Effects of Nicotine on Schizophrenia and Antipsychotic Medications: A Systematic Review

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Abstract

Background: Majority people with schizophrenia who smoke cigarettes, tend to be heavy smokers than other psychiatric patients and general population. Nicotine is one of the main components of cigarettes that can produce nicotinic interactions with antipsychotic drugs. Nicotine can also alleviate psychotic symptoms of schizophrenia. Aim: The objective for this systematic review is to examine the effects of nicotine and nicotine-based products in the treatment of schizophrenia, in comparison with placebo, no treatment or antipsychotic medication. Results: All studies comparing nicotine or other related products as the only treatment or adjunctive treatment for schizophrenia patients excluding the animal studies and case studies are reviewed. The use of traditional or known as typical antipsychotics may cause the patients to smoke frequently while patients taking atypical antipsychotics may smoke less. Patients who smoke may metabolize antipsychotics faster than non-smoking patients. There is less report related to smoking cessation among the schizophrenia patients. Conclusion: Neurobiological and psychosocial factors reinforce the high use of nicotine by patients with schizophrenia. Prior to smoking cessation implementation, it is crucial to understand on the ways and reasons for schizophrenia patients to consume nicotine for self-medicate symptoms which may lead to the development of new treatments for schizophrenia and nicotine dependence.

Keywords: Nicotine, Schizophrenia, Antipsychotics, Smoking

Introduction

Schizophrenia is a chronic, deteriorating and complex disorder that can affect the perception, language and communication. It also affect thought processes, volition and drive, attention and executive function of the individual [1]. A study showed that 68% of people with schizophrenia who smoked were classified as heavy smokers (25 or more cigarettes daily) compared with 11% of the general smoking population [2]. One of psychoactive component of tobacco is nicotine. Nicotine affects central nervous system and improves symptoms of schizophrenia by producing its positive reinforcing and addictive properties by activating dopaminergic pathway [3].
There are several reasons that cause the schizophrenia patient to smoke. The reasons are to break the monotony associated with the disorder, attain social contact, experience some pleasure, self medicate some of the symptoms of schizophrenia or side effects of antipsychotic medication and/or cope with nicotine withdrawal [1].

However, there are reports that some smokers with schizophrenia experience an acute increase in psychotic symptoms during attempts to quit smoking which favour a self medication model [4]. The positive symptoms include delusions, hallucinations, disorganized speech, and catatonic motor behaviors. The negative symptoms involve affective flattening, alogia and avolition [5]. The symptoms of schizophrenia may be explained by abnormalities in dopaminergic synaptic transmission that seems to produce excessive dopamine and leads to overactivity of synapses in the mesolimbic and prefrontal cortex.

Smoking may affect more significantly the negative than the positive symptoms of schizophrenia [6]. Individuals with schizophrenia who smoke or are administered nicotine improve on neuropsychological and psychophysiological test measures example attention and vigilance. Tobacco cessation among patients with schizophrenia has been associated with slowed motor speed but not with worsening of cognitive performance [1]. Some smokers with schizophrenia experience an acute increase in psychotic symptoms during temptation to quit smoking [3].

Significant attention should be put on the smoking cessation in schizophrenia patients [2]. Future studies should be focused on some pharmacotherapy strategies involving a higher-dose nicotine patch, combining nicotine gum and a patch, and augmentation medication to nicotine replacement [7]. Pharmacotherapies for schizophrenia may aim at the positive or negative symptoms, cognitive deficits and/or reduction of extrapyramidal symptoms.

**Objectives**

Hence, the objectives of this review are to study the effects of nicotine and nicotine-based products in the treatment of schizophrenia, in comparison with placebo, no treatment or antipsychotic medication. Besides, studies were reviewed to determine how nicotine can affect the usage of antipsychotic drugs. This could trigger a new study to be done in the future for developing a suitable therapy for smokers of schizophrenia patients.

