IMPLEMENTATION OF NICOTINE REPLACEMENT THERAPY IN PATIENTS WITH SEVERE MENTAL ILLNESS ISOLATED IN A COVID-19 SPECIFIC ACUTE PSYCHIATRIC WARD

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Covid-19 Spesifik Akut Psikiyatri Servisinde İzole Edilmiş Ağır Ruhsal Hastalığı Olan Hastalarda Nikotin Replasman Tedavisinin Uygulanması

ÖZET

Amaç: Çalışmamızın amacı, psikiyatri servisinde yatarak tedavi gören, COVID-19 tanılı, ağır ruhsal hastalığı olan ve sigara içen hastaların tedavisinde nikotin replasman tedavisi (NRT) uygulamasına ve psikiyatrik hastalık seyrine dair bir deneyim sunmaktır. Yakın zamanda yaşanan pandemi süreci de düşünüldüğünde, ağır ruhsal hastalığa eşlik eden fiziksel hastalık, enfeksiyon hastalıkları ve özellikle COVID-19 enfeksiyonu olan psikiyatri hastalarında, eş zamanlı hastalıkların ve enfeksiyonun tedavisinde daha iyi sonuçlar alınması açısından kapalı serviste yatan hastalara sigara bırakmanın önerilmesi ve hastalara tedavi desteği sağlanması büyük önem taşımaktadır.

Yöntem: Araştırmamıza ağır ruhsal hastalık nedeni ile psikiyatri servisinde yatarak tedavi gören ve COVID-19 enfeksiyonu geçiren 23 hastadan sigara içen 18 hasta dahil edildi. FNBT ile PANSS-EC'deki azalma oranı ve hastanede kalma süresi gibi değişkenler arasındaki ilişki araştırıldı.

Bulgular: Çalışmaya katılan 18 hastanın 16'sı erkek ve ikisi kadındı, 14 hasta psikotik spektrum bozuklukları, dört hasta ise bipolar bozukluk tanısı ile takip edildi. Geliş FNBT skorları ile taburculuktan sonraki 30. gün FNBT skorları karşılaştırıldığında, anlamlı bir azalma gözlemlendi.

Sonuç: Tütün kullanımının kısıtlandığı psikiyatri servisinde yatan ve sigara içen hastalarda nikotin yoksunluk belirtilerinin dikkate alınması ve NRT'nin yatarak tedavi programının bir bileşeni olarak düşünülmesi önem taşımaktadır. Ancak sonuçlarımıza göre NRT sigara bırakma tedavisinde tek başına yeterli olmamıştır. Bireysel terapi, danışmanlık ya da psikoeğitimlerle desteklenmelidir. Ayrıca araştırmamızda hastaların, COVID-19 enfeksiyonu nedeniyle akut ve dışsal bir motivasyonla hareket ederek sigarayı bırakmış olmaları taburcu olduktan sonra nüks etmelerine neden olan etkenler arasında sayılabilir. Bu nedenle, psikiyatri hastaları için kapsamlı sigara bırakma tedavisi ve NRT, pandemi sırasında ve sonrasında da yataklı tedavi programlarının ayrılmaz bir parçası olmalıdır.

Anahtar Kelimeler: COVID-19, nikotin replasman tedavisi, ajitasyon, nikotin yoksunluğu, ağır ruhsal hastalık

Implementation of Nicotine Replacement Therapy in Patients with Severe Mental Illness Isolated in a COVID-19 Specific Acute Psychiatric Ward

ABSTRACT

Objective: The aim of our study is to present our experience with the application of nicotine replacement therapy (NRT) and the course of psychiatric illness in hospitalized smokers with severe mental illness and COVID-19. Considering the recent pandemic, it is crucial to recommend smoking cessation and provide treatment support to psychiatric patients with severe mental illness accompanied by physical illnesses, infectious diseases, and especially COVID-19 infection, to achieve better outcomes in the treatment of comorbidities and infections.

