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UNIVERSIDADE  
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FACULDADE DE  
**MEDICINA**  
LISBOA

# **TRABALHO FINAL**

## **MESTRADO INTEGRADO EM MEDICINA**

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Clínica Universitária de Psiquiatria e Psicologia Médica

### **Tobacco and first-episode psychosis: a systematic review**

Adriana Rodrigues Ferreira

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**Julho'2019**



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**Orientado por:**

Dr. Ricardo Coentre

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## **Abstract**

The first episode psychosis is a variable syndrome defined by the presence of positive and negative symptoms with a continuous duration of at least one week. Typically it begins in adolescence or young adulthood. The prevalence of tobacco use in patients with first episode psychosis is markedly high, about 59%, higher than in the general population. Most of the existing studies currently refer to patients with chronic psychotic disorders. Thus, there has been crescent interest in understanding the concrete origin of the relationship between tobacco and the first psychotic episode. This systematic review reunites the studies published until March 2018, through a search in Pubmed and Web of Knowledge databases, in order to study three main aims that could contribute to the existence of the relationship between tobacco and first psychotic episode: 1) Tobacco smoking as a potential risk factor to first episode psychosis; 2) Nicotine use in the form of tobacco smoking in first episode psychosis: the self-medication hypothesis; and 3) Tobacco use as a marker of greater illness severity in first episode psychosis. Ten original articles were included, of which: one studied the first topic mentioned above; four studied the second; and the remaining five studied the third hypothesis. This review concludes that the relationship between tobacco and the first psychotic episode is undeniable, and, in spite of being difficult to reach the nature of this association, there was a trend towards a greater contribution of the hypothesis "Tobacco smoking as a potential risk factor to first episode psychosis" comparative to the "Nicotine use in the form of tobacco smoking in first episode psychosis: the self-medication hypotheses". The last hypothesis "Tobacco as a marker of disease severity" was the one that was most corroborated, with four of the five studies included in this topic supporting this hypothesis. In one study, it is suggested that poor adherence to medication may be a causal factor that mediates the association between smoking and increased severity of the disease. It was found that, although further studies on this associations are necessary, if fully tested, it may be very useful in clinical practice, primarily in a view of prevention and also in the staging of the disease.

**Keywords:** first episode psychosis; tobacco smoking; nicotine

The Final Work expresses the opinion of the student and not that of the Faculdade de Medicina da Universidade de Lisboa.

## **Resumo**

O primeiro episódio psicótico é uma síndrome variável que se define pela presença de sintomas positivos e negativos com uma duração contínua mínima de uma semana. Tipicamente tem início na adolescência e idade adulta jovem. A prevalência do uso de tabaco em doentes com primeiro episódio psicótico é marcadamente elevada, cerca de 59%, superior comparativamente à da população em geral. A maioria dos estudos existentes atualmente refere-se a doentes com doença psicótica crónica. Desta forma, tem-se manifestado interesse em entender a origem concreta da relação entre o tabaco e o primeiro episódio psicótico. Esta revisão sistemática reuniu os estudos publicados até março de 2018, através da pesquisa nas bases de dados Pubmed e Web of Knowledge, sobre a relação referida de forma a estudar três tópicos principais que poderão contribuir para a associação entre o tabaco e o primeiro episódio psicótico: 1) Tabaco como fator de risco do primeiro episódio psicótico; 2) A exposição à nicotina, através do tabaco, como comportamento de auto-medicação, e 3) Tabaco como marcador de gravidade da doença. Foram incluídos dez artigos originais, dos quais: um estudou o primeiro tópico acima referido; quatro estudaram o segundo; e os restantes cinco estudaram a terceira hipótese. Esta revisão permite concluir que a relação entre o tabaco e o primeiro episódio psicótico é inegável, e, apesar de ser difícil de alcançar a verdadeira génese da mesma, houve uma tendência para mostrar uma maior contribuição da hipótese “Tabaco como fator de risco do primeiro episódio psicótico” em relação à hipótese “A exposição à nicotina, através do tabaco, como comportamento de auto-medicação”. A última hipótese “Tabaco como marcador de gravidade da doença” foi aquela que mais foi corroborada, com quatro dos cinco estudos incluídos neste tópico a apoiar esta hipótese. Num dos estudos, sugere-se que a fraca adesão à medicação possa ser um fator causal que medeia a associação entre o tabaco e uma maior severidade da doença. Constatou-se, desta forma, que, apesar de serem necessários mais estudos sobre estas associações, no caso de serem totalmente provadas, poderão ter uma utilidade clínica muito vantajosa, primeiramente, numa perspetiva de prevenção e ainda no estadiamento da doença.

**Palavras-chave:** primeiro episódio psicótico; tabaco; nicotina

O Trabalho Final exprime a opinião do autor e não da Faculdade de Medicina da Universidade de Lisboa.

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## 1. Introduction

The first episode psychosis (FEP) is defined as a variable syndrome, lasting continuously for at least one week, characterized by the presence of positive symptoms, predominantly hallucinations and delusional ideas, and other accompanying symptoms, including negative, affective and cognitive symptoms. Typically, its begin during adolescence and young adulthood (1).

