

Smoking in schizophrenic patients: A critique of the self-medication hypothesis

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Abstract

A common remark among laypeople, and notably also

among mental health workers, is that individuals with mental illnesses use drugs as self-medication to allay clinical symptoms and the side effects of drug treatments. Roots of the self-medication concept in psychiatry date back at least to the 1980s. Observations that rates of smokers in schizophrenic patients are multiple times the rates for regular smoking in the general population, as well as those with other disorders, proved particularly tempting for a self-medication explanation. Additional evidence came from experiments with animal models exposed to nicotine and the identification of neurobiological mechanisms suggesting self-medication with smoking is a plausible idea. More recently, results from studies comparing smoking and non-smoking schizophrenic patients have led to the questioning of the self-medication hypothesis. Closer examination of the literature points to the possibility that smoking is less beneficial on schizophrenic symptomology than generally assumed while clearly increasing the risk of cancer and other smoking-related diseases responsible for early mortality. It is a good time to examine the evidence for the self-medication concept as it relates to smoking. Our approach is to focus on data addressing direct or implied predictions of the hypothesis in schizophrenic smokers.

Key words: Nicotine; Nicotinic receptor; Dopamine; Positive-negative symptoms; Side effects; Age of onset; Smoking cessation

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Core tip: The high rates of smoking in mentally ill people have led to the uncritical acceptance that these individuals smoke to self-medicate with nicotine. A self-medication hypothesis (SMH) proposed three decades ago set the stage for explanations for smoking associated with mental illness. Here, we review the origins of the SMH and apply stated and implied predictions to smoking in patients. Our conclusions are that there is some support for the SMH explanations for smoking in schizophrenic patients.

However, there are sufficient contradictory data, and predictions not adequately tested, to justify continued empirical studies and new alternative hypotheses to the self-medication concept.

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INTRODUCTION

That smoking cigarettes is common among people suffering psychiatric disorders has given renewed popularity of the idea that patients may be self-medicating. Particular attention to self-medicating by smoking has been on schizophrenic patients.

The self-medication concept is reminiscent of an equally popular belief about cravings for certain types of food, given credence in psychology and physiology as "specific hungers"^[1]. Anecdotal observations pointed to humans craving certain foods with pregnancy or other states accompanying marked changes in one's nutritional needs. The implication is that the person lacks a necessary nutrient and somehow that unconscious deficiency is transmitted into a specific hunger signal. Both the specific hunger and self-medication concepts recall the famous book by Cannon entitled "Wisdom of the Body"^[2]. Subsequent research^[3] and anecdotal observations question the generality of the concept.

The specific hungers concept also could be criticized by failures to identify neural mechanisms explaining nutrient deficiency inducing specific motivations. The self-medication concept, however, has that criticism covered. Plausible, neural mechanisms are well established that provide a means by which smoking could influence the brain. Nicotine is the major psychoactive component in tobacco and nicotine has a direct influence on cholinergic neurotransmitter pathways. Let us now turn to basics of the self-medication concept.

SELF-MEDICATION HYPOTHESIS

The initial formal presentation in the psychiatric literature of the self-medication hypothesis (SMH) often is attributed to Khantzian^[4]. In an attempt to understand substance abuse, Khantzian noted clinical observations that the drug of choice by drug abusers is not random. Drug-dependent individuals under care for a psychiatric condition chose a drug related to the symptoms accompanying their specific mental disorder. Khantzian observed that cocaine is most often abused by psychiatric patients because of the stimulant qualities of the drug that "relieve distress associated with depression, hypomania, and hyperactivity"^[4].

Thus, the self-medication concept could be described as being composed of several principles: (1) Diagnosed or undiagnosed mental disturbances precede initial substance use; (2) Mentally ill individuals are drawn to psychoactive substances more than are healthy people; (3) Deriving continuous symptomatic relief from the drug, the mentally ill person is led to excessive use with the consequence that they are disproportionately represented in addiction groups; and (4) The class of drug most attractive to the person is determined by the symptoms suffered by the person^[5].

Although Khantzian's writings on the SMH remain focused on abuse of illicit drugs^[6,7], the concept has been expanded to use of licit drugs, most notably alcohol and nicotine. For the latter, expansion was stimulated by epidemiological studies revealing that a remarkably high percentage of schizophrenic patients are regular smokers^[8].

The SMH also has been expanded to suggest that smoking relieves psychiatric symptoms, but also the side effects of antipsychotic medications. Indeed, recent authors have emphasized the latter far more than the former to explain smoking by schizophrenic patients. The effects of nicotine on the brain and behavior would seem a plausible mechanism to alleviate well-known side effects of the medications, especially those induced by typical neuroleptics.