**Rational of study**

To understand the effects of nicotine and the nicotine-based products in the treatment of schizophrenia.

**Method**

**Data Sources**

A systematic review was conducted by using databases for example Springer Link, and Science Direct to search for relevant articles for this study. Google Scholar and the literature search of Mendeley were used as the important search engines which are related to these databases. The keywords ‘nicotine’, ‘schizophrenia’ and ‘antipsychotics’ were used to search all major research databases. All studies searched were examined by looking to its abstracts related to the objectives of this systemic review, although not all were reviewed here. The review focuses on studies published since 1997 with the relevant evidences.
**Inclusion Criteria And Exclusion Criteria**

This review only includes the articles that present the data of effects of nicotine on schizophrenia patients with or without the treatment using antipsychotic medications. However, it also includes other antipsychotic disorders as comparison to schizophrenia. Only research articles between year 1997 to 2014 are considered in this systemic review.

Several studies related to the animal case studies and related to narcoleptic–induced movement disorders, nicotinic receptor interactions and molecular mechanisms underlying the etiology of schizophrenia were excluded from this systematic review.

**Search Strategy**

PRISMA checklist flow diagram was used to guide the systematic analysis for all the research papers located. The Science Direct database found 3059 articles. The Springer Link search yielded 1050 articles while Google Search provided 19 500 articles. The duplications of articles between these databases were removed and found 185 articles. After screening all the articles related to the inclusion criteria outline, only 48 full text articles are assessed for eligibility. The research articles with too detail scientific information regarding the pharmacologic effects of nicotine on brain, animal studies and case reports were excluded. The total of 30 articles is reduced to 16 articles after thorough qualitative analysis. Then, the data were extracted to be included in this systematic review.
PRISMA 2009 Flow Diagram

1.1 IDENTIFICATION

- Records identified through database searching (n=3059 Sciencedirect)
- (n=1050 Springer Link)

1.2 ELIGIBILITY

- Additional records identified through books (n=0)

1.3 INCLUDED

- Records after duplicates removed (n=185)

1.4 SCREENING

- Records screened (n=48)
- Full-text articles assessed for eligibility (n=30)
- Studies included in qualitative synthesis (n=16)

- Full-text articles excluded, with reasons (n=10)
Results

Description of studies

Excluded studies

About 18 references are identified and rejected as not relevant on the basis of information provided in the title and abstract and these articles had wide inclusive criteria. Due to the reasons of lack of randomization and irrelevant interventions or outcomes, about 10 studies were excluded. The most important reason of being excluded is because the studies were based on experiment in vitro.

Besides, due to the inappropriate study participants, one study needs to be excluded. Although it had normal healthy people and schizophrenia patients but no useful data can be extracted from it. One study is excluded as it concerns on the relationship between cigarette smoking and DNA methylation without relating to schizophrenia specifically. Some studies have inappropriate interventions as the interventions were not nicotine.