The prevalence of tobacco use in first episode psychosis patients is markedly high, about 59%, higher than in the general population (2).

In a study of a population of the United States of America, against age and sex, was observed a 12-month mortality among young people after a diagnosis of first episode psychosis at least 24 times greater than the general population (3). Also, it is suggested that cardiovascular mortality in schizophrenia has been increasing relative to the general population, a large part of the excess mortality probably attributed to the effects of smoking. (4)

On the other hand, the fact that tobacco dependence is a high financial burden also contributes to the social disadvantage and consequent decline of many of these patients. (5)

Several theories have been proposed to explain the reason why individuals with psychosis are more vulnerable to initiate and maintain tobacco use.

A causal role of tobacco in the first episode psychosis has been suggested, taking into account the interpretation of results as the association between tobacco use and an increased risk of psychosis, despite the awareness that this effect may be modest. (6)

In fact, there is some biological plausibility in this association. Tobacco contains almost 5,000 different chemicals, with nicotine being the most important pharmacologically active and psychogenic component because of its interaction with nicotinic acetylcholine receptors (nAChRs) (7), which exhibit distinct patterns of expression that are in parallel with major developmental events within the cholinergic system which are in turn critical regulators of brain maturation from prenatal development to adolescence. (8)

Several studies on smoking suggest that nicotine may alter the signaling of dopaminergic, cholinergic and glutamatergic neurotransmitter systems (9, 10) and thus may influence brain development, as suggested by studies on nicotine exposure in adolescents (9). Excessive exposure to nicotine during early adolescence is associated with abnormal

maturation of the white matter in adults (11) and chronic smoking has been associated with structural brain changes, such as decreased gray matter in the prefrontal cortex, which correspond to areas where functional changes occur due to exposure to nicotine (12).

Early intervention in psychosis was the one that showed the greatest progress on the classical pessimism associated with the disease, possible through the identification of the patients with ultra-high risk of psychosis and consequent possibility of intervening therapeutically at an earlier stage (13). Also, giving to the first episode psychosis patients the evidence based interventions effective in this phase of the disorder. It becomes more and more important to identify possible risk factors for the development of the disease in order to prevent or reduce exposure to them.

In another point of view, the question has been raised if the widespread smoking behavior that is seen in this patient group is in fact a relation of cause-effect or it is instead a manifestation of a common underlying physiology, being tobacco an attempt to self-medication.

There are different types of nicotinic receptors once multiple subtypes of pentameric structures with unique combinations form at least twelve ( $\alpha 2$ – $\alpha 10$ ,  $\beta 2$ – $\beta 4$ ) genetically-distinct subunits (14). The existence of these different types of nAChRs leads to the consequence that different doses of nicotine will promote different pharmacological effects (15). Since inhalation of cigarette smoke results in almost immediate absorption of nicotine, it might be possible for a smoker to control their nicotine dose to achieve the desired effect(s) (15).

Nicotinic acetylcholine receptors appear to be associated with different functional systems, by modulating the effects of different transmitter pathways, including the cholinergic system itself (by both pre- and post-synaptic mechanisms), and the dopamine (DA), glutamate, GABA, 5-HT, norepinephrine, opioid, and histaminergic systems (16). In the case of dopamine system, the pleasurable and reinforcing effects of nicotine are believed to arise via an interaction of the drug with the mesocorticolimbic system (15), once nicotine elicits dopamine release in the Ventral Tegmental Area (VTA), which projects to many brain regions like prefrontal cortex (PFC), dorsal striatum, nucleus accumbens (NAc), ventral pallidum (VP), hippocampus and amygdala (17) and which is known to play an important role in drug addiction (14).

It has been described a possible therapeutic role of nicotine for negative symptoms in psychosis. This effect is thought to be due to a raise in the dopamine levels in the nucleus accumbens and prefrontal cortex (18).

In fact, according to the dopaminergic theory, the negative symptoms present in this disorder are caused by hypoactivation of the dopaminergic mesocortical projections, which results in a hypostimulation of the D1 receptors. Also corroborating this hypothesis, atypical antipsychotics, which have shown the potential to decrease negative symptoms, are thought to do so by serotonergic antagonistic activity (5-HT) since, by blocking these receptors, there is an increase in the release of dopamine in the mesocortical pathway (1).

In this way, it calls attention for a possible common underlying physiology between nicotine and atypical antipsychotics.

Still on this subject, typical antipsychotics, through blocking the D2 receptors in the mesolimbic dopaminergic pathway, reduces the positive symptoms, such as hallucinations; however, the blockade is not limited to the mesolimbic pathway, simultaneously blocking other dopaminergic pathways, which aggravates negative symptoms and promotes the onset of extrapyramidal effects by blocking D2 receptors in the nigrostriatal dopaminergic pathway (1). Giving raise to the self-medication theory, reports showed reduced rates of smoking in patients treated with atypical antipsychotics compared to those treated with typical antipsychotics (19).

