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Associations between health risk behaviors and symptoms of schizophrenia and bipolar disorder: a systematic review

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Abstract

Objective—To systematically review the literature to determine if health risk behaviors in patients with schizophrenia or bipolar disorder are associated with subsequent symptom burden or level of functioning.

Method—Using the PRISMA systematic review method we searched PubMed, Cochrane, PsychInfo and EMBASE databases with key words: *health risk behaviors, diet, obesity, overweight, BMI, smoking, tobacco use, cigarette use, sedentary lifestyle, sedentary behaviors, physical inactivity, activity level, fitness, sitting AND schizophrenia, bipolar disorder, bipolar illness, schizoaffective disorder, severe and persistent mental illness, and psychotic* to identify prospective, controlled studies of greater than 6 months duration. Included studies examined associations between sedentary lifestyle, smoking, obesity, physical inactivity and subsequent symptom severity or functional impairment in patients with schizophrenia or bipolar disorder.

Results—Eight of the 2130 articles identified met inclusion criteria and included 508 patients with a health risk behavior and 825 controls. Six studies examined tobacco use and two studies examined weight gain/obesity. Seven studies found that patients with schizophrenia or bipolar illness and at least one health risk behavior had more severe subsequent psychiatric symptoms and/or decreased level of functioning.

Conclusion—Tobacco use and weight gain/obesity may be associated with increased severity of symptoms of schizophrenia and bipolar disorder or decreased level of functioning.

Keywords

Health risk behaviors; severe and persistent mental illness; obesity; sedentary behavior

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Background

Health risk behaviors such as sedentary lifestyle [1], tobacco use [2], poor diet [3] and obesity [4] have been associated with increased risk of developing chronic medical disorders. These health risk behaviors account for approximately 40% of deaths in the United States [5]. Depression is associated with the incidence of health risk behaviors such as obesity, smoking and lack of exercise potentially causing early development of chronic illnesses such as coronary heart disease (CHD) and diabetes [6]. Once chronic illnesses develop depression is associated with poor self-care including lack of change in diet, increasing exercise, cessation of smoking and taking medications as prescribed [7–9]. In patients with comorbid depression and CHD adverse health risk behaviors have been found to mediate the relationship between depression and morbidity and mortality [8]. Other severe psychiatric disorders such as schizophrenia, schizoaffective disorder and bipolar disorder are also associated with a higher prevalence of health risk behaviors and poor self-care (ie adherence to diet, exercise, cessation of smoking and taking medications as prescribed) [10–14]. Thus there is likely a bidirectional relationship between depression and other psychiatric illnesses and chronic medical illnesses [8]. Health risk behaviors may contribute to this bidirectional relationship in patients with depression or severe and persistent mental illnesses (SPMI). For this paper, the term SPMI will refer to only schizophrenia, bipolar disorder and schizoaffective disorder.

Numerous studies have documented that many chronic illnesses are more prevalent in patients with SPMI compared to the general population [15–19]. For example, Leucht, et al. [15] performed a systematic review and found that cardiovascular diseases, obesity, diabetes mellitus, HIV infection and other chronic infectious diseases, hepatitis, osteoporosis, impaired lung functioning, poor dental status, altered pain sensitivity, sexual dysfunction, obstetric complications, thyroid dysfunction, and hyperlipidemia were consistently found to have an increased prevalence in populations of patients with schizophrenia compared to control populations. Notably, many of these disorders, including cardiovascular diseases, obesity, diabetes mellitus and hyperlipidemia, are strongly associated with health risk behaviors such as sedentary lifestyle, smoking, poor diet and obesity.

The importance of identification and treatment of health risk behaviors and general medical problems in patients with SPMI has recently been emphasized due to data showing that patients with SPMI are dying of chronic medical illnesses one to two decades earlier than community populations [20–29]. A high prevalence of obesity, lack of exercise and tobacco use in patients with SPMI has often been described [13,30,31]. Although these studies call attention to the adverse medical outcomes associated with health risk behaviors, fewer studies have specifically addressed the associations of poor general health or risk behaviors with the course and symptoms of SPMI.

