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COVID-19 Pandemic Detrimentally Affects Craving and Quality of Life in Patients Under Medication-Assisted Treatment with Buprenorphine and Methadone: The Issue of Medication Dose

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Abstract: The COVID-19 pandemic crisis has increased the vulnerability and decreased the retention in treatment of patients receiving medication-assisted treatment (MAT). Therefore, the aim of the present study was to investigate the impact of COVID-19 on craving and quality of life (QoL) of MAT patients and to reveal the potential role of medication dose. Thus, 562 volunteers were divided into the control group (n = 100) comprising healthy volunteers without prior contact with substances of abuse, and into the experimental group (n = 462), which included patients receiving MAT, who were stratified into sub-groups of patients under methadone and buprenorphine. The groups were further divided into two sub-groups, based on whether the participants were infected by SARS-CoV-2 or not. The heroin craving questionnaire (HCQ), and the Nottingham health profile (NHP) instrument were used for craving assessment and QoL evaluation respectively. The MAT patients who were infected by SARS-CoV-2 had higher levels of craving compared to their non-infected counterparts, and COVID-19 restriction measures reduced QoL mainly of non-infected MAT patients. Furthermore, low craving and high QoL were largely associated with medium or low medication dose. It appears that focused interventions and modifications to medication doses could lead to better clinical outcomes of the MAT programs and relapse prevention.

Keywords: methadone; buprenorphine; COVID-19 pandemic crisis; craving; quality of life; SARS-CoV-2

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1. Introduction

According to recent published data in the Report of the European Monitoring Centre for Drugs and Drug Addiction [1], substance dependence remains at high levels in Europe. Indeed, 83.4 million adults have used illicit drugs, and opioids accounted for the greatest share of harms attributed to illicit drug use. This number experienced a rising tendency due to the COVID-19 pandemic, while only 17% of the patients with opioid use disorders (OUDs) attend a medication-assisted treatment (MAT) program with methadone and buprenorphine [2].

Infection by SARS-CoV-2, which induced an extremely severe pandemic crisis a few years ago, affects multiple organs, mainly the respiratory system, with fever, cough, dyspnea, fatigue, and myalgia being the most common symptoms, and psychosocial effects including anxiety, mood swings, and depression, which influence mental health, have also been observed [3,4]. Together with restriction measures and social distancing, the COVID-19 pandemic has led to the increase in both anxiety and depression, whilst its

impact was much worse in vulnerable groups, such as patients with OUDs [5,6]. Thus, these susceptible groups experienced the impact of the pandemic crisis to a great extent, worsening their daily living [7]. Furthermore, medical problems due to drug use, such as cardiovascular diseases, HIV, and chronic hepatitis C, among others, are present in OUD patients [8,9]. These health issues, along with the immunosuppressive consequences of chronic opioid use, and the COVID-19 impact of enhancing stress and isolation, have exacerbated social vulnerability of OUD patients receiving MAT, leading to reduced retention in treatment, craving, and relapse affecting quality of life (QoL) [3,10–12].

MAT with methadone and buprenorphine is undoubtedly a helpful practice in reducing opioid abuse, craving, and drug-related risk behaviors, as well as in improving overall emotional and physical health resulting in a better QoL [13–15]. Although buprenorphine and methadone are considered beneficial for OUD treatment, they have been related to serious side effects that negatively affect the therapeutic process. Indeed, they have been incriminated in sleep disturbances, cognitive impairment, and oxidative stress, which, accompanied by a stressful condition such as SARS-CoV-2 infection, may boost craving and drug-seeking behavior, reducing QoL of patients [16,17]. However, the medication dose could appear as a decisive factor for their efficiency. It has been recently shown that the dose regimen of xenobiotics is crucial for their effects on biochemical pathways that can severely affect cellular function and structure [18,19]. Limited findings have demonstrated that QoL and craving of patients receiving MAT are influenced by the COVID-19 pandemic, since MAT potentially exacerbates the cellular functions that have been dysregulated by SARS-CoV-2, leading progressively to drug-seeking behaviors and relapse [17].

Based on the above, the dose of these medicines, along with parameters that dysregulate normal organismal function, such as in the stressful COVID-19 pandemic crisis, could be determinant factors for their efficacy against OUDs. Therefore, the goal of the present study was to investigate the impact of the COVID-19 pandemic on craving and QoL of patients receiving MAT, aiming to identify the effects of a wide range of MAT doses on craving and QoL, and to build a prediction model for the aforementioned parameters through elements from patients' demographic data, offering clinical guidance for their efficient rehabilitation from opioid use.

2. Materials and Methods

2.1. Inclusion and Exclusion Criteria of the Participants

Patients with OUDs receiving MAT were included in the present investigation. All participants were fully informed about the purpose of the study, as well as provided assurance about the confidentiality of the obtained data, and a consensus form was signed for study participation and data publication. According to the inclusion criteria, all patients of the experimental group were over 20 years of age, were long-term opioid drug users, suffered from physical and mental dependence due to use, and should have been active members in MAT programs for at least three quarantine periods during the pandemic crisis from 2020 up to 2022. Patients with severe psychopathology and serious medical problems incompatible with the monitoring of the program were excluded. All patients infected by SARS-CoV-2 were outpatients and appeared with mild to moderate symptoms, including fever, cough, myalgia, and fatigue. All participants anonymously completed the self-reported instruments to evaluate the impact of the pandemic on craving and their QoL, and demographic data were also obtained.

2.2. Medication

The participants receiving methadone maintenance treatment (i.e., MMT) and buprenorphine maintenance treatment (i.e., BMT) were administered methadone hydrochloride solution (10 mg/mL) and buprenorphine and buprenorphine/naloxone tablets (2–8 mg), respectively. Based on the dose of medication, the patients were divided into three groups. For the MMT patients, the stratification was as follows: low dose (2–45 mg, n = 40), moderate dose (45–85 mg, n = 39), and high dose (>85 mg, n = 35) [20]; whereas the BMT pa-

tients were similarly stratified into low dose (2–10 mg, n = 118), moderate dose (10–18 mg, n = 121), and high dose (>18 mg, n = 109) [21].

