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REVIEW ARTICLE

A systematic review of tobacco use in first-episode psychosis

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Abstract
Background and objectives: The prevalence of tobacco use in patients with first-episode psychosis is elevated, higher than in the general population. Classically studies in first-episode psychosis are few with most current studies referring to patients with chronic psychotic disorders. However, in recent years there has been increasing interest in understanding the concrete origin of the relationship between tobacco use and the first-episode psychosis. This study provides a systematic review of current research on the relationship between tobacco use and first-episode psychosis.
Methods: A comprehensive systematic review of electronic databases PubMed and Web of Science was conducted. Articles were included if they mentioned the relationship between tobacco use and first-episode psychosis. Ten original articles were selected.
Results: The prevalence of tobacco use in first-episode psychosis patients was high, ranging from 36.7% to 72%. Results are divergent regarding gender differences and tobacco use in first-episode psychosis. Some studies have found that tobacco-using first-episode psychosis patients were younger than non-tobacco-using patients. Three hypotheses have been proposed to explain the relationship between tobacco use and first-episode psychosis: 1) tobacco smoking as a potential risk factor for first-episode psychosis; 2) nicotine use as a form of self-medication treatment; and 3) tobacco use as a marker for greater illness severity in first-episode psychosis.
Conclusions: This review demonstrates that the relationship between tobacco use and the first-episode psychosis seems clear. Primary and secondary preventive strategies regarding tobacco use would be useful for first-episode psychosis patients, and included in early intervention in psychosis teams.

Abbreviation: PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analysis.

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Introduction

Psychotic disorders, and particularly schizophrenia, are serious illnesses which typically first manifest during the period of adolescence and emerging adulthood.[1] 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.[2]

The prevalence of tobacco use in first-episode psychosis patients is higher than in the general population.[3] On the one hand, it has been observed that the higher mortality after first-episode psychosis it is partially due to cardiovascular disease and a large percentage of the excess mortality as 70% of smoking related diseases.[4,5] On the other hand, the fact that tobacco dependence poses a high financial burden also contributes to the social disadvantage and consequent decline of many of these patients with psychotic illnesses.[6]

Several theories have been proposed to explain 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 an association between tobacco use and an increased risk of psychosis. Despite this awareness, this effect may be modest.[7] In fact, there is some biological plausibility regarding this association. Tobacco contains almost 5000 different chemicals, with nicotine being the most important pharmacologically active and psychogenic component because of its interaction with nicotinic acetylcholine receptors (nAChRs).[8] Nicotine exhibits 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.[9] Several studies on smoking suggest that nicotine may alter the signaling of the dopaminergic, cholinergic and glutamatergic neurotransmitter systems,[10,11] and thus may influence brain development, as suggested by studies on nicotine exposure in adolescents.[10] Excessive exposure to nicotine during early adolescence is associated with abnormal maturation of the white matter in adults[12] and chronic smoking has been associated with structural brain changes, such as decreased gray matter in the prefrontal cortex, which corresponds to areas where functional changes occur and are associated with psychosis.[13]

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 is instead a manifestation of a common underlying physiology, with tobacco use being an attempt at self-medication. There are different types of nicotinic receptors with multiple subtypes of pentameric structures whose unique combinations form at least twelve ($\alpha2$–$\alpha10$, $\beta2$–$\beta4$) 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 the 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 such as the prefrontal cortex (PFC), dorsal striatum, nucleus accumbens (NAc), ventral pallidum (VP), hippocampus and amygdala,[17] and which are known to play an important role in drug addiction.[14]

A possible therapeutic role of nicotine for negative symptoms in psychosis has been described. 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 the hypostimulation of the D1 receptors. Also corroborating this hypothesis, atypical antipsychotics, which have demonstrated 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.[18]