Method: Our study included 18 smoking patients out of 23 with severe mental illness who were hospitalized in the psychiatric ward and had COVID-19 infection. The correlation between FTND and variables such as the rate of reduction in PANSS-EC and length of hospital stay was investigated.

Results: Two-thirds of the patients had high nicotine dependence with FTND scores ≥ 6. A significant decrease was observed when comparing baseline FTND scores with FTND scores on the 30th day post-discharge.

Conclusion: It is important to consider nicotine withdrawal symptoms in patients who smoke and are admitted to a psychiatric unit where tobacco use is restricted, and to consider NRT as part of the inpatient treatment programme. However, according to our results, NRT alone is not sufficient for smoking cessation treatment. It should be supported by motivational interviewing, individual counselling or psychoeducation. In addition, the fact that the patients in our study quit smoking with acute and extrinsic motivation due to COVID-19 infection may be one of the factors that caused them to relapse after discharge. Therefore, comprehensive smoking cessation treatment and NRT for psychiatric patients should be an integral part of inpatient treatment programmes during and after the pandemic.

Keywords: COVID-19, nicotine replacement therapy, agitation, nicotine withdrawal, severe mental illness

INTRODUCTION

Tobacco use is a significant public health concern, representing one of the most preventable causes of disability and death globally (1). Every year, thousands of people die prematurely or suffer from severe diseases due to smoking or exposure to secondhand smoke (2). Recent studies highlight smoking as a major risk factor for susceptibility to respiratory infectious diseases, heightening the likelihood of transmission, poor prognosis, and adverse outcomes, particularly in tuberculosis and COVID-19 infections (3,4). Both the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) advocate for smoking cessation or a reduction in daily consumption to mitigate the risk of harm, particularly during the pandemic (2,5).

Individuals with severe mental illness (SMI) are one of the groups that are considered at risk for the consequences of smoking. Smoking rates are very high among patients in this group, and they tend to be less informed about the long-term health risks of smoking (6). Approximately 70%–85% of patients with schizophrenia and 50%–70% of patients with bipolar disorder are smokers (7,8). Smokers with SMI may resort to nicotine as a form of self-medication to alleviate symptoms such as anxiety, irritability, agitation, and aggression (9–11). In many countries worldwide, smoking is prohibited indoors in most psychiatric inpatient units to minimize exposure to secondhand smoke, with partial smoking restriction policies implemented in some units (12–14). Nicotine restriction in psychiatric wards may lead to the onset of nicotine withdrawal symptoms such as dysphoria, irritability, agitation and insomnia, and may worsen the psychiatric condition of patients with behavioural dysregulation due to psychosis and mania symptoms (15,16).

Nicotine replacement therapy (NRT) has been demonstrated to alleviate nicotine withdrawal symptoms effectively (17,18). Additionally, previous studies have indicated that nicotine patches can mitigate agitation and aggressiveness in psychiatric patients who smoke. These patches have shown good tolerance in studies conducted by Allen et al. (15,16,19,20). Some studies suggest that NRT may reduce aggression in both smokers and nonsmokers (16). Although the underlying mechanism is not fully understood, it has been hypothesized that the reduction in agitation associated with NRT could be linked to improvements in cholinergic dysfunction (11,19). Controlled nicotine administration has been reported to alleviate cravings and withdrawal symptoms rapidly while also enhancing treatment adherence (13,20).

Seasonal or pandemic infections present a window of opportunity to counsel patients who smoke to quit (3). Especially in light of the recent pandemic, it is crucial to strongly recommend smoking cessation and offer support to patients in inpatient psychiatric wards, where the risk of transmission is elevated. Therefore, establishing a comprehensive treatment plan for smoking cessation in psychiatric inpatient units becomes crucial when implementing smoking restrictions (12,13,16). NRT emerges as a significant treatment option for managing nicotine withdrawal symptoms in acute psychiatric inpatients, potentially aiding in agitation reduction.