2.3. Description of the Instruments Used to Assess Quality of Life and Craving

Nottingham Health Profile (NHP): The NHP questionnaire was used for the assessment of the pandemic impact on the participants' QoL. The questionnaire consists of two parts: the first part assesses the parameters *activity*, *pain*, *emotional reaction*, *sleep*, *social isolation*, and *mobility*, whereas the second part evaluates the effects of health or disease on the activities of daily living using yes-or-no answers. Each parameter score receives a value in the 0–1 interval and the overall QoL score ranges from 0 to 7, wherein a higher score reflects better QoL. The questionnaire is highly valid and reliable (i.e., test–retest reliability coefficients and Spearman's R-value range between 0.77 and 0.86) [22].

Heroin Craving Questionnaire (HCQ): The HCQ was used for the assessment of the effects of the pandemic on craving. It consists of five dimensions, namely *desire to use heroin*, *intentions and planning to use heroin*, *anticipation of positive outcome*, *relief from withdrawal or dysphoria*, and *lack of control over use*. Each of these includes nine questions. The score of each dimension is equally weighted on a 7-point Likert scale ranging from 1 (i.e., strongly disagree) to 7 (i.e., strongly agree), resulting in a total craving score, wherein the higher the number the higher the level of craving. It is a reliable and validated questionnaire with Cronbach's alpha equal to 0.90 [23].

2.4. Ethical Approval

All procedures followed were in accordance with the ethical standards of the responsible committee in human experimentation (institutional and national) and with the Declaration of Helsinki 1975, as revised in 2013. It was also approved by a University Department and the Institutional Review Board (ref. number 44482-2/11/2020).

2.5. Statistical Analysis

The sample size (n') was calculated by the following equation:

$$n' = \frac{n}{1-r}$$

where r is the anticipated non-response rate and n is the sample size without correction regarding the non-response rate (desired sample size), which is defined as follows:

$$n = \frac{z^2 P(1-P)}{d^2}$$

where z is the z statistic for the level of confidence, P is the expected prevalence, and d is the allowable margin of error. The formula for estimating n was selected based on the fact that the population of patients receiving MAT in Greece is equal to 12,000, while the collected sample has a size of 463 patients, which leads to a sampling fraction of 3.860%, which is, thus, smaller than 5% [24]. More precisely, a 95% confidence interval was selected for the sample size estimation; therefore, the z statistic value is equal to 1.96, while a non-response rate of 10% of the desired sample size was anticipated. Additionally, the expected prevalence was set to 50% due to the absence of previous studies, while the allowable margin of error was set to 5%, which, according to the literature, is a reasonable choice given the setting of the expected prevalence [24]. The substitution of the aforementioned values into the previously presented formulas yields a sample size corrected for non-response equal to 427 patients. No missing data were observed.

Furthermore, in order to determine differences and associations between the dimensions of the instruments and the demographic variables, one-way analysis of variance, the Kruskal–Wallis test using the Pearson correlation coefficient, or Kendall's tau were used [25,26]. The independent sample *t*-test, Welch's *t*-test, and Wilcoxon–Mann–Whitney test were also applied to determine variations in instrument scores between groups [26].

Tukey's Honest Significant Difference test and Dunn's test with Šidák's *p*-value adjustment method for multiple comparisons were used to identify differences between the dimensions of the instruments and the dose levels of methadone or buprenorphine [27,28].

Additionally, regression trees on QoL and craving for each administered medication treatment were constructed, based on total scores of dependent variables and the demographic variables, substance dose, and pandemic crisis. The train and test splits were retrieved by random sampling as an 80% to 20% ratio, respectively, while the minimum number of observations per leaf was set to 10 and 20 for MMT and BMT patients, respectively, to mitigate the overfitting phenomenon [29,30]. The previously presented and described regression trees achieve a mean absolute error (MAE) on the above tests equal to 1.061 and 1.202, respectively. The statistical significance threshold for all *p*-values was set to 5% and the analysis was conducted using the R programming language (version 4.1.2).

3. Results

3.1. Demographic Data and Participant Characteristics

The demographic characteristics of the participants are presented in Table 1. No statistically significant difference was found between demographic data and MAT. Regarding the characteristics of the participants, a total of 562 individuals, based on statistical power calculation, voluntarily participated in the present investigation and were divided into the control and the experimental groups. The first group comprised 100 healthy volunteers without prior contact with substances of abuse, and in the second group 462 patients attending MAT programs were included. The volunteers of the experimental group were divided into the MMT (n = 114) and the BMT sub-groups (n = 348). Moreover, the participants were further stratified according to whether they were infected by SARS-CoV-2 or not. In particular, the experimental group comprised 31 infected and 83 non-infected patients under MMT, and 42 infected and 306 non-infected patients under BMT, whereas 16 infected and 84 non-infected patients were included in the control group.

Table 1. The demographic data of the participants.

Demographic Data		**Control n (%)**	**MMT n (%)**	**BMT n (%)**
Gender	Female	26 (26)	30 (26.3)	77 (22.1)
	Male	74 (74)	84 (73.7)	271 (77.9)
Education level	Illiterate	2 (2)	1 (0.9)	7 (2.0)
	Primary school	5 (5)	18 (16.0)	39 (11.3)
	Secondary	44 (44)	70 (62.0)	246 (71.5)
	U.G/P.G	49 (49)	24 (21.2)	52 (15.1)
Family Status	Married	20 (20)	28 (24.4)	45 (13.2)
	Single	60 (60)	61 (53.0)	234 (68.6)
	Widowed	3 (3)	3 (2.6)	9 (2.6)
	Div./Sep.	17 (17)	23 (20.0)	53 (15.5)
Work Status	Employed	80 (80)	39 (34.5)	102 (29.5)
	Unemployed	20 (20)	74 (65.5)	244 (70.5)
Place of residence	Urban	64 (64)	104 (91.2)	267 (78.8)
	Rural	36 (36)	10 (8.8)	72 (21.2)
Chronic disease	Diabetes	3 (3)	1 (0.9)	10 (2.9)
	Cancer	1 (1)	4 (3.5)	1 (0.3)
	C.V	6 (6)	6 (5.3)	12 (3.5)
	COPD	6 (6)	11 (9.7)	18 (5.2)
	Systemic Disease	5 (5)	3 (2.6)	6 (1.7)
	PS.D.	18 (18)	30 (26.3)	98 (28.2)
	None	61 (61)	59 (51.8)	203 (58.3)
COVID-19 data	Non-infected	84 (84)	83 (72.8)	306 (87.9)
	Infected	16 (16)	31 (27.2)	42 (12.1)