It was still suggested that tobacco use could serve as a marker of severity in psychotic illness (20), as it has been associated with an increase in negative (21, 22) and positive (23) symptoms, as well as poorer global functioning (24) and also social adjustment (25). However, it may not be representative of first episode psychotic individuals once those clinical outcomes are from patients who have a chronic disease.

This systematic review reunites the current evidence of three main aims: 1. Tobacco smoking as a potential risk factor to first episode psychosis; 2. Nicotine use in the form of tobacco smoking in first episode psychosis: the self-medication hypothesis; 3. Tobacco use as a marker of greater illness severity in first episode psychosis. The major objective was to understand the true connection between tobacco use and first episode psychosis.

## **2. Methods**

Pubmed and Web of Knowledge databases were searched for published articles using keywords “tobacco” OR “tobacco use” OR “tobacco smoking” AND “first episode psychosis” OR “first episode schizophrenia”. In addition, a secondary search was performed by reviewing reference lists of sources identified as relevant in initial search to find more articles to this review. The articles were included if they were original articles and written in English. This systematic review included articles until March 2018. Studies were excluded if were related to chronic schizophrenia patients or psychiatric populations other than first-episode psychosis. In case of multiple publications deriving from the same study population, we selected the articles reporting the largest or the most recent data. In case of conflict between these two last criteria, the sample size was the priority.

### **3. Results**

Ten articles were included in the systematic review.

One article was included that studied tobacco as a potential risk factor to first episode psychosis (26), four articles that examined the self-medication hypothesis (27-30) and five articles that studied tobacco use as a marker of greater illness severity in first episode psychosis (31-35).

A total of 2567 patients were included, sample size ranged from 41 to 503 patients, with mean age from 20,5 to 29,9 years, with male percentage from 28,1 to 72,5 %. Two studies are from Canada, four are from Spain, one is from UK, one study is from Australia, one study is from USA and one study is from Poland. Three studies were published between 2008 and 2012 and seven between 2015 and 2018 (inclusive).

#### **3.1. Prevalence of smoking**

The prevalence of smoking in first episode psychosis patients ranged from 36,7% to 72,0 %. In one article it was not possible to determine the prevalence of smoking (26).

There was no significant gender difference on tobacco use in first episode psychosis patients in most studies, with the exception of three studies: one study in which when the FEP group was stratified by smoking status, significant differences emerged in gender, with 65% of males smokers versus 47% of female smokers (29); other second study, in which the male smoker percentage was 64,8% against the male general percentage of 56,9% (30); and a third study, in which statistically significant associations were found between smoking status and gender, with male subjects more than three times as likely to smoke as females (35).

In one study, when the FEP group was stratified by smoking status, significant differences emerged in age, with a mean age of 28,1 in smokers and 32,3 in non-smokers (29). In a second study, also smokers showed a mean age of 28,2, while non-smokers showed a mean age of 32,2 (30). Lastly, heavy smokers were older than light/moderate smokers and non-smokers (34).

### **3.2. Tobacco smoking as a potential risk factor to first episode psychosis**

In 2009, a study showed that the mean age at starting smoking was earlier than the onset of psychosis, which can be suggestive of a causal role of the tobacco in the onset of psychosis (26). Besides this, the proportion of patients who started smoking by the onset of a functional decline was significantly high comparative to the general population. In more detail, the percentage of patients who smoked for patients aged 20 years or more was 70% and lower for teenager patients (49%), which also suggests that some patients initiate smoking after their first referral for treatment. In addition and also supporting the idea of tobacco smoking as a risk factor for psychosis, smoker patients showed a nonsignificant better functioning compared to nonsmoker patients and also those patients who started smoking had better premorbid social functioning than those who did not smoke, which is contrary to what was expected in case smoking were initiated in response to early prodromal features of illness.

### **3.3. Nicotine use in the form of tobacco smoking in first episode psychosis: the self-medication hypothesis**

The four articles included in this systematic review were divergent with a general conclusion that goes against the self-medication hypothesis.

Recently, in 2018, a study (27) tested the following hypothesis: tobacco using FEP patients have better non-social and social cognitive performance than non-tobacco using FEP patients; tobacco smoker patient group presented worse non-social and social cognitive performance than the tobacco-smoker and non-smoker control group. The results showed no differences between the patient groups (tobacco users and non-tobacco users). Taking into account these results, this study suggests that tobacco use in FEP patients is not related to better non-social or social cognitive performance, which do not support the self-medication hypothesis. Despite this, it's important to be aware of a limitation of this study, which is the lack of IQ matching between patients and healthy controls, specifically, the control group had a significantly higher IQ compared to the patient group and this difference remained significant when the sample was subdivided into the four subgroups and after controlling by the covariate variables.

Misiak et al. investigated the relationship between nicotine dependence and psychopathology in FEP patients, in particular, and with more interest for this review, it was studied the association between the severity of nicotine dependence and scores of negative and positive symptoms. It was found that cigarette smoking is associated with lower severity of negative symptoms, although this difference is significant only in the comparison of severe nicotine dependence patients and non-smokers (28), indicating that cigarette smoking might be enrolled in the psychopathology of this illness, by inducing less severe negative symptoms.

