TECHNICAL COMMENTARY

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SCHIZOPHRENIA LIBRARY

Smoking

Introduction

Tobacco smoking is very common among people with schizophrenia, who often show particularly heavy usage. This poses considerable health risks, potential interference with the metabolism of antipsychotic medications, as well as financial burden for the individuals. Heavy cigarette use may contribute to the increased mortality and reduced life expectancy reported within the schizophrenia population. This topic considers the effects of smoking among people with schizophrenia. Please also see the smoking topic in comorbid conditions for the rates of smoking in this population.

Method

We have included only systematic reviews with detailed literature search, methodology, and inclusion/exclusion criteria that were published in full text, in English, from the year 2000. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Reviews with pooled data are prioritized for inclusion. Reviews reporting fewer than 50% of items on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA[1]) checklist have been excluded from the library. The evidence was graded guided by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found eight systematic reviews that met inclusion criteria[3-10].

- Moderate to high quality evidence found small effects of more severe positive symptoms and less severe extrapyramidal symptoms in smokers with schizophrenia compared to non-smokers with schizophrenia. There were no differences in negative symptoms, depression, anxiety, tardive dyskinesia, or parkinsonism.
- Moderate quality evidence suggests the most commonly reported reasons for smoking were relaxation/stress reduction, dysphoria relief, sociability, craving/addiction. The most commonly reported reasons for quitting were self-control, health concerns, social influence. The following factors were barriers to smoking cessation: cravings and addiction, perceived risk of negative affect, social pressures, stress and boredom reduction, and weight management. Knowledge about health risks of smoking, physician advice and social pressures to quit helped facilitate smoking cessation.
- Moderate to high quality evidence suggests no differences in the age at onset of psychosis between people who use tobacco and people who do not use tobacco.
- Moderate to high quality evidence found a medium-sized effect of increased craving scores in people with schizophrenia and a substance use disorder compared to people without schizophrenia and a substance use disorder. Scores were greater for relief (desire for the reduction of negative effects of withdrawal) than reward (desire for the rewarding effects of drugs).
- Moderate to high quality evidence suggests a medium-sized effect of reduced clozapine blood levels in smokers compared to non-smokers with schizophrenia. Clozapine dose was higher in the smoking group; those who quit smoking could have clozapine dose decreased.
- High quality evidence found small impairments in attention, working memory, learning, reasoning/problem solving, and speed of processing in smokers vs. non-smokers with schizophrenia. There were no differences in delayed memory, executive functioning (abstraction/shifting or inhibition), or language.

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Coustals N, Martelli C, Brunet-Lecomte M, Petillion A, Romeo B, Benyamina A

Chronic smoking and cognition in patients with schizophrenia: A meta-analysis

Schizophrenia Research 2020; 222: 113-21

View review abstract online

Comparison	**Cognition in smokers vs. non-smokers with schizophrenia.**
Summary of evidence	**High quality evidence (large samples, consistent, precise, direct) found small impairments in attention, working memory, learning, reasoning/problem solving, and speed of processing in smokers vs. non-smokers with schizophrenia. There were no differences in delayed memory, executive functioning (abstraction/shifting or inhibition), or language.**

Cognition

Small effects showed chronic smoking in patients with schizophrenia was associated with significant impairment in;

Attention: 12 studies, N = 3053, SMD = -0.12, 95%CI -0.22 to -0.02, $p = 0.02$, $I^2 = 19\%$

Attention impairment was increased by older age and higher PANSS total score.

Working memory: 6 studies, N = 1,473, SMD = -0.23, 95%CI -0.34 to -0.12, $p < 0.001$, $I^2 = 0\%$

Learning: 8 studies, N = 2,840, SMD = -0.18, 95%CI -0.26 to -0.10, $p < 0.001$, $I^2 = 0\%$

Reasoning/problem solving: 7 studies, N = 2,802, SMD = -0.18, 95%CI -0.27 to -0.10, $p < 0.001$, $I^2 = 5\%$

Speed of processing: 8 studies, N = 1,593, SMD = -0.19, 95%CI -0.29 to -0.08, $p < 0.001$, $I^2 = 0\%$

There were no significant differences in delayed memory, executive functioning (abstraction/shifting or inhibition), or language.