Table 1. *Cont.*

Demographic Data	Control n (%)	MMT n (%)	BMT n (%)
	Control Mean ± SD	**MMT Mean ± SD**	**BMT Mean ± SD**
Age	42.8 ± 10.3	48.7 ± 8.2	49.0 ± 8.1
Age of onset		18.9 ± 6.5	17.5 ± 5.2
Years of drug use (before MAT admission)		18.0 ± 8.3	16.3 ± 9.6
Years in MAT programs		10.3 ± 6.5	6.6 ± 4.8
Dose (mg/24 h)		67.8 ± 35.6	15.6 ± 10.5
BMI		24.7 ± 4.5	25.6 ± 16.0

MMT: patients under methadone maintenance treatment; BMT: patients under buprenorphine maintenance treatment; U.G: Undergraduate; P.G: Postgraduate; C.V: Cardiovascular disease; COPD: Chronic obstructive pulmonary disease; PS.D.: Psychiatric disorders; BMI: Body mass index.

3.2. Craving

The infected patients both under MMT and BMT had increased craving in all dimensions of the HCQ, in comparison to their non-infected counterparts (Table 2). No statistically significant differences between MAT both in infected and non-infected patients were observed. Furthermore, the patients under a medium dose of methadone (i.e., MMT patients) had, overall, a decreased craving level compared to their high- and low-dose counterparts (Table 3). This result was depicted in the following dimensions of HCQ: desire and use of heroine, anticipation of positive outcome, and relief from withdrawal or dysphoria. The overall findings were also the same in BMT patients in all HCQ dimensions, reinforcing the notion that dose modification during an infection is probably imperative. In addition, no significant differences between HCQ dimensions and the MAT doses of non-infected patients were found.

Table 2. The results of craving for infected and non-infected patients in terms of MAT.

HCQ Dimensions	Non-Infected		Infected		p ** Non-Infected vs. Infected MMT	p ** Non-Infected vs. Infected BMT
	MMT Mean ± SD	**BMT Mean ± SD**	**MMT Mean ± SD**	**BMT Mean ± SD**		
Desire to use heroin	31.71 ± 7.27	31.83 ± 5.89	46.65 ± 7.72	45.16 ± 7.37	**0.001**	**0.001**
p *	0.97		0.40			
Intentions, planning to use heroin	30.16 ± 7.26	30.75 ± 5.88	46.62 ± 6.84	43.97 ± 7.85	**0.001**	**0.001**
p *	0.24		0.12			
Anticipation of positive outcome	32.1 ± 7.98	32.42 ± 7.19	46.56 ± 7.68	43.69 ± 8.10	**0.001**	**0.001**
p *	0.87		0.07			
Relief from withdrawal, dysphoria	30.37 ± 9.35	29.58 ± 8.46	44.31 ± 8.48	41.64 ± 8.78	**0.001**	**0.001**
p *	0.59		0.23			
Lack of control over use	33.84 ± 9.52	33.13 ± 7.93	46.84 ± 7.70	44.90 ± 6.94	**0.001**	**0.001**
p *	0.39		0.17			
Total score	19.38 ± 3.67	19.33 ± 3.24	27.81 ± 4.23	26.47 ± 4.00	**0.001**	**0.001**
p *	0.96		0.09			

HCQ: Heroin Craving Questionnaire; MMT: methadone maintenance treatment; BMT: buprenorphine maintenance treatment. SD: Standard deviation; * Results of craving through comparison of MAT both in infected and non-infected patients in each HCQ dimension. ** Results of craving in the same medication through comparison between infected and non-infected patients in each HCQ dimension. Bold numbers indicate statistically significant difference ($p < 0.05$).

Table 3. The results of craving for infected patients in terms of MAT and medication dose.

	Infected Patients											
	MMT						BMT					
HCQ Dimensions	**L Mean ±SD**	**M Mean ±SD**	**H Mean ±SD**	***p* ** H–L**	***p* ** H–M**	***p* ** L–M**	**L Mean ± SD**	**M Mean ± SD**	**H Mean ± SD**	***p* ** H–L**	***p* ** H–M**	***p* ** L–M**
Desire to use heroin	51.72 ± 4.40	42.57 ± 5.25	44.71 ± 8.93	0.07	0.79	**0.02**	54.33 ± 2.91	43.26 ± 5.75	42.16 ± 6.54	**0.001**	0.94	**0.001**
p *		**0.01**						**0.001**				
Intentions, planning to use heroin	50.00 ± 5.27	44.00 ± 5.22	45.28 ± 7.89	0.06	0.92	0.64	54.55 ± 2.78	41.53 ± 6.58	40.72 ± 5.80	**0.001**	0.93	**0.001**
p *		0.08						**0.001**				
Anticipation of positive outcome	52.18 ± 3.51	42.71 ± 7.40	44.07 ± 8.03	**0.01**	0.87	**0.006**	54.66 ± 2.5	40.86 ± 6.89	40.55 ± 5.91	**0.001**	1.0	**0.001**
p *		**0.002**						**0.001**				
Relief from withdrawal, dysphoria	49.27 ± 5.53	39.57 ± 3.45	42.78 ± 10.34	0.11	0.65	**0.04**	52.33 ± 3.60	39.93 ± 7.86	37.72 ± 7.04	**0.001**	0.72	**0.004**
p *		**0.03**						**0.001**				
Lack of control over use	50.45 ± 7.20	44.00 ± 7.74	45.42 ± 7.51	0.07	0.09	0.07	53.88 ± 3.68	44.86 ± 5.19	40.44 ± 4.87	**0.001**	0.16	**0.01**
p *		0.14						**0.001**				
Total score	30.54 ± 2.16	25.28 ± 3.35	26.92 ± 4.82	0.06	0.62	**0.02**	32.00 ± 2.00	25.60 ± 2.77	24.44 ± 3.05	**0.001**	0.82	**0.002**
p *		**0.01**						**0.001**				

MMT: patients under methadone maintenance treatment; BMT: patients under buprenorphine maintenance treatment; HCQ: Heroin Craving Questionnaire; SD: Standard deviation; L: low dose; M: medium dose; H: high dose; * Comparison of each HCQ dimension with doses as a whole. ** Comparison between doses in each HCQ dimension; Bold numbers indicate statistically significant difference ($p < 0.05$).