In this paper, we report the results of a systematic review of the literature assessing whether associations exist between health risk behaviors and the course and symptoms of schizophrenia and bipolar disorder measured by standardized measures of symptom severity or functional impairment. Finding an association between health risk behaviors and higher symptom burden or impaired functioning in patients with SPMI could lead to a wider implementation of health risk behavior screening and management in psychiatric clinics.

Methods

We followed the PRISMA method of conducting a systematic review [32], but did not register the review using a pre-specified protocol. We searched the PubMed, Cochrane, PsychInfo and EMBASE databases [last search run on March 30th, 2012] using the

following term combinations: *health risk behaviors, diet, obesity, overweight, BMI, smoking, tobacco use, cigarette use, sedentary lifestyle, sedentary behaviors, physical inactivity, activity level, fitness, sitting AND schizophrenia, bipolar disorder, bipolar illness, schizoaffective disorder, severe and persistent mental illness, and psychotic* to identify reports in English published between January 1980 – March 2012. The reference lists of selected studies were scanned to identify additional articles. Unblinded eligibility assessment was performed by one author (JMC). The search strategy was developed by the authors in consultation with a librarian with expertise in literature searches.

Titles and abstracts of studies returned from the search were screened, and selected full-text articles were assessed for eligibility. We included prospective observational studies or intervention studies of greater than 6 months duration examining as primary or secondary outcomes the associations between health risk behaviors (sedentary lifestyle, smoking, obesity, and physical inactivity) and psychiatric outcomes measured by standardized measures of symptom severity or functional impairment in patients with schizophrenia and bipolar disorder diagnosed by clinical interview, standardized measures or chart review. Included studies were also required to have a control group. Changes in standardized symptom measures or measures of functioning were the principal outcomes.

Information was extracted by one author from each included trial including: patient demographics, inclusion and exclusion criteria, control group, type of study, health risk behaviors studied, outcome measures, effects, and miscellaneous comments. The PRISMA method includes the assessment of risk of bias using the Cochrane Risk of Bias Tool for intervention studies only [33]. Our review returned only observational studies, so the risk of bias tool was not used.

Results

Study characteristics

The results of our search are shown in Figure 1. Two thousand one hundred and thirty studies were identified and screened after duplicates were removed. Full articles were pulled and assessed for eligibility for ninety-three of these studies. Eight studies met our inclusion criteria and were included in the review. The 8 studies included 508 patients with SPMI and a health risk behavior and 825 control patients with SPMI without a health risk behavior. Study size ranged from 19 to 147 patients and 15 to 322 control patients. Study duration ranged from 9 months to 10 years.

One study examined the effects of obesity [34], 1 examined effects of weight gain [36] and 6 examined the effects of cigarette use on symptoms of SPMI [35,37–41]. Three studies included patients with bipolar disorder only [34–36], one study included those with bipolar disorder and schizoaffective disorder [37], two included patients with schizophrenia only [38,39], one included patients with first episode psychosis only [40] and one included patients with a first manic or mixed episode only [41]. Two studies [36, 41] included adolescent and adult patients while the rest included only adult patients.

Bipolar disorder

Fagiolini, et al [34] assessed the association of obesity and numerous markers of bipolar disorder severity including time spent in acute episode treatment, time until recurrence of mood episode, and scores on standardized symptom scales. The authors compared 62 patients with bipolar disorder and obesity (defined as BMI >30) to 113 non-obese patients with bipolar disorder prospectively over 2 years. The authors found that obesity was associated with poorer outcomes on all three outcome measures. (See Table for details).

Bond, et al [36] prospectively observed the association of weight gain with symptom severity and degree of functioning in 19 patients with bipolar disorder and weight gain (defined as >7% increase in body weight over 1 year) compared to 27 patients with bipolar disorder who did not gain >7% body weight over one year. This trial included patients between ages 14–35 years. Patients with weight gain showed more impairment in functioning, but showed no significant differences in mood symptom or episode relapse outcomes. However, patients with weight gain showed numerically more days with depressive symptoms compared to those without weight gain. Weight gain, level of functioning and mood symptoms were all measured prospectively. Therefore, in this study, it is unclear if weight gain preceded functional impairment and depressive symptoms, or if functional impairment and depressive symptoms preceded weight gain. The authors also noted that it was very likely that this study had limited statistical power to detect an association between weight gain and mood symptoms.

