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Smoking in Schizophrenia: Dependancy Assessment, Neurobiological Aspects and Management Difficulties

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Abstract **Original Research Article**

Tobacco is the leading cause of preventable death worldwide. Numerous studies have shown that the frequency of smoking in schizophrenic patients is significantly higher than in the general population or in other psychiatric disorders, which hinders both treatment strategies and the efficacy of antipsychotics. The objectives of our study are: to highlight the prevalence of smoking in this population, to assess its dependence on nicotine, as well as to support the difficulties of its management. We conducted a cross-sectional study of 186 patients, hospitalized at Ar-razi Hospital in Salé, using the Fagerström scale, associated with a questionnaire that included age, marital status, educational level, occupation, duration of psychiatric follow-up, somatic comorbidities, current treatment, other substances used, withdrawal attempts, age of first cigarette, family history of smoking, and finally, number of cigarettes per day before and then after psychiatric diagnosis. The frequency of tobacco use in our schizophrenic patients was high. Unfortunately, these patients remain poorly aware of the harms of tobacco, hence the need to integrate a tobacco control strategy into the hospital management of schizophrenia.

Keywords: Smoking, Nicotine, Schizophrenia.

INTRODUCTION

The tobacco epidemic is one of the most serious threats ever to global public health. It kills more than 8 million people worldwide each year [1]. According to the WHO, all forms of tobacco are harmful and there is no safe level of exposure, so it remains the leading preventable cause of mortality and morbidity in North America and worldwide [2].

In the United States, it is estimated that nearly half of the cigarettes consumed in that country were consumed by people who had a mental illness in the past month. Schizophrenia remains the psychiatric disorder with the highest proportion of smokers, with a smoking-related mortality rate five times higher than that normally expected in the general population [3].

Smokers with schizophrenia not only consume more cigarettes, but also extract more nicotine per cigarette. They experience greater reinforcing effects of smoking and more severe withdrawal symptoms during abstinence than non-schizophrenic smokers. Thus, these subjects are more likely to develop nicotine dependence, and smoking cessation in them remains very difficult [4].

In this article, we will highlight the prevalence of smoking in this population, assess their nicotine dependence, and finish by discussing the neurobiological aspects of this comorbidity, the difficulties of withdrawal, and the impact of smoking on the treatment of schizophrenia and on the efficacy of antipsychotics.

METHODOLOGY

We conducted a descriptive cross-sectional study, analyzing the epidemiology and assessment of smoking in schizophrenic patients.

The recruitment of participants was carried out at the level of the hospital services of the Psychiatric Hospital Ar-razi of Salé.

The context and objectives of the study were explained to the participants, and the data collection was carried out in the respect of anonymity and confidentiality of the patients' information.

The variables of our study were organized in two groups:

- Patient variables: age, marital status, place of residence, education level and occupation.
- Illness variables: duration of psychiatric treatment, somatic comorbidities, current treatment
- Variables related to smoking: attempts to quit, age of first cigarette, number of cigarettes per day before and after psychiatric diagnosis, and finally, other substances used).

We then used the Fagerström test, which is a test to screen and quantify the level of tobacco dependence [5], consisting of 06 questions, and depending on the answers given, a score from 0 to 10 is obtained; dependence is thus judged as nil if the score is 0 to 2, low from 3 or 4, medium from 5 or 6, high from 7 or 8 and very high from 9 or 10 [6].

Inclusion criteria included meeting DSM-V criteria for schizophrenia. Exclusion criteria were inability to respond to the interview due to disorganized speech or thought content.

RESULTS

I. Sociodemographic Data:

The total number of participating patients in our study was 186, with 156 male patients (83.87%).

The age of the patients ranged from 20 to 62 years, with an average age of 34 years. 86 of our patients were single (46.24%), 62 married (33.33%), while 38 were divorced (20.43%). It was also noted that 34 of the participants in our study had stopped at elementary school (18.28%), 31 at middle school (16.67%), 63 at high school (33.87%), while 58 participants had gone to university (31.18%).

Regarding employment, only 32 patients were employed (17.20%), while 4 patients were retired (2.15%).

II. Clinical Data:

The average duration of psychiatric follow-up in our patients ranged from 1 to 35 years, with a mean duration of 13 years.

The somatic comorbidities present in our patients were diabetes, hypertension, asthma, viral hepatitis C, Chron's disease and epilepsy.