3.3. Quality of Life

The patients of the experimental group had overall lower QoL compared to the healthy volunteers of the control group, as indicated from the total score (Table 4). This result was depicted in the following dimensions of NHP: energy level, emotional reactions, sleep, and social isolation. Moreover, both the infected and non-infected patients of the experimental group showed compromised QoL in the same dimensions (apart from energy level in the infected participants). Notably, the patients who receive a low or medium methadone dose have better QoL compared to those who take a high dose. On the contrary, low buprenorphine dose scarcely affected QoL (Table 5). No significant differences were found in NHP dimensions compared to substance doses in infected patients.

Table 4. Quality of life assessed in the control and experimental groups as a whole, and after their stratification based on COVID-19 infection (i.e., infected and non-infected).

	Total Sample		Non-Infected		Infected	
NHP Dimensions	**Control Mean ± SD**	**Experimental Mean ± SD**	**Control Mean ± SD**	**Experimental Mean ± SD**	**Control Mean ± SD**	**Experimental Mean ± SD**
Energy level	0.75 ± 0.1	0.60 ± 0.2	0.79 ± 0.13	0.60 ± 0.20	0.54 ± 0.28	0.61 ± 0.37
p *	**<0.001**		**<0.001**		0.43	
Pain	0.83 ± 0.11	0.81 ± 0.18	0.86 ± 0.12	0.83 ± 0.17	0.76 ± 0.23	0.80 ± 0.18
p *	0.78		0.28		0.44	

Table 4. *Cont.*

NHP Dimensions	Total Sample		Non-Infected		Infected	
	Control Mean ± SD	Experimental Mean ± SD	Control Mean ± SD	Experimental Mean ± SD	Control Mean ± SD	Experimental Mean ± SD
Emotional reactions	0.79 ± 0.3	0.58 ± 0.1	0.79 ± 0.21	0.58 ± 0.34	0.77 ± 0.11	0.55 ± 0.35
p *	**<0.001**		**<0.001**		**0.01**	
Sleep	0.85 ± 0.25	0.53 ± 0.12	0.87 ± 0.11	0.53 ± 0.27	0.76 ± 0.23	0.54 ± 0.42
p *	**<0.001**		**<0.001**		**0.008**	
Social isolation	0.91 ± 0.03	0.63 ± 0.1	0.90 ± 0.06	0.64 ± 0.33	0.95 ± 0.05	0.60 ± 0.32
p *	**<0.001**		**<0.001**		**<0.001**	
Physical abilities	0.83 ± 0.1	0.83 ± 0.3	0.84 ± 0.1	0.83 ± 0.12	0.78 ± 0.16	0.82 ± 0.12
p *	0.12		0.17		0.45	
Activities of daily living	0.44 ± 0.21	0.46 ± 0.13	0.43 ± 0.27	0.47 ± 0.36	0.45 ± 0.25	0.41 ± 0.31
p *	0.76		0.50		0.42	
Total score	5.43 ± 1.35	4.47 ± 1.27	5.53 ± 2.61	4.49 ± 1.43	4.93 ± 2.16	4.36 ± 2.12
p *	**<0.001**		**<0.001**		0.25	

NHP: Nottingham Health Profile; * Comparison of the control and experimental groups in each NHP dimension. Bold numbers indicate statistically significant difference ($p < 0.05$).

Table 5. Quality of life on non-infected patients in terms of MAT and medication dose.

NHP	Non-Infected											
	MMT						BMT					
	L Mean ± SD	M Mean ± SD	H Mean ± SD	*p* ** H–L	*p* ** H–M	*p* ** L–M	L Mean ± SD	M Mean ± SD	H Mean ± SD	*p* ** H–L	*p* ** H–M	*p* ** L–M
EL	0.65 ± 0.39	0.55 ± 0.40	0.39 ± 0.39				0.63 ± 0.39	0.59 ± 0.39	0.65 ± 0.37			
p *		0.06		0.1	0.09	0.07		0.51		0.09	0.62	0.91
Pain	0.8 ± 0.17	0.68 ± 0.34	0.79 ± 0.27				0.82 ± 0.24	0.82 ± 0.24	0.83 ± 0.25			
p *		0.27		0.38	0.44	0.06		0.75		0.51	0.74	0.99
EM	0.66 ± 0.34	0.64 ± 0.31	0.48 ± 0.32				0.63 ± 0.27	0.53 ± 0.34	0.61 ± 0.31			
p *		0.08		0.15	0.12	0.16		0.12		0.32	0.46	0.82
SL	0.67 ± 0.28	0.58 ± 0.29	0.38 ± 0.30				0.56 ± 0.27	0.50 ± 0.32	0.56 ± 0.32			
p *		**0.003**		**0.003**	**0.04**	0.69		0.32		0.13	0.09	0.47
SI	0.77 ± 0.36	0.70 ± 0.33	0.53 ± 0.32				0.68 ± 0.32	0.57 ± 0.35	0.67 ± 0.35			
p *		**0.01**		**0.01**	0.17	0.58		**0.03**		0.9	**0.04**	0.19
PA	0.86 ± 0.18	0.76 ± 0.20	0.79 ± 0.23				0.81 ± 0.26	0.83 ± 0.23	0.86 ± 0.19			
p *		0.18		0.16	0.12	0.07		0.56		0.83	0.32	0.45
ADL	0.55 ± 0.34	0.48 ± 0.31	0.39 ± 0.29				0.48 ± 0.31	0.46 ± 0.32	0.48 ± 0.29			
p *		0.22		0.07	0.28	0.85		0.80		0.21	0.17	0.14
Total score	5.03 ± 1.69	4.42 ± 1.52	3.78 ± 1.60				4.65 ± 1.47	4.33 ± 1.64	4.68 ± 1.51			
p *		**0.02**		**0.01**	0.38	0.31		0.23		0.62	0.73	0.74

NHP: Nottingham Health Profile; EL: energy level; EM: emotional reactions; SL: sleep; SI: social isolation; PA: physical activities; ADL: activities of daily living; L: low dose; M: medium dose; H: high dose; MMT: methadone maintenance treatment; BMT: buprenorphine maintenance treatment. * Results of QoL through comparison of each NHP dimension with doses as a whole. ** Results of QoL through comparison between doses in each NHP dimension; Bold numbers indicate statistically significant difference ($p < 0.05$).