These dynamics have called attention to a possible common underlying physiology between nicotine and atypical antipsychotics. Still on this subject, typical antipsychotics, by blocking the D2 receptors in the mesolimbic dopaminergic pathway, reduce 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. Giving rise to the self-medication theory, reports have revealed reduced rates of smoking in patients treated with atypical antipsychotics compared to those treated with typical antipsychotics.[19]

It is 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 symptoms,[23] as well as poorer global functioning[24] and social adjustment.[25]

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.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) methodology was used.[26] Pubmed

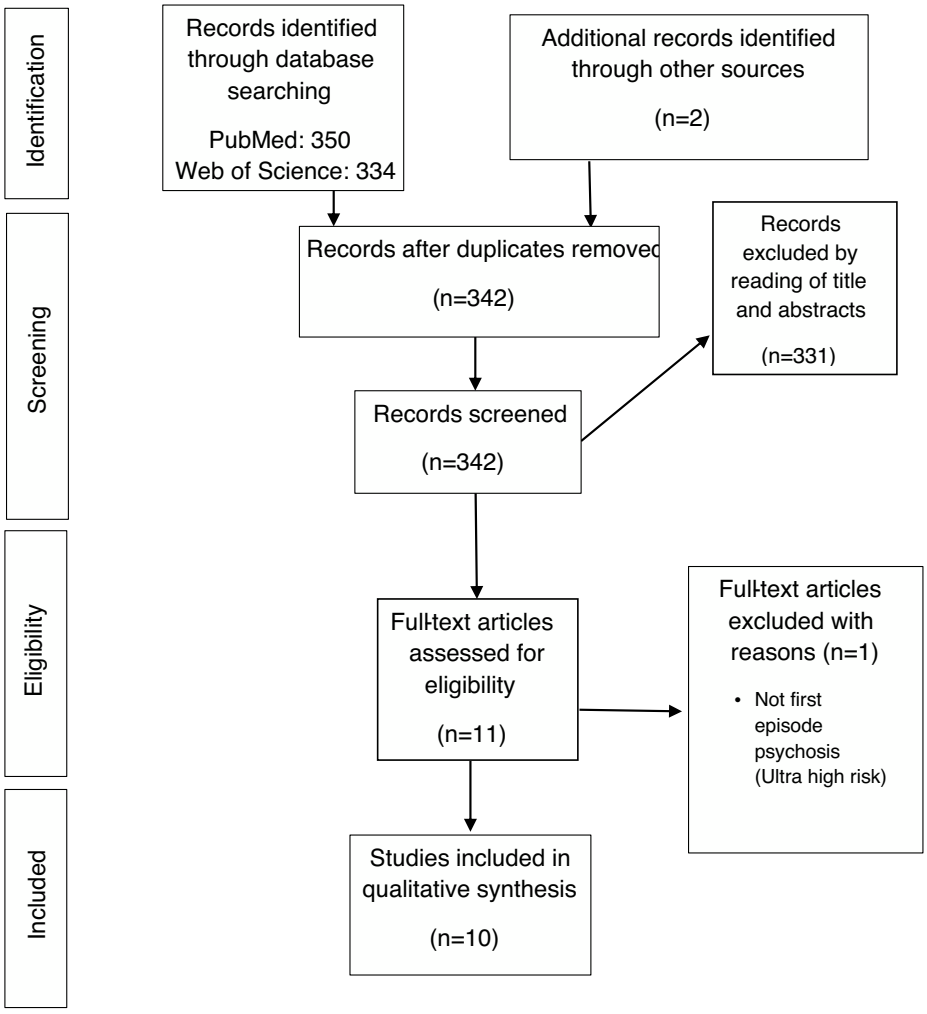

Fig. 1 Flow Chart of systematic identification of papers following PRISMA Guidance.