Ostacher, et al [35] studied the association between suicidal behavior and smoking over 9 months in 31 patients with bipolar disorder compared to 85 non-smoking patients with bipolar disorder. Cigarette use was associated with higher scores on measures of suicidality, and patients who smoked made more suicide attempts compared to non-smokers. Patients who smoked also had higher rates of lifetime substance abuse (61% compared to 33%, $P<0.05$). Although the authors controlled for lifetime substance use using multivariate regression, it is likely that the difference in rates of substance use were proxies for many other differences in the populations that were not controlled for.

Dodd, et al [37] followed 122 patients with tobacco use and either bipolar disorder ($n=86$) or schizoaffective disorder, bipolar type ($n=36$) over 2 years and compared several measures of symptom severity compared to non-smoking patients with bipolar disorder ($n=89$) or schizoaffective disorder, bipolar type ($n=28$). At 2 years, patients who used tobacco had worse Clinical Global Impression (CGI) – Depression and CGI – Overall Bipolar scores and spent more days hospitalized compared to those who did not smoke. As in the Ostacher, et al [35] study, patients who used tobacco were also more likely to use alcohol. Smoking patients in this study were also significantly younger than non-smoking patients. Multivariate analysis was used to control for age, sex, diagnosis, length of hospitalization, smoking status, medication use over past 24 months, and length of time treated with mood stabilizers, antipsychotics and hypnotics. The analysis did not control for other health risk behaviors such as sedentary lifestyle.

Schizophrenia

Wang, et al [38] examined the rate of cigarette use and associated clinical characteristics in patients with schizophrenia discharged from an acute care hospital living in China. They followed 52 patients who smoked cigarettes and 322 patients who did not smoke for at least 12 months (patients were followed between 12–26 months). The main outcomes were schizophrenia symptom severity measured by standardized scales. Patients who smoked had more hospitalizations than those who did not smoke, and demonstrated less reduction in the hostility-excitement subscore of the PANSS. Otherwise, symptom measures were not significantly different between the two groups. The majority of patients who smoked were men (45 men and 7 women) compared to a mixed population of non-smokers (127 men and 195 women). This study included a multivariate analysis to control for these differences, although other differences that were not controlled for may have been present in the two populations.

Kotov, et al [39] followed patients after first episode psychosis for 10 years and aimed to determine if cigarette use was associated with symptom severity in patients with schizophrenia. Although patients with schizoaffective disorder and bipolar disorder were

originally included in this assessment, the study's main aim was to observe only patients with schizophrenia. One hundred and forty seven smokers with schizophrenia and 82 non-smokers with schizophrenia completed the 10 year observation. The authors used standardized scales as outcome measures. After 10 years, cigarette use was associated with a significant, but modest difference in negative symptom severity as measured by the Scale for Assessment of Negative Symptoms (SANS) and was otherwise not associated with any significant differences in severity of schizophrenia symptoms.

First episode psychosis

One study [40] used neuropsychological assessments to determine the association between cigarette use and cognitive functioning in 41 patients with first-episode psychosis (26 smokers and 15 non-smokers) who completed the 1 year observation. Specific diagnoses were assessed over the 12 months and in both groups the most common diagnosis was schizophrenia. Measures of symptom severity were also performed. The authors found no significant longitudinal differences between the groups in cognitive functioning measured by numerous neuropsychological measures. However, after 12 months, compared to non-smoking controls patients who smoked showed greater increases in total and negative symptoms subscale on the Positive and Negative Syndrome Scale (PANSS) scores compared to their baseline scores. Comparisons between patients who did and did not smoke showed no significant differences in symptom severity.