Our study, a descriptive research, aims to share our experiences with applying NRT and to explore the progression of nicotine dependence in SMI individuals who smoke and have COVID-19 during inpatient treatment, along with its impact on psychiatric conditions and agitation. Throughout the COVID-19 pandemic, in accordance with the recommendations of the infection control committee, patients in the COVID-19-specific acute psychiatric ward of Erenkoy Mental and Nervous Diseases Training and Research Hospital were informed and received brief psychoeducation on tobacco use. NRT was administered with their consent.

METHOD

Study Design and Sample

We conducted a retrospective case series study using data extracted from electronic records of 18 smokers who participated in the study out of 23 patients admitted to the COVID-19-specific acute psychiatric ward between April 9 and July 1, 2020. Two patients, for whom the COVID-19 diagnosis was not confirmed during hospitalization, and three non-smoking patients were excluded from the study. All patients were involuntarily admitted to the hospital due to severe acute psychotic symptoms. Due to the challenging conditions of operating in a mental health hospital, we only admitted patients who were asymptomatic or exhibited mild symptoms. Patients with severe symptoms and/or three or more COVID-19 symptoms, as well as those requiring intensive care unit treatment, were transferred to affiliated general hospitals.

Patients were administered NRT in the form of a 25-mg nicotine transdermal patch during their hospitalization. Additionally, within the first week of hospitalization, they received haloperidol, biperiden, and lorazepam for psychotic symptoms and agitation, with doses ranging from 15–20 mg/d, 5–10 mg/d, and 2–3 mg/d, respectively. Invariably, the patients also received supportive treatment, which included zinc tablets (30 mg/day), vitamin C (1000 mg/day), and vitamin D (2400 IU/day). These supplements were chosen for their roles as essential nutrients and potential fortifiers of antiviral immunity (21–23).

The COVID-19 diagnosis for each patient was determined by infectious disease specialists following the guidelines provided by the Turkish Ministry of Health. Approval for the study was granted by the Ethics Board of the Marmara University Faculty of Medicine (Approval No. 220/09/02/2024) and the COVID-19 Scientific Re-

search Review Board of the Turkish Ministry of Health.

Outcome Measure

Patients enrolled in the study underwent an evaluation of nicotine dependence severity using the FTND (24). This self-assessment scale comprises six questions, offering Likert-type measurements between 0 and 1 and 0 and 3. An FTND score ≥ 6 is categorized as high dependence. The validity and reliability of the Turkish version of the original FTND form have been reported by Uysal (25).

We utilized the PANSS-EC, derived from the original Positive and Negative Syndrome Scale (PANSS) developed to evaluate the severity of schizophrenia (26). The PANSS-EC comprises five components from the PANSS scale, namely, excitement (P4), hostility (P7), tension (G4), uncooperativeness (G8), and poor impulse control (G14). Each item is rated on a seven-point scale, where 1 indicates "absent" and 7 indicates "extreme". The validity and reliability of the Turkish version of the original PANSS form have been previously reported by Kostakoğlu (27). As PANSS-EC scores are rated on a 1–7 scale and the minimum score is 5 (indicating no symptoms), we subtracted five points before the analysis, as recommended for PANSS assessment (Leucht et al., 2010).

Data were collected on the first and seventh day of hospitalisation and on the 30th day after discharge. The Fagerström test and PANSS-EC were administered on the first day of hospitalisation. After assessing the degree of nicotine dependence on the Fagerström test, patients were subsequently treated with NRT accordingly. The PANSS-EC was repeated on the seventh day. The Fagerström test was repeated on the 30th day after discharge.

Statistical Analysis

Statistical analysis was performed using SPSS 20.0 statistical software. Descriptive statistics, frequencies, and rates were calculated for both continuous and categorical sociodemographic and clinical variables. A paired t-test was used to compare the baseline and 30th-day FTND scores after discharge, as well as the baseline and seventh-day PANSS-EC scores. Partial correlation analysis was conducted to explore the correlation between variables such as the baseline FTND, the reduction rate (%) of PANSS-EC, and the duration of hospitalization. This analysis controlled for chlorpromazine drug equivalent doses, as antipsychotic doses may impact the reduction rate of PANSS-EC scores and hospitalization duration. A p-value lower than 0.05 was deemed statistically significant.