The different treatments used varied between classical neuroleptics in 58 patients (31.18%) and atypical antipsychotics in 128 others (68.81%).

The most commonly used substance was Cannabis, used by 134 of our patients who smoked (72.04%), followed by alcohol, benzodiazepines and then organic solvents.

104 of our patients had already tried to quit (55.91%), only 12 patients were able to maintain their abstinence (6.45%).

III. Tobacco dependence:

123 patients had a very strong nicotine dependence (66.12%).

The average daily tobacco consumption was 12 cigarettes per day before the onset of psychiatric symptoms, rising to 20 cigarettes per day after the psychiatric diagnosis.

92 Patients reported smoking their first cigarette within 5 min after waking up (49.47%), 58 within 6 to 30 min (31.18%), 24 within 31 to 60 min (12.90%) and only 12 waited more than 60 min before smoking the first cigarette of the day (6.45%).

137 patients reported difficulties in abstaining in places where smoking was prohibited (73.66%), 127 reported difficulties in giving up a cigarette other than the first one of the day (68.28%).

Only 16 patients reported smoking less than 10 cigarettes per day (8.60%), 102 between 11 and 20 cigarettes per day (54.84%), 20 between 21 and 30 (10.75%) and 48 patients reported smoking more than 31 cigarettes per day (25.80%).

75 patients reported smoking at closer intervals during the first hours of the morning than during the rest of the day (40.32%), and 132 reported smoking even in spite of an illness that would require them to stay in bed all day (70.97%).

DISCUSSION

I. Prevalence of smoking in schizophrenic patients:

Schizophrenia is the psychiatric condition associated with the highest risk of smoking; this risk is greater in men than in women [7, 8]. The prevalence of smoking in patients with schizophrenia, estimated to be between 64 and 79%, is significantly higher than in the general population [9].

The meta-analysis by De Leon *et al*., of 42 studies from 20 countries estimated that the mean prevalence of lifetime smoking was 62% in patients with schizophrenia (52-95% depending on the study). This prevalence is higher in men than in women (71% vs. 44%). However, the prevalence of smoking among patients with schizophrenia is lower in some countries (Japan, China, India, Turkey, Colombia), approaching that observed in the general population [10]. This may be due to different social and family situations - for

example, in India, due to strong family support, and restrictions on smoking.

II. Neurobiology of the co-occurrence of smoking and schizophrenia:

Nicotine plays an important role in smokers by modulating dopamine and glutamate transmission in the central nervous system. By directly activating nicotinic cholinergic receptors located on dopamine neurons, nicotine increases the release and turnover of dopamine in the mesolimbic system.

After chronic use, nicotine receptors become desensitized [3]. Nicotine can also stimulate glutamatergic neurons in the prefrontal cortex, which increases dopamine and glutamate activity in the basal ganglia. Some components of tobacco smoke may also increase dopamine activity by inhibiting monoamine oxidase type B, the enzyme responsible for its breakdown. A decrease of almost 40% in the activity of this enzyme can lead to a decrease in dopamine activity. Cholinergic neurons in the pedunculopontine nucleus (PPN) are in contact with dopaminergic neurons in the ventral tegmental area (VTA) through nicotinic receptors. Activation of these receptors by nicotine increases dopamine levels in the VTA, which contributes to the reinforcing effects of nicotine. Chronic activation of cholinergic neurons in the MPN may also result in over-activation of dopaminergic neurons in the VTA, thereby increasing the positive symptoms of schizophrenia. In addition, activation of the thalamus, again by the same neurons, may contribute to the disorganization of thought observed in schizophrenic subjects [3, 12].

The cholinergic neurons of the MPN could also be activated more easily in schizophrenics; this phenomenon has been associated with differences in sleep patterns observed in these individuals. Indeed, compared to healthy subjects, schizophrenics show a decrease in the amplitude and duration of delta sleep or an early onset of REM sleep, events that are related to the degree of cholinergic activity [12, 13].