and Web of Science electronic databases were searched for published articles, using the keywords ''tobacco'' OR ''tobacco use'' OR ''tobacco smoking'' AND ''first-episode psychosis'' OR ''first-episode schizophrenia''. Abstracts were screened and the full texts of suitable studies were obtained. In addition, a secondary search was performed by reviewing reference lists of sources identified as relevant in the initial search to find more articles for this review. The articles were included if they were original articles and written in English. This systematic review included articles until March 2019. Studies were excluded if they were related to chronic schizophrenia patients or psychiatric populations other than first-episode psychosis and also proceeding abstracts. Two authors (AF and RC) did the search, data extraction and selected the final studies included in the systematic review. Conflicts were resolved by discussion between these two authors. In case of multiple publications deriving from the same study population, we selected the articles reporting the largest or most recent data. In case of a conflict between these last two criteria, the sample size was the priority. See Fig. 1 for the PRISMA diagram documenting this process.

Results

Selected articles were divided into three groups for rational reasons: 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. Ten articles were included in the systematic review. One article studied tobacco as a potential risk factor to first-episode psychosis,[27] four articles examined the self-medication hypothesis[28–31] and five articles studied tobacco use as a marker of greater illness severity in first-episode psychosis.[32–36]

A total of 2567 patients were included, the sample size ranged from 41 to 503 patients, with the mean age from 20.5 to 29.9 years, with the male percentage between 28.1% and 72.5%. Two studies are from Canada, four from Spain, one from the UK, one from Australia, one from the USA and one from Poland. Three studies were published between 2008 and 2012 and seven between 2015 and 2019, which reveals the growth of interest in this field of knowledge. Table 1 resumes the major findings of included studies.

Table 1 Characteristics of included studies.

Reference number	Country	Sample size	Age mean (SD)	Male percent	Diagnosis	Main aim	Prevalence	Relevant findings
Risk factor[27]	Canada	115	20.5 (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.
The self-medication hypothesis								
[28]	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.
[29]	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.
[30]	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.
[31]	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								
[32]	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.

Table 1 (*Continued*)

Reference number	Country	Sample size	Age mean (SD)	Male percent	Diagnosis	Main aim	Prevalence	Relevant findings
[33]	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.
[34]	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% premorbid nicotine dependence at baseline and 59.5% nicotine dependence in the 1 year follow-up evaluation.	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.
[35]	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.
[36]	Australia	193	22.0 (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.

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.[27] Most studies reported no significant gender difference in tobacco use in first-episode psychosis patients, with the exception of three studies: one study in which, when the FEP group

was stratified by smoking status, significant differences emerged in terms of gender, with 65% of male smokers versus 47% of female smokers[30]; a second study, in which the male smoker percentage was 64.8% against the male general percentage of 56.9%[31]; 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.[36]

Regarding age, there is a trend to consider smokers younger than non-smokers. In one study, when the FEP group was stratified by smoking status, significant differences emerged in terms of age, with a mean age of 28.1 in smokers and of 32.3 in non-smokers.[30] In a second study, smokers also indicated a mean age of 28.2, while non-smokers indicated a mean age of 32.2.[31] Lastly, heavy smokers were older than light/moderate smokers and non-smokers.[35]

Tobacco smoking as a potential risk factor for first-episode psychosis

One study included in this systematic review reported tobacco use as a potential risk factor for first-episode psychosis. This study demonstrated that the mean age of starting smoking was earlier than the onset of psychosis, which can be suggestive of a causal role of tobacco use in the onset of psychosis.[27] Besides this, the proportion of patients who had 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 older was 70% and lower for teenaged patients (49%), which also suggests that some patients initiate smoking after their first referral for treatment. In addiction and also supporting the idea of tobacco smoking as a risk factor for psychosis, smoker patients demonstrated nonsignificant better functioning compared to non-smoker 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 had been initiated in response to early prodromal features of illness.