NEUROBIOLOGY OF NICOTINE

The most common form of self-administration of nicotine is smoking cigarettes. The main components of tobacco smoke are nicotine and the various particulate matters from the burning of tobacco collectively termed as tars.

Tars are carcinogens and responsible for most if not all smoking-related diseases^[9,10]. Nicotine clings to tar droplets to be absorbed by tissues in mouth, nose, throat and, especially, alveoli of lungs. Over decades of smoking, these tissues begin to reveal pathology that often continues into development of disease states. The contribution of nicotine to tobacco-related diseases is its addictive properties that motivate the smoker to continue exposing himself to the tars of cigarettes^[11].

Nicotine is the main neurologically active agent in tobacco. Nicotine from a puff of smoke is rapidly delivered to the brain *via* venous circulation, the left ventricle of the heart and then the arterial bloodstream. Time of this route to the brain is 10-20 s^[12]. It is the rapid rise in blood levels and delivery to the brain thought to be key to addiction to a drug^[13].

Nicotine binds nicotinic receptors that are targets for the endogenous neurotransmitter acetylcholine (ACh) in the peripheral and central nervous systems^[14]. The nicotinic receptor (nAChR) is one of two subtypes in cholinergic pathways; the muscarinic subtype is the other one. There are also subtypes of nicotinic receptors^[15], identified with Greek letters and numbers.

Cholinergic pathways have their origins primarily

in the basal forebrain cholinergic complex and the pontomesencephalotegmental cholinergic complex^[16]. Cholinergic neurons, and nAChRs, are strategically positioned in forebrain, midbrain and hindbrain to influence most of the other neurotransmitters in the central nervous system (CNS), most notably the monoamines and amino acid transmitters^[17,18].

A particularly striking feature of nicotine exposure is its capacity to increase the numbers of the nicotinic receptors in the brain. Findings in both humans and animal models have confirmed that long-term exposure to nicotine upregulates central nAChR numbers^[19-21].

ACH, SMOKING AND THE NEUROPATHOLOGY OF SCHIZOPHRENIA

Schizophrenia is an intractable neurological disease most often first diagnosed after a psychotic episode in the late teens and early twenties. Although the worldwide prevalence rates of schizophrenia are likely less than the commonly cited 1%^[22], patients are impaired in every aspect of daily functioning. Characterizing schizophrenia symptomology as positive (delusions, auditory hallucinations) and negative (anhedonia, apathy, cognitive degradation) have proven useful for treatment and prognosis^[23].

Neurotransmitter systems have been a particular focus of research to identify underlying mechanisms of schizophrenia. Dopamine (DA) was the neurotransmitter initially implicated in the disorder. The DA hyperactivity hypothesis was proposed after revelations that the D2 receptor subtype was blocked by the original anti-psychotic medications^[24,25]. Involvement of DA remains central to most schizophrenia hypotheses because only drugs that antagonize the D2 receptor are effective anti-psychotics^[26]. The involvement of ACh in schizophrenia may be the capacity of nAChR to regulate dopamine activity^[27].

Most commonly, activation of the nAChR increases the release of dopamine in DA pathways^[28]. Nicotine interacts with DA neurons in midbrain sites that are the origins of projections to subcortical and cortical regions. The substantia nigra projects *via* the nigrostriatal DA pathway to the striatum and is considered a key to positive symptoms of schizophrenia. The ventral tegmental area sends DA projections to limbic and cortical structures. Activation of the mesolimbic pathway is likely the source of nicotine dependency. This pathway continues to the cortex as the mesocortical pathway, also known as the mesocorticolimbic pathway^[29].

It was ultimately recognized that the DA hyperactivity hypothesis was too broad to describe the various features of schizophrenia. Patients often have abnormally high DA activity in nigrostriatal regions but abnormally low prefrontal DA activity^[30]. A revision of the DA model concluded the negative symptoms are from prefrontal hypoactivity and the positive symptoms from striatal hyperactivity. The revision also explained the

effectiveness of DA antagonist anti-psychotic drugs being most effective on the positive symptoms and less so on negative symptoms.

Other neurotransmitters and hypotheses emerged with the development of atypical anti-psychotic medications that antagonize serotonin (5-HT). Unlike the older, typical neuroleptics that normally do not provide improvement in negative symptoms, clozapine and other atypicals relieved both negative and positive symptoms in some patients. Because clozapine is both a dopamine and serotonin antagonist, these observations were followed by hypotheses for the involvement of 5-HT in schizophrenia^[31].