Hickling et al. analyzed the relationship between chronic exposure to nicotine through tobacco smoking on cognitive performance and there was no significant difference in any of the cognitive areas between smokers and non-smokers in the FEP group and also in the healthy group (29).

Still within this topic, Hickling et al. published a study which focused on the effects of tobacco smoking on age of onset of psychosis and psychotic symptoms in a first-episode psychosis population. The study conclusion was that tobacco smoking had no effect on psychopathology at initial presentation or treatment response at 6 weeks (30).

### **3.4. Tobacco use as a marker of greater illness severity in first episode psychosis**

Four of the five studies included in this topic supported this hypothesis.

An observational study (31) was conducted to determine if there is cognitive benefit achieved via smoking by comparing the cognitive performance of smoking and non-smoking FEP patients. In their baseline report, it was found that smoking FEP patients performed better in tasks measuring attention and working memory than non-smoking patients after stabilization (36). In the present longitudinal report, these patients were followed up in order to determine possible differences in attention and working memory between smoking and non-smoking patients 1 year after the initiation of antipsychotic treatment and the secondary objective was to explore the relationship between smoking and the symptoms and side effects of antipsychotics. It was observed that, after 6 months the initiation of antipsychotic treatment, baseline differences in selective attention and working memory parameters were no longer significant between smokers and non-smokers, with the exception of Stroop-I mean RT (Stroop Color-Word Test Interference

score/Stroop-I, the measure of selective attention) and after 1 year, performance was similar between the groups. Another point that deserves attention is that smokers did not show any cognitive response to SGA, with no synergic effects observed for nicotine and antipsychotics. In addition, although the results of this study indicate that the initial clinical presentation is the same between groups, it was found that negative symptoms worsen significantly in smokers. With respect to the exploration of the association between smoking and symptoms and side effects of medication, this study results do not support that FEP patients smoke in order to reduce the side effects of antipsychotic drugs, once smokers did not show fewer extrapyramidal side effects comparative to non-smokers (31).

In another study it was found that cigarette smoking was consistently associated with higher ratings of psychiatric symptoms and functional impairment, more missed pills and lower ratings of quality of life (32). This study results encourage the hypothesis of tobacco being a marker of greater illness severity.

In a one year follow-up study of first episode psychosis (33), the following hypotheses were addressed: firstly, if substance use (including tobacco) following illness onset impairs medication adherence; secondly, if substance use is associated with poor outcome at 1 year follow-up, and finally if the poor medication adherence mediates this effect. The results indicate that in fact nicotine dependence in the first year after psychosis onset affect medication adherence. Furthermore, poor medication adherence predicts non-remission and lastly nicotine dependence in the first year after psychosis onset are associated with increased probability of non-remission during the one year follow-up and medication adherence is involved in it by mediating these effects.

A recent study demonstrated that neurocognitive and functional impairments are more prominent in light/moderate and heavy cigarette smokers with FEP relative to non-smoking patients at initial presentation for treatment (34), which reinforces the theory that cigarette smoking may be indicative of a greater illness severity.

In a 7.5-year follow-up study of a first episode psychosis cohort, the conclusion was that there were not any impact of smoking on clinical outcomes in individuals after a first episode psychosis (35), disapproving the primary hypothesis of the study which was that smoking would be associated with poorer clinical and functional outcomes and also

contrasting with the previous conclusions in this review that connected smoking with a greater illness severity in first episode psychosis.

| Authors and published year                           | Country | Sample size | Age Mean (SD) | Male percent | Diagnosis                                  | Main Aim  | Prevalence | Relevant findings   |
|--|---------|-------------|---------------|--------------|--|---|------------|---|
| <b><u>Risk factor</u></b><br>(26)                    | Canada  | 115         | 20,5<br>(5,5) | 69,6%        | FEP: Affective and non-affective psychosis | Determine the predictors of starting to smoke in patients with first episode psychosis.   |            | The mean age at starting smoking was earlier than the onset of psychosis, which can be suggestive of a causal role of the tobacco in the onset of illness.  |
| <b><u>The self-medication hypothesis</u></b><br>(27) | Spain   | 503         | 24,0          | 28,1%        | FEP: Affective and non-affective psychosis | Test if tobacco using FEP patients have better non-social and social cognitive performance than non-tobacco using FEP patients. | 67,8%      | No differences were revealed in the comparison between the patient groups (tobacco users and non-tobacco users), suggesting that tobacco in FEP patients is not related to better non-social or social cognitive performance. |
| (28)   | Poland  | 109         | 27,7          | 56,0%        | First-episode schizophrenia                | Investigate the relationship between nicotine dependence and psychopathology in FEP patients.                                   | 36,7%      | Cigarette smoking is associated with lower severity of negative symptoms.   |

|      |       |     |      |       |  |   |       |  |
|------|-------|-----|------|-------|--|---|-------|--|
| (29) | Spain | 460 | 29,9 | 59%   | FEP: Affective and non-affective psychosis | Analyze the relationship between chronic exposure to nicotine on cognitive performance.                         | 57%   | No difference in cognitive ability was found between smokers and non-smokers.                      |
| (30) | Spain | 397 | 29,8 | 56,9% | FEP: Affective and non-affective psychosis | Analyze the effects of tobacco smoking on age of onset of psychosis and psychotic symptoms in a FEP population. | 58,7% | Smoking had no effect on psychopathology at initial presentation or treatment response at 6 weeks. |

