

# Prevalence of depressive symptoms in a large series of smokers intending to quit. Effective implications for clinics in the field of internal medicine

*Prevalența simptomelor depresiei într-un grup mare de fumători cu sevraj tabagic. Implicații clinice în domeniul medicinei interne*

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## Abstract

**Background.** The association linking nicotine addiction with depression is known, described and clinically significant. Tobacco addiction has much in common with the dependence on illegal drugs, but it results significantly a more lethal factor. When compared with the general population, patients with depression smoke two times more, and among this population there was not noticed any downward trend in the prevalence of smoking as it is widely reported in the general population. The bond between smoking and depressive disorders is complex. While some studies indicate that no significant relapse has been observed during the cessation in patients with a history of affective disorders, others underline the development of an increased risk of manic episodes and/or recurrent depression during the 6 months following smoking cessation. The current guidelines do not suggest specific assessments with diagnostic screening for depression, nor do they consider the utility of an eventual anti-depression treatment prior to the smoking cessation intervention, although having quite a few anti-depressive drugs among those used as first and second choice treatment for smoking cessation. The aim of the study is to assess the prevalence and the degree of depression at baseline of a large cohort of smokers intending to quit.

**Methods.** A cross-sectional investigation was carried out on a population of 1110 smokers attending the Medical Service at Verona University Hospital. The degree of nicotine addiction was measured by the Fagerstrom Test of Nicotine Dependence (FTND) and current mood tested by the Self-rating Depression Scale (SDS), a commonly used and well validated instrument to assess depressive mood.

**Results.** 132 subjects (12%) were depressed at baseline (SDS test score  $\geq 50$ ). Bivariate analysis, using the SDS score dichotomised at the cut-off of 50 as dependent variable, shows that female gender and degree of nicotine dependence were correlated to depression.

**Conclusions.** The study showed a high degree of pre-treatment depression in smokers intending to quit. Although the association between depression and nicotine dependence has been consistently reported many times, and it is well known that depressed subjects may encounter more difficulty to quit, most guidelines do not seem to consider this issue. These findings suggest the need for baseline assessment of depression by screening all smokers seeking assistance in quitting.

**Keywords:** smoking cessation, nicotine, treatment, depression, gender, SDS

## Rezumat

**Context general.** Asocierea dintre dependența de nicotină și depresie este cunoscută, descrisă și cu semnificație clinică. Adicția de nicotină este foarte asemănătoare cu dependența de alte droguri ilegale, dar generează consecințe posibil letale. Pacienții cu depresie fumează de două ori mai mult decât populația generală, iar în rândul lor nu s-a observat tendința de scădere a prevalenței fumatului, așa cum se raportează în populația generală. Legăturile dintre fumat și afecțiunile depresive sunt complexe. În timp ce unele studii nu au arătat recidive semnificativ mai multe în timpul sevrajului tabagic la cei cu afecțiuni afective, altele subliniază un risc crescut de apariție a episoadelor maniacale și/sau a depresiei recurente în primele 6 luni de la sevrajul de tutun. Ghidurile curente nu sugerează evaluare de screening pentru depresie, nici nu consideră necesar vreun tratament antidepressiv anterior sevrajului tabagic, deși există unele medicamente antidepressiv printre cele de linia întâi sau a doua utilizate în sevrajul tabagic. Scopul acestui studiu este evaluarea prevalenței și a gradului de depresie inițială în cadrul unei cohorte largi de fumători cu sevraj de tutun.

**Metode.** S-a efectuat un studiu cross-sectional în rândul unei populații de 1110 de fumători care s-au adresat serviciilor medicale la Spitalul Universitar din Verona. Gradul de dependență nicotinică a fost evaluat prin Testul Fagerstrom (Fagerstrom Test of Nicotine Dependence; FTND), iar starea dispoziției a fost evaluată prin Scala de depresie autoevaluată (Self-rating Depression Scale; SDS), un instrument validat și utilizat în mod curent pentru aprecierea dispoziției depresive.