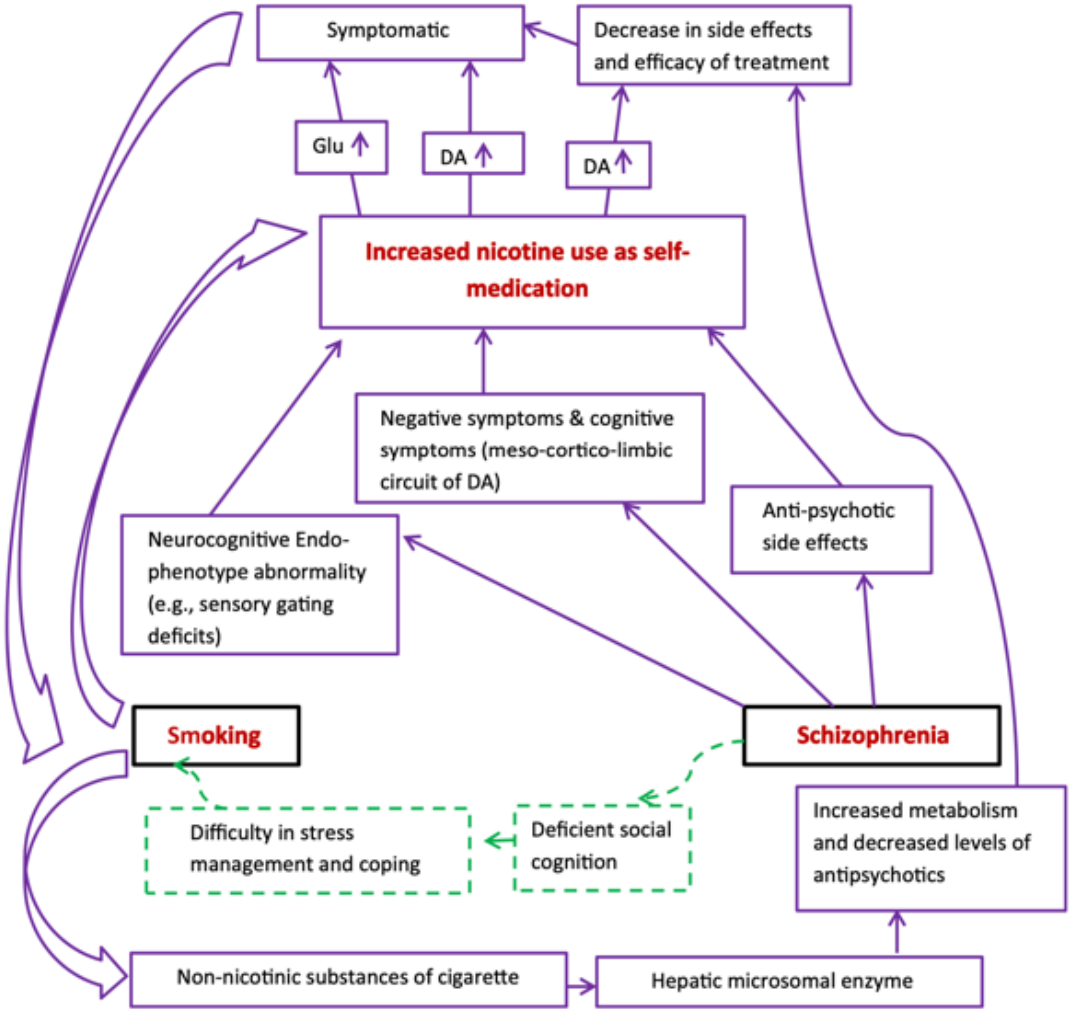

Figure 1: Neurobiology of the co-occurrence of smoking and schizophrenia.

III. Factors promoting tobacco use in schizophrenic patients:

While it was once thought that schizophrenic patients smoked mainly out of boredom or due to the lack of stimulating living conditions, several authors have suggested that tobacco use is a form of self-medication, particularly of the cognitive symptoms of schizophrenia, by promoting glutamatergic and dopaminergic transmission at the level of the prefrontal cortex.

Furthermore, nicotine could improve attention and working memory by attenuating the effects of thalamocortical dysconnectivity found in schizophrenia, notably by increasing glutamatergic transmission at the nerve endings of thalamocortical projections on the prefrontal cortex [13, 14].

Smoking could also be promoted by the administration of neuroleptic treatments, as smoking attenuates certain extrapyramidal and cognitive adverse effects induced by neuroleptics. Some authors have shown that the initiation of haloperidol treatment is followed by an increase in tobacco consumption. However, others have pointed out that smoking began in 90% of cases before the initiation of medication.

The high frequency of this comorbidity may also be related to abnormalities in brain reward circuitry in schizophrenia, which favors tobacco use.