**Greater illness**

**severity**

|      |       |    |      |       |  |   |       |   |
|------|-------|----|------|-------|--|---|-------|---|
| (31) | Spain | 41 | 27,8 | 68,2% | FEP: Affective and non-affective psychosis | Determine if there is cognitive benefit achieved via smoking by comparing the cognitive performance of smoking and non-smoking FEP patients and explore the relationship between smoking and the symptoms and side effects of antipsychotics. | 63,4% | Smoking patients lost their superior baseline performance, did not obtain any cognitive benefit after treatment and worsen their symptoms. Also smokers did not show fewer extrapyramidal side effects. |
|------|-------|----|------|-------|--|---|-------|---|

|      |     |     |      |       |  |   |                |  |
|------|-----|-----|------|-------|--|---|----------------|--|
| (32) | USA | 404 | 23   | 72,5% | FEP: Affective and non-affective psychosis | Examine the effect of recent tobacco and other substances use on psychiatric symptoms and quality of life outcomes and assess the illness severity and missed antipsychotic pills.  | 51,4%          | Cigarette smoking was associated with higher ratings of psychiatric symptoms and functional impairment, more missed pills and lower ratings of quality of life.  |
| (33) | UK  | 205 | 29,6 | 63,4% | FEP: Affective and non-affective psychosis | Test: if substance use (including tobacco) following illness onset impairs medication adherence; if substance use is associated with poor outcome at 1 year follow-up and lastly if the poor medication adherence mediates this effect. | 53,2%<br>59,5% | Nicotine dependence in the first year after psychosis onset affects medication adherence. Poor medication adherence predicts non-remission. Nicotine dependence in the first year after psychosis onset is associated with non-remission. Medication adherence mediates these effects. |

|      |           |     |               |       |  |   |       |   |
|------|-----------|-----|---------------|-------|--|---|-------|---|
| (34) | Canada    | 140 | 23,2          | 70,7% | FEP: Affective and non-affective psychosis | Determine the prevalence and patterns of smoking and its co-use with cannabis in FEP and examine demographic, clinical, cognitive, and functional characteristics associated with smoking status, after adjusting for cannabis use. | 53,0% | Neurocognitive and functional impairments are more prominent in light/moderate and heavy cigarette smokers with FEP relative to non-smoking patients at initial presentation for treatment. |
| (35) | Australia | 193 | 22,0<br>(3,3) | 70,5% | FEP: Affective and non-affective psychosis | Clarify the impact of smoking on clinical outcomes  | 72,0% | There are not any impact of smoking on clinical outcomes in individuals after a first episode psychosis.  |

## Discussion

The current systematic review provides convincing evidence that tobacco use have high rates in the first-episode psychosis, being in agreement, in fact, with the prior knowledge from previous studies (2).

A meta-analysis of worldwide studies suggests that smoking begins before the first referral for treatment (37) and two prospective cohort studies indicated that smoking may begin before the onset of psychosis (38, 39).

About this first topic “Tobacco smoking as a potential risk factor to first episode psychosis”, it was observed that, in spite of the percentage of patients who smoked for patients aged 20 years or more was superior than for teenage patients, suggesting that part of them started to smoke after the outset of the illness, in general, the mean age at starting smoke was significantly earlier than the functional decline and the onset of psychosis. In addition, smoker patients showed a nonsignificant better functioning compared to nonsmoker patients. Those patients who started smoking had better premorbid social functioning than those who did not smoke, which is contrary to what was expected in case smoking were initiated in response to early prodromal features of illness (26). These results make it possible to have a cause-effect relationship instead of tobacco smoking being just a consequence of first-episode psychosis, which is in line with the literature (37-39).

Interestingly, Cannon and colleagues showed evidence for a relation between increased rate of conversion to psychosis and any substance use when entered in a prediction algorithm along with other predictors, although in multivariate analyses no specific substance class of the 7 tested (alcohol, hypnotics, cannabis, amphetamines, opiates, cocaine, and hallucinogens) (40). In this regard, it’s possible that the importance of substance use can be through its interactive effects with other substances, symptom severity or current level of functioning and therefore, the role of tobacco use for risk of conversion may be better tapped by multivariate prediction algorithms incorporating multiple variables implicated in psychosis onset.