3.4. Correlations Between Quality of Life and Craving

According to Kendall's tau correlation, in MMT patients, the dimension emotional reactions (i.e., NHP) were significantly negatively correlated with the HCQ dimensions of relief from withdrawal or dysphoria and lack of control over use (r = −0.14, p = 0.03 for both correlations) (Table 6). Furthermore, the NHP dimension of social isolation was significantly negatively correlated with the HCQ dimensions of relief from withdrawal or dysphoria (r = −0.14, p = 0.04). With respect to BMT patients, the HCQ dimension of relief from withdrawal or dysphoria and the total craving score were significantly negatively correlated with almost all NHP dimensions, apart from sleep and activities of daily living. In addition, the HCQ dimension of lack of control over use was significantly negatively correlated with the NHP dimensions of emotional reactions and physical abilities (r = −0.08, p = 0.02 and r = −0.10, p = 0.01, respectively). Finally, a significantly negative correlation between total craving score and total QoL score was found (r = −0.11, p = 0.002).

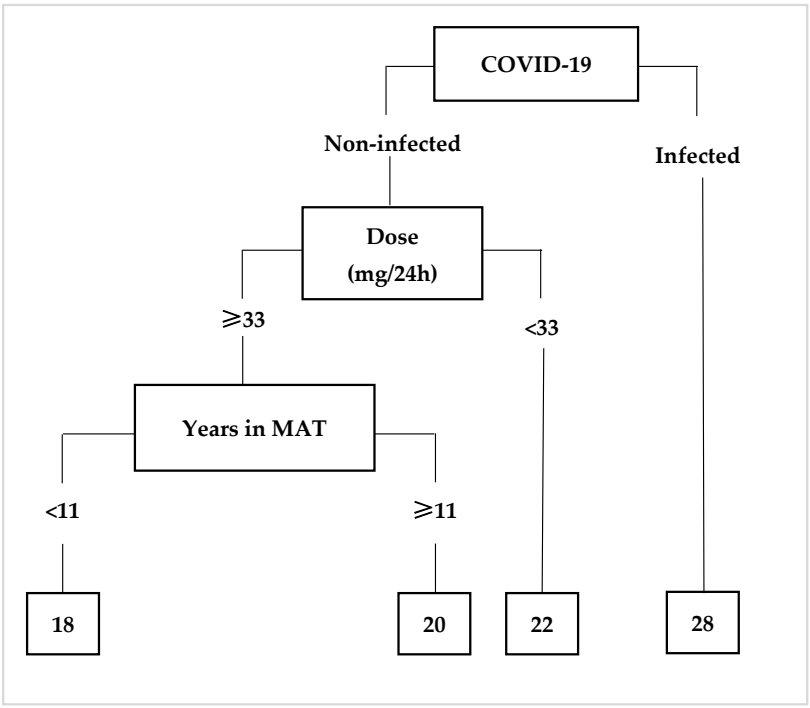
Table 6. Correlation between the NHP and HCQ dimensions in MMT and BMT patients.

NHP Dimensions		HCQ Dimensions: Desire to Use Heroin		Intentions and Planning to Use Heroin		Anticipation of Positive Outcome		Relief from Withdrawal or Dysphoria		Lack of Control Over Use		Total Craving Score	
		MMT	**BMT**	**MMT**	**BMT**	**MMT**	**BMT**	**MMT**	**BMT**	**MMT**	**BMT**	**MMT**	**BMT**
Energy level	r	−0.02	−0.03	−0.04	0.04	−0.01	−0.04	−0.04	−0.10	−0.006	−0.03	−0.05	−0.08
	p *	0.74	0.44	0.57	0.27	0.79	0.29	0.50	**0.01**	0.89	0.38	0.48	**0.04**
Pain	r	−0.01	−0.05	−0.05	0.02	−0.01	−0.03	−0.03	−0.09	0.009	−0.07	−0.006	−0.10
	p *	0.78	0.24	0.46	0.56	0.84	0.36	0.59	**0.02**	0.89	0.06	0.95	**0.01**
Emotional reactions	r	−0.08	−0.03	−0.04	0.02	−0.01	−0.03	−0.14	−0.09	−0.14	−0.08	−0.13	−0.11
	p *	0.20	0.37	0.46	0.59	0.80	0.41	**0.03**	**0.01**	**0.03**	**0.02**	0.05	**0.004**
Sleep	r	−0.06	−0.05	−0.07	0.02	−0.004	−0.02	−0.12	−0.06	−0.13	−0.01	−0.08	−0.07
	p *	0.33	0.18	0.27	0.52	0.94	0.49	0.06	0.10	0.05	0.65	0.24	0.05
Social isolation	r	−0.12	−0.05	−0.01	0.03	−0.02	−0.04	−0.14	−0.09	−0.10	−0.05	−0.13	−0.10
	p *	0.07	0.17	0.78	0.04	0.70	0.23	**0.04**	**0.02**	0.14	0.14	0.05	**0.009**
Physical abilities	r	−0.01	−0.02	−0.02	0.04	−0.03	−0.04	−0.10	−0.10	−0.05	−0.10	−0.07	−0.11
	p *	0.86	0.59	0.70	0.28	0.57	0.33	0.13	**0.01**	0.40	**0.01**	0.29	**0.007**
Activities of daily living	r	−0.05	0.009	−0.04	0.002	0.003	−0.04	−0.10	−0.05	−0.12	−0.03	−0.11	−0.04
	p *	0.45	0.81	0.51	0.94	0.96	0.22	0.13	0.13	0.05	0.37	0.10	0.28
Total QoL Score	r	−0.06	−0.04	−0.05	0.03	−0.01	−0.05	−0.11	−0.10	−0.08	−0.06	−0.09	−0.11
	p *	0.31	0.25	0.43	0.31	0.82	0.17	0.08	**0.004**	0.16	0.06	0.13	**0.002**