Included studies

No studies really met the inclusion criteria for this study. However, there is a study by Matthews and her colleges that discussed about the effects of typical and atypical antipsychotic drugs to smoking behavior of schizophrenia patients. This study suggested that typical antipsychotics may increase basal smoking and decrease patient’s ability to stop smoking whereas atypical antipsychotics decrease basal smoking and promote smoking cessation [8].
<table>
<thead>
<tr>
<th>No</th>
<th>Author</th>
<th>Year</th>
<th>Publisher</th>
<th>Study Type</th>
<th>Title</th>
<th>Summary</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Ücok et al.</td>
<td>2004</td>
<td>Psychiatry and Clinical Neurosciences</td>
<td>Case series</td>
<td>Cigarette smoking among patients with schizophrenia and bipolar disorders.</td>
<td>To investigate the ratio of smokers and the relationship of cigarette smoking to clinical features in patients with schizophrenia and bipolar disorders.</td>
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<tr>
<td>2</td>
<td>Kelley et al.</td>
<td>2011</td>
<td>Schizophrenia Bulletin</td>
<td>Case control study</td>
<td>Cigarette smoking and mortality risk in people with schizophrenia.</td>
<td>Cigarette smoking, particularly in people aged 35–54 years, contributes to an increased risk of death. Greater smoking severity significantly increases this risk. Smoking cessation in people with schizophrenia deserves significant attention.</td>
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<td>3</td>
<td>Ziedonis &amp; George</td>
<td>1997</td>
<td>Schizophrenia Bulletin</td>
<td>Cross sectional studies</td>
<td>Schizophrenia and nicotine use: report of a pilot smoking cessation program and review of neurobiological and clinical issues.</td>
<td>Pharmacotherapy strategies of a higher-dose nicotine patch, combining nicotine gum and a patch, and augmentation medication to nicotine replacement should be evaluated in future studies in this population.</td>
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<td>4</td>
<td>Tsuda, Saruwatari, &amp; Yasui-Furukori,</td>
<td>2014</td>
<td>BMJ Open</td>
<td>Meta analysis</td>
<td>Meta-analysis: the effects of smoking on the disposition of two commonly used antipsychotic agents, olanzapine and clozapine.</td>
<td>This study suggest that the doses of olanzapine and clozapine should be reduced by 30% and 50%, respectively, in non-smokers compared with smokers in order to obtain an equivalent olanzapine or clozapine concentration.</td>
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<td>5</td>
<td>Spring, Pingitore, &amp; McChargue</td>
<td>2003</td>
<td>The American Journal of Psychiatry</td>
<td>Qualitative study</td>
<td>Reward value of cigarette smoking for comparably heavy smoking schizophrenic, depressed, and nonpatient smokers.</td>
<td>Schizophrenic and depressed smokers recognize have many drawbacks associated with smoking, but compared to nonpatients who smoke as heavily, they also perceive more benefits and find cigarettes more appealing than alternative rewards.</td>
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<tr>
<td>No.</td>
<td>Author(s)</td>
<td>Year</td>
<td>Journal</td>
<td>Study Design</td>
<td>Mediation</td>
<td>Findings</td>
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<td>6</td>
<td>Wijesundera, Hanwella, &amp; de Silva</td>
<td>2014</td>
<td>Annals of General Psychiatry</td>
<td>Cross-sectional studies</td>
<td>Antipsychotic medication and tobacco use among outpatients with schizophrenia: a cross-sectional study.</td>
<td>Prevalence of smoking was less than in many countries. This is influenced by prevalence in the general population and low affordability. Risk of tobacco use was significantly less among patients treated with clozapine.</td>
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<td>7</td>
<td>Robert et al.</td>
<td>2002</td>
<td>Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology</td>
<td>Randomised control clinical trials</td>
<td>Effects of cigarette smoking and nicotine nasal spray on psychiatric symptoms and cognition in schizophrenia.</td>
<td>These results suggested that acute smoking of cigarettes may transiently decrease negative symptoms in patients with schizophrenia, but it is unclear whether this effect is attributable to nicotine, other components of cigarettes, or the act of smoking.</td>
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<td>8</td>