Consistency in results‡	Consistent
Precision in results§	Precise
Directness of results‖	Direct

Donde C, Achim AM, Brunelin J, Poulet E, Mondino M, Haesebaert F

A meta-analysis of craving studies in schizophrenia spectrum disorders

Schizophrenia Research 2020; 222: 49-57

View review abstract online

Comparison	**Craving scores in people with schizophrenia and a substance use disorder vs. people without schizophrenia and a substance use disorder. Substances included tobacco, cannabis, or cocaine.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) found a medium-sized effect of increased craving scores in people with schizophrenia and a substance use disorder compared to people without schizophrenia and a substance use disorder. Scores were greater for relief (desire for the reduction of negative effects of withdrawal) than reward (desire for the rewarding effects of drugs).**

Craving

A medium-sized effect showed increased craving scores in people with schizophrenia and a substance use disorder;

16 studies, N = 1,219, r = 0.20, 95%CI 0.15 to 0.26, $p < 0.001$, $Qp = 0.006$

Subgroup analysis showed a significantly greater effect for relief (desire for the reduction of negative effects of withdrawal) than reward (desire for the rewarding effects of drugs).

There were no moderating effects of substance type.

Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Huang H, Dong M, Zhang L, Zhong B-L, Ng CH, Ungvari GS, Yuan Z, Xiangfei M, Xiang Y

Psychopathology and extrapyramidal side effects in smoking and non-smoking patients with schizophrenia: Systematic review and meta-analysis of comparative studies

Progress in Neuro-Psychopharmacology & Biological Psychiatry 2019; 92: 476-82

Smoking

View review abstract online	
Comparison	**Effects of smoking in people with schizophrenia vs. non-smokers with schizophrenia.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) suggests small effects of more severe positive symptoms and less severe extrapyramidal symptoms in smokers with schizophrenia. There were no differences in negative, depression, anxiety, tardive dyskinesia, or parkinsonism symptoms.**
Symptoms	
Positive symptoms *Small effect showed smokers had more severe positive symptoms;* 24 studies, N = 4,641, SMD = 0.33, 95%CI 0.16 to 0.50, *p* = 0.0002, I^2 = 85% This effect was increased in non-European and non-Western Pacific regions, and in lower socioeconomic regions. Younger age and shorter illness duration also increased the effect size. There were no moderating effects of gender, diagnostic or outcome assessment tools used, or inpatient vs. outpatient status. Negative symptoms *There were no significant differences between groups;* 24 studies, N = 5,048, SMD = 0.14, 95%CI -0.01 to 0.29, *p* = 0.06, I^2 = not reported Younger age increased the effect size. There were no other moderating factors. Depression symptoms *There were no significant differences between groups;* 4 studies, N not reported, SMD = 0.11, 95%CI -0.06 to 0.28, *p* = 0.06, I^2 = not reported Anxiety symptoms *There were no significant differences between groups;* 2 studies, N = not reported, SMD = 0.06, 95%CI -0.27 to 0.38, *p* = 0.73, I^2 = not reported	
Extrapyramidal side effects	
Any extrapyramidal side effect *Small effect showed smokers had less severe extrapyramidal symptoms* 7 studies, N = 2,602, SMD = -0.20, 95%CI -0.38 to -0.02, *p* = 0.03, I^2 = 70% This effect increased with more males in the study. There were no other moderating factors. Tardive dyskinesia *There were no significant differences between groups;*	

4 studies, N = not reported, SMD = -0.01, 95%CI -0.13 to 0.11, p = 0.89, I^2 = not reported Parkinsonism *There were no significant differences between groups;* 2 studies, N = not reported, SMD = 0.17, 95%CI -0.54 to 0.88, p = 0.65, I^2 = not reported	
Consistency in results	Inconsistent where reported.
Precision in results	Precise
Directness of results	Direct

Lum A, Skelton E, Wynne O, Bonevski B

A systematic review of psychosocial barriers and facilitators to smoking cessation in people living with schizophrenia

Frontiers in Psychiatry 2018; 9: 565

View review abstract online

Comparison	**Barriers and facilitators of smoking cessation in people with schizophrenia.**
Summary of evidence	**Moderate quality evidence (large overall sample, unable to assess precision or consistency, direct) finds the following factors are barriers to smoking cessation: cravings and addiction, perceived risk of negative affect, social pressures, stress and boredom reduction, and weight management. Knowledge about health risks of smoking, physician advice and social pressures to quit helped facilitate smoking cessation.**
Smoking cessation	
23 studies, N = 3,557 *Barriers to smoking cessation;* 9 studies reported cravings and addiction 7 studies reported a perceived increased risk of negative affect 7 studies reported social pressures 5 studies reported stress reduction 5 studies reported boredom reduction 5 studies reported stimulation	

4 studies reported weight management *Facilitators to smoking cessation;* 8 studies reported health risks 7 studies reported physician advice 2 studies reported social pressures to quit	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Mitchell AJ, Vancampfort D, De Hert M, Stubbs S

Do people with mental illness receive adequate smoking cessation advice? A systematic review and meta-analysis