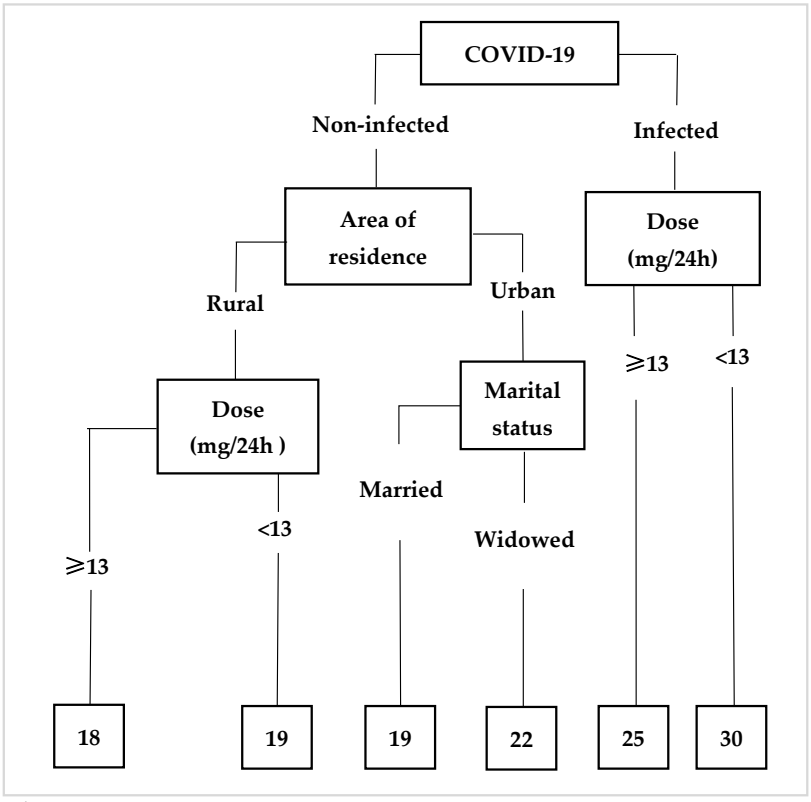
HCQ: Heroin Craving Questionnaire; NHP: Nottingham Health Profile; MMT: patients under methadone maintenance treatment; BMT: patients under buprenorphine maintenance treatment. r: Kendal's tau correlation coefficient. * Results through comparison between NHP and HCQ dimensions. Bold numbers indicate statistically significant correlation (p < 0.05).

3.5. Regression of Craving with Demographic Data

According to the regression tree for MMT patients (Figure 1a), the total craving score appears to be determined by COVID-19 infection, since the infected patients had the higher craving level (i.e., score equal to 28) in comparison to the non-infected. Among the latter, the dose of methadone is a determinant, as those who receive a dose lower than 33 mg/24 h have a higher level of craving (i.e., 22) than those who receive higher doses. For the patients of the second category, the number of years of attending MAT programs determines the total craving score, since the patients with less than 11 years have the lowest score (i.e., 18), which equates to a lower craving level.



(a)



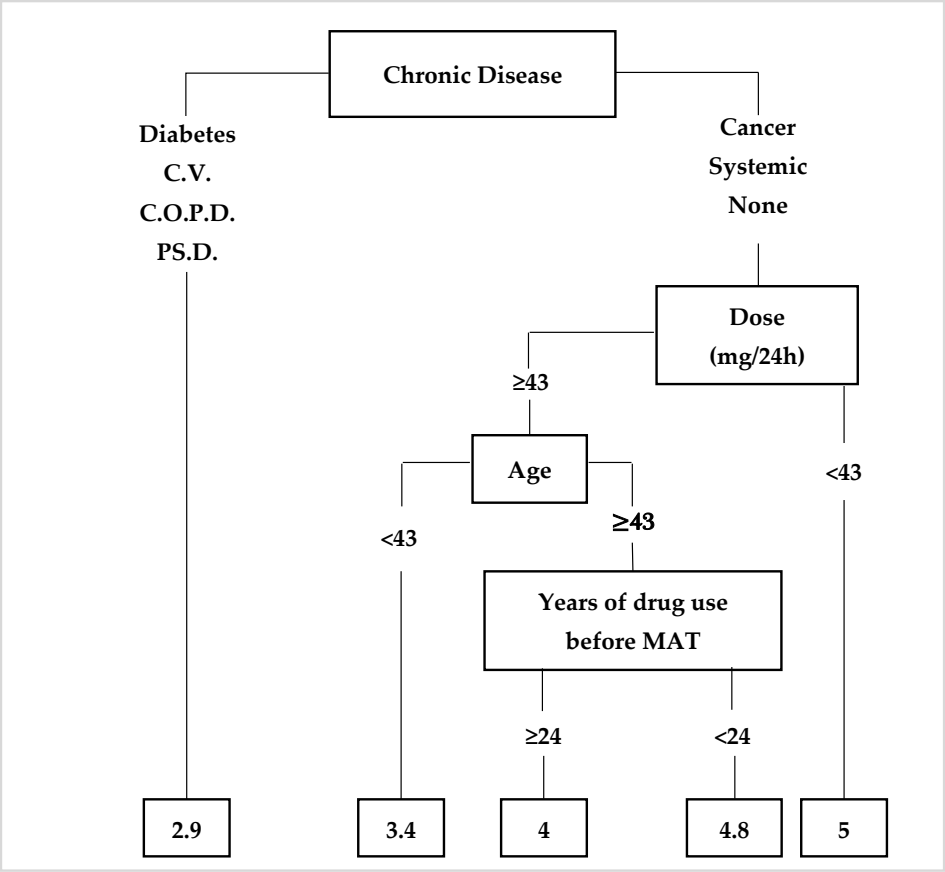
(b)

Figure 1. Regression trees indicating determinants for craving on MMT (**a**) and BMT (**b**) patients. MMT: patients under methadone maintenance treatment; BMT: patients under buprenorphine maintenance treatment; MAT: medication-assisted treatment. The main determinant was COVID-19 infection in both MMT and BMT participants, since infected patients had a higher craving score level than their non-infected counterparts.

For BMT patients (Figure 1b), COVID-19 infection is also the main determinant of craving. The craving score of the infected patients is equal to 25 or 30, depending on whether they receive a buprenorphine dose higher or lower than 13 mg/24 h, respectively. Concerning the non-infected participants, the area of residence mainly determines the total craving score. Citizens of rural places have a lower craving (i.e., score equal to 18 or 19, depending on whether they receive a buprenorphine dose higher or lower than 13 mg/24 h) than their counterparts in urban areas. For the latter, marital status seems to determine craving. Indeed, married patients have a lower craving (i.e., score equal to 19) than widowed, separated, or divorced participants, whose craving is higher (i.e., score equal to 22). The regression trees of Figure 1 show MMT and BMT achieve an MAE on the test set equal to 1.92 and 2.57, respectively.