More recently, glutamate hypoactivity has been hypothesized as contributing to the pathophysiology of schizophrenia^[32]. Antagonists of the NMDA subtype of glutamate receptor leads to less stimulation of γ -aminobutyric acid (GABA) interneurons. The downstream consequence is increased DA release in limbic structures^[33].

Acetylcholine has emerged as another candidate neurotransmitter in the etiology of schizophrenia. Although antipsychotic drugs reduce some psychotic symptoms by antagonizing the D2 receptor, the medications have other pharmacological properties that may mitigate cellular mechanisms underlying the disease^[34]. Indeed, several of the atypical anti-psychotic drugs show high affinity for ACh receptors^[35]. Also, preclinical findings have confirmed interactions between ACh and DA. For example, nicotine binding of nAChR can influence DA release in cortical and subcortical areas^[27,36].

SMH APPLIED TO SCHIZOPHRENIA

Khantzian's self-medication concept can be applied to cigarette smoking. Adapting the self-medication model to smoking by schizophrenic patients would appear to make specific predictions related both to the psychiatric symptoms of the disease and to the side effects of drug therapies used as treatments. Although not an exhaustive list, we have generated a set of predictions that appears in Table 1.

There are both direct and indirect findings in the literature in relation to all of these predictions. We now will review the evidence for each.

If smoking relieves symptoms in schizophrenia, patients should be more likely to smoke than healthy people

There is overwhelming evidence throughout the world that people with schizophrenia are more likely to smoke cigarettes than are healthy people^[37]. The prodigiously high 80%-90% smoker rates cited in the literature and in popular media are questionable^[38,39]. Nonetheless, the more reasonable figure of 60%-65%^[8] is significantly higher than the approximately 25% prevalence rate among North Americans.

Moreover, a schizophrenic smoker consumes more cigarettes each day and with a greater preference

Table 1 Predictions for the self-medication hypothesis as applied to smoking in schizophrenic patients

Item	Prediction
A	If smoking relieves symptoms in schizophrenia, patients should be more likely to smoke than healthy people
B	Smoking behaviors and their effects in patients and healthy people should be different
C	Age of onset for regular smoking should correspond to the age of appearance of the first psychotic symptoms
D	Smoking and non-smoking patients should show behavioral differences
E	If smoking relieves side effects of antipsychotic medications, smoking in patients should change with drug treatments
F	If they smoke for reasons other than simply the addictive properties of nicotine, success of smoking cessation programs should be lower in schizophrenic smokers than in healthy smokers
G	Schizophrenic smokers who are successful at smoking cessation should experience worsening of symptoms of the disease or medications
H	The pathology of neurobiological systems (brain regions, circuits and neurotransmitters) underlying schizophrenia should be the same as those influenced by the nicotine in cigarette smoke

for unfiltered, high nicotine and high tar cigarettes than does a smoker in the general population^[40]. Schizophrenics also extract more nicotine per cigarette than do healthy smokers^[41].

That cigarettes and nicotine hold a unique sway over schizophrenic individuals is suggested by comparisons with other psychiatric patients. Schizophrenic patients are more likely to smoke than patients diagnosed with other psychiatric conditions^[8]. These data stand in contrast to the use of other unprescribed drugs. Although alcohol and illicit drug use by schizophrenic outpatients are estimated at circa 50%, this is no higher than many other psychiatric populations. Individuals diagnosed with major depression, attention deficit hyperactivity disorder and post-traumatic stress disorder are also attracted to illicit drugs and alcohol at rates similar to schizophrenic patients^[42].

Smoking behaviors and their effects in patients and healthy people should be different

As predicted by the SMH, there are differences between the responses of schizophrenic smokers and healthy smokers. Yet, the overall data are mixed, with some supporting the SMH and others contradicting the hypothesis.

Schizophrenic patients report that they smoke for many of the same reasons indicated by smokers in general. However, there are differences in the ratings of certain motivations. For example, schizophrenic patients highly rank the stimulant properties of cigarettes^[43], suggesting they associate smoking with relief from schizophrenia symptoms or, more likely, from medication side effects.

Interestingly, two extensive studies on the motivation to smoke found that healthy controls more prominently cited increased social activity than schizophrenic smokers^[43,44]. This is surprising because a prominent symptom of the disease is asociality, and one would expect relief from asociality would be attractive to patients. Indeed, an experiment designed to assess the social influences of nicotine failed to support the SMH. Schizophrenic and healthy smokers were administered nicotine after 24 h abstinence from smoking. There were no group differences on social cognition or facial affect recognition. Moreover, there were no differences

in subjective stress reports^[45].