General Hospital Psychiatry 2015; 37: 14-23

View review abstract online

Comparison	**Receipt of smoking cessation advice in people with schizophrenia vs. people without a mental disorder.** **Note: results are for schizophrenia samples only.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, imprecise, direct) suggests no difference in smoking cessation advice between people with schizophrenia and people without a mental illness.**
Smoking cessation advice rates	
No significant difference in smoking cessation advice rates between those with and without schizophrenia; 3 studies, N = 542,129, RR = 1.09, 95%CI 0.68 to 1.70, Q_w = 109, $p < 0.001$ Authors report no evidence of publication bias.	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Myles N, Newall H, Compton MT, Curtis J, Nielssen O, Large M

The age at onset of psychosis and tobacco use: a systematic meta-analysis

Social Psychiatry Psychiatric Epidemiology 2012; 47: 1243-1250

View review abstract online

Comparison	**The impact of tobacco use on age at onset.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests no differences in the age at onset between people who use tobacco and people who do not use tobacco.**
Age at onset	
No differences between groups; 29 studies, N = 5,062, *d* = -0.03, 95%CI -0.14 to 0.08, *p* = 0.59, I^2 = 60.6% Authors report that no study or sample characteristic contributed significantly to between-study heterogeneity. These characteristics were male vs. female, first episode vs. chronic patients, age at first treatment vs. onset of positive symptoms, different measurement of tobacco use, different measurement of diagnosis, schizoaffective disorder vs. schizophrenia, differences in study quality, and study recruitment techniques.	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Sabe M, Zhao N, Kaiser S

Cannabis, nicotine and the negative symptoms of schizophrenia: Systematic review and meta-analysis of observational studies

Neuroscience and Biobehavioral Reviews 2020; 116: 415-25

View review abstract online

Comparison	**Negative symptoms in people with schizophrenia with current nicotine use vs. negative symptoms in people with**

	schizophrenia with no nicotine use.
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests no differences in negative symptoms between people with schizophrenia and current nicotine use and people with schizophrenia with no nicotine use.**
Current nicotine use	
No significant differences between groups; 45 studies, N = 8,942, SMD = 0.03, 95%CI -0.06 to 0.12, p = 0.55, I^2 = 65% There were no moderating effects of comorbid substance use.	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Thornton LK, Baker AL, Johnson MP, Lewin TJ

Attitudes and perceptions towards substances among people with mental disorders: a systematic review

Acta Psychiatrica Scandinavica 2012; 126: 87-105

View review abstract online

Comparison	**Attitudes towards substances in people with schizophrenia.**
Summary of evidence	**Moderate quality evidence (medium to large samples, unable to assess consistency or precision, direct) suggests the most commonly reported reasons for smoking were relaxation/stress reduction, dysphoria relief, sociability, craving/addiction. The most commonly reported reasons for quitting were self-control, health concerns, social influence.**
Attitudes to substances	
5 studies (N = 959) reported that people with schizophrenia who smoked cited reasons for use including: relaxation/stress reduction, dysphoria relief, sociability, craving/addiction. 1 study (N = 298) reported reasons for quitting were self-control, health concerns, social influence.	
Consistency in results	Unable to assess; no measure of consistency is reported.

Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Wagner E, McMahon L, Falkai P, Hasan A, Siskind D

Impact of smoking behavior on clozapine blood levels - a systematic review and meta-analysis

Acta Psychiatrica Scandinavica 2020; 142: 456-66

View review abstract online

Comparison	**Clozapine blood levels in smokers with schizophrenia vs. non-smokers with schizophrenia.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests a medium-sized effect of reduced clozapine blood levels in smokers compared to non-smokers with schizophrenia. Clozapine dose was higher in the smoking group. Authors suggest that patients on clozapine who quit smoking could have clozapine dose subsequently decreased with monitoring of clozapine blood levels.**

Clozapine blood levels

A medium-sized effect showed clozapine blood levels were significantly lower in smokers compared to non-smokers;

16 studies, N = 7,110, SMD = -0.39, 95%CI -0.55 to -0.22, $p < 0.001$, $I^2 = 80\%$

The effect size was greater in studies with more males. There were no consistent moderating effects of study quality, age, or region.

Clozapine dose was higher in the smoking group.

Authors suggest that patients on clozapine who quit smoking could have dosage subsequently decreased with monitoring of clozapine blood levels.

Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Explanation of acronyms

BPRS = Brief Psychiatric Rating Scale, CI = confidence interval, *d* = Cohen's d standardised mean difference, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, OR = odds ratio, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), PANSS = Positive and Negative Syndrome Scale, Q = Q statistic for the test of heterogeneity, *r* = correlation coefficient, RCT = randomised controlled trial, RR = relative risk, SMD = standardised mean difference, vs. = versus, WMD = weighted mean difference

Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[11].

† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) that allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect[11].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[12]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

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Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They can provide an indirect indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity.

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed[13].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C that allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

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