The cognitive approach to the self-medication hypothesis is supported by several studies (41-49). On the contrary, two studies found no significant differences in the general neurocognitive (non-social) functioning between nicotine user and non-user patients with psychosis (50, 51). In addition, regarding social cognition, one study published in 2013

did not find nicotine effects on social cognitive tasks (facial affect recognition) or on social competence (52), however the sample of schizophrenia patients in this study unexpectedly did not perform significantly worse in the facial affect recognition task than the healthy controls. Therefore, a precondition for showing performance-enhancing effects of nicotine in schizophrenia patients was not given, which may have contributed to the lack of nicotine effect on facial affect recognition.

Regarding the second topic “Nicotine use in the form of tobacco smoking in first episode psychosis: the self-medication hypothesis”, the results of the current systematic review were, in an overall analysis, against the proposed hypothesis and the knowledge taken from previous studies. One study verified the association between severe dependence and lower severity of negative symptoms (28), supporting the self-medication hypothesis. On the other hand, one study included did not support the mentioned theory once no significant difference in cognitive ability has been found between smokers and non-smokers (29) and another one concluded that tobacco smoking had no effect on psychopathology at initial presentation or treatment response at 6 weeks (30). Lastly, one of the included studies does not allow us to fully draw conclusions about this concern which shows that tobacco use in FEP patients is not related to better non-social or social cognitive performance, meanwhile, there was a lack of IQ matching between patients and healthy controls with the control group having higher IQ (27). So future longitudinal studies with healthy controls with a similar IQ and also measures of pre and post substance-use and FEP-onset cognitive function could overcome this limitation.

Previously, published studies related to the association “Tobacco use as a marker of greater illness severity in first episode psychosis” are inconsistent.

Some studies demonstrated that current smokers with schizophrenia exhibit greater working memory impairments than non-smokers (53) and worse cognitive and functional outcomes than past smokers or those who had never smoked (54). In addition, in a cohort of 542 inpatients with psychosis who were followed for 10 years after first hospitalization, smokers exhibited greater functional impairment than non-smokers, and depressive symptoms positively covaried with cigarette smoking over a 10-year period (55). And still, one study suggests that severe forms of schizophrenia with poor outcome were associated with heavy smoking (20).

Despite these findings, the clinical outcomes of patients who are chronically ill as the populations in the studies above mentioned may not be representative of the first-episode psychosis population.

In this systematic review, as we have seen, this third topic was in line with the findings from chronically ill psychosis patients. The first study mentioned in this review on this topic, reached the conclusion that, although cognitive performance was better in patients with FEP who smoked than in non-smoking patients in selective attention and working memory soon after the first stabilization, in a different way, after 6 months initiation of antipsychotic treatment, baseline differences in selective attention and working memory parameters were no longer significant between smokers and non-smokers, with the exception of Stroop-I mean RT (Stroop Color-Word Test Interference score/Stroop-I, the measure of selective attention) and after 1 year, performance was similar between the groups (31). This could be explained once non-smokers might obtain more benefit from practice effects, since they start with a more disadvantageous performance than smokers, as various studies have pointed out that worse baseline scores predict greater cognitive improvement (56, 57). Another explanation for the improvements in non-smokers might be through the therapeutic effects of SGA on cognition. Olanzapine and risperidone, for example, have been reported to provide a modest cognitive improvement during the early phase (58), so this may have led non-smokers to achieve the superior baseline cognitive performance of smokers, which was probably obtained through nicotinic stimulation. In this case, once nicotine use leads to a cognitive benefit also achievable from antipsychotic medication during the early course of the illness (6–12 months), it could be a support for the self-medication hypothesis. In addition, once smokers seem to have difficult to benefit from practice effects from medication, it gives strength to the hypothesis that smoking may be a marker of more severe illness. Another point that deserves attention is that smokers did not show any cognitive response to SGA, with no synergic effects observed for nicotine and antipsychotics. Explanations for the lack of an additional cognitive benefit in smokers promoted by the SGA, can be a possible ceiling effect of the agonist activity that may be obtained through smoking and/or SGA or the possibility of an etiologically differentiated system with more marked alterations among smokers, which might prevent smokers from benefitting from practice effects, suggesting that smoking may be a marker of more severe illness and/or of its neurodevelopmental phenotype, as it was suggested by some authors (15, 20). Also supporting this hypothesis, although the