This is in contrast to the conclusions of other authors that smoking schizophrenics are more sensitive to acute nicotine abstinence^[46]. Upon finding abstinence-induced decrements in visuospatial working memory task only in the schizophrenic smokers, the authors concluded that patients experience greater cognitive declines than in non-patient smokers^[47].

Other studies in this literature have used various measures of cognition to distinguish between schizophrenic and healthy smokers. Smoking in both groups has been reported to enhance some aspects of cognitive function, working memory and, especially, sustained attention to visual cues^[48]. However, patients who smoke may benefit more; for example, schizophrenic subjects had better information processing scores than healthy smokers on a selective attention task^[49]. A review of the cognition literature concluded that nicotine from smoking was effective in remediating many of the cognitive deficits accompanying schizophrenia whereas evidence for gains in cognitive performance in healthy smokers was more suspect^[50].

Age of onset for regular smoking should correspond to the age of appearance of the first psychotic symptoms

A key principle for Khantzian in his SMH was that mentally ill individuals seek out drugs, including nicotine, to mollify the symptoms of their condition. We interpreted this to predict that non-smoking patients would initiate smoking upon development of full-blown psychosis. Yet that is rare. A report of 176 patients found that only few nicotine users had started after onset of psychoses^[51]. More commonly, regular smoking of cigarettes precedes a schizophrenia diagnosis.

Timing of the onset of the smoking habit with onset of schizophrenia has been a fertile field for speculation. There is little doubt that the onset of smoking most often begins prior to diagnosis. The debates are about its meaning.

For many, the significant time lapse between smoking onset and psychosis is the most damning of the predictions from the SMH. Others have dismissed the age of onset differential as being expected because symptoms may appear before a formal diagnosis. Indeed, we know that adults who develop schizophrenia

may show distinctive neuromotor function as early as 2 years of age^[52]. However, it is unclear how neuromotor activity is related to the array of cognitive, communication and motivational symptoms of adult schizophrenia^[53].

Other symptoms that more closely match the disease could, of course, emerge and beginning the cigarette habit could correspond to first blush of those early and presumably subclinical symptoms. This is a position that resists careful scrutiny because the ontogeny of schizophrenia is unknown. It is difficult to know when schizophrenia begins. The premorbid stage is characterized by deficits shared by myriad other disorders^[54].

The prodromal phase, the period when psychosis onset is not far off, for the distinguishing positive symptoms of the disease is unlikely to extend past 1-2 years prior to diagnosis^[23]. As pointed out by Tandon *et al*^[23], there is an unsubstantiated assumption that premorbid features are accurate precursors of the prodromal symptoms leading to schizophrenia. More striking is that most individuals with psychotic symptoms in a presumed prodromal phase do not go on to develop schizophrenia.

An imperfect attempt at an empirical resolution is to use retrospective data to identify the age of onset of smoking relative to age at which disruptive symptoms would have occurred. The literature offers some support for close timing of smoking relative to psychosis onset that supports the SMH while other reports do not.

Initiation of regular smoking has been cited to be about 2 years before the age of onset of schizophrenia^[55], suggesting that smoking was within the time frame of the prodromal period. These data are consistent with an earlier report that the age of onset for smoking was 2.3 years before symptomatic onset^[56]. Importantly, the latter study found that regular smoking was more closely tied to disease onset with schizophrenia than the 8.6 years differential observed with other psychotic diagnoses. Also, there is some evidence that prodromal symptoms and early psychotic episodes are associated with a progressive increase in smoking behavior^[57]. Finally, a significant number of schizophrenic patients began regular smoking into their late thirties, which likely corresponds with manifestation of symptoms and, especially, chronic exposure to medications^[58].

In opposition are studies reporting a longer differential between onset of smoking and schizophrenia, and the absence of data of initial symptoms when smoking was initiated. Most schizophrenic patients report they began smoking around the same age as healthy controls, *i.e.*, in their teenage years and well before the onset of symptoms^[59]. Individuals diagnosed with schizophrenia, mood disorders and healthy controls reported similar onset of smoking for all three groups^[58].

A study by Smith *et al*^[60] poses a particularly strong challenge to the SMH prediction on the time from between onset of smoking and initial symptoms.

Smoking history was assessed in a community-wide sample of 115 first episode patients. Of the 67 patients who smoked, 80% had started to smoke around 14 years of age. Yet, those individuals experienced functional declines or psychosis at around 19 years of age. The authors concluded, "In most cases, smoking preceded illness onset and was not a response to early features of illness"^[60].