Common genetic vulnerability factors for tobacco dependence and schizophrenia have also been reported. In families of schizophrenics, the frequency of smoking is higher in relatives of schizophrenic patients, for example 83.3% in the Lyons study. Freedman described a genetic anomaly at the gene locus encoding the alpha-7 nicotinic receptor located on chromosome [15]. This receptor is associated with decreased P50 wave inhibition in schizophrenic patients and some of their family members, which is indicative of the attentional problems found in this population and which is transiently corrected by nicotine [14, 15].

Several studies in the general population have shown that certain personality traits favor tobacco use, in particular extreme sensation seeking, disinhibition and impulsivity [3, 16].

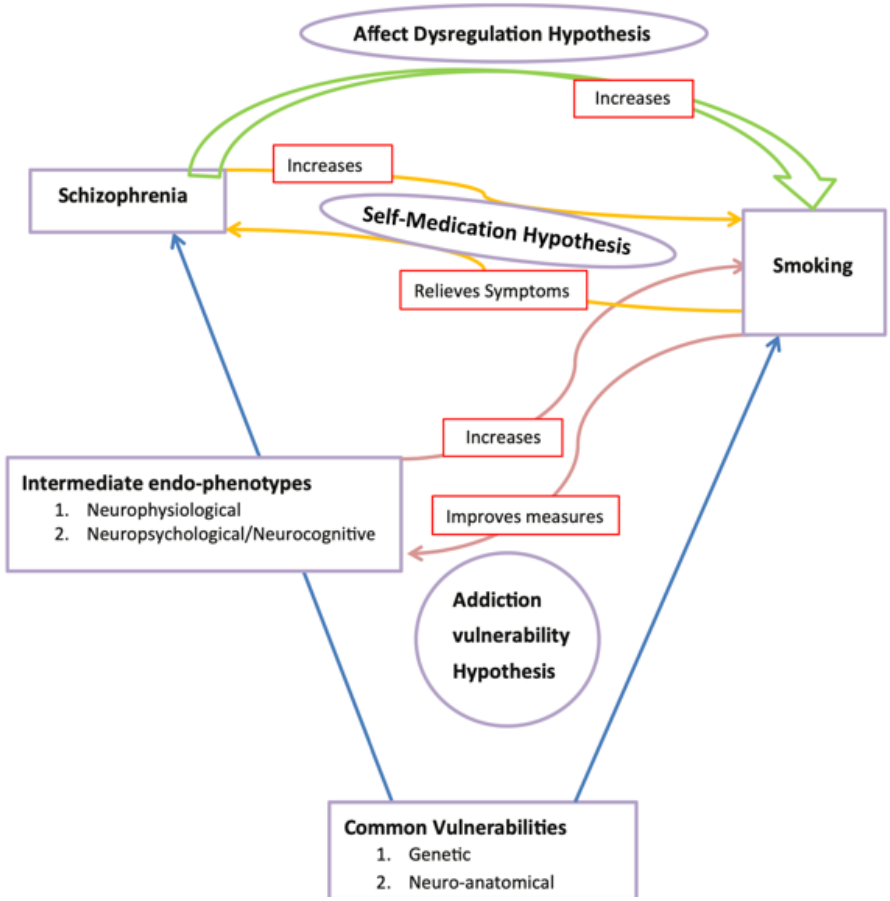

Figure 2: Factors promoting tobacco use in schizophrenic patients:

IV. Nicotine-antipsychotic interactions:

Smoking schizophrenic patients receive higher doses of antipsychotics than non-smoking patients. Some constituents of tobacco, particularly polycyclic aromatic hydrocarbons, accelerate the metabolism of antipsychotics through the cytochrome P450 CYP1A2

pathway; as a result, they decrease the blood levels, and thus the efficacy, of antipsychotics metabolized through this pathway. Dosage adjustments for antipsychotic medication should therefore be anticipated when a patient starts or stops smoking.

Several studies have shown that smoking reduces the extrapyramidal side effects of neuroleptic treatments. These effects could be related to decreased neuroleptic blood levels, increased subcortical dopaminergic transmission, and/or the action of nicotine on the gabaergic and glutamatergic systems. Thus, nicotine would improve bradykinesia and rigidity, and to a lesser extent, tremor in schizophrenic patients treated with haloperidol [17, 18].