**Rezultate.** 132 de subiecți (12%) erau depresivi (scorul la testul SDS  $\geq 50$ ). Analiza bivariată, utilizând scorul SDS dihotomizat cu pragul de 50 ca variabilă dependentă, a arătat că sexul feminin și gradul de dependență nicotinică erau corelate cu depresia.

**Concluzii.** Studiul a arătat o prevalență ridicată a depresiei anterior inițierii tratamentului pentru sevrajul nicotinic la fumătorii cu intenție de a renunța la fumat. Deși asocierea dintre depresie și dependența de nicotină a fost în mod repetat raportată în numeroase studii și este bine cunoscut faptul că pacienților depresivi le este mai greu să renunțe la fumat, cele mai multe ghiduri nu par să ia în considerare acest aspect. Rezultatele recomandă necesitatea evaluării bazale a depresiei prin aplicarea de teste de screening tuturor fumătorilor care solicită consult medical în vederea sevrajului tabagic.

**Cuvinte-cheie:** sevraj tabagic, nicotină, tratament, depresie, sex, SDS

## Introduction

Tobacco is the only legalised drug that may cause death to most of its consumers<sup>(1)</sup>. There is no other dependence in which a person self administers the substance so many times by day, repeating hundreds of times the same gestures, creating a chain of behavioural automatisms, so that countless actions, environments, emotions, feelings, daily internal and external cues are related to the act of smoking cigarettes<sup>(2,3)</sup>. Smoked nicotine quickly reaches the targeted brain areas, permitting the smoker to have an excellent control on the desired effect of the drug. By means of the frequency and the depth of the inhaled smoke, the smoker can calibrate, in a kind of self treatment, the substance, depending on the psychological and physical needs of the moment: more nicotine if the smoker feels nervous, and the answer will be a relaxing effect; less nicotine but in a more constant manner, if one looks for a mild stimulating outcome, and a positive modulation of his or her mood. In fact, nicotine, on one hand, increases the feeling of well-being, producing both activation and relaxation, helping to maintain concentration, controlling both appetite and weight<sup>(2,4)</sup>; and on the other hand, however, smoking is frequently associated to depression, which is co-present in smokers in the rate of 22-61%, compared to 17% in the general population<sup>(5-9)</sup>. The association between depression and cigarette smoking is known and studied for many years<sup>(10-12)</sup>. Compared to non smokers, daily smokers show more depressive symptoms<sup>(14)</sup>, more frequent and severe episodes of depression, higher rates of suicidal ideations<sup>(15-18)</sup> and of suicide<sup>(16-18)</sup>. Smokers with a history of depression who attempt to stop smoking have a higher risk of failure than non-depressed smokers. Anecdotal and post-hoc data suggest that those who abstain are at increased risk of depression compared with individuals who continue to smoke.

However, these studies confound effects of abstinence and history of depression<sup>(19)</sup>. Depression may be frequently associated to abstinence because tobacco smoke contains also MAO inhibitors (I-MAO). MAO inhibition fosters the synaptic presence of neurotransmitters such as dopamine, serotonin, norepinephrine, which play an important role for feelings such as pleasure and well-being. Also, nicotine stimulates the effect of antidepressant tricyclic drugs which have a similar effect on the same neurotransmitters; however, the association between tobacco smoke and depression does not enlighten the direction of the causal bond<sup>(20-22)</sup>. Surely, individuals who suffer from anxiety or depression disorder are at a two-fold higher risk to become regular smokers<sup>(23,24)</sup>, but tobacco dependence at turn enhances the onset of symptoms of depression<sup>(4,25)</sup>. The bonds between depression and tobacco use disorder (TUD) are of neurobiological and behavioural nature. Abstinence from tobacco smoke may enhance depressive-like symptoms or the onset of clinical depression, which may be a higher risk for those who already had a history of depressive episodes<sup>(11,26)</sup>.