Another report was of schizophrenic patients starting to smoke during adolescence and at least 5 years before initiation of psychiatric medication. The authors interpreted their data as indicating that symptomology, anti-psychotic drugs or the prodromal period could adequately confirm an association between schizophrenia and smoking^[61].

In a sample of 406 including both hospitalized and outpatient schizophrenics, there was no difference in the onset of the disease between smokers and nonsmokers^[62]. In the same study, up to 90% of schizophrenic smokers reported the time between initiation of smoking and disease onset was circa 5 years. The conclusion was, "the psychotic phase of the disease per se is not the major factor leading to the increased frequency of smoking"^[62].

Still others have raised the possibility that nicotine use itself might elevate the risk for developing schizophrenia. Supporting data are from longitudinal studies showing that beyond cannabis and alcohol use, early consumption of tobacco increases the risk for psychosis^[63].

Finally, an important study by Weiser *et al*^[64] examined records kept by Israeli agencies on adolescents to determine the onset of smoking and subsequent risk for schizophrenia. It represents the rarest of studies, a longitudinal study of smoking prior to diagnosis and, presumably, detectable symptoms of a mental illness. A random sample of adolescents were screened and determined to present no signs of a major psychopathology. The adolescents then were administered a questionnaire on smoking, finding that 28.4% smoked at least one cigarette per day. The cohort was followed for 4 to 16 years to determine development of schizophrenia (0.3%) and its relation to prior smoking. Findings were a significant linear relation between adolescence daily smoking levels and risk of developing schizophrenia during adulthood. The authors concluded early smoking was unrelated to symptomatic relief. The more likely explanation was that smoking worsens the neurophysiological bases for the disease in genetically susceptible people.

To summarize, all studies cited above agree that age of smoking onset begins well before symptom onset. That smoking onset is well before individuals were diagnosed with schizophrenia suggests to us that smoking was not in response to early symptoms. Still, one cannot dismiss that possibility completely.

What we can say without controversy is that onset of smoking prior to development of schizophrenia is unrelated to alleviating side effects of antipsychotic

medications. Smoking begins in patients long before they begin drug therapies.

Smoking patients should show different symptomology than non-smoking patients

On the question of behavioral differences between patients who smoke and patients who do not, the evidence is mixed. Support for the SMH comes from studies comparing cognitive performance, particularly improvements in attention. Conflicting data emerges from comparisons of the symptoms of smoking and non-smoking patients.

A battery of neuropsychological tests was used to assess the influence of an acute administration of nicotine to schizophrenic samples that did or did not smoke^[65]. Across domains of learning and memory, language or visuospatial abilities there were no differences. The only domain to show improvement from nicotine was attention.

Deficits in attentional gating of sensory input are common symptoms accompanying schizophrenia. First episode schizophrenic patients not yet prescribed antipsychotic drugs were evaluated for sensory gating. Results indicated that both smoking and non-smoking patients showed worse sensory gating than healthy smoking or non-smoking controls. However, the smoking patients showed less of a sensory decrement^[66]. This is one of the few reports that give us a glimpse into smoking prior to diagnosis and drug treatment. And the results offer support for the SMH in that prior smoking allays a common deficit in schizophrenia.

Another study tested schizophrenic patients and found smokers displayed improved attention performance over non-smoking schizophrenics^[67]. These findings were also observed in first-episode psychosis (FEP) patients. Smokers scored better than non-smokers on attention tasks and also exhibited faster working memory reaction times^[39].

Segarra *et al*^[68] followed patients with first-episode psychosis during their initial year of antipsychotic treatment. At baseline, they found that smokers with FEP performed faster during a selective attention task than non-smokers. Although their reaction times were comparable to that of non-smokers, smokers exhibited fewer omission errors in a working memory task than non-smokers.

It is of interest that the smoking patients showed no cognitive improvements over the year. Cognitive performance of non-smoker patients, however, improved from baseline to 12 mo during the course of antipsychotic treatment^[68]. And, although more smokers than non-smokers self-reported smoking as a means to improve concentration, their nicotine intake did not correlate with behavior in the attention paradigms^[69]. These data suggested to the authors that "subjective or objective attentional benefits are unlikely the primary driving force of tobacco consumption" in schizophrenia.