First mixed or manic episode

Heffner et al [41] followed adolescent (n=72) and adult (n=41) patients for 1 year after hospitalization for their first mixed or manic episode to determine the association between cigarette use and bipolar disorder symptom severity measured by time to recovery from first episode, percentage of time with mood symptoms and service utilization outcomes. The authors found no significant differences between those who smoked (n=26 adolescents, n=23 adults) and those who did not smoke (n=46 adolescents, n=18 adults) on any study outcome measure. The only difference between groups was found in the adolescent sub-population where tobacco use was associated with cannabis and alcohol use.

Discussion

Findings and Implications

This systematic review found 8 studies that have prospectively examined the associations among health risk behaviors and symptoms of SPMI. The only health risk behaviors assessed in these studies were weight gain/obesity and tobacco use. No studies have examined other health risk behaviors such as sedentary lifestyle or physical inactivity. Health risk behaviors were associated with adverse outcomes based on either symptoms of SPMI or level of functioning (or both) in 7 out of 8 studies. Outcome measures included duration of episodic symptoms (e.g. time spent in acute treatment, time until recurrence of mood episode), severity of mood and psychotic symptoms (e.g. PANSS, HAM-D), standardized measures of suicidality and functional impairment, and service utilization (e.g. hospitalizations). It remains unanswered whether health risk behaviors are markers of severity of chronic mental illness or whether health risk behaviors influence subsequent symptom severity and functional impairment.

The four studies [34–37] that examined outcomes of patients with bipolar disorder included 198 patients with bipolar disorder and 36 patients with schizoaffective disorder bipolar type plus a health risk behavior. Obesity and weight gain were studied in this population, but not in the population with schizophrenia. The study by Fagiolini, et al [34] suggests that the observed bidirectional relationship between depression and obesity may also be present in

bipolar disorder in patients with a BMI > 30. Furthermore, Bond, et al [36] showed that gaining more than 7% body weight over one year is associated with significantly more impairment in functioning after controlling for mood symptoms, even in patients with BMI of less than 30. The authors did not find an association between weight gain and mood symptoms. This study had a small sample size of 19 patients and 27 control patients. Future studies should examine larger populations to assess whether weight gain, obesity or both are associated with worsening symptoms of bipolar disorder or impaired functioning.

Six studies [35,37–41] assessed associations between cigarette use and subsequent symptom severity. Two studies [35,37] were in patients with bipolar disorder, two studies [38,39] in patients with schizophrenia and two in patients with first episode psychosis [40], mania or mixed episode [41]. Only one [45] of these studies did not show an association between cigarette use and poorer outcomes on standardized measures. However, in that study of adolescents and adults with first episode mania or mixed episode, cigarette use was associated with development of cannabis or alcohol use in adolescents [41]. Only one study [40] did not include multivariate analysis in comparing patient populations.

The two studies [38,39] examining outcomes in 199 total patients with schizophrenia who smoked cigarettes found that tobacco use was associated with higher scores on PANSS measurements. The patients in the study by Kotov, et al [39] were followed for 10 years which suggests that the associations observed are stable over time, although the differences between patients who smoked and did not smoke were minor (though significant). The prevalence of tobacco use among patients with schizophrenia is as high as 88% [42], and the most common preventable diseases in the United States are related to smoking [43]. Reducing tobacco use in patients with schizophrenia should have significant health benefits, but may also be associated with reduction in severity of schizophrenia symptoms.

Health risk behaviors associated with SPMI may also lead to early development of chronic medical disorders which may in turn worsen the course of SPMI. However, none of the studies identified in this review examined whether the association of health risk behaviors with subsequent severity of SPMI symptoms is mediated by development or complications from chronic medical disorders. Several authors have suggested ways in which chronic medical disorders may contribute to symptoms of SPMI. Psychiatrists may be less likely to treat schizophrenia in patients with chronic medical disorders [44], the presence of general medical disorders may be associated with prominent depressive and cognitive symptoms in schizophrenia [45,46], common pathophysiologic processes may contribute to the general medical problems and the worsening of symptoms of SPMI [47], or general medical disorders may contribute directly to functional impairment in patients with SPMI, which may in turn lead to worsening of the psychiatric disorder [45,48]. Future studies should address the associations among health risk behavior, chronic medical disorders, symptoms of SPMI, and overall level of functioning.

