016/j.ejphar.2007.09.042.
45. Bora E, Yücel M, Fornito A, Pantelis C, Harrison BJ, Cocchi L, et al. White matter microstructure in opiate addiction. Addict Biol. 2012 Jan;17(1):141–8. https://doi.org/10.1111/j.1369-1600.2010.00266.x.