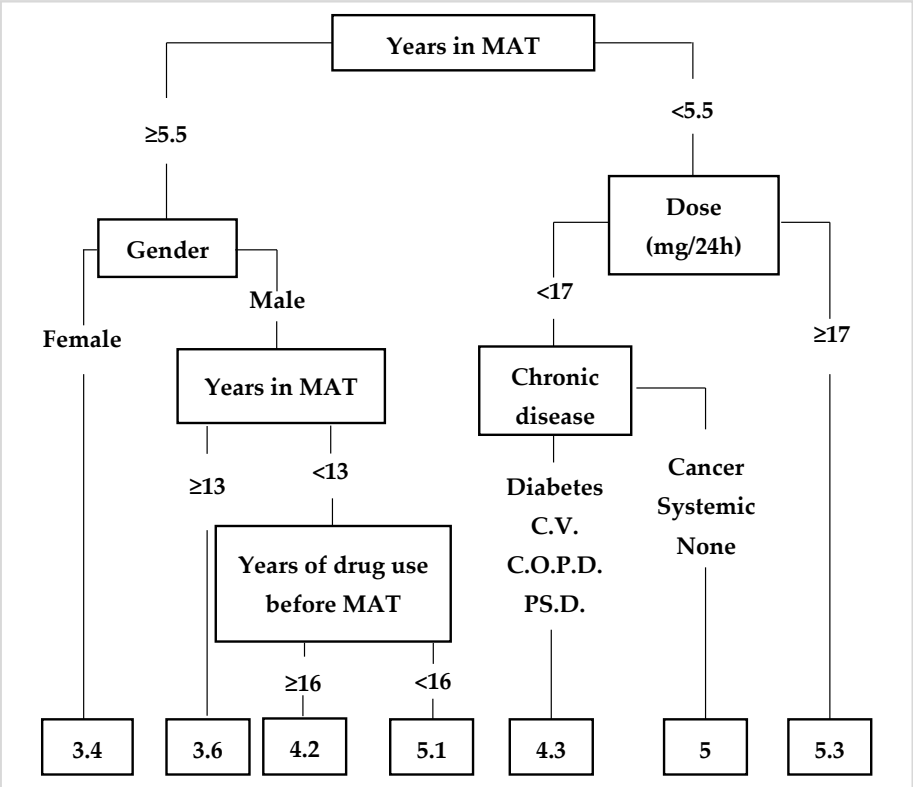
3.6. Regression of Quality of Life with Demographic Characteristics

In regards to the regression tree for MMT patients (Figure 2a), chronic illness is the primary factor that determines QoL. The patients with diabetes, cardiovascular disease, or COPD have the lowest score (lowest QoL), whereas QoL of patients with other chronic illnesses (i.e., cancer or a systemic disease) or none depends on methadone dose. Thus, those who receive a methadone dose lower than 43 mg/24 h have the best QoL score (i.e., 5), whilst those who take methadone in a dose greater or equal to 43 mg/24 h, and are younger than 43 years of age, have a lower QoL score (i.e., 3.4) than their older counterparts. Among the patients who are 43 years old or older, the number of years of opioid use prior to their admission in MAT programs plays an important role in QoL. Indeed, MMT patients who used opioids for less than 24 years achieve a better QoL score (i.e., 4.8) compared to those who use opioids for more than 24 years (i.e., 4).



(a)

Figure 2. *Cont.*



(b)

Figure 2. Regression trees indicating determinants for quality of life on MMT (**a**) and BMT (**b**) patients. MMT: patients under methadone maintenance treatment; BMT: patients under buprenorphine maintenance treatment; MAT: medication-assisted treatment; C.V.: cardiovascular disease; C.O.P.D.: chronic obstructive pulmonary disease; PS.D.: psychiatric disorders. The primary determinant for QoL on MMT patients was chronic disease whereas on their BMT counterparts was years in MAT programs.

For BMT patients (Figure 2b), years in MAT is the main determinant for QoL. The patients with less than 5.5 years in MAT achieve a better score than those with 5.5 or more years in MAT. In further detail, buprenorphine dose affects QoL of the patients with less than 5.5 years in MAT programs, since those with a dose equal to or greater than 17 mg/24 h have better QoL (i.e., score equal to 5.3) than their counterparts. For patients who receive a dose of buprenorphine lower than 17 mg/24 h, chronic illness is a determinant of QoL. Interestingly, the patients who suffer from diabetes, cardiovascular disease, or chronic obstructive pulmonary disease have lower QoL score (i.e., 4.3) compared to those who suffer from cancer or systemic disease or none (i.e., 5). Moreover, concerning the BMT patients who attend MAT programs for 5.5 years or more, gender seems to highly determine QoL. Female patients have the lowest score (i.e., 3.4), whereas, regarding male patients, QoL score seems to be determined by the years of participation in MAT programs. Those who participate in MAT programs for 13 years or more have a lower QoL score (i.e., 3.6) than those with less than 13 years. Notably, the QoL score of the latter is governed by the years of drug use before admission in MAT, since those that used drugs for less than 16 years have a better QoL score (i.e., 5.1) than their counterparts with 16 or more years in drug use (i.e., 4.2). These regression trees of QoL in MMT and BMT patients achieved a mean absolute error (MAE) on the test set equal to 1.06 and 1.20, respectively.

4. Discussion

This investigation highlights the severe impact of the COVID-19 pandemic on psychosocial parameters of patients with OUDs receiving MAT, while also examining the issue of medication dose. According to the findings, the patients who were infected by SARS-

CoV-2 had higher levels of craving compared to their non-infected counterparts, regardless of MAT. Furthermore, the patients who received medium doses of either buprenorphine or methadone had lower craving than the others. For QoL, the patients under OUDs had worse QoL compared to the healthy volunteers. Unlike craving, QoL was not affected by SARS-CoV-2 infection. Moreover, the patients who received a low or medium MAT dose had better QoL. Finally, suffering from COVID-19 was the main determining factor for craving both in MMT and BMT patients, whereas chronic disease in MMT patients and the years attending MAT programs for their BMT counterparts were key determinants for QoL.