Depression reduces the probability of smoking cessation, worsens withdrawal symptoms and increases the risk of relapse<sup>(27,28,30,50)</sup>. In economically developed countries, major depression is more frequent among females, particularly of Caucasian race, middle aged, severely overweight (BMI $\geq$ 30), in poor economical conditions, in smokers and in individuals with former diagnosis of major depression<sup>(29,31,36)</sup>. For women, depression is one of the main causes of disability. Epidemiological studies constantly underlined that lifetime prevalence of major depression in women is at least two times higher than in men. This ratio is found in many different countries and ethnic groups. This gender disparity appears around the age of ten, and is constant until around the age of fifty, when it begins to vanish<sup>(36)</sup>. The risk factors for depression are related to patterns that are not yet fully clear. Even if numerous, and sometimes debated, the reasons of this higher prevalence of major depression in females are grouped, for simplification, in two areas: biological factors (genetic, hormonal) and psychosocial factors. Estrogens expose women to a higher vulnerability for the initiation and the maintenance of tobacco smoking dependence, whereas progesterone seems to have a protective role<sup>(32,33,34)</sup>. Studies that aimed to schedule "quit days" according to the menstrual cycle phases gave contradictory outcomes<sup>(32,35)</sup>. More frequently than for males, the need to smoke in females is associated with a reduction of the mood, sadness, anxiety, solitude, uncertainty, anger and frustration. Smoking helps to cope with unpleasant situations, nervous states and stress<sup>(37-39)</sup>.

Even if they show an average less pharmacological dependence for nicotine than men, women have more trouble quitting to smoke and have poorer compliance towards cessation treatments<sup>(39-41)</sup>. The guidelines do not give precise indications on the utility of an eventual anti-depressant treatment before the smoking cessation intervention. However, almost paradoxically, for the treatment of tobacco dependence there are used antidepressant drugs such as bupropion (first choice) or amitriptylin (second choice)<sup>(28,42)</sup>, although varenicline has shown to be efficient and safe even for patients with depression, in spite of being an antidepressant drug<sup>(26,43)</sup>.

## Purpose of the study

Clinical experience shows that individuals who seek help to nursing services for tobacco cessation are quite willing to talk about their motivations, or eventual physical harm, present or feared, consequences of smoking, but they are less willing to talk about their emotional state.

Assessing systematically, with agile tools, the presence of depression symptoms in individuals with tobacco use disorders, and correlating them to gender difference and severity of addiction, could be an adequate assessment and improves the efficacy of interventions of the services that treat tobacco use disorders. From 2006 to 2016, many people who desired to quit smoking addressed to the Smoking Cessation ambula-

tory, managed by the Medical Ward of the University and Hospital of Verona. The purpose of this study was to gather homogeneous data of this population, focusing upon:

- the rate of nicotine addiction;
- the presence and severity of depressive symptoms at the acceptance, measured by a screening test;
- the evaluation of possible correlations between depressive symptoms, rate of nicotine dependence, gender and other demographic aspects.

## Materials and methods

The data was gathered in the Medical Service from outpatient folders opened from January 2006 to June 2016. The group admitted to the study is composed by a population of 1110 smokers willing to quit smoking. Patients were assessed at the entry and individually followed-up in a time interval of 8-12 weeks. We noted from the outpatient folders homogeneous data such as:

- personal data (age, sex);
- scholarship, professional condition;
- marital status (unmarried; separated/divorced, widow);
- comorbidities, use of prescribed drugs;
- cohabitation with other smokers;
- level of nicotine dependence;
- age of onset;
- previous attempts to quit smoking, length of eventual abstention period;
- mood evaluation.

## Results

Out of 1,110 patients, 663 were males (59.73%) and 447 were females (40.27%). The average age was 48.75 years old.