<td>Mcneill</td>
<td>2001</td>
<td>Smoke-free London.</td>
<td>Systematic reviews</td>
<td>Smoking and mental health</td>
<td>Smokers with mental health problems are motivated to quit and can be successfully helped to stop smoking. Effective treatments include group therapy, NRT and bupropion.</td>
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<td>9</td>
<td>Zammit et al.</td>
<td>2003</td>
<td>The American Journal of Psychiatry</td>
<td>Cohort study</td>
<td>Investigating the Association Between Cigarette Smoking and Schizophrenia in a Cohort Study Stanley</td>
<td>The authors investigated whether cigarette smoking alters the risk of subsequently developing schizophrenia. No longitudinal studies have previously examined this relationship. Cigarette smoking may be an independent protective factor for developing schizophrenia.</td>
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<td>10</td>
<td>Allen, et al.</td>
<td>2011</td>
<td>The American Journal of Psychiatry</td>
<td>Random, placebo control study</td>
<td>Effect of Nicotine Replacement Therapy on Agitation in Smokers With Schizophrenia: A Double-Blind, Randomized, Placebo-</td>
<td>Participants were 40 smokers 18–65 years of age with schizophrenia were screened for agitation with the excited component subscale of the Positive and Negative Syndrome Scale (PANSS) and for nicotine dependence with the Fagerström Test for</td>
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<tr>
<td></td>
<td>Controlled Study</td>
<td>Nicotine De-pendence.</td>
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<td>11</td>
<td>Matthews at al.</td>
<td>CNS drugs Review The role of antipsychotic in smoking and smoking cessation. The study show a better characterization of what features of antipsychotic medications alter smoking behaviours which may lead to new treatments.</td>
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<td>12</td>
<td>Harris et al.</td>
<td>Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology Cross sectional study Effects of Nicotine on Cognitive Deficits in Schizophrenia Attentional function was increased in non-smokers but decreased in nicotine-abstinent smokers after nicotine administration.</td>
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<td>13</td>
<td>Kumari &amp; Postma</td>
<td>Neuroscience and Biobehavioral Reviews Review Nicotine use in schizophrenia: The self medication hypothesis This review relating the behaviour to sensory gating and cognitive deficits in this disorder that have been viewed as major support for the self-medication hypotheses.</td>
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<td>14</td>
<td>Lyon</td>
<td>Psychiatric Services Review A review of the effects of nicotine on schizophrenia and antipsychotic medications. Nicotine affects both schizophrenia and antipsychotic medications.</td>
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<td>15</td>
<td>Montoya &amp; Vocci</td>
<td>NIH Public Access Review Medications Development for the Treatment of Nicotine Dependence in Individuals with Schizophrenia Nicotine improves neuropsychological deficits associated with schizophrenia such as in the P50 evoked auditory potentials, spatial working memory, and attention. Studies have evaluated the efficacy of smoking cessation medications in patients with schizophrenia.</td>
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<td>16</td>
<td>Punnoose &amp; Belgamwar</td>
<td>The Cochrane Collaboration Review Nicotine for schizophrenia This review included all the randomised clinical trial comparing nicotine and placebo. Further research of nicotine for schizophrenia by parallel group design randomised controlled trials</td>
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generally, the findings show that nicotine has some effects on schizophrenia and antipsychotic medications. daily cigarette consumption among the patients with schizophrenia was higher than that for the bipolar patients, and control group. recent data indicate that the smoking rate in schizophrenia is somewhat higher than in other psychiatric disorders, such as mood disorder [9] and bipolar disorder [10]. analysis of other psychotic illnesses including affective psychoses and substance-induced psychoses did not show the same association with smoking, suggesting that smoking may have a rather specific effect in reducing the development of schizophrenia but not of other psychotic disorders [11].