Another paradigm in the literature is to test

the possibility that smoking would be different in patients with predominantly positive and negative symptomatology. The interaction of nicotine with dopamine predicts that smoking would be more closely related to positive symptomatology. Results have yielded every possible outcome with some reporting smoking related to positive symptomatology, to negative, to both positive and negative symptomatology^[41,70] or to neither positive nor negative symptoms^[51].

Aguilar *et al*^[71] explored the association between frequency of smoking among Spanish schizophrenia patients and symptoms, medication side effects and outcome. Results were that mildly dependent smokers had fewer high positive symptoms and total PANSS (Positive And Negative Syndrome Scale for Schizophrenia) scores than non-smokers or, importantly, highly dependent smokers. The authors concluded, considering all of their data, they had found little support for the SMH.

Other reports suggest smoking may be related, rather than to schizophrenic symptomology, to depressive symptoms commonly comorbid with psychosis. For example, rates of smoking were found to be similarly elevated with schizophrenia and other psychotic disorders. Smoking was not associated with psychotic symptoms, but cigarette consumption over time covaried with depression^[37].

Also, there were no differences in nicotine dependence between patients with schizophrenia and those with a mood disorder^[58]. These data are notable because patients with schizophrenia complain far more about side effects than people treated with drugs for mood disorders.

There are other data suggesting that smoking worsen the symptoms of schizophrenia. In the Spanish cohort cited above^[71] comparing positive symptom scores among smokers and non-smokers, highly dependent smokers had the most severe symptoms of schizophrenia. A recent report found that tobacco use and weight gain/obesity was associated with increased severity of symptoms of schizophrenia and decreased functioning^[72].

Smoking of another substance, cannabis, also has been reported to be a risk factor for development of schizophrenia. High potency cannabis and frequent cannabis use was associated with an earlier age of onset of psychosis. Adolescents who used cannabis before the age of 15 were at a greater risk of developing psychosis earlier in life than their peers who began smoking at a later age^[73]. Although there was a progressive increase in cannabis use upon onset of the prodromal phase^[57], the self-report for reasons for smoking cannabis was mainly to enhance mood. Self-medication for symptomatic relief was ranked last^[74].

If smoking relieves side effects of antipsychotic medications, smoking in patients should change with drug treatments

Should nicotine be able to relieve side effects of antipsy-

chotic drugs, smoking should either be initiated or increase after diagnosis. Early studies by McEvoy *et al.*^[75,76] are often cited as confirming the SMH. Typical antipsychotic drugs are more often accompanied by adverse side effects than are atypical antipsychotics. Smoking frequency should track a change in medications. Those were the results as schizophrenic patients switched from typical neuroleptics to the atypical drug clozapine, which decreased their smoking frequencies.

Later, de Leon *et al.*^[77] cast serious doubt on these findings. They addressed five of the basic conclusions of the previous studies. None of the five analyses demonstrated that clozapine had major effects on smoking. Indeed, by replicating the McEvoy *et al.*^[76] procedures as closely as possible, their findings of no relation between drug and smoking was a particularly striking repudiation of the SMH.

Matthews *et al.*^[38] reviewed the literature for evidence of the suggestion that atypical antipsychotics decrease smoking and promote smoking cessation while the typical medications may increase smoking and decrease the ability to stop smoking. However, the authors found that the studies used small sample sizes, were generally of moderate quality and reported conflicting data. Moreover, there are enough exceptions to question generalization to other antipsychotic drug classes^[78].

Attempts to test the influences of smoking on the side effects of typical and atypical antipsychotic medications include assessment of extrapyramidal symptoms (EPS). Indirect support for relief of EPS comes from evidence that smoking decreases the effectiveness of antipsychotics. Smoking decreases serum levels of the atypical drugs clozapine and olanzapine, likely by increasing hepatic drug metabolism by activating enzymes of the cytochrome P450 enzymatic family^[79]. It could be expected, then, that these patients would experience fewer side effects, should they be regular smokers, and those data have been reported^[80].

The suggestion that smoking is a response to the side effects of antipsychotic medications has been questioned. Smoking and non-smoking schizophrenia patients did not differ on side-effect profiles with drug treatments. Incidences of tardive dyskinesia, for example, were the same in smokers and non-smokers^[51]. Another study found no significant association between smoking in schizophrenic patients and antipsychotic usage or development of EPS^[81].

A corollary of Prediction E is that if smoking relieves medication side effects, patients who are being treated with a drug producing fewer side effects should smoke less than drugs that produce more side effects. That question has been addressed and results supported the SMH. On a test of motivation to smoke, scores for sedative and anxiolytic effects of smoking were significantly associated with the dose and anticholinergic load of the medications^[43].