**Table 1** The presence of depressive symptoms (Zung SDS>50) in absolute values and as percentage

Gender	No	Yes	Total
Males	603 (91.50%)	56 (8.50%)	659 (100%)
Females	369 (82.92%)	76 (17.08%)	445 (100%)
Total	972 (88.04%)	132 (11.96%)	1104 (100%)

P Value=0.05; In six cases, the test was invalidated.

A significant difference between the two genders was found: 8.5% for males and 17.08% for females (p=0.05).

**Table 2** The Severity of depressive symptoms (Zung Score SDS) in absolute values and as percentage

Gender	Mild	Moderate	Severe
Males	48 (85.71%)	7 (12.50%)	1 (1.79%)
Females	59 (77.63%)	15 (19.74%)	2 (2.63%)
Total	107 (81.06%)	22 (16.67%)	3 (2.27%)

P Value=0.009

The severity of nicotine dependence was assessed by the Fagerstrom test (FTND). The FTND is a validated instrument, widely used, easily understood, and useful for auto-administration<sup>(44)</sup>. The test is very sensitive and specific for pharmacological dependence of medium and strong severity, and less for lower grades of tobacco use disorders. Mood levels were assessed by means of the Zung self-rating Depression Scale (SDS), a frequently used and widely validated screening instrument, auto-administrated and usually accepted by patients<sup>(45)</sup>. The test assesses the presence of depression-like symptoms, offering only indicative guidelines, and thus not considerable as a diagnostic test for depression. Its easy use in outpatient settings, however, fosters the gathering of clinical indications at the assessment, and in this study it is used only for this purpose. The Zung scale has three different outcomes:

- scores from 50 to 59: mild depression;
- scores from 60 to 69: moderate depression;
- scores from 70 to 80: severe depression.

## Data analysis

The chi-square test was used for categorical independent variable comparison, with independent samples *t*-test or analysis of variance (ANOVA) for continuous data. Logistic regression analysis was carried out to independently assess the correlation of various factors with mood. For all analyses, statistic significance was defined at 95%. Statistical analysis and data management were carried out using statistical software SPSS 11.5 (SPSS Inc., Chicago, IL).

**Table 3** FTND score in relationship with the presence or absence of depression symptoms, divided by gender, in absolute values and as percentage

	ZUNG>50	No	Yes
	FTND test score		
Males	Mild	47 (7.90%)	1 (1.89%)
	Moderate	106 (17.82%)	6 (11.32%)
	High	196 (32.94%)	16 (30.19%)
	Very high	246 (41.34%)	30 (56.60%)
	Total	595 (100%)	53 (100%)
Females	Mild	29 (7.92%)	4 (5.63%)
	Moderate	58 (15.85%)	3 (4.23%)
	High	144 (39.34%)	26 (36.62%)
	Very High	135 (36.89%)	38 (53.52%)
	Total	366 (100%)	71 (100%)

P Value=0.05

When the Zung SDS test gives positive scores, most of the studied patients show a score corresponding to a mild level of depressive symptoms (81.6%). As confirmed by literature, there is a significant prevalence of moderate depressive symptoms in women with respect to men (19.74% vs. 12.5%), and – even if the sample number is very small – women with highest scores for depressive symptoms are almost two-fold with respect to men.

There is evidence of a correlation between percentages of high Zung test scores and dependence level calculated by means of FTND test. We evidenced that the more severe was the dependence level assessed by the Fagerström nicotine dependence test, the higher in percentage were the depression symptoms; this phenomenon was equally verified in both sexes. It is interesting to know that, on the contrary, among patients who showed a mild to moderate level of dependence, the absence of depressive symptoms, with no significant differences between the two sexes, was found.

Among males, 53 patients out of 595 (8.91%) showed symptoms of depression with Zung test scores >50. Among females, the percentage was 19.3%, as confirmed by literature data. In both males and females, the presence of depression correlated with dependence severity calculated with FTND test scoring.