results of this study indicate that the initial clinical presentation is the same between groups, it was found that negative symptoms worsen significantly in smokers (31). With respect to the exploration of the association between smoking and symptoms and side effects of medication, this study results do not support that FEP patients smoke in order to reduce the side effects of antipsychotic drugs, once smokers did not show fewer extrapyramidal side effects comparative to non-smokers (31). The second one study mentioned, documented that cigarette smoking was consistently associated with higher ratings of psychiatric symptoms and functional impairment, more missed pills and lower ratings of quality of life (32), also encouraging the hypothesis of tobacco being a marker of greater illness severity. In other study included in this systematic review (33), the results also agree with the assumption, showing that in fact nicotine dependence in the first year after psychosis onset affects medication adherence, poor medication adherence predicts non-remission and lastly nicotine dependence in the first year after psychosis onset is associated with increased probability of non-remission during the one year follow-up suggesting a role to poor medication adherence in this as a causal pathway by mediating this connection. This study evaluated the impact of substance use, both premorbid and after psychosis onset, on medication adherence and the conclusion was that premorbid substance use does not affect medication adherence during the one year follow-up but its use during the year after psychosis onset predicted poor medication adherence at follow-up. Moreover, one study showed that substance use increases the risk of non-remission, with a more than 2-fold increased likelihood of not achieving remission in the case of nicotine dependent patients (59). These results make emerge a new possible explanation for the association between tobacco use and worst outcomes at follow-up which is poor medication adherence as a causal pathway by mediating this connection. In the study of Grossman and colleagues (34), it was observed that neurocognitive and functional impairments are more prominent in light/moderate and heavy cigarette smokers with FEP relative to non-smoking patients at initial presentation for treatment, also reinforcing this theory. The last one was the only which disapproved the hypothesis once after adjustment for cofounders, the conclusion was that there are not any impact of smoking on clinical outcomes in individuals after a first episode psychosis (35). One possible explanation for this disagreement is that the first episode psychosis study population that participated in this study may not be a real representative of this psychiatric population.

## **Conclusion**

As it has been analyzed, the evidence supporting the existence of an association between tobacco use and first episode psychosis patients is undeniable. The discrepancy in the nature of this association mainly in relation to the first two hypothesis “Tobacco smoking as a potential risk factor to first episode psychosis” and “Nicotine use in the form of tobacco smoking in first episode psychosis: the self-medication hypothesis” makes it difficult to clearly understand which hypothesis contributes more to the aforementioned relationship, although, according to this meta-analysis, a trend towards a greater contribution of the first proposed hypothesis. The third topic “Tobacco use as a marker of greater illness severity in first episode psychosis” seems to be the one with the greatest confidence. One of the studies included makes emerge a new possible explanation for the association between tobacco use and worst outcomes at follow-up which is poor medication adherence as a causal pathway by mediating this connection. It is clear that more studies will be needed to overcome some of the limitations of the previous studies that have been mentioned; however, the conclusion of this meta-analysis, if duly proven, may be very useful in clinical practice, primarily in a view of prevention through anti-smoking measures in risk groups and also tobacco use may be used as an accessory marker of staging of the disease with a probably prognostic value involved.

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## **Resumo Extenso em Português**

O primeiro episódio psicótico define-se como uma síndrome variável, com duração mínima de uma semana e que se caracteriza pela presença de sintomas positivos, predominantemente alucinações e delírios, e outros sintomas acompanhantes que incluem os negativos, os afetivos e o abuso de substâncias. Tipicamente, apresenta o seu início na adolescência ou no início da idade adulta.

A prevalência do uso do tabaco em doentes com primeiro episódio psicótico é marcadamente alta, cerca de 59%, sendo superior à da população em geral.

Têm sido propostas diversas teorias com o objetivo de explicar a razão pela qual os doentes com primeiro episódio psicótico apresentam uma maior predisposição para iniciar e manter o uso do tabaco.

Foi sugerida a existência de uma relação de causa-efeito do tabaco em relação à doença, tendo em conta resultados observados na associação entre o uso do tabaco e um risco aumentado de psicose.

Por outro lado, também emergiu a questão de que a alta prevalência de tabagismo neste grupo de doentes poderia ser justificada como uma tentativa de auto-medicação (the self-medication behaviour).

Foi ainda sugerido que o uso do tabaco poderia servir como marcador de uma maior gravidade da doença psicótica, tendo em conta que o tabagismo foi associado a um aumento dos sintomas negativos e positivos, assim como a uma pior função global e capacidades sociais. No entanto, isto poderá não ser representativo da população referente ao primeiro episódio psicótico, uma vez que os resultados clínicos provêm de doentes com doença psicótica crónica.

Esta revisão sistemática reuniu os estudos publicados até ao março de 2018, através da pesquisa nas bases de dados Pubmed e Web of Knowledge, sobre a relação referida de forma a estudar três tópicos principais que poderão contribuir para a associação entre o tabaco e o primeiro episódio psicótico: Tabaco como fator de risco do primeiro episódio psicótico; A exposição à nicotina, através do tabaco, como comportamento de auto-medicação; e Tabaco como marcador de maior gravidade da doença. Foram incluídos dez artigos originais, dos quais: um estudou o primeiro tópico acima referido; quatro estudaram o segundo; e os restantes cinco estudaram a terceira hipótese.

No total, foram incluídos 2567 doentes, com um tamanho de amostra que variou entre 41 a 503 doentes, com média de idade entre 20,5 e 29,9 anos, com percentagem de sexo masculino entre 28,1 e 72,5%. Dois dos estudos são provenientes do Canadá, quatro de Espanha, um do Reino Unido, um da Austrália, um dos Estados Unidos da América e um da Polónia. Três dos estudos foram publicados entre 2008 e 2012 e sete entre 2015 e 2018.

Em relação à prevalência do tabagismo nos doentes com primeiro episódio nos artigos incluídos nesta revisão sistemática, esta variou entre 36,7% e 72,0%, sendo que em um dos artigos não foi possível determinar a mesma.