the reasons for the widespread smoking behavior seen in schizophrenia are not well understood but several possible mechanisms have been advanced. most of these suggest that nicotine as a form of self-medication to reduce the side effects of antipsychotic medications, to enhance the therapeutic effect of antipsychotics and so alleviate negative symptoms and or to improve a number of cognitive deficits associated with schizophrenia [12].

smoking cessation in people with schizophrenia deserves significant attention, since smoking cigarettes will increase the risk of death [2]. moreover, some antipsychotic medications were affected with smoking cigarettes. for example, olanzapine and clozapine should be reduced by 30% and 50%, respectively, in non-smokers compared with smokers in order to obtain an equivalent olanzapine or clozapine concentration [13].

the heightened reward value of smoking warrants attention in tailoring tobacco control interventions for schizophrenic smokers. this is because the prevalence of smoking in schizophrenia is higher than in the general population. biological, psychological and social factors influence smoking in patients with schizophrenia [14]. therefore, smoking cessation medications should also be considered for schizophrenia patients since many studies have evaluated the efficacy of smoking cessation medications in patients with schizophrenia [1].

discussion

effects of nicotine

nicotine interacts with nicotinic receptors on nerves throughout the body and brain. in the brain, nicotine acts on nicotinic acetylcholine receptors (nachr) causing transmitter to release and metabolized. chronic nicotine use causes inactivation of the receptors which might cause a subsequent increase in their number. the brains of smokers have an increased number of high affinity nicotinic receptors [15]. however, people with schizophrenia have a lower number of nicotinic receptors. leonard hypothesized that this might be due to an abnormality of the genes relating to neuronal nicotinic receptors in schizophrenia.
Nicotine causes an elevation of concentrations of circulating hormones for example norepinephrine and epinephrine and an increase in the release of vasopressin, beta-endorphin, ACTH and cortisol which are thought to cause stimulatory effects of nicotine on the central nervous center. Thus, nicotine causing positive reinforcing and addiction. There is also an evidence of improved focusing of attention in smokers over nonsmokers [16]. The future schizophrenia patients smoke cigarettes to improve pre-morbid anxiety and depression [17]. In patients with various disorders, have indicated that cigarette smoking and/or nicotine may improve memory, attention, and spatial perception [6].

**Antipsychotic medications for schizophrenia**

People with schizophrenia and some other mental health disorders are often treated with antipsychotic medications. Generally, antipsychotic drugs block dopamine receptors in the brain which block the passage of nerve signals by dopamine. Hence, they reduce the symptoms of schizophrenia [18] As the serotonin (5-HT) system also interacts with the dopaminergic system, 5-HT may also be involved [19].

Antipsychotic medications are divided into first generation (typical) and second generation (atypical) drugs. Typical Medications such as Haloperidol were introduced into the market from the 1960s onwards. Atypical medications such as Clozapine were developed during the 1990s and work on a wider range of symptoms and tend to be associated with fewer side effects [20].

There are two types of symptoms in schizophrenia, which are positive symptoms and negative symptoms. Positive symptoms (such as voices, hallucination, delusion and confusion) are thought due to excess of dopamine in brain, whereas negative symptoms (such as withdrawal, anhedonia, inertia, lack of motivation) are due to concurring deficits of dopamine in the cortex [21].

People with schizophrenia who smoke present more positive psychiatric symptoms of schizophrenia than nonsmokers [22]. Antipsychotic medication more effectively controls positive symptoms of schizophrenia than negative symptoms. Newer drugs appear also to act more effectively on negative symptoms. The example is Clozapine, which have shown the potential to decrease negative symptoms, are thought to do so by increasing cortical dopamine levels, possibly in a similar way to nicotine [23].

**Smoking and antipsychotics**

Cigarette smoking can decrease levels of many antipsychotics used to treat schizophrenia by as much as 50 percent by increasing metabolism of that medications [24]. This leads to the need of a higher dosage in smokers with schizophrenia to achieve therapeutic blood levels relative to non-smoking schizophrenia patients [7].

A recent study on schizophrenia patients in British Columbia found that patients treated with atypical (second generation) antipsychotics especially Clozapine had significantly lower expired air carbon monoxide values (an indicator of smoke inhalation) than patients treated with depot (injected) neuroleptics [25]. Clozapine may reduce smoking through its specific action of reducing cognitive deficits. Another possibility is that the improved therapeutic response to Clozapine also reduces risk of smoking [14].
Decreased smoking rates do not appear to be associated with other atypical antipsychotic medications [26].

A study of 39 patients with schizophrenia spectrum disorder found that patients on typical (first generation) antipsychotics for example Haloperidol had the highest prevalence of smoking [26]. Typical antipsychotic drugs have a strong dopamine blocking action and smoking might able to relieve some of the side effects through its efficacy in stimulating dopamine release. However, typical antipsychotics are probably less effective than Clozapine in correcting abnormal sensory processing and cognitive impairment associated with schizophrenia [27].