Identifying associations among these behaviors and disorders could lead to a deeper understanding of the premature mortality in patients with SPMI. Long-standing observations of the decreased life expectancy in patients with severe psychiatric disorders have been reconfirmed in newer population based studies and reviews [49–52]. In patients with schizophrenia, some chronic medical problems are also associated with reduced quality of life [53]. These findings have led researchers to develop ways to deliver or coordinate general medical care to this patient population [20]. These new interventions [20,54] have found positive associations between increased access to primary care and improved general health, though the impact on life expectancy remains unknown.

Limitations

This review has several limitations. Although our search strategy yielded 2130 unique articles, only 8 studies fit our inclusion criteria. The small sample size in the majority of studies is a major limitation. Having one adverse health risk behavior is often correlated with a higher likelihood of having multiple health risk behaviors such as sedentary lifestyle, poor diet, use of alcohol and other substances, and lack of use of preventive care [55]. However, most studies did not evaluate and control for a full range of health risk behaviors and quality of medical care received. Using less-stringent inclusion criteria would have increased the number of studies included in our qualitative analysis and increased the total number of patients studied. However, broader inclusion criteria may have also limited the conclusions we could draw from our findings. Our findings are also limited by the databases we searched and the English language restriction. Three studies [35,37,38] also had significant differences in characteristics of patients with the health risk behavior and control populations.

It is notable that all included studies were observational. No studies examined whether an intervention targeting reduction in a health risk behavior (such as increased activity, reduced weight or reduction in cigarette use) was associated with improved outcomes. Positive findings from intervention studies would further strengthen the evidence for an association between health risk behaviors and symptom severity.

Conclusions

We found that 7 out of 8 published prospective studies found negative associations between health risk behaviors and subsequent severity of symptoms of SPMI or decreased level of functioning. No conclusion on the direct impact of health risk behaviors on symptom severity or level of functioning can be made. Large prospective studies are needed that control for socioeconomic variables and a full range of health risk behaviors and quality of medical care. If negative associations between health risk behaviors and SPMI symptoms were consistently shown, then interventions targeting health risk behaviors in patients with SPMI may be associated with reduction in psychiatric disorder symptom severity or improved level of functioning.

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Figure 1.