Also, patients switched from the EPS-inducing typical medications to the atypical drug clozapine exhibit lower rates of smoking than those treated with typical antipsychotic drugs. However, the generalization to other atypical drugs, risperidone for instance, has not been confirmed^[68].

More detailed analyses of smoking and atypical drugs have revealed another inconsistency. Among smokers and non-smokers, serum concentration of clozapine or olanzapine were reduced in the smokers. However, numbers of cigarettes smoked was unrelated to serum values. Patients who smoked 7-12, 13-19 or 20+ cigarettes per day had similar serum concentrations of the medications^[82]. Because minimal smoking would relieve side effects similarly to heavy smoking, the elevated rates of daily smoking cannot be explained by the side effects prediction.

If they smoke for reasons other than simply the addictive properties of nicotine, success of smoking cessation programs should be lower in schizophrenic smokers than in healthy smokers

A clear prediction from the SMH is that mentally ill people have a greater dependency on the effects of nicotine on the brain. As a result, patients should have considerable difficulty stopping smoking. There is firm evidence that schizophrenic smokers have more difficulty quitting the habit than do healthy smokers^[83].

With the well-known health consequences from long-term use, smoking is a concern for families and care providers of patients. Yet, smoking cessation rates among schizophrenic individuals are markedly lower than among both the general population and non-schizophrenic psychiatric patients^[84]. Yet, the majority of patients say they would like to quit. Despite both internal and external motivations to quit, continuing to smoke suggests patients are accruing benefits from cigarettes^[50].

Studies of the reasons for the cessation failure in schizophrenia focus on self-reports and type of drug therapy. Compared to healthy controls, patients self-report more often stress reduction, stimulation and increasing concentration^[85]. However, the ability of patients to self-report accurately was questioned by an experiment using an attention task. Although participants with and without schizophrenia cited smoking helps their concentration, nicotine status predicted changes in attention in the healthy controls but not patients^[69].

The similarly, high rates of smoking between people newly diagnosed and long-term patients suggests that drug treatments are not the cause of smoking. A similar case could be made for smoking cessation^[59]. Type of antipsychotic medication has been examined in patients who were successful in cessation. Once again, the results are contradictory^[38].

The general expectation was that atypical drugs would have fewer side effects and would promote

cessation. Although somewhat dependent upon the classification system used, successful smoking cessation did not align along typical-atypical medications. Rather, specific drugs appeared to be associated with smoking cessation. The atypical drug clozapine, but also various typical drugs, correlated to decreased cigarettes smoked per day^[78]. Other atypical drugs, however, were relatively ineffective. The authors interpreted their findings as pointing to a greater blockage of the D2 dopamine receptor being a key to successful smoking cessation.

Schizophrenic smokers who are successful at smoking cessation should experience worsening of symptoms of the disease or medications

This prediction is possibly surprising, but it clearly follows logically from the SMH. It is based on the assumptions that smoking allays psychiatric symptoms of schizophrenia but only as long as the patient smokes. That is, smoking does not permanently change brain or behavior. Rather the current levels of nicotine determines reductions of symptoms.

There are anecdotal reports of exacerbated symptoms of schizophrenia following nicotine withdrawal^[86], but systematic assessments on the influence of smoking cessation have revealed no major effect on the symptoms of schizophrenia^[87]. Indeed, changes in smoking habits over years could not be linked to any systematic effects on symptom load, symptom improvement or subsiding of side effects^[51]. Also, interventions that have proven effective in stopping smoking in individuals with mental illness do not appear to worsen psychiatric symptoms. Bupropion is a pharmacological treatment to aid smoking cessation in healthy people. When bupropion was employed to assist smoking cessation in schizophrenic patients, there were no change in their symptoms^[88]. The interpretation is that the SMH failed in this basic prediction of the model.

The pathology of neurobiological systems underlying schizophrenia should be the same as those influenced by the nicotine in cigarette smoke

A prediction from the SMH is that the nicotine from smoking should influence the same brain regions and neurotransmitters that are pathological in schizophrenia. Results from studies of nicotine in animal models and some data from patients support the hypothesis. Yet, there are troubling inconsistencies in schizophrenia studies.

Much of the relevant research has focused on neural mechanisms underlying nicotine and the regional basis of different symptoms of the disease and of medication side effects.

Nicotinic ACh receptors are present throughout the human brain but in different concentrations in distinct brain areas. The highest density of nAChR are found in the substantia nigra, thalamus and caudate nucleus,

and in moderate to- low densities in the frontal, parietal, temporal and occipital cortex, hippocampus, and cerebellum^[89]. In contrast to conventional wisdom that an agonist down regulates receptor numbers, long-term nicotine exposure upregulates brain nAChRs. Postmortem binding studies have revealed increased binding sites in the brains of smokers compared to non-smokers^[90].