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 tested the following hypothesis: tobacco-using FEP patients have better non-social and social cognitive performance than non-tobacco-using FEP patients; the tobacco smoker patient group presented worse non-social and social cognitive performance than the tobacco smoker and non-smoker control group.[28] The results revealed 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 does not support the self-medication hypothesis. Misiak et al. investigated the relationship between nicotine dependence and psychopathology in FEP patients, in particular, and more interesting for this review, they 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 in patients and non-smokers,[29] 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: 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.[30] 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 six weeks.[31]

Tobacco use as a marker for greater illness severity in first-episode psychosis

Four of the five studies included on this topic supported this hypothesis. An observational study was conducted to determine whether a cognitive benefit is achieved from smoking by comparing the cognitive performance of smoking and non-smoking FEP patients.[32] 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.[37] 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 one year after the initiation of antipsychotic treatment. The secondary objective was to explore the relationship between smoking and the symptoms and side effects of antipsychotics. It was observed that, six months after the initiation of antipsychotic treatment, the baseline differences between smokers and non-smokers in selective attention and working memory parameters were no longer significant. In addition, although the results of this study indicate that the initial clinical presentation is the same for the two groups, it was found that negative symptoms worsened significantly in smokers. With respect to the exploration of the association between smoking and the 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.[32] 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.[33] These study results encourage the hypothesis of tobacco being a marker for greater illness severity. In a one-year follow-up study of first-episode psychosis,[34] the following hypotheses were addressed: first, whether substance use (including tobacco) following illness onset impairs medication adherence; second, whether substance use is associated with poor outcome at one-year follow-up; and finally, whether the poor medication

adherence mediates this effect. The results indicate that in fact nicotine dependence in the first year after psychosis onset affects medication adherence. Furthermore, poor medication adherence predicts non-remission and, lastly, nicotine dependence in the first year after psychosis onset is associated with an increased probability of non-remission by the one-year follow-up and medication adherence is involved in this by mediating these effects.

A recent study has 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,[35] which reinforces the theory that cigarette smoking may be indicative of greater illness severity. In a 7.5-year follow-up study of a first-episode psychosis cohort, the conclusion was that smoking did not have any impact on clinical outcomes in individuals after a first-episode psychosis,[36] disproving 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 of this review that connected smoking with greater illness severity in first-episode psychosis.

Discussion

The current systematic review provides convincing evidence of high rates of tobacco use in first-episode psychosis, being in agreement, in fact, with the prior knowledge from previous studies.[3] A meta-analysis of worldwide studies suggests that smoking begins before the first referral for treatment[38] and two prospective cohort studies have indicated that smoking may begin before the onset of psychosis.[39,40]

Regarding the first topic, tobacco smoking as a potential risk factor for first-episode psychosis, it was observed that, in spite of the percentage of patients aged 20 years or older who smoked being greater than the percentage of teenaged patients, suggesting that a percentage of them started to smoke after the onset of the illness, in general the mean age of starting to smoke was significantly earlier than the age of functional decline and the onset of psychosis. In addition, smoker patients indicated nonsignificant better functioning compared to non-smoker patients. Those patients who started smoking had better premorbid social functioning than those who did not smoke, which is contrary to what would be expected if smoking had been initiated in response to early prodromal features of illness.[27] These results make it possible to have a cause–effect relationship instead of tobacco smoking simply being a consequence of first-episode psychosis, which is in line with the literature.[38–40]

Interestingly, Cannon and colleagues provided evidence for a relationship between an 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 seven tested (alcohol, hypnotics, cannabis, amphetamines, opiates, cocaine, and hallucinogens) dominated.[41] In this regard, it is possible that the importance of substance use can be because of its interactive effects with other substances, symptom severity or the 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.[42–50] By contrast, two studies found no significant differences in the general neurocognitive (non-social) functioning between nicotine user and non-user patients with psychosis.[51,52] 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[53]; 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 indicating performance-enhancing effects of nicotine in schizophrenia patients was not given, which may have contributed to the lack of a 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 the overall analysis, against the proposed hypothesis and the knowledge gained from previous studies. On the one hand, one study verified the association between severe dependence and lower severity of negative symptoms,[29] supporting the self-medication hypothesis. On the other hand, another study included did not support the theory once no significant difference in cognitive ability was found between smokers and non-smokers[30] and yet another concluded that tobacco smoking had no effect on psychopathology at initial presentation or on treatment response at six weeks.[31] Lastly, one of the included studies does not allow us to fully draw conclusions about this concern, as it indicated that tobacco use in FEP patients was 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 IQs.[28] So future longitudinal studies with healthy controls with similar IQs and also measures of pre- and post-substance use and FEP-onset cognitive function could overcome this limitation.