Table 1

Study	Patients	Study methods	Control	Health risk behaviors	Outcome measures	Effects	Comments
Fagiolini, et al. (34)	62 obese patients with bipolar disorder between ages 18–65.	Two year prospective study assessing the effects of patients' baseline characteristics, including BMI, on the course of bipolar disorder and acute and maintenance treatment outcomes	113 non-obese patients with bipolar disorder between ages 18–65	Obesity, defined as body mass index >30	<ul style="list-style-type: none"> Time spent in acute treatment (weeks). Time until recurrence of mood episode (weeks) measured by Hamilton Rating Scale for Depression (HAM-D) Bech-Rafaelsen Mania Scale 	<ul style="list-style-type: none"> Obese patients required more time in acute treatment of mood episode (39.5 wks vs. 30.0 wks, $p<0.005$) A higher percentage of obese patients experienced recurrence of mood episode (54.3% vs 35.4%, $p<0.04$) Time to depressive recurrence was shorter in obese group (log rank $X^2 = 7.33$, $df=1$, $p<0.007$) 	Other health risk behaviors were not assessed
Ostacher, et al. (35)	31 smokers with bipolar disorder with mean age of 37.3 years SD 10.8 years	Nine month prospective, longitudinal study of cigarette smoking and suicidality in patients with bipolar disorder	85 non-smokers with bipolar disorder with mean age of 46.7 years SD 13.5 years	Cigarette smoking, defined as any cigarette use in the past month	<ul style="list-style-type: none"> Suicidality measured by the Suicide Behaviors Questionnaire (SBQ), and by presence or absence of attempted suicide 	<ul style="list-style-type: none"> Cigarette use was associated with higher SBQ scores at baseline and at 9 month follow-up ($p=0.042$) Eight patients (7%) attempted suicide during the 9 month period – 5/31 smokers vs 3/85 nonsmokers ($p=0.031$, OR 5.25, CI 1.2–23.5) 	Patients who smoked also had higher rate of lifetime substance abuse (61% vs 33%, $p<0.05$)
Bond, et al. (36)	19 patients with bipolar disorder 14–35 years old who experienced first manic or mixed episode and >7% increase in body weight in 1 year	One year, prospective naturalistic study of patients with bipolar disorder subsequent to first manic or mixed episode, assessing association of weight gain, bipolar	27 patients with bipolar disorder 14–35 years old who experienced first manic or mixed episode without >7% increase in body weight in 1 year	Weight gain, defined as >7% increase in baseline body weight	<ul style="list-style-type: none"> Weight and height Functional outcomes measured by the Multidimensional Scale of Independent Functioning (MSIF) Clinical status measured by numerous standardized rating 	<ul style="list-style-type: none"> Patients with >7% increase in body weight showed significantly more impairment in global functioning (2.42 vs. 1.93, $F=6.491$, $df=1$, $p=0.015$) and role functioning (3.05 vs 2.26, $F=9.627$, $df=1$, $p=0.004$) on MSIF 	Differences in functional impairment remained after controlling for mood symptoms, baseline weight and demographics

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Dodd, et al. (37)	122 patients with daily cigarette use with bipolar I disorder (n=86) or schizoaffective disorder, bipolar type (n=36)	Two year, prospective, observational study of patients with bipolar I disorder or schizoaffective disorder, bipolar type, assessing association of tobacco use and bipolar symptoms	117 non-daily smoking patients with bipolar I disorder (n=89) or schizoaffective disorder, bipolar type (n=28) (55 patients never smoked, 51 were ex- smokers, 8 were occasional smokers and 3 “experimented a few times”	Smoked tobacco use, defined as daily cigarette use	<ul style="list-style-type: none"> Young Mania Rating Scale (YMRS), HAM-D, Clinical Global Impression (CGI)- Bipolar, Current Major Depressive/Mania Checklist, Short Form-36 (SF-36) and other patient reported measures 	<ul style="list-style-type: none"> Weight gain was not associated with total number of days with mood symptoms, or with relapse to a mood episode ($\chi^2=0.046$, $df=1$, $p=NS$) At 2 years, daily smokers had worse CGI-Depression and Bipolar scores than non-daily smokers (2.87 vs 2.63, $p=0.034$; 3.16 vs 2.9, $p=0.0257$) All other measures were numerically worse, but not significantly, for daily smokers vs non-daily smokers at 2 years Daily smokers spent more days hospitalized (median of 4 compared to 0, $p=0.012$) 	Daily smokers were significantly younger than non-daily smokers (38.17 years $\pm$ 10.99 vs 45.67 years $\pm$ 13.26, $p<0.0001$), and more daily smokers had a history of alcohol dependence (24.6% vs 9.4%, $p=0.002$)
Wang, et al. (38)	52 patients with schizophrenia and tobacco use (13.2 $\pm$ 8.2 cigarettes/day), less than 8 weeks after an acute episode	Twelve month long prospective study assessing the association between smoked tobacco use and schizophrenia symptom progression. Some patients were observed up to 26 months	322 patients with schizophrenia 18–65 years old less than 8 weeks after an acute episode who did not use tobacco	Smoked tobacco use, defined as any cigarette use	<ul style="list-style-type: none"> Brief Psychiatric Rating Scale (BRPS) Positive and Negative Syndrome Scale, Chinese version (PANSS) 	<ul style="list-style-type: none"> On multiple logistic regression analysis, smoking was associated with more hospitalizations during the study period (1.9 vs. 1.6, $p=0.01$), less reduction in hostility-excitement subscores on the PANSS (0.3 $\pm$ 2.7 vs. 1.0 $\pm$ 3.0, $p=0.004$) and no differences in changes in PANSS positive or negative scores. (Note – on Spearman 	Sample of smokers with schizophrenia had 45 men and 7 women compared to 127 men and 195 women in nonsmoking group ($p<0.001$)