The COVID-19 pandemic, due to restricted measures with repeated lockdown and quarantine periods, detrimentally affected the life of patients with OUDs and led to increased anxiety and craving [31,32]. SARS-CoV-2 infection induces release of cytokines, which are positively correlated with craving, drug-seeking behavior, and relapse [17,33]. Thus, it appears that the detrimental effects of COVID-19 on craving observed herein have a biochemical footing. An important issue herein is that of medication dose, since a medium MAT dose is equal to low levels of craving. Scarce evidence from the literature has demonstrated that methadone doses of 60 mg or higher are considered more effective than lower doses in increasing patient retention in treatment and reducing drug-seeking behavior [34,35]. These findings are consistent with those of our study and with others reporting that higher buprenorphine doses (i.e., 8 mg or higher) were more effective on craving reduction [36].

With the aim of offering clinically significant observations, a regression was performed and determinant factors for craving were revealed. It seems that SARS-CoV-2 infection plays the main role in the prediction of craving, both in MMT and BMT patients. Concurrently, factors such as area of residence and medication dose are also important. These results are in line with previously published findings, according to which the dose of medication and the distance from rehab centers affect the retention in treatment and patients' craving [37]. In addition, results during the pandemic have indicated that geographical distance and the restrictions on traveling magnified the risk of relapse on OUD patients who lived in rural areas, due to limited access to treatment, therefore increasing the risk of overdose [38,39].

Concerning QoL, the fact that patients receiving MAT showed compromised QoL compared to the healthy population has been reported previously, but not in the context of a pandemic crisis [40]. Patients with prolonged opioid use are more likely to present unstable social interactions associated with negative emotional reactions, and to experience loneliness suffering from stigma-based social isolation and exclusion [41]. This negative emotional condition is accompanied by stress and sleep dysregulation, relating to craving and relapse [42,43]. Notably, the fact that QoL of both infected and non-infected groups was affected similarly implies that the restricted measures for the COVID-19 pandemic affected the patients to a greater extent than the virus itself. Interestingly, COVID-19 restriction measures have induced a strong impact on aspects related to QoL, such as physical mobility, sleep, and social isolation of mentally ill patients [44]. In terms of medication, a high methadone dose induced sleep disturbances and social isolation. Even though there is no evidence in MMT patients, a correlation between daily methadone dose (>72.5 mg/24 h) and sleep disorders has been reported [45]. Although there are no available results in BMT, a previous study has shown that a low dose of buprenorphine decreased social rejection and increased ratings of social interaction in healthy adults [46]. The overall correlation of QoL with craving revealed negative relations in BMT patients, indicating a lower level of craving with high QoL. It has been shown that, in the non-COVID period, relief from withdrawal or dysphoria and lack of control over use were related with the sociability and maintenance of social networks, implying the strong relationship between craving and QoL [47]. Notably, research evidence has also demonstrated that retention in treatment is better in MMT patients than their BMT counterparts [48,49].

Regarding regression prediction models for QoL, our results showed that factors such as comorbidity and the number of years in MAT programs are the main determinants

for both MMT and BMT patients. Secondary factors, namely medication dose for both patient categories, as well as gender for BMT and age for MMT patients, are also crucial. It is obvious that patients receiving MAT need additional support for dose modification and treatment of health problems that reduce QoL, especially in severe conditions [50,51]. Additionally, before the COVID-19 era, patients with more than 10 years in MAT programs had lower QoL than patients with 7 or 8 years [50,52]. Regarding age, surprisingly the patients who were older than 43 years old showed better QoL outcomes, in contrast to previous pre-COVID-19 results, wherein increase in age was related with poorer QoL [53]. However, research studies during the COVID-19 pandemic support our result, highlighting the impact of the crisis on opioid use and drug toxicity, especially on patients younger than 40 years old with an increased rate of overdose deaths [54,55]. Furthermore, our findings indicate that female patients have worse QoL than males. This fact is attributed to the enhanced barriers they face in the health systems and the higher magnitude of stigma, compared to males, since it is more likely that they are rejected by their families and social network [50,56].

It must be noted that this study has the following limitations. First, even though a large number of volunteers participated in this study, most of them were males; thus, these study results lack generalizability given that women also experience, to a great extent, changes in their QoL [57]. Secondly, MMT patients were fewer than their BMT counterparts. This is due to the fact that the number of rehab centers with methadone as MAT is much lower than those who host patients under buprenorphine. Further research interventions with a larger number of women and MMT patients could probably partly address these limitations.

5. Conclusions

To our knowledge, this is the first study to reveal the impact of the COVID-19 pandemic and the significance of medication dose on craving and QoL of patients receiving MAT. SARS-CoV-2 infection reduced craving, which is probably the most crucial clinical parameter for assessing rehab, whereas it did not largely affect QoL. Moreover, medication dose seems to play a pivotal role in both craving and QoL, with a low or medium dose displaying superiority over a high MAT dose. Furthermore, COVID-19 is the main determinant for craving, whilst the presence of chronic diseases and the number of years in MAT programs are crucial factors for QoL prediction in MMT and BMT patients, respectively. The COVID-19 pandemic showed similar characteristics as other physical or epidemiological disasters. Indeed, it led to significant disruption of health services and increased overall stress, a factor that detrimentally affected craving and QoL of MAT patients [10]. To that end, the findings of the current investigation suggest that the modification of the medication dose is a parameter that could putatively give insight into the confrontation of similar future public health issues. It is apparent that there is a window of improvement in the conditions of MAT programs with focused interventions and modifications in contributing factors that affect craving and QoL of patients with OUDs, leading to essential harm reduction and better daily living.

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Institutional Review Board Statement: This study approved by the Nursing Department of the University of Peloponnese (Tripoli, Greece) and the scientific committee board of Greek Organization Against Drugs (OKANA) (ref. number 44482-2/11/2020). All procedures followed were in accordance with the ethical standards of the responsible committee in human experimentation (institutional and national) and with the Declaration of Helsinki 1975, as revised in 2013.

Informed Consent Statement: Written informed consent for study participation and data publication was provided by all participants before the study began.

Data Availability Statement: The data used to support the findings of this study are available upon request.

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