Previously, published studies on tobacco use as a marker for greater illness severity in first-episode psychosis were inconsistent. Some studies have demonstrated that current smokers with schizophrenia exhibit greater working memory impairments than non-smokers[54] and worse cognitive and functional outcomes than past smokers or those who had never smoked.[55] 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.[56] One study suggested 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 mentioned above, 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 terms of selective attention and working memory soon after the first stabilization, in a different way, six months after the initiation of antipsychotic treatment, the baseline differences in terms of selective attention and working memory parameters were no longer significant between smokers and non-smokers, with the exception of Stroop-I mean RT, and after one year performance was similar between the groups.[32] This could be explained if 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.[57,58] Another explanation for the improvements in non-smokers might be because of 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,[59] so this may have led non-smokers to achieve a baseline cognitive performance superior to 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 support the self-medication hypothesis. In addition, once smokers seem to have difficulty to benefit from practice effects from medication, it gives strength to the hypothesis that smoking may be a marker for more severe illness.

Another point that deserves attention is that smokers did not demonstrate 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 by 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 for more severe illness and/or its neurodevelopmental phenotype, as 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 for the two groups, it was found that negative symptoms worsened significantly in smokers.[32]

With respect to the exploration of the association between smoking and the symptoms and side effects of medication, these study results do not support that FEP patients smoke in order to reduce the side effects of antipsychotic drugs, since smokers did not exhibit fewer extrapyramidal side effects comparative to non-smokers.[32] A second study 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,[33] also encouraging the hypothesis of tobacco being a marker for greater illness severity. In yet other study included in this systematic review,[34] the results also agree with this assumption, demonstrating 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 an increased probability of non-remission by the one-year follow-up, suggesting the role of poor medication adherence 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 at the one-year follow-up, but its use during the year after psychosis onset predicted poor medication adherence at follow-up. Moreover, one study indicated that substance use increases the risk of non-remission, with a more than twofold increased likelihood of not achieving remission in the case of nicotine-dependent patients.[60] These results may suggest a possible new explanation for the association between tobacco use and worse outcomes at follow-up, which is poor medication adherence as a causal pathway by mediating this connection.

In the study of Grossman and colleagues,[35] 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 study was the only one which disproved the hypothesis since, after adjustment for cofounders, the conclusion was that there is no impact of smoking on clinical outcomes in individuals after a first-episode psychosis.[36] One possible explanation for this disagreement is that the first-episode psychosis study population that participated in this study may not be truly representative of this psychiatric population.

Conclusion

Based on this research study's analysis, 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 hypotheses – ''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 review, there is a trend toward a greater contribution by the first proposed hypothesis. The third hypothesis, ''Tobacco use as a marker for greater illness severity in first-episode psychosis,'' seems to be the one that can be asserted with the greatest confidence. One of the studies included suggested a possible new explanation for the association between tobacco use and worse 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 systematic review, if duly proven, may be very useful in clinical practice, primarily in view of prevention through anti-smoking measures in risk groups. Furthermore, tobacco use may be used as an accessory marker of staging of the disease, with a probable prognostic value. It is evident that primary and secondary preventive strategies in respect of tobacco use would be useful in first-episode psychosis, and should be included in early intervention in psychosis teams.

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Conflict of interest

The authors have no conflict of interest to declare.

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