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Kotov, et al. (39)	147 smokers with schizophrenia who completed the 10 year follow-up	10 year prospective, observational study evaluating the association between longitudinal symptoms and cigarette consumption	82 non- smokers with schizophrenia who completed the 10 year follow-up	Smoked tobacco use, defined as any cigarette use over the 30 days preceding assessment at baseline, or over preceding 6 months at follow-up	<ul style="list-style-type: none"> PANSS Scale for the Assessment of Positive Symptoms (SAPS) Scale for the Assessment of Negative Symptoms (SANS) HAM-D 	<ul style="list-style-type: none"> In patients with schizophrenia, smoking status was associated with symptom or illness severity on only one measure at 10 years: the difference in SANS scores (0.34, $p<0.05$) 	correlation analysis, there were no significant differences in any PANSS scores.)
Segarra, et al. (40)	26 smokers with first episode psychosis 15–65 years old (8 patients with schizophrenia, 2 with schizoaffective disorder, 4 with bipolar disorder, 12 with other explanations for first episode psychosis	1 year prospective, observational study evaluating the association between cigarette use, positive and negative symptoms, and cognitive functioning. Included only patients who completed 1 year follow-up.	15 non- smokers with first episode psychosis 15–65 years old (5 patients with schizophrenia, 2 with schizoaffective disorder, 1 with bipolar disorder, 7 with other explanations for first episode psychosis	Smoked tobacco use, defined as ≥ 15 cigarettes/day	<ul style="list-style-type: none"> PANSS Montgomery Asberg Depression Rating Scale (MADRS) Numerous neuropsychological assessments 	<ul style="list-style-type: none"> No significant cognitive differences detected between groups at 12 months Patients with first episode psychosis who smoked had greater increase in PANSS score over 12 months compared to patients with first episode psychosis who did not smoke (smokers change of 10.44+/- 21.65, $p=0.045$ vs non-smokers change of 0.86 +/-21.60, $p=0.615$). Smokers showed significant differences in PANSS negative subscale scores compared to non-smokers (mean difference 3.52 +/- 7.38, $z=-2.020$, $p=0.043$) 	<ul style="list-style-type: none"> Smokers were younger (25.08+/- 6.22 years compared to 32.53+/- 13.11 years, $p=0.082$)

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Hefner, et al. (41)	26 adolescent patients (mean age 14.9 years $\pm$ 1.6 years) and 23 adult patients (mean age 24.7 years $\pm$ 6.7 years) with first episode mania or mixed episode who also smoked cigarettes	1 year prospective study evaluating the association of tobacco use with symptoms of bipolar disorder and alcohol and cannabis use	46 non- smoking adolescent patients (mean age 13.9 years $\pm$ 1.5 years) and 18 non- smoking adult patients (mean age 26.1 years $\pm$ 8.3 years) with first episode mania or mixed episode	Smoked tobacco use defined as self-report of any cigarette use over the month prior to baseline assessment and during the first four months of prospective observation	<ul style="list-style-type: none"> YMRS HAM-D Addiction severity index (ASI) 	<ul style="list-style-type: none"> No significant differences in MADRS scores Among adolescents and adults, tobacco use was not associated with post-hospitalization time to recovery (p=0.58 for adolescents, p=0.77 for adults), percentage of weeks with mood syndromes (p=0.10 for adolescents, p=0.57 for adults), suicide attempts (p=0.36 for adolescents) or need for hospitalization (p=0.63 for adolescents, p=0.97 for adults). Baseline tobacco use predicted development of cannabis or alcohol use in adolescents (p=0.02), but not in adults (p=0.30) 	<ul style="list-style-type: none"> Adolescent smokers were on average 1 year older than non-smokers