RESULTS

Out of the 18 patients enrolled in the study, 16 were males and two were females, with a mean age of 38.9 ± 12 years. The most common diagnosis was an acute episode of schizophrenia (33.3%, n=6), followed by schizoaffective disorder (n=4), bipolar disorder (n=4), atypical psychosis (n=3), and brief psychotic disorder (n=1). Fourteen patients were admitted with a diagnosis of psychotic spectrum disorders, and four with bipolar disorder. Psychiatric diagnoses were established based on the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) criteria (29). The average duration of hospitalization was 29.2 days (SD=18.9), and the chlorpromazine drug equivalent dose ranged from 200 to 900 (mean=616.6; SD=191.7).

Two-thirds of the patients had FTND scores of ≥ 6, indicating high nicotine dependence. On the first day, PANSS-EC scores ranged from 2 to 28 (mean=16.9; SD=7.8), and on the seventh day, they ranged from 0 to 22 (mean=10.1; SD=6.6). The sociodemographic and clinical data of the sample are presented in Table I. The PANSS-EC scores decreased in nearly all patients by the end of the first week (16.9±7.8 vs 10.1±6.7; t: 7.542; $p<0.001$). The mean reduction rate (%) in PANSS-EC score was 43.1% (median=42.5; SD=25.2) on the seventh day.

Four patients (22.2%) exhibited a reduction of less than 25% in PANSS-EC scores. Seven patients (38.9%) demonstrated a reduction rate of 25%–49%, six patients (33.3%) fell within the 50%–74% reduction range, and a reduction of more than 75% was observed in only one patient. All patients experienced recovery from COVID-19 without serious complications, and the majority showed positive outcomes for psychiatric conditions.

Considering that antipsychotic drugs may influence PANSS-EC scores, duration of hospitalization, and FTND scores, we conducted a partial correlation analysis while controlling for chlorpromazine drug equivalent doses. We identified a moderate positive correlation between baseline FTND scores and the reduction rate in PANSS-EC scores, as well as a moderate negative correlation between baseline FTND scores and the duration of hospitalization. Both of these correlations were statistically significant. The data for the partial correlation of baseline FTND, reduction rate of PANSS-EC, and duration of hospitalization are provided in Table II.

On the 30th-day assessment after discharge, patients were evaluated for both their smoking status and psychiatric condition. All patients were found to have relapsed into smoking after discharge, with 44% having FTND scores of 6 or higher. When comparing the baseline FTND scores (mean=6.3; SD=2.1) to the FTND scores on the 30th day after discharge (mean=5.7; SD=2.2), a significant decrease was observed (t: 2.829; $p<0.01$).

DISCUSSION

The key findings of our study are as follows: (i) those with higher nicotine dependence levels during inpatient care saw greater reductions in agitation; (ii) individuals with higher nicotine dependence had shorter hospital stays;

(iii) every patient who received NRT experienced a relapse post-discharge; and (iv) despite resuming smoking, patients displayed notably decreased levels of nicotine dependence.