## Discussion

Even if well described since quite a while, little is known about the association between depression and smoking behavior by age, socioeconomic status, or race/ethnicity or with regard to the use of tobacco products other than cigarettes<sup>(30,43)</sup>. There is no full agreement in recent studies in evaluating the impact that depression has on smoking cessation processes: according to a recent review, individuals with depression have greater difficulty in quitting cigarette smoking, and community-based and public health approaches may need to begin considering the links between depression and smoking in order to target the current smokers in the

population better, and develop more effective tobacco control campaigns<sup>(30)</sup>. According to others, on the other hand, even if the finding of depressive symptoms is a common event in individuals intentioned to quit smoking, this would not give worse outcome for smoking cessation<sup>(46,47)</sup>. In our study, available data in literature is confirmed: smokers show a significant (almost two-fold with respect to the general population) prevalence of depressive symptoms<sup>(24,30)</sup>. Furthermore, we confirmed the higher prevalence of depressive symptoms in women<sup>(30,39)</sup>. The Italian 2013 PASSI report evidenced a 6.5% prevalence of depressive symptoms in the general population, with higher rates among women. Women are more sensitive than men towards social events happening in their environment, to the point that living with smokers, at home or at workplace, undermines the possibility to reach and maintain nicotine abstinence<sup>(48)</sup>. Women are more likely to think that interpersonal proximity of operators would give them important support during a smoking cessation treatment<sup>(38,39)</sup>. They tend to expect more help from emotional supporting (listening, encouragement, understanding) than from actions which target specific factors of relapse<sup>(42)</sup>. Maybe, also for this important aspect of gender vulnerability, empathic listening and motivational support are the most useful tools to personalise interventions and to cope with difficulty and resistance.

The guidelines for tobacco cessation suggest a highly pragmatic approach to help the patient to proceed through the states of change, and just as strong indications for pharmacologic therapy which include among first and second choices bupropion and amitriptylin, which are both anti-depressant drugs. But no smoking cessation guideline recommends investigating upon mood disorders. The smoking patient comes to the cessation services to quit smoking, not to move his or her internal world, not to cope with a perceived emotional distress, not for a psychotherapy, even if there is no doubt that quitting smoking entails an important change of the individual psychic world. Even with the

differences discussed above, there is a prevalent belief that mood affects the confidence of being able to quit smoking, influences the choice of treatment and modifies outcomes with time. Regarding, for example, the treatment and specific gender differences, a recent article shows how, only for the female gender, the effectiveness of a treatment of 16 weeks with fluoxetine, starting 8 weeks before the quitting day, was apparently demonstrated (sequential fluoxetine). This treatment seems to be able to reduce depressive symptoms emerging before the smoking cessation, to mitigate the negative effects of abstinence and to reduce the extent of craving<sup>(39)</sup>. From earlier studies<sup>(31,38)</sup>, it is known that – as reported for the general population – also in smokers the female gender is significantly correlated with depression, whereas other social and demographic variables are less or not correlated at all. In smoke cessation guidelines, there are no widely accepted evaluation scales for depressive symptoms assessment. In our experience, auto-evaluation tests, such as SDS, are well accepted, particularly in those who tend to underestimate their own symptoms<sup>(38)</sup>. They are useful for follow-up purposes, as they allow us to monitor the mood pattern in the evolution of withdrawal, in situations of triggered craving or relapse. We think that during smoking patient's assessment, it is useful, at least by means of a screening test, to evaluate the initial mood status, even if this evaluation may not be easily approached; patients have the tendency to not mention their depressive symptoms, maybe because of a lack of awareness on the possible existence of psychological difficulties in those who maintain a good social and workplace function. If the presence of depression-like symptoms is to be revealed by means of an auto-evaluation test and discussed, before starting a process of smoking cessation, prescription of anti-depressant drugs may be better accepted with less negative effects on motivation and on the patient's sense of self-efficacy. Mood monitoring could be even more important for female smoking patients. More than men, women fear difficulties due to abstinence and anticipate with anxiety the negative aspects of smoking withdrawal<sup>(27)</sup>. In depressed women, "atypical" symptoms (i.e., hypersomnia, hyperphagia, hypersensitivity to stress, perception of cognitive impairment), that may be due to withdrawal symptoms during nicotine deprivation, are more frequent than in men. In our sample of 1110 patients, the severity of depressive symptoms evaluated with the screening test (Zung SDS) correlated with the severity of nicotine dependence, measured by means of FTND test. The Fagerström test measures the biological dependence to nicotine, and does not allow to assess the influence of contextual situations (such as environment in which there are other smokers, stress conditions, perception of the quality of life, negative emotions such as solitude, isolation, frustration, apathy etc.). There are no systems of evaluation at hand regarding gender differences (at a biological level), for example neuro-endocrine adaptive capacity towards stress, which may explain further dif-