**Smoking/Nicotine reduction**

According to a study [28], it showed that there is no difference in the effect of wearing nicotine or placebo patches during withdrawal on psychotic symptoms. This data suggests that problems patient might have during the early stage of smoking or nicotine withdraw for example agitation are not related to increased psychotic symptoms.

A recent study involved 101 patients with schizophrenia in which antipsychotic medication was discontinued. At baseline, smokers had more positive symptoms and were apparently more functionally impaired than nonsmokers. This difference was however no longer evident after a 30-day medication discontinuation period [1]. This suggests an interaction between the medication, smoking and positive symptoms of schizophrenia.

Based on a study finding [29], the transdermal delivery of nicotine is important for its predictability but nicotine gum should also be effective and has a rapid onset. Hence, it may be necessary to combine gum with the patch or otherwise obtain higher doses of antipsychotics to better manage agitation for nicotine dependence population. The nicotine replacement in addition to usual care reduces agitation by about one-third.

Another study [30] was consistently using a combination of antipsychotic medication and nicotine transdermal patch. It is possible that commonly used smoking cessation aids may alter the effects of antipsychotics on smoking. More research is required to better understand the effects of antipsychotics on smoking cessation attempts and how any positive effects might be enhanced by combination with other medications.

The findings of another study [1] showed that the patients appreciated the drawbacks of smoking as fully as the non-psychiatric comparison subjects but considered them outweighed by smoking’s advantages. The schizophrenic and depressed smokers chose smoking twice as often as the normal subjects than other pleasant activities. Thus, the voluntary smoking cessation is quite difficult unless the benefits of smoking cessation are higher than the non-psychiatric subjects received. This exhibit greater nicotine dependence in schizophrenic and depressed patients than normal subjects. The smokers need to experience a decline in the perceived advantages of smoking in an attempt to quit smoking [31]. Nevertheless, the studies on the ‘self-medication’ hypotheses about smoking and mental illnesses have shown mixed results. One study has shown that patients treated with clozapine reduced smoking and this reduction is due to reduction in positive and negative symptoms [32]. However another studies by Frakenburg and colleagues have shown no effects on measures of akathisia, positive or negative symptoms, global
symptoms reading or vocabulary scores. This study showed that the smoking cessation in patients treated with clozapine was associated with weight gain and it also suggests that smoking might be used to counter the sedating effects of antipsychotics [33]. Hence, definitely stating that smoking is associated with self-medication had lack of evidences and requires further research to be done on this issue.

Conclusion

Nicotine in cigarettes has significant implications for schizophrenia patients who take antipsychotic medications. Nicotine may increase dopamine which believed to improve negative symptoms of schizophrenia. Typical antipsychotics are likely to increase smoking whereas the atypical antipsychotics may decrease this behavior. Heavy smoking may decrease the blood levels of antipsychotic medication by 50 percent. There are several recommendations based on the studies reviewed. The schizophrenia patients should try to stop smoking to avoid addiction and other health problems. Patients with schizophrenia who are dependent on nicotine should not be denied smoking opportunities without being provided alternatives. The use of cigarettes should be monitored. The clinicians conducting psychiatric evaluations of schizophrenia patients should determine how many patients smoke and consider prescribing antipsychotic medications for them. This is due to the fact that smoking can alter the metabolism of psychotic drugs. Special smoking cessations programs for schizophrenia patients should be developed especially for the chronic inpatients.

Limitation

Research regarding the therapeutic effects of smoking on individuals with schizophrenia has produced mixed results, which may be primarily due to study design. Many studies had very small sample sizes, lacked information on confounders, and, in some cases, were cross-sectional rather than longitudinal, thus only capturing data at a single point in time. The journals obtained did not undergo critical appraisal to know the quality of the journals. Some relevant journals could not be obtained as the journals need to be purchased online.

References


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