Most commonly, activation of the nAChR increases the release of dopamine in DA pathways^[28]. This provides a convenient mechanism for smoking to help relieve negative symptoms and cognitive deficits of schizophrenia. But, it proves troublesome for alleviation of the positive symptoms.

Recall that earlier we presented the dogma on dopamine and schizophrenia. Essentially, schizophrenics show hyperactivity in nigrostriatal DA pathways and hypoactivity in mesocortical DA pathways^[30]. Importance of dopamine in the disease is highlighted by the well-documented findings that, although the different typical and atypical drugs influence different arrays of neurotransmitters, all effective antipsychotics block the D2 dopamine receptor subtype^[91].

Hyperactivity of the nigrostriatal DA pathway is thought to be responsible for positive symptoms, explaining the clinical effectiveness of antipsychotic drugs' antagonism of the D2 receptor. Relative ineffectiveness of neuroleptics in treating negative symptoms is explained by DA antagonism presumably decreasing further the existing hypoactivity of mesocortical DA pathways.

Problems for the SMH emerge, first, when seeking to understand the attraction to smoking in unmedicated schizophrenics or individuals in prodromal and prodromal stages of the disease. On the one hand, the neurophysiological data suggests smoking could help relieve the negative symptoms of the unmedicated person by opposing DA mesocortical hypoactivity. Nicotine would increase mesocortical DA activity and, consequently, prefrontal cortical function.

On the other hand, it makes little sense for unmedicated individuals to self-administer nicotine and further increase DA activity in brain regions impacted by an already hyperactive nigrostriatal DA pathway. Yet, we have seen subclinical symptoms as an explanation by the SMH for the onset of smoking being well before a schizophrenic diagnosis and drug therapy^[60]. An outlet to resolve the dilemma would be to demonstrate that prodromal or prodromal symptoms are primarily negative. However, we do not yet know the predominant symptoms of the individual when age of onset of smoking was years before diagnosis^[92].

The SHM has been invoked to explain smoking to counter the adverse side effects of medication-induced reductions of nigrostriatal DA activity. Although perhaps predicted by the neurophysiological data, there is little evidence for greater relief of side effects of antipsychotics in patients who smoke^[8].

The interested reader is directed to an excellent

review by Dome *et al.*^[87] for other neural data questioning the self-medication concept. Included is their observation that much of the support for the SMH comes from researchers funded by the tobacco industry.

The take-away for this final prediction is that smoking can modulate the same thought and emotional processes that are interwoven with the expression of schizophrenia^[93]. Nicotinic receptors are found in brain regions that influence these same processes and chronic nicotine exposure has at least some effects that would appear to indicate a central involvement in allaying aspect of the disease^[19]. However, there are inconsistencies in the findings and important data are lacking in the literature to conclude strong support for the neurophysiological predictions of the SMH. In particular, resolution of the dopamine effects on positive-negative symptomology will require clever experiments and insightful interpretations^[94].

CONCLUSION

We generated a list of predictions from the self-medication hypothesis applied to smoking in schizophrenic patients. There are surely more predictions that could be generated from such a broad model. The ones selected here struck us as particularly relevant to the SMH.

We found support in the literature for certain predictions of the SMH. For example, patients smoke more than healthy people and, importantly, more than people with other mental illnesses. Patients cite reasons for smoking that are different from healthy smokers and that are related to symptoms of the disease. Smoking schizophrenics perform better on cognitive tasks, particularly attention paradigms, than non-smoking patients. And, there are neural mechanisms to support a self-medication concept.

On the other hand, we found the findings on age of onset of smoking relative to development of clear symptoms particularly troubling for the SMH unless unique and questionable assumptions are made about the early symptoms. Other creative interpretations of the neurophysiological data are required to resolve the opposing actions of nicotine-dopamine interactions on positive and negative symptoms. Finally, the evidence is conflicting that smoking patients have fewer symptoms than non-smoking patients. There are no data regarding a central component of the SMH, that is, that smoking allays undesirable side effects of antipsychotic drugs while leaving untouched the beneficial effects of the drugs.

Our conclusion is that there are sufficient data that appear contrary to expectations with the SMH explanation of smoking and to give us pause in continuing to accept the hypothesis without question. Our hope is that the generation of predictions presented in this review provides direction for future empirical tests of the SMH.

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