The sociodemographic and clinical characteristics of the sample revealed that our patients were predominantly middle-aged males with SMI and high nicotine dependence. The majority of the patients were diagnosed with psychotic spectrum disorders, with schizophrenia being the most prevalent. Our results revealed that patients with higher levels of nicotine dependence who received NRT had significantly higher reduction rates of agitation. This finding holds particular significance, as agitation is commonly associated with nicotine withdrawal symptoms (15). In a randomized controlled trial, Allen et al. reported that NRT decreased levels of agitation in patients with schizophrenia. The NRT group had a 33% greater reduction in agitation at 4 hours and a 23% greater reduction at 24 hours than the placebo group. Moreover, individuals with lower FTND scores demonstrated greater responsiveness to NRT in terms of agitation (16). The inconsistency in findings regarding baseline FTND scores and reduction rates in agitation in our study may be attributed to several factors, such as the differences in the clinical characteristics of the study samples and methodologies. Allen et al.'s study was conducted in an emergency service setting, likely with patients who did not require hospitalization, and assessed agitation reduction within the first 24 hours. By contrast, our sample consisted of acute psychiatric inpatients with severe symptoms who were involuntarily hospitalized, and agitation reduction was evaluated on the seventh day of hospitalization. In another study, Prochaska et al. reported that psychiatric inpatients who smoked and did not receive NRT exhibited higher levels of irritability and agitation compared to nonsmokers and smokers who received NRT (13). Additionally, two case report articles, one involving a patient with autism and the other involving two patients with dementia, indicated reduced agitation with a 21-mg nicotine transdermal patch (19,30). Our findings corroborate previous studies, suggesting that NRT has a positive impact on alleviating agitation in psychiatric patients with SMI during nicotine withdrawal.

Baseline nicotine dependence scores were observed to have a negative correlation with the duration of hospitalization. In patients with a higher level of nicotine dependence, NRT may have played a role in improving agitation, which is closely associated with better outcomes in mental illness and shorter hospital stays during nicotine withdrawal. (31). The mean chlorpromazine equivalent dose calculated in our study was 616.6±191.7. Smoking has been associated with the need for increased drug doses in patients with schizophrenia (32). Polycyclic aromatic hydrocarbons resulting from smoking are well-known to induce the metabolism of antipsychotic drugs through enzyme induction, leading to decreased plasma levels of antipsychotics. Enzyme synthesis for the induction of drug metabolism is typically completed two weeks after smoking cessation (10). Our findings on drug equivalent doses are consistent with studies that have reported significantly higher antipsychotic doses in psychiatric patients who smoke (33,34). We also found no significant relationship between nicotine dependence levels and drug equivalent doses. This observation can be explained as follows: the quantity of nicotine taken by the patient, which induces hepatic enzymes, may not directly correlate with the level of nicotine dependence. There is extensive interindividual variation in cytochrome enzyme activity and the rate of metabolism of nicotine and other psychopharmacologic agents (35).

Outcome in Smoking

All patients in our sample reported upon examination on the 30th day after discharge that they had stopped using nicotine transdermal patches and had resumed smoking. However, we noted a significant decrease in the severity of nicotine dependence levels. Patients may engage in self-medication for negative symptoms, reducing anxiety and social inhibition, and improving behavioral arousal and relaxation through nicotine consumption (36). Those with positive symptoms and aggression may use higher doses of cigarettes to induce sedation, as nicotine exerts an increasing effect on dopamine concentration in the striatum (37).

Previous studies have indicated that patients with mental illness, especially those with schizophrenia, are less likely to quit smoking (6). Another study looked retrospectively at smoking cessation outcomes in hospitalised psychiatric patients and found that smoking cessation rates were lower in psychiatric patients than in other patients (38). In a case series presented during the COVID-19 pandemic, three psychotic patients received NRT and counselling, were informed about the increasingly risky consequences of smoking, and the patients quit smoking (39). It was concluded that the effects of COVID-19 are an important motivational factor for smoking cessation, especially in people with severe mental illness (39). However, it is not known how long this abstinence lasted, as the long-term results of this case series were not reported.

Although all patients in our study resumed smoking after being discharged, it was observed that the level of addiction had decreased. Post-discharge relapse could be linked to the external motivation that led patients to quit smoking due to the dangers of COVID-19 infection. The spread of misinformation in the media suggesting that smoking can protect against COVID-19 may have encouraged individuals to continue smoking during this time. Furthermore, the heightened vulnerability of these individuals to the challenges of quitting may contribute to the elevated rates of relapse during stressful periods like the pandemic (40). However, given that smoking is a major cause of ex-

cess mortality in people with SMI, the reduction in nicotine dependence observed in our patients after discharge is an extremely important outcome (41,42). The hospital setting is a promising setting for smoking cessation treatment of inpatient psychiatric patients. However, further studies are needed to identify adjunctive treatment approaches for long-term abstinence (38). Indeed, due to the challenging conditions of a COVID-19-specific acute psychiatric ward, we may have overlooked the importance of implementing a detailed smoking cessation program. Therefore, we recommend that smoking cessation treatment and NRT be included as integral parts of inpatient treatment programs for psychiatric patients both during and after the pandemic, with the aim of achieving better outcomes.