V. Management of nicotine dependence:

A. Pharmacological treatments:

1. Nicotine substitutes:

Available in the form of transdermal devices (patches) or chewing gums, they consist of daily intakes of nicotine in progressively decreasing doses over several weeks

Abstinence rates at 12 weeks after substitution with transdermal systems are however lower in schizophrenic patients (36-42%) than in the general population (50-70%).

The Afssaps recommendations stipulate that the total duration of nicotine replacement therapy during initial smoking cessation should be between 6 weeks and 6 months depending on the patient [17].

2. Bupropion:

Mixed antidepressant, norepinephrine and dopamine reuptake inhibitor, amphetamine structure. It acts through two neuronal pathways, dopaminergic and serotonergic.

This product has proven to be a suitable therapy for smoking cessation, but its benefit-risk balance is unfavorable in smoking cessation [17].

Subjects motivated to reduce their consumption but not to stop smoking were given bupropion (300 mg/d) and ST support sessions for 14 weeks, but none of them stopped smoking [18].

3. Varenicline

A partial nicotinic receptor agonist, this drug is reported to be significantly more effective than Bupropion in aiding smoking cessation, in terms of complete abstention between the 9th and 12th week of treatment and reduction in craving. It has not been studied in a psychotic patient population and has not been reported [17].

In several studies, men not motivated to quit smoking were given varenicline (2 mg/d) for 9 weeks. At the end of the study, a reduction in daily cigarette consumption and a decrease in plasma cotinine concentration were noted. The point prevalence of abstinence at the end of treatment was 16.6%.

Administration of varenicline (2 mg/d) combined with cognitive behavioral therapy sessions for 12 weeks with a point prevalence at the end of treatment between 47.3 and 60.4% [19].

4. Combinated therapies:

Subjects motivated to quit smoking received a 3-month ST combination of bupropion (300 mg/d), 21 mg/24-hour patches, nicotine gum or tablets, and behavioral and cognitive therapy sessions.

The point prevalence of abstinence at the end of month 15 was 64.7%. The rates of continuous abstinence (4 weeks before the end of the study) and prolonged abstinence from months 6 to 12 were 58.8% and 23.5%, respectively.

The choice of medication (SN, bupropion, or varenicline) and duration of treatment depends on patient and physician preference [19].

B. Supportive psychotherapies and other supportive modalities:

1. Cognitive and behavioral therapies:

Combined with ST medications, they have been shown to be effective in smokers without psychiatric pathologies, but also in patients with schizophrenia, with improved compliance with antipsychotics, increased social skills and facilitation of the management of stressful situations. The combination of pharmacological treatment and cognitive behavioral therapy is a predictive factor for smoking abstinence [18, 20].

2. Social skill building and psychosocial management:

An enhanced program tailored to schizophrenia (with motivational enhancement, mental health education, social skills training, and relapse prevention), combined with nicotine patches and group cessation support sessions resulted in a significantly higher point prevalence of abstinence, with a significant decrease in positive and negative symptoms of schizophrenia due to increased psychosocial skills, including feelings of self-efficacy and social skills in patients with schizophrenia [20, 21].

VI. Withdrawal difficulties in patients with schizophrenia:

Smoking cessation rates are approximately two times lower in patients with schizophrenia than in the general population. 20-40% of schizophrenics report wanting to quit smoking but are unable to do so. These difficulties in achieving cessation could in fact be linked to the cognitive disorders of schizophrenia, as mentioned above. The re-learning of a life without

tobacco could also be longer in schizophrenic patients than in subjects without psychotic pathology [23].

The period of stabilization of psychiatric disorders is therefore the appropriate time to consider withdrawal. The doses of antipsychotics should be systematically re-evaluated after weaning, since it is common to observe an increase in the plasma levels of these drugs after smoking cessation, due to the removal of the interaction of tobacco related to cytochrome P450 CYP1A2 [24].

CONCLUSION

Schizophrenic patients form a population not only predominantly smoking but also more addicted than the average general population.

Nicotine is the psychoactive product responsible for the phenomenon of tobacco dependence, in the interaction with psychotropic drugs, in the participation of co-addictions (alcohol and cannabis, even coffee), in the acuity of clinical symptoms and in a possible associated anxiety-depressive state.

Smoking, which has long been tolerated and unfortunately underestimated, is under-treated by health care providers.

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