ferences for women to quit smoking, and their higher relapse rate. Our study does not establish a causality relationship between nicotine addiction and onset of depression, meaning that it does not help to explain if individuals with depression smoke more than the general population or if cigarette smoking fosters the insurgence and maintaining of mood disorders. In literature, the association between smoking and anxiety disorders is significant, whereas the diagnosis of major depression is found in 50% of patients with panic attack, in 42% of patients with generalised anxiety disorder, in 67% of patients with obsessive compulsive disorder, and in 34-70% of patients with social phobia. Furthermore, anxiety disorders precede mood disorder and studies suggest that one third of the individuals with major depression have life long comorbidity with an impulse control disorder<sup>(20,22,29)</sup>.

Other aspects that our study did not consider are: the percentage of patients who were already taking prescribed antidepressive drugs at the beginning of the treatment and how many patients were not depressed at the beginning but showed depressive symptoms during treatment and follow-up. The decision to not include these elements was due to the extreme heterogeneity of pharmacological treatment, which do not allow any kind of comparison. Moreover, our work did not aim to evaluate the course or the follow-up of the patients cared for. It must be underlined that this study was done in a typical setting of internal medicine, quite common in services of Pulmonology, Cardiology, Diabetology etc. Those engaged caregivers thus had less diagnostic capacity for psychiatric disorders. The presence of medium or severe depressive symptoms should indicate the opportunity of activating network actions with services in the psychiatric field, to manage depressive aspects, or activation of specific consultants. In outpatient cabinet for smoking cessation teams, the SDS test may be a useful tool for assessment and, together with others, may contribute in orienting the pathway of smoking cessation. An indication of a screening for depressive symptoms would enable to program an adequate pathway, both in timing and in ways, in order to not let motivation run out and to support self-efficacy. Other studies could investigate upon the hypothesis of latent depression treatment in smokers, with which drugs and protocols, and to evaluate results in terms of efficacy of treatment and prevention of relapse. Finally, a recent study by Frank Bandiera and his colleagues of the University of Texas (USA) assessed a sample of 5445 college students in Texas in a 6-month and 1-year follow-up study for eventual correlations between depressive symptoms and e-cigarette (e-cig) use, and evidenced how depressive symptoms predicted e-cig use and not vice versa. The authors observed a temporal correlation between more severe depression symptoms among college students predictive of e-cig use six months after. This may encourage more studies that would establish associative mechanisms and eventual causal associations between depression, nicotine use and tobacco smoking<sup>(51)</sup>.

## Conclusions

The study showed a high degree of pre-treatment depression in smokers intending to quit. Although the association between depression and nicotine dependence has been consistently reported many times, and it is well known that depressed subjects find it more difficult to quit, however most guidelines seem not to con-

sider this connection. These findings suggest the need for baseline assessment of depression by screening all smokers seeking assistance for quitting. ■

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