This study has several limitations. Due to its retrospective design, the sample size is small as the study focused on a specific population of acute psychiatric inpatients with COVID-19. Also, the lack of a control group prevented the comparison of the effectiveness of NRT. Additionally, this helps avoid making broad conclusions based on the findings.

CONCLUSION

To the best of our knowledge, this is the first study to present the experience of NRT administration during inpatient treatment of acute psychiatric inpatients with SMI and COVID-19 who smoke and to investigate its effect on nicotine dependence. According to the results of our study, NRT was unsuccessful in maintaining smoking cessation after discharge in psychiatric inpatients with COVID-19 who smoked. NRT may help reduce agitation during the withdrawal period in psychiatric patients, but may not be sufficient for smoking cessation treatment alone. Additionally, this might be related to patients' lack of motivation to quit smoking. It is important to thoroughly assess patients during the smoking cessation treatment process, addressing their motivation and tailoring treatment to their individual needs. Nicotine replacement therapy should be implemented in an inpatient programme, but should be supported by motivational interviewing, psychoeducational sessions and behavioral counselling. The findings of this study suggest that further large-scale and comparative studies are needed to determine the effectiveness of NRT in the management of agitation among psychiatric inpatient smokers with COVID-19. Therefore, the findings of our study were not able to be generalized, but were instead shared as personal experiences.

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TABLES

Table I. Sociodemographic and clinical variables

N:18	
	n (%)/Mean ±SD
Gender (n)	
Female	2(11.1)
Male	16(88.9)
Age (yr)	38.9 ±12
Education (yr)	9.2 ± 3.2
Marital Status (n)	
Single	13(72.2)
Married	2(11.1)
Divorced	3(16.7)
Habitation (n)	
Alone	5(27.8)
Family	12(66.7.4)
Homeless/Nursing Home	1(5.6)
Occupational status (n)	
Working	8(44.4)
Not working	9(50)
Retired	1(5.6)
Diagnosis (n)	
Schizophrenia	6(33.3)
Schizoaffective Disorder	4(22)
Bipolar Disorder	4(22)
Atypical psychosis	3(16)
Brief Psychotic Disorder	1(5)
Duration of illness (yr)	11 ±9,3
First episode (n)	3(16.7)
Prior psychiatric admissions (n)	4,6 (4,46)
Alcohol use (n)	2(11.1)
Substance use (n)	7(38.9)
Baseline PANSS-EC scores	16,9 ± 7,8
7th day PANSS-EC scores	10,1 ± 6,6
FTND scores at admission day	6,3 ± 2,1
FTND scores at 30th day after discharge	5,7± 2,2
Duration of hospitalization (days)	29,2 ± 18,9
Chlorpromazine drug equivalent dose	616,6 ± 191,7

FTND: Fagerström Test for Nicotine Dependence, PANSS-EC: Excited Component Subscale of the Positive and Negative Syndrome Scale

Table II. Partial correlation of the baseline FTND scores, reduction rate (%) in PANSS-EC, duration of hospitalization controlling for chlorpromazine drug equivalent doses

	FTND Scores	
	r	**p**
Reduction Rate (%) of PANSS-EC	0,559	0,02*
Duration of Hospitalization	-0,608	0,01*

*FTND: Fagerström Test for Nicotine Dependence, PANSS-EC: Excited Component Subscale of the Positive and Negative Syndrome Scale, r: partial correlation analysis, *p <0,05*