Os resultados acerca do primeiro tópico “Tabaco como fator de risco do primeiro episódio psicótico” apoiaram a hipótese. Mais especificamente, o artigo incluído mostrou que, apesar da percentagem de doentes fumadores com idade superior ou igual a 20 anos ser superior à percentagem de doentes fumadores com idade inferior, sugerindo, neste caso, que parte dos doentes começaram a fumar apenas após o início da doença, por outro lado, no geral, a média de idade de início do tabagismo foi significativamente inferior ao declínio funcional e início do primeiro episódio psicótico. Além disto, no mesmo artigo os doentes fumadores apresentaram um melhor desempenho funcional não significativo comparativamente aos doentes não fumadores e ainda aqueles doentes que começaram a fumar mostraram ter melhores resultados nas capacidades sociais a nível pré-morbido em relação aos doentes que não fumaram, o que contraria o que seria expectável no caso do tabagismo ser iniciado como resposta aos sintomas iniciais da doença. Estes resultados tornam possível a existência de uma relação causa-efeito e não apenas o uso do tabaco como consequência da manifestação da doença.

Acerca do tópico “A exposição à nicotina, através do tabaco, como comportamento de auto-medicação”, os quatro artigos incluídos obtiveram resultados divergentes com um resultado geral que não apoia a hipótese sugerida. Um dos estudos verificou a associação entre a dependência severa à nicotina e uma redução da severidade dos sintomas negativos, suportando a hipótese sugerida. Por outro lado, um dos estudos não apoiou a mesma, uma vez que não foram observadas diferenças nas funções cognitivas entre doentes fumadores e não fumadores e, ainda, mais um dos estudos incluídos, concluiu que o tabaco não tinha qualquer efeito na psicopatologia nem na apresentação inicial da doença nem na resposta ao tratamento às 6 semanas. Por último, um dos estudos não permitiu totalmente extrapolar conclusões uma vez que o tabagismo nos doentes incluídos

não se relacionou com melhores resultados nas funções cognitivas, no entanto, o estudo referido apresenta uma falta de concordância relativamente ao QI entre o grupo dos doentes e o grupo controlo, com o último a apresentar um valor de QI superior.

Em relação ao último tópico “Tabaco como marcador de maior gravidade da doença”, quatro dos cinco artigos incluídos suportam a hipótese. Num dos artigos referidos, os doentes fumadores, após 6 meses e 1 ano de seguimento, perderam a superioridade que apresentavam anteriormente relativa às funções cognitivas, os sintomas negativos agravaram-se de forma mais marcada nos doentes fumadores e estes não mostraram apresentar diminuição dos efeitos extra-piramidais, sugerindo que o uso do tabaco não é iniciado ou mantido de forma a diminuir os efeitos adversos dos fármacos anti-psicóticos. Num segundo estudo referido, o tabaco mostrou estar associado a taxas superiores de sintomas psicóticos e a um maior compromisso funcional. No terceiro estudo, foi concluído que: a dependência à nicotina um ano após o primeiro episódio psicótico diminui a adesão à terapêutica; a fraca adesão à terapêutica prediz a não remissão da doença; e a dependência à nicotina um ano após o primeiro episódio psicótico está associado à não remissão da doença. Sugere-se assim que a adesão à terapêutica apresenta um papel de mediador da relação entre o tabaco e um maior grau de gravidade do primeiro episódio psicótico. Ainda, um dos artigos incluídos mostrou que o comprometimento a nível neurocognitivo e funcional é mais proeminente em doentes fumadores em relação aos não fumadores na apresentação inicial da doença. Por último, apenas um dos artigos, não apoiou a hipótese, tendo em conta que mostrou não existir qualquer impacto do tabaco nos resultados clínicos dos doentes após o primeiro episódio psicótico.

Como foi analisado, existe bastante evidencia que suporta a associação entre o tabagismo e o primeiro episódio psicótico. No entanto, a discrepância observada nos resultados, principalmente em relação aos tópicos “Tabaco como fator de risco do primeiro episódio psicótico” e “A exposição à nicotina, através do tabaco, como comportamento de auto-medicação” dificulta a compreensão da verdadeira natureza desta relação, apesar de, segundo esta meta-análise, haver uma tendência para uma maior contribuição da primeira hipótese na génese da mesma. Em relação à hipótese “Tabaco como marcador de maior gravidade da doença”, esta foi aquela que mais foi corroborada, com a quase totalidade dos estudos incluídos a suportar esta hipótese.

Deste modo, no caso de as hipóteses “Tabaco como fator de risco do primeiro episódio psicótico” e “Tabaco como marcador de maior gravidade da doença” serem totalmente provadas estas poderão ter uma utilidade clínica muito vantajosa. No caso da primeira hipótese, numa perspetiva de prevenção através de medidas anti-tabágicas nos grupos de risco; na segunda, a utilização do uso do tabaco como marcador do estadiamento do primeiro episódio psicótico, inclusivamente com um provável